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SUBMISSION DATES: 9/29/93
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6/15/94

METFORMIN HCl (500 & 850 MG TABLETS)
GLUCOPHAGE®

ALPHA PHARMACEUTICALS, INC.
NEW YORK, N.Y.

REVIEWERS: M. DANIEL GORDIN, PH.D.
JOHN HUNT

TYPE OF SUBMISSION: ORIGINAL NDA FOR A NEW NME

CODE: 1P

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[Note: Appendix II contains more detailed information/data that can be obtained from the Division of Biopharmaceutics.]

RECOMMENDATION

The Division of Biopharmaceutics (DB) has reviewed NDA 20-357 for Metformin HCl (Glucophage®) that was originally submitted on September 29, 1993 by Lipha Pharmaceuticals, Inc. Based upon the evaluation of the submitted pharmacokinetic, etc. information, DB is of the opinion that the sponsor has overall adequately provided sufficient information to support the NDA's approval as related to meeting the Agency's biopharmaceutic regulatory requirements (21 CFR 320). However, in the sponsor's proposed package insert (PI), the Dosage and Administration section recommends/allows Glucophage® to be given concomitantly with any (by inference) of the US commercially available sulfonylurea drugs that are approved for treating hyperglycemia if Glucophage® monotherapy fails. Of concern is the availability of clinical data (particularly safety data), as well as pharmacokinetic drug-drug interaction data, for concomitant administration of Glucophage® with sulfonylurea drugs other than glyburide. Therefore, to help address this concern, the sponsor should attempt to determine what information might be available in the literature, etc. on concomitant administration for the other sulfonylurea drugs and submit it to the Agency for review.

The Recommendation, as appropriate, General Comment No. 1 (page 10) and Labelling Comment Nos. 1-8 (pages 11-13) should be forwarded to Lipha Pharmaceuticals, Inc.

7/6/94

M. Daniel Gordin, Ph.D.
John Hunt
Pharmacokinetics Evaluation Branch II

Biopharm Day: 5/31/94 (Drs. Collins, Ludden, Malinowski, Hepp, Fleischer, Chen)

Concurred by Mei-Ling Chen, Ph.D. 7/6/94

cc: NDA 20-357, HFD-510, HFD-426 (Fleischer), HFD-427 (M. Chen, Hunt), Drug, Chron, Reviewer, and HFD-19 (FOI), HFD-340 (Viswanthan), A, E, F, G, DI, RI

BACKGROUND

A. Drug

Metformin was developed approximately 30 years ago and it is on the market in over 50 countries. Metformin is an oral antihyperglycemic agent that is to be used in the management of non-insulin dependent diabetes mellitus (NIDDM) i) as monotherapy for those patients uncontrolled by diet alone or ii) as concomitant therapy with an oral sulfonylurea antihyperglycemic agent in patients who are no longer controlled by diet and monotherapy with either metformin or a sulfonylurea given at their respective maximum recommended doses. Glucophage® is to be contraindicated in patients with abnormal kidney or liver function, patients with serious acute or chronic cardicrespiratory disease, patients with hypersensitivity to the drug, patients undergoing radiologic studies with parental iodinated contrast materials, and alcoholic patients and patients >70 years of age.

The mechanism of action for the antihyperglycemic effect of metformin is not completely understood, although it is probably multifactorial. Metformin does not lower blood glucose by stimulation of insulin secretion as do the sulfonylureas. Possible mechanisms include: increased cellular glucose uptake; decreased hepatic gluconeogenesis; potentiation of insulin action at the receptor or post receptor level; decreased intestinal glucose absorption; increased insulin receptor binding; and/or stimulation of anaerobic glycolysis. One proposed mechanism suggests that metformin could inhibit glucose absorption by inhibiting Na-glucose transport across brush border enterocytes. The degree of glucose transport inhibition could be linked to the concentration of metformin in the small intestine. Thus, the less metformin absorbed, the more inhibition and less glucose ultimately absorbed [Vidon N et.al.; Metformin in the digestive tract; *Diabetes Research and Clinical Practice* 4:223 (1988)].

The most serious and life threatening side effect of metformin is lactic acidosis which is due to the overproduction of lactate through the inhibition of mitochondrial respiration and increased anaerobic glycolysis and decreased lactate utilization by inhibition of gluconeogenesis. Other side effects include cramping, nausea, diarrhea among others.

Metformin HCl, a biguanide hydrochloride salt of N,N-dimethylimidodicarbonimidic diamide, does not have any chiral centers. It is freely soluble in water and practically insoluble in inorganic solvents.

B. **Dosage & Administration**

From the sponsor's proposed package insert (see pages 32 - 35) it indicates that for Glucophage® there is no fixed dosage regimen. Dose is to be individualized on the basis of effectiveness and tolerance. During initial titration, Glucophage® should be given with meals at a low dose to reduce gastrointestinal side effects (e.g., one tablet per day). The maximum recommended daily dose is 2550 mg. Glucophage® monotherapy (i.e., started because diet alone or diet with a sulfonylurea drug doesn't work) can be followed by concomitant therapy with an oral sulfonylurea if Glucophage® maximum dose monotherapy does not work. Blood glucose and glycosylated hemoglobin are to be periodically monitored to help determine i) the minimum effective dose and ii) to detect drug/dose failures.

From the March 18, 1994 Advisory Committee Meeting for this NDA, the committee recommended approval of the drug with two provisos:

> [1] That dosing be done in the following manner in individual patients: After measuring their glycated hemoglobin values, patients should initially be administered 500 mg/day or 850 mg/day, followed within a week or two with an upward titration to 850 mg b.i.d. This dose should be maintained for three months after which glycated hemoglobin should be measured again. If the results are not satisfactory, the patients should be given 850 mg t.i.d. for another three months after which glycated hemoglobin should be measured again. If the third glycolated hemoglobin value shows an improvement over the second, the dosage should be maintained. If not, the patient should be returned to the 850 mg b.i.d. dose.
>
> [2] That a post-marketing surveillance be instituted to assess the rate of mortality of patients treated with metformin.

The reviewing medical officer for the NDA's efficacy evaluation portion is suggesting that the company perform a dose-response study prior to engaging in post-marketing surveillance.

PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD), etc. SUMMARY

A. BIOAVAILABILITY

From one published study by Pentikainen et. al. (Appendix I, page 15), it was determined that metformin's oral absolute bioavailability was about 50-60% following single fasting oral (1 X 500 mg ^{14}C-metformin HCl tablet) and intravenous (500 mg ^{14}C-metformin HCl) doses. In another fasting study (No. 89-11-6023, Appendix I, page 16), 1 X 850 mg market tablet was shown to be bioequivalent to an 850 mg oral solution.

B. SINGLE DOSE KINETICS

Following a single 500 mg intravenous (iv) dose (Appendix I, page 15), metformin's plasma level profile was defined by a three compartment open model where the mean plasma terminal elimination half-life determined between 3 - 10 hr post-dose was 1.7 hr. Metformin is not metabolized and 99.9% of the iv dose was excreted unchanged in urine. The mean terminal elimination half-life determined from urinary excretion rate data was 8.9 hr. The mean iv plasma clearance and renal clearance values were 459 ml/min and 454 ml/min, respectively, and the mean volume of distribution (Vd_{ss}) was 69 L.

For oral administration of a 500 mg tablet dose in the same study, the mean terminal elimination half-life from urinary excretion rate data was 8.4 hr. About half of the administered dose was recovered in urine as unchanged drug and the mean renal clearance value was 444 ml/min. The high net iv and oral renal clearance values indicate that renal tubular secretion is occuring. Following oral administration, one subject had 61.1% of the dose recovered in urine over 48 hr plus 29.4% recovered in feces following one week of fecal sample collection.

For metformin there is no plasma protein binding as determined by equilibrium dialysis and ultrafiltration but metformin has been shown to distribute into RBCs. The whole blood elimination half-life was found to be approximately 18 hours for which it is felt that RBCs act as a deep distribution compartment.

C. MULTIPLE DOSE KINETICS

From Study No. 89-12-6023 (Appendix I, page 20), metformin's pharmacokinetics in healthy subjects (n = 9) and NIDDM patients (n = 9) were determined i) following a single 1 X 850 mg market tablet fasting dose and ii) following 6 days administration (i.e., dose #19 which was an AM dose on Day 7) using the highest recommended daily dose of 2550 mg and the most frequent dosing regimen (i.e., t.i.d.). The study's results demonstrated that:

1. Metformin's single dose and multiple dose PK were not different in normal healthy subjects and NIDDM patients.

2. Linear kinetics were observed following multiple doses using the highest recommended daily dose and the most frequent dosing regimen.

3. There is little metformin accumulation using the t.i.d. dosing regimen.

D. DOSE PROPORTIONALITY

From two separate single dose studies that used the to-be-marketed tablets given under fasting conditions, there was a less than proportional increase in metformin's systemic plasma drug levels (AUC) with increased dose.

		"X" Fold Increase	
		Theoretical	Observed
1. Study #89-11-6023	1x850 mg tab[1] / 1x500 mg tab	1.7	1.5
2. Study #89-12-6023	2x850 mg tab[1] / 1x850 mg tab	2.0	1.5
	3x850 mg tab[1] / 1x850 mg tab	3.0	2.0
	2x850 mg tab[2] / 1x850 mg tab	2.0	1.6
	3x850 mg tab[2] / 1x850 mg tab	3.0	2.1

1 - Healthy subjects.
2 - NIDDM patients.

Plasma Cmax values were also less than proportional with dose to approximately the same degree as AUC. Mean Tmax ranged from 1.8 to 3.6 hr but showed no apparent relationship to dose.

E. METABOLISM

The sponsor did not conduct a study to assess metformin's metabolism. However, from a publication by Pentikainen et. al. it was determined that metformin is not metabolized.

F. FOOD EFFECT

The results of a food effect study (No. 89-11-6023; Appendix I, page 17) showed that when metformin was administered with a high fat breakfast, the rate and extent of metformin absorption from the

GI tract were less than when metformin was administered under fasting conditions. Mean AUC and Cmax fed values were 21% and 39% less when compared to respective fasting values. [Note: The PI recommends that metformin be taken with meals in order to decrease the gastrointestinal side effects associated with metformin.]

G. SPECIAL POPULATIONS

1. Gender

From two separate PK studies (Appendix I, page 46) where males and females received single fasting 1 X 850 mg tablet doses, data analyses indicated that the disposition of metformin was not significantly different between men and women. The numbers per gender per PK study were somewhat small but the two studies findings support each other.

2. Elderly

From Study No. 90-13-6023 (Appendix I, Page 28), the results demonstrated a decrease in both metformin plasma clearance (-37%) and renal clearance (-35%) in an elderly group (n=12; age 65-81) compared to a young group (n=6; age 25-37). These clearance changes resulted in 76% and 60% increases in respective mean plasma Cmax and AUC(inf) values. [Note: On page 26 of the PI (Precautions Section) it raises caution regarding the use of metformin in patients >65-70 years of age and on PI pages 26 and 34 the sponsor contraindicates metformin's use in patients >70 years of age.]

3. Renal Patients

The elimination of metformin is renally dependent. On page 11 of the proposed PI it states the following.

"1. GLUCOPHAGE is contraindicated in patients with abnormalities of renal function, e.g., serum creatinine levels ≥ 1.5 mg/dL (males), ≥1.4 mg/dL (females). Even mild impairment of renal function can result in GLUCOPHAGE accumulation and increases the risk of lactic acidosis (see WARNINGS and PRECAUTIONS for additional information)."

Also, the PI (page 13) indicates that when lactic acidosis occurs, metformin plasma levels are generally ">5 mg/L".

From Study No. 90-13-6023 (Appendix I, page 28), the PK of metformin in patients with different degrees of renal impairment was studied. All patients received a single fasting 1 X 850 mg tablet dose. For the mildly (n=5), moderately (n=4) and severely impaired (n=6) renal

patients, the mean metformin Cl_{ren} values were 384, 108 and 130 ml/min, respectively, as compared to 636 ml/min for healthy subjects (n=6). The corresponding mean plasma CL/F values were 852, 238, 259, and 1155 ml/min while mean plasma t1/2 values were respectively 17.3, 16.2, 17.2, and 6.9 hr. The mean single dose metformin plasma Cmax values for the renally impaired patients, in order of decreasing kidney function were 1.9, 4.1 and 3.9 mcg/ml. Further multivariate regression analysis by the sponsor demonstrated that both renal function (as measured by creatinine clearance adjusted for body surface) and age are predictors of metformin clearance (both total and renal). While creatinine clearance as a single covariate was significant, age was only significant when creatinine clearance was considered and was not significant as a single covariate (Appendix I, page 29).

H. **PK/PD**

From Study No. 89-12-6023 (Appendix I, page 19), following single dose administration of 850 mg, 1700 mg, and 2250 mg metformin, the average plasma glucose concentration across the doses did not differ significantly. The sponsor stated that due to this finding, a concentration-effect data analysis was not performed. Following multiple dose administration at the top dose of 2250 mg, there were however significant decreases in average fasting, 2 hr postprandial and 6 hr postprandial glucose concentrations in NIDDM patients. Example, the average (± SD) fasting plasma glucose concentration was 131 ug/dl (± 27) after multiple doses of metformin compared to 172 (± 42) ug/dl with placebo.

I. **FORMULATIONS**

Clinical studies and the PK studies used the to-be-marketed tablet formulations. The batch sizes for the tablet lots used in the PK studies represented at least half of what full scale production size batches will be. The US commercial tablets are to be manufactured in the UK. The tablet formulations, which are proportional in active to inactive ingredients, are as follows:

	500 mg	850 mg
Metformin HCl	500	850

J. DISSOLUTION

The sponsor's proposed in vitro dissolution method is that of the British Pharmacopoeia 1988 (Vol. II, pp. A143-A144, Appendix XIID).

Basket Method (Identical to USP XXII Apparatus I Method)
100 rpm
1000 ml pH 6.8 buffer
37 ± 0.5°C
N = 5 tablets

Specification: "Not less than in 45 min" is proposed in the submission.

Dissolution profiles for i) two production size batches (Nos. CMC and ACE) for each tablet strength, ii) three clinical trial lots and iii) dissolution in 0.1N HCl are as follows. (Note: All tablet lots used in the PK studies had about 100% dissolution in 45 min.)

1. Batch No. CMC (Control No. 109448) – 500-mg Tablets

	Amount released after:-				
Tablet No.	5 min	15 min	25 min	35 min	45 min
1					
2					
3					
4					
5					
Mean	41.7%	86.4%	99.2%	99.0%	97.8%
Adjusted*	41.7%	86.8%	100.5%	101.3%	101.1%

2. Batch No. ACE (Control No.110179) – 850-mg Tablets

	Amount released after:-				
Tablet No.	5 min	15 min	25 min	35 min	45 min
1					
2					
3					
4					
5					
Mean	40.8%	92.0%	99.9%	99.1%	98.0%
Adjusted*	40.8%	92.4%	101.2%	101.5%	101.4%

3. 500-mg Tablets Used in Clinical Trials

a) In pH 6.8 buffer medium

	Amount released after:-			
Lot No.	5 min	15 min	28 min	45 min
123				
137				
146				
Mean	45%	89%	100%	102%

b) In 0.1N Hydrochloric Acid

	Amount released after:-					
Formula	5 min	10 min	15 min	30 min	45 min	60 min
UK 3-500						

GENERAL COMMENT

1. The in vitro dissolution method and specification that are proposed for Glucophage® need modification. First, the method should require the testing of a minimum of six (6) dosage units per run instead of five (5) dosage units which appears to be what is currently proposed. Additionally, the "Acceptance Table" approach as described on page 1579 of USP XXII/NF XVII (1990) should also be employed. Lastly, a specification of Q = in 30 minutes should be adopted for both tablet strengths.

LABELING COMMENTS

1. According to the proposed package insert for Glucophage®, it allows Glucophage® to be given concomitantly with the marketed US sulfonylurea products that are indicated for treating hyperglycemia. Knowing that systemically absorbed metformin is only eliminated via the kidney and that it is renally excreted by active processes, there is a concern that there could be possible drug-drug interactions between Glucophage® and sulfonylurea drug products that it may be given with. The basis for this concern is founded on the urinary excretion information that has been published by Oates et.al. [*The New England Journal of Medicine* 321:1231 (1989)] for the drugs acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide and tolbutamide. From that publication it indicates that 98%, 61%, 85%, 47%, 93% and 98% of administered doses for the respective drugs are excreted via the kidney as metabolites. (Note: Some are active for certain drugs.) For glyburide, the drug interaction study (No. 89-2B-6023) that was submitted in the NDA indicated no significant drug interaction. However, of all the sulfonylurea drugs, glyburide has the least urinary excretion of its metabolites. Therefore, in the package insert a statement should be made that identifies those sulfonylurea drugs where there is clinical and/or pharmacokinetic drug-drug interaction data available for concomitant metformin administration and a statement should be made that identifies those sulfonylurea drugs where there is no such information available for metformin concomitant administration.

2. Currently FDA is attempting to standardize the content and presentation of information/data that is to be given in the **Pharmacokinetics** section of the **Clinical Pharmacology** section of a product's package insert. Therefore, it is recommended that the package insert's **Pharmacokinetics** section be reorganized to present appropriate information/data under the subheadings of **Absorption, Distribution, Metabolism**, and **Excretion.** Following this, there should then be a section with the heading of **Special Populations** and appropriate pharmacokinetic (PK) data should be included under the subheadings of **Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency** and **Drug-Drug Interactions.** Where relevant information/data are lacking it should be so stated.

Lastly, a table with PK parameters to include Absolute Bioavailability, Tmax, Oral Clearance, Apparent Volume of Distribution, Half-life (including effective half-life) and Renal Clearance for normals and each special population, including the drug's intended target population (and where numbers of subjects/patients are indicated), should be prepared. For metformin, since there appears to be a plasma concentration (i.e., >5 mcg/ml) that is associated with the occurrence of lactic acidosis, then peak metformin plasma concentration information should also be included for the different doses/dosing regimens in

the different populations studied. Mean values (with the coefficients of variation) and 95% confidence intervals should be provided.

3. Carried out have been a number of pharmacokinetic (PK) studies where the same dose(s) of metformin was given and where collected blood/plasma/urine samples were assayed at the same facility using the same assay methodology. Therefore, for providing mean PK parameter values for the package insert, all the relevant and appropriate data from across the different studies should be used.

4. For the information that is currently provided for the effect of meals on metformin's absorption, the data for the comparison of the tablet given with and without meals should replace those for the tablet given with meals versus the oral solution given under fasting conditions.

5. Currently the proposed package insert makes a banket statement that contraindicates the use of Glucophage® in patients >70 years of age which does not appear to be based upon pharmacokinetic principles. Additionally, patients with all degrees of compromised kidney function are also contraindicated from using metformin. Knowing that the pharmacokinetic characteristics of this drug have been evaluated as related to both age and kidney function, it is regrettable that an effort was not made to address possible dose adjustment strategies so that patients in these contraindication categories could also be allowed the possible efficacy benefits of metformin therapy.

6. In the submitted NDA, the results of six single dose drug-drug interaction pharmacokinetic studies were provided. For metformin, the bases for potential drug-drug interactions could be due to i) effects on metformin's absorption processes (which are not understood at this time) and ii) effects on metformin's renal excretion processes. Of the drugs that were evaluated for concomitant metformin administration, cimetidine, which competes for metformin's urinary excretion processes, appears to be the drug of most concern for potential clinical consequences. For the other drugs that were tested (i.e., based on single dose data) the results would probably suggest that there is less of a clinical concern.

However, there are a number of other drugs that were not tested where it could be hypothesized that there could be significant interactions with metformin. Example, other drugs that might compete with metformin's renal elimination via the cationic tubular secretion pathway (e.g., amiloride, digoxin, morphine, procainamide, trimethoprim, ranitidine, etc.). Therefore, the sponsor should attempt (via a consultant if necessary) to identify all drugs that might have a potential for interaction with metformin or vice versa. In making these assessments drug kinetics, administered doses and dosing frequency for the other

drugs that would be given with metformin should be considered. Lastly, for this requested drug-drug interaction evaluation, an assessment should be made as to what the clinical safety and efficacy consequences might be for each drug that is covered. Ultimately, following this evaluation additional statements in the package insert may be needed.

7. In the package insert under the Drug Interactions section, the blood/plasma PK parameter results for the metformin-furosemide drug interaction study are summarized. The changes that were observed for these parameters for each drug were speculated to be the result of changes in each drug's biovailability. However, since the urinary excretion results for both drugs don't strongly support the conclusions that there were changes in each drug's bioavail .bility, the related statements that infer this should be deleted.

8. In the package insert under the Contraindications section it indicates that patients with abnormalities of renal function, as assessed by certain serum creatinine levels, should be contraindicated. This section should be updated to also indicate what creatinine clearance values should be used to contraindicate patients in case creatinine clearance is determined in some cases for patients.

APPENDIX I

Pentikainen P.J., et.al. Pharmacokinetics of Metformin after Intravenous and Oral Administration to Man. Eur. J. Clin. Pharmacol. 16:195 (1979).

[A study (ies) in which metformin was administered intravenously in order to determine its oral absolute bioavailability and to determine its metabolism was not performed by the sponsor. This journal article was however referenced which is abstracted below.]

The kinetics of ^{14}C-metformin HCl were studied in healthy subjects (3 F and 2 M) after 500 mg oral (as a tablet) and iv doses that were administered following an overnight fast. All 5 subjects received oral administration but only 3 sujects received iv administration. Blood samples were obtained at 0, 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post oral dose. Following the iv dose, 2 and 15 min blood samples were also obtained. Urine was collected at 0-1, 1-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-32, and 32-48 h after drug administration. Fecal samples were collected for one week following the iv (3 subjects) and oral (1 subject) doses. Saliva samples were collected 1, 2, 3, 5, 8, and 12 h after drug administration. Total radioactivity in plasma, urine, and feces was measured by liquid scintillation counting. Urine samples were extracted several times with n-butanol after adding sodium hydroxide. The extracts were subjected to two-dimensional thin layer chromatography (TLC). Also chromatograms of urine samples were run directly without pre-extraction.

RESULTS: The publication summarizes the study's findings as follows.

"The intravenous dose was distributed to a small central compartment of 9.9 ± 1.61 L (X±SE), from which its elimination could be described using a three-compartment open model. The elimination half-life from plasma was 1 7 ± 0.1 h. Urinary excretion data revealed a quantitatively minor terminal elimination phase with a half-life of 8.9 ± 0.7 h. After the intravenous dose, metformin was completely unchanged in urine with a renal clearance of 454 ±47 ml/min. Metformin was not bound to plasma proteins. The concentration of metformin in saliva was considerably lower than in plasma and declined more slowly. The bioavailability of metformin tablets averaged 50-60%. The rate of absorption was slower than that of elimination, which resulted in a plasma concentration profile of "flip-flop" type for oral metformin."

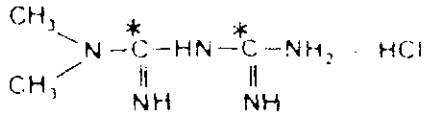


Fig. 1. Structural formula of metformin HCl with asterisks showing the position of ^{14}C label

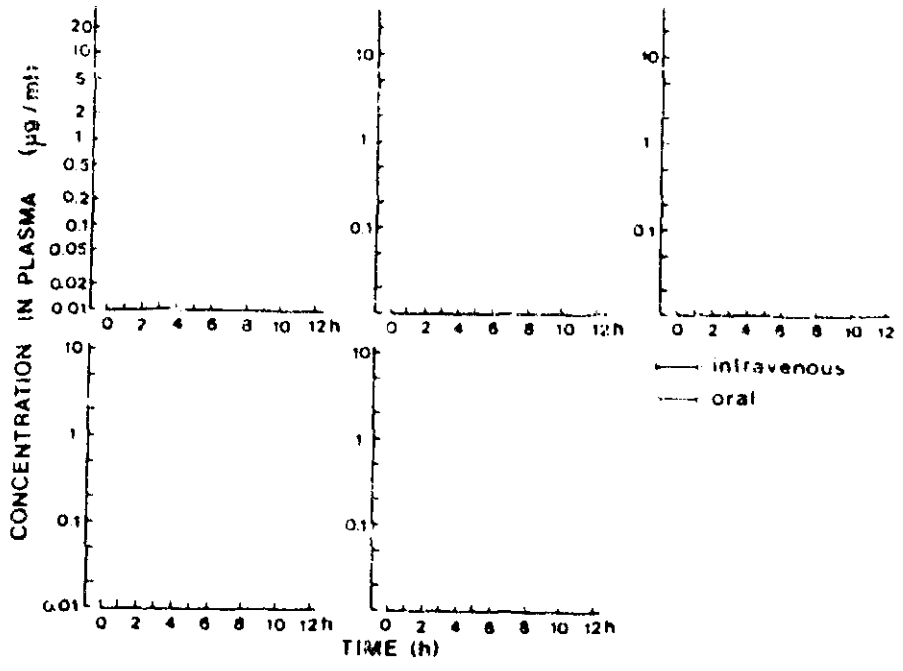


Fig. 3. Plasma concentration of metformin and computer-determined best fitting pharmacokinetic functions for five healthy volunteers who received i. v. and oral doses of 4.4 μCi/500 mg ^{14}C-metformin HCl

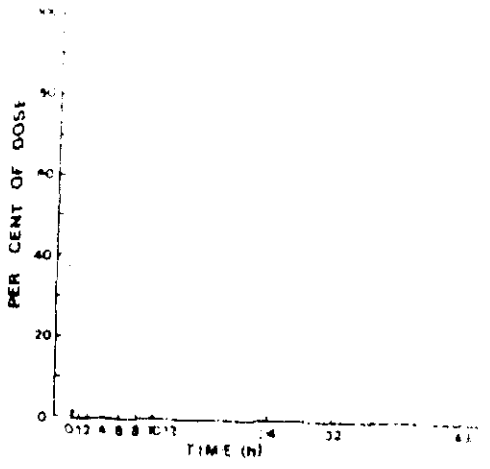


Fig. 4. Cumulative excretion of metformin in urine in [illegible] healthy volunteers following administration of 4.4 μCi, 500 mg ^{14}C-metformin HCl intravenously (N = 3) and orally (N = 5, excluding those [illegible] intravenous dose). mean ± SE

Table 3. Model independent parameters of ^{14}C-metformin[a] pharmacokinetics, calculated from intravenous injection experiments in three healthy volunteers

Parameter	Subject	Mean	SE
Plasma clearance ml/min		459	6
Renal clearance; ml/min		454	47
Elimination half-life determined from plasma h[b]		1.74	0.11
Terminal half-life determined from excretion rate in urine h[c]		8.93	0.68
AUC_∞ μg × h × ml^{-1}		17.64	0.38
Vd_{area} l		69.0	4.5
Recovery in urine, % of dose[d]		39.9	0.8

[a] Dose 4.4 μCi/500 mg metformin HCl.
[b] Based on plasma concentrations between 3 and 10 h after drug administration.
[c] Based on urinary excretion rate between 12 and 48 h. after drug administration.
[d] During 48 h following administration of the drug.

Table 4. Observed pharmacokinetic parameters of ^{14}C-metformin[a] following oral administration to five healthy volunteers

Parameter	Subject	Mean	SE
T_{max} h[b]		3.9	0.43
C_{max} μg ml^{-1}[c]		1.55	0.24
AUC_∞ μg × h × ml^{-1}		9.08	1.54
AUC_∞ AUC_∞ × 100		59.6	8.3
Half-life of absorption h		2.63	0.18
Terminal elimination half-life h[d]		8.41	0.58
Renal clearance ml/min		344	23
Recovery in urine, % of dose[e]		51.6	5.2

[a] Dose 4.4 μCi/500 mg metformin HCl.
[b] Time of peak plasma concentration following drug intake.
[c] Peak plasma concentration.
[d] Determined from urinary excretion rate between 12 and 48 h after drug intake.
[e] During 48 following drug intake.

TITLE: BIOEQUIVALENCE AND FOOD/FASTING STUDY OF METFORMIN FORMULATIONS IN 24 HEALTHY MALE SUBJECTS (Study # 89-11-6023, Volume 1.42)

INVESTIGATORS:

OBJECTIVES: To compare 500 mg and 850 mg metformin tablets to an 850 mg solution and to assess the effect of a standard, high fat, high caloric breakfast.

DESIGN:

Open-label, single dose, crossover study involving 24 healthy, male subjects who were randomized into 4 treatments separated by a 1 week washout:

Treatment A - 500 mg metformin tablet fasting (overnight+4 h)
Treatment B - 850 mg metformin tablet fasting "
Treatment C - 850 mg metformin solution fasting "
Treatment D - 850 mg metformin tablet given within 15 minutes of a high fat breakfast (2 scrambled eggs, 2 slices bacon, 8 oz whole milk, 4 oz hash browns, 1 piece toast, and 1 pat butter)

Blood samples obtained at 0, 20, 40, 60 min, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, & 48 hrs post dose. Urine samples were collected at -1-0, 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hr.

ANALYTICAL:

RESULTS:

Key Pharmacokinetic Parameters, Lipha U.S. Study No. 89-11-6023 Bioequivalence and Food/Fasting Study of Metformin Formulations in 24 Healthy Male Subjects

PARAMETER*	METFORMIN DOSE AND DOSAGE FORM			
	850 MG SOLUTION, FASTING	850 MG TABLET, FASTING	850 MG TABLET, WITH FOOD	500 MG TABLET FASTING**
C_{max} (µg/ml):				
Plasma:	1.50±0.41	1.58±0.40	0.97±0.19	**1.75±0.55**
Blood:	1.01±0.30	1.03±0.24	0.67±0.17	**1.17±0.03**
t_{max} (hr):				
Plasma:	2.49±0.71	2.77±0.71	3.35±1.30	2.75±0.81
Blood:	2.73±0.91	2.86±0.78	3.32±1.14	2.73±0.84
AUC (µg/ml•hr):				
Plasma:	9.31±2.71	9.82±2.71	7.41±1.59	**11.14±3.00**
Blood:	8.86±3.56	9.00±3.02	6.92±2.20	**10.43±2.90**
AUCX (µg/ml•hr):				
Plasma:	9.59±2.80	10.07±2.76	7.65±1.59	**11.47±3.01**
Blood:	10.66±4.23	10.43±3.48	8.88±4.34	**12.07±3.32**
k_a (hr^{-1}):				
Plasma:	0.147±0.053	0.133±0.043	0.142±0.044	0.153±0.054
Blood:	0.050±0.035	0.064±0.044	0.057±0.040	0.058±0.033
Oral plasma clearance (CL/F) (ml/min)	**1,243±313**	**1,182±308**	**1,508±377**	**1,028±235**
Renal clearance: (CL_R) (ml/min)	605±127	573±155	633±163	598±132
Time of peak urinary excretion rate (hr)	3.04±1.80	3.27±1.91	4.55±2.63	2.67±1.52
Peak excretion rate (mg/hr)	41.8±9.2	41.5±9.8	30.7±8.8	**47.1±10.5**
Urinary excretion in mg (% of administered dose, corrected for HCl)	323±73.1 (49%)	329±86.4 (50%)	276±54.5 (42%)	**385±62.9 (58%)**

* Values given are means, ± standard deviation.

** Values for Cmax, AUCUN, AUCX, peak excretion rate and urinary excretion, shown in bold, are normalized to 850 mg. Actual values are: 1.03±0.33, 6.55±1.75, 8.75±1.77, 27.7±8.20, and 227±36.1, respectively

CONCLUSIONS:

1. Following single doses, metformin was not exactly proportional between 1 X 500 mg tablet and 1 X 850 mg tablet under fasting conditions. For a 70% increase in dose, mean plasma AUC(inf) increased only 40%, plasma Cmax increased 60%. Employing the bioequivalence (BE) Two One Sided Tests Procedure on AUC(inf) for 1 X 850 mg tablet (test) versus 1 X 500 mg tablet (reference) whose AUC(inf) values were normalized to a 850 mg dose, the 90% C.I. was 75.7% to 99.9%. The sponsor stated that because renal clearance (Clr) did not differ significantly, this may reflect dose dependent absorption rather than elimination.

2. When given with a high fat breakfast, the metformin 850 mg tablet mean AUC(inf) and Cmax plasma values were 24% and 39%, respectively, lower compared to fasting which is significant.

3. Metformin partitions into blood RBCs and its elimination rate from blood is slower than that from plasma [i.e., Kel_{blood} = 0.057 hr^{-1} (t1/2 = 12 hr) versus Kel_{plasma} = 0.144 hr^{-1} (t1/2 = 4.8 hr)]. This suggests that RBCs may act as a deep compartment.

4. The PK parameters for the 850 mg oral solution (reference) and the 850 mg market tablet administered under fasting conditions were not significantly different. The BE 90% C.I. values for plasma untransformed AUC(inf) and Cmax were 98% to 112% and 97.1% to 114%, respectively. The Tmax values were 2.5 hr and 2.8 hr, respectively.

TITLE: SINGLE AND MULTIPLE DOSE STUDY OF METFORMIN IN HEALTHY SUBJECTS AND IN NIDDM PATIENTS (Study # 89-12-6023; Volume 1.44)

INVESTIGATORS:

OBJECTIVES: To assess the multiple dose kinetics and dynamics of metformin.

DESIGN:

This study consisted of two treatment phases: a single-blind, randomized crossover Single Dose Phase followed by an open-label Multiple Dose Phase involving 9 NIDDM patients (4F&5M; 12 originally randomized but 2 dropped out due to AEs of nausea and vomiting, and 1 due to personal reasons) and 9 healthy subjects (4F&5M; 10 originally but 1 dropped out due to personal reasons). Treatments in the Single-Dose Phase were separated by a 1 week washout. The treatments were as follows:

Single Dose Phase

Trt A fasting; 1 X 850 mg tablet + 2 placebo tablets
Trt B fasting; 2 X 850 mg " + 1 placebo tablet
Trt C fasting; 3 X 850 mg " - .
Trt D fasting; 3 placebo tablets

Multiple Dose Phase

Trt E 1 X 850 mg tablet tid with main meals at 8 am, 12 noon, and 6 pm (as outpatients) for 16 doses followed by 3 doses given every 8 hr under fasting conditions within the clinic.

Blood samples obtained during treatments A, B, C, and D were 0, 20, 40, 60 min, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hr post-dose. Urine samples were collected at -1-0, 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hr. For treatment E, trough levels were taken before the am doses. On Day 6 subjects took their 8:00 am dose (Dose 16) with breakfast and thereafter continued on an every 8 hr dosing schedule without concomitant food administration [i.e., Dose 17 (4:00 pm), Dose 18 (midnight), Dose 19 (8:00 am)]. Following the last dose (Dose 19, Day 7), blood was obtained at 0, 20, 40, 60 min, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 48 hr post-dose. Two ml aliquots of each whole blood sample were assayed for metformin and harvested plasma samples were assayed for metformin, glucose, lactate and insulin. (Note: Only plasma samples up to 10 hr were assayed for glucose, lactate and insulin.) Urine samples collected at -1-0, 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hr.

RESULTS:

Trough (Eight-Hour Post-Dose) Plasma Metformin Concentrations in 9 Subjects with NIDDM and 9 Healthy Subjects Following Single and Multiple 850 mg Oral Doses of Metformin (U.S. Study No. 89-12-6023)

TREATMENT (A = single dose; E = multiple doses)	Time Since First Dose of Treatment		Plasma Metformin Concentration (ng/ml) (Mean ± S.D.)		
	Days	Hours	All Subjects	NIDDM	Non-diabetic
A	0	8	655.6±335.0	741.3±443.6	569.8±158.4
E	1	24	211.9±78.7	212.7±96.6	211.2±61.8
E	2	48	269.8±165.6	255.4±117.4	286.0±215.3
E	3	72	276.9±127.7	278.3±120.5	275.6±141.9
E	4	96	346.0±173.3	364.2±168.4	325.5±188.0
E	5	120	313.8±133.9	304.6±107.3	327.7±177.1
E	6	144*	923.9±327.6	947.9±413.9	896.6±221.1
E	6	152*	705.2±298.6	769.2±376.5	641.2±196.2

* - Just prior to the last dose

* - Eight hours after the last dose

PARAMETER ESTIMATES RELATED TO PLASMA METFORMIN IN [illegible] HEALTHY SUBJECTS AFTER METFORMIN HCL SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E) [illegible]

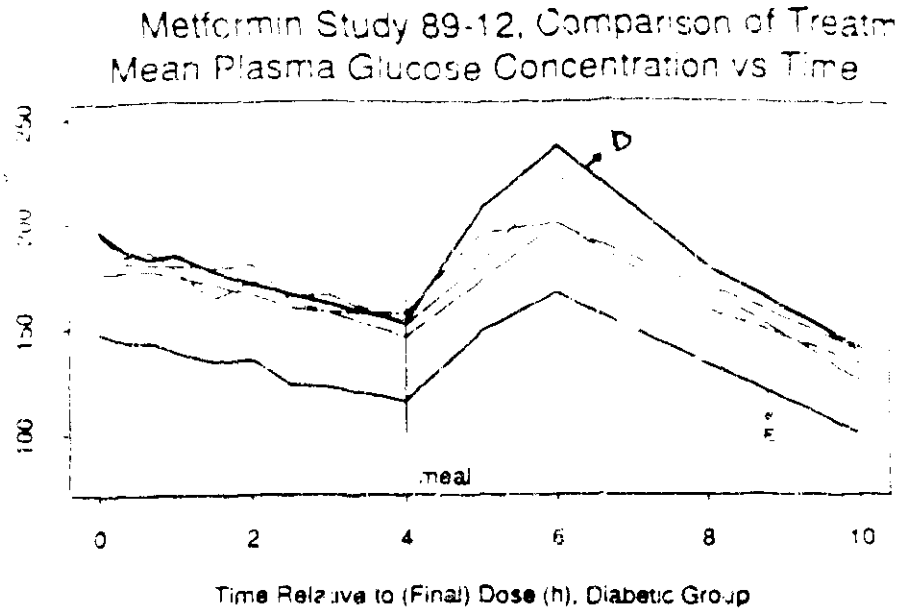
Parameter	Estimate (mean ± SD)				ANOVA POSTHOC*	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
t_{max} (h)	2.92 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
C_{max} (µg/ml)	[illegible] (0.61)	2.01 (0.56)	3.64 (1.16)	2.01 (0.42)	NA	NA
Norm C_{max}* (µg/ml)	1.81 (0.61)	1.30 (0.28)	1.21 (0.39)	2.01 (0.42)	C B A	NA
AUC (µg h/ml)	12.00¶ (3.22)	17.85 (3.85)	24.03 (7.75)	NA	NA	NA
Norm AUC* (µg h/ml)	12.00¶ (3.22)	8.93 (1.92)	8.01 (2.58)	NA	C B A	NA
AUCX§ (µg h/ml)	12.23 (3.30)	18.20 (3.89)	24.32 (7.72)	10.73 (2.78)	NA	NA
Norm AUCX* (µg h/ml)	12.23 (3.30)	9.10 (1.95)	8.13 (2.56)	10.73 (2.78)	C B A	E D
k (h^{-1})	0.167 (0.038)	0.127 (0.049)	0.095 (0.042)	0.066 (0.028)	C B A	E D
$t_{1/2}$ (h)	4.6 (2.2)	6.3 (2.5)	8.2 (2.4)	13.0 (7.7)	A B C	A E
CL/F (L/h)	58.1 (16.5)	76.2 (17.9)	89.1 (27.2)	81.2 (29.5)	A B C	A E
CL_R (L/h)	31.5 (10.3)	27.3 (7.0)	27.7 (6.8)	38.5 (10.4)	B C A	A E

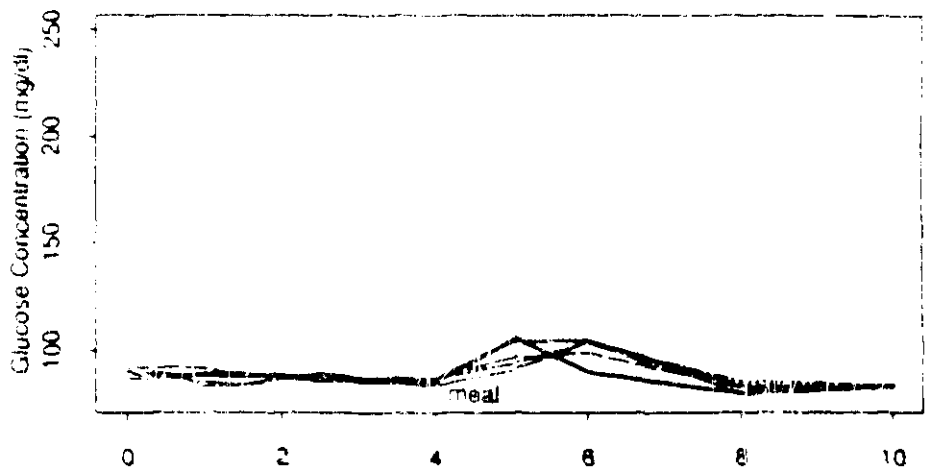
* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.
‡ Normalized to 850 mg
§ $AUC_{0-\infty}$ for single doses and $AUC_{0-8\ h}$ for Treatment E.
¶ $AUC_{0-8\ h}$ for Treatment A = 9.28 ± 2.39 µg.ml

PARAMETER ESTIMATES RELATED TO PLASMA METFORMIN IN 9 SUBJECTS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS AFTER METFORMIN HCL SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E)
(DSU #89-12/LIPHA #89-12-6023)

Parameter	Estimate (mean ± SD)				ANOVA POSTHOC*	
	850 mg x 1 (Tx A)	850 mg x 2 (Tx B)	850 mg x 3 (Tx C)	850 mg MD† (Tx E)	Tx A vs Tx B vs Tx C	Tx A vs Tx E
t_{max} (h)	3.28 (1.15)	3.12 (1.44)	2.41 (1.02)	2.01 (1.22)	C B A	NA
C_{max} (µg/ml)	1.51 (0.46)	2.62 (0.53)	3.29 (1.00)	1.90 (0.62)	NA	NA
Norm C_{max}* (µg/ml)	1.51 (0.46)	1.31 (0.27)	1.10 (0.33)	1.90 (0.62)	C B A	A E
AUC (µg h/ml)	11.41¶ (3.78)	18.55 (4.20)	24.06 (8.69)	NA	NA	NA
Norm AUC* (µg h/ml)	11.41¶ (3.79)	9.27 (2.10)	8.02 (2.90)	NA	C B A	NA
AUCX§ (µg h/ml)	11.66 (3.82)	18.91 (4.14)	24.42 (8.65)	10.83 (4.03)	NA	NA
Norm AUCX* (µg h/ml)	11.65 (3.82)	9.45 (2.07)	8.14 (2.89)	10.83 (4.03)	C B A	E A
k (h^{-1})	0.145 (0.078)	0.103 (0.062)	0.114 (0.045)	0.049 (0.023)	B C A	E A
$t_{1/2}$ (h)	7.2 (5.6)	9.5 (5.7)	7.1 (2.9)	19.8 (15.9)	C A B	A E
CL/F (L/h)	62.0 (18.0)	72.6 (28.5)	90.1 (31.8)	67.1 (19.5)	A B C	A E
CL_R (L/h)	28.9 (8.3)	28.5 (8.3)	34.0 (23.0)	33.0 (9.6)	B A C	A E

* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.
‡ Normalized to 850 mg
§ $AUC_{0-\infty}$ for single doses and $AUC_{0-8\ h}$ for Treatment E.
¶ $AUC_{0-8\ h}$ for Treatment A = 8.30 ± 2.65 µg.ml





CONCLUSIONS:

1. Overall, the pharmacokinetics of metformin were not significantly different between healthy subjects (n = 9) and NIDDM patients (n = 9) following single doses of 850, 1700, and 2550 mg and following multiple doses using the PI's highest recommended daily dose of 2550 mg.

2. The dosing schedule for Trt E was tid for which patients were instructed to take their doses at 8 am, 12 noon, and 6 pm with meals for 6 days. Blood samples for Cmin determination were obtained every morning before the 8 am dose; consequently, there was a 14 hr gap between the 6 pm dose (given with a meal) and the 8 am dose. For the last 3 doses however, patients were sequestered in the clinic and then given drug every 8 hr under fasting conditions. Therefore, these factors account for the lack of consistency seen in Cmin values from Day 1 to Day 6 for Trt E.

3. For orally administered metformin, if it is assumed/concluded that its "effective half-life" is about 4-5 hr (i.e., about 50% of an orally absorbed metformin dose is excreted via the kidney in about 4-5 hr), then, assuming linear kinetics, steady state in this study should have been essentially reestablished by the 8:00 am dose (Dose 19) on Day 7 following the switch on Day 6 from the dosing regimen where metformin was given at intervals of 4, 6, and 14 hr to the regimen where it was given every 8 hr. Comparison of the mean plasma AUC infinity value (AUCX) for Trt A (1 X 850 mg

tablet) to the steady state AUC_{τ} value for Trt E within healthy volunteers and within NIDDM patients indicate that mean steady state AUC_{0-8} values were only 11% and 5%, respectively, smaller than the single dose AUCX values, suggesting/indicating that linear kinetics were maintained following multiple dosing using the highest recommended metformin daily dose.

4. Inspection of Trt A (1 X 850 mg tablet) and Trt E (1 X 850 mg tablet q8h) fasting mean plasma PK parameters of Cmax, Cmin and AUC_{0-8} indicate that there is limited metformin accumulation upon multiple dosing using a tid regimen.

	Healthy Subjects		Accumulation	NIDDM Patients		Accumulation
	SD	MD	Ratio	SD	MD	Ratio
Cmax (mcg/ml)	1.81	2.01	1.11	1.51	1.90	1.26
Cmin (mcg/ml)	0.57	0.64	1.12	0.74	0.77	1.04
AUC_{0-8}	9.28	10.7	1.15	5.30	10.8	1.30

5. In both healthy subjects and NIDDM patients the plasma t1/2 after single dose administration was about 2-3 times smaller than that after multiple dose administration. Assay sensitivity limits precluded an accurate assessment of a longer terminal elimination phase following single dose administration as compared to multiple dose administration where plasma metformin concentrations were maintained above the assay's sensitivity limit longer.

6. Following increasing single fasting doses of 1 X 850 mg tablet (Trt A), 2 X 850 mg tablet (Trt B) and 3 X 850 mg tablet (Trt C) in both healthy subjects and NIDDM patients, there was a less than proportional increase in systemic drug availability. See page ... for ratio analyses of dose proportionality.

7. Following single metformin doses of 850 mg, 1700 mg, and 2250 mg, the average fasting plasma glucose (FPG) concentration across the doses did not differ significantly. The sponsor stated that due to this finding, a concentration effect relationship was not examined. Following multiple dose administration at the top daily dose of 2250 mg, average FPG, 2 hr postprandial and 6 hr postprandial glucose concentrations in the NIDDM patients significantly decreased. Example, the average FPG concentration was 131 mg/dl(±27) after multiple doses of metformin compared to 172 mg/dl (±42) with placebo. Metformin's effects on plasma insulin concentrations were similar to those of glucose concentrarions. For average fasting and postprandial plasma lactate concentrations they were significantly increased after single 2550 mg dose and after multiple doses in both groups.

TITLE: THE ACUTE EFFECTS OF ORAL SINGLE DOSING WITH METFORMIN ON GLYCEMIC CONTROL OF NIDDM PATIENTS (Study #MET/GB/89/HOCKA; Volume 1.63)

INVESTIGATOR:

OBJECTIVES:

To determine i) the PK of metformin, ii) the acute effects of different single doses of metformin on basal glucose and glucose tolerance profiles, and iii) to assess any dose-response relationships between metformin and plasma insulin and lactate levels.

DESIGN:

This was a double blind, placebo controlled, randomized, single dose, 4 way crossover study in 10 fasting NIDDM patients (5 M & 5 F; mean weight 77.9 kg; mean age 57.5) with stable glycemic control and body weight. Treatments consisted of the following and were administered with a minimum washout period of six days:

Trt A	1 x 500 mg tablet + 2 x placebo tablet
Trt B	2 x 500 mg " + 1 x " "
Trt C	3 x 500 mg "
Trt D	3 x placebo tablet

Each treatment day followed the same schedule and procedures as defined in Table A.

Table A
Study Schedule

Time (min) of Blood Sampling	Periods
-20,-10 and 0	Pre-Dosing
0	Treatment administered (Placebo or METFORMIN)
20,40,60,80,100,120 and 140	Post-Dosing Baseline
100, 120, 140	Pre-Glucose
140	GTT administered
160,180,200,220, 240 260,280, and 300	Post-Glucose

Metformin plasma levels were determined for 0 - 300 min and glucose, insulin, and lactate plasma levels were measured during pre-dosing and post-dosing periods before and during the glucose tolerance test (GTT) where 75 g of glucose was given in 300 ml of water that was followed by a 50 ml water wash.

RESULTS:

Key Pharmacokinetic Parameters in 12 NIDDM Subjects following Single Doses of Metformin (Non-U.S. Study No. MET GF 89 HOCKA)

	SINGLE DOSE TREATMENT GROUP *		
	500 mg X 1	500 mg X 2	500 mg X 3
C_{max} (ug/ml)	1.89±0.20	2.92±0.31	3.80±0.39
$C_{ss,max}$ (ug/ml)	1.89±0.20	**1.46±0.15**	**1.27±0.26**
t_{max} (hr)	3.33±0.19	3.57±0.23	2.77±0.19
AUC_{0-8} (ug/ml•hr)	6.12±0.62	10.13±0.11	13.54±0.13
$AUC_{ss,0-8}$ (ug/ml•hr)	6.12±0.62	**5.06±0.09**	**4.53±0.02**

* - Parameters normalized to 500 X 1 dose shown in bold, are Cmax and AUC.

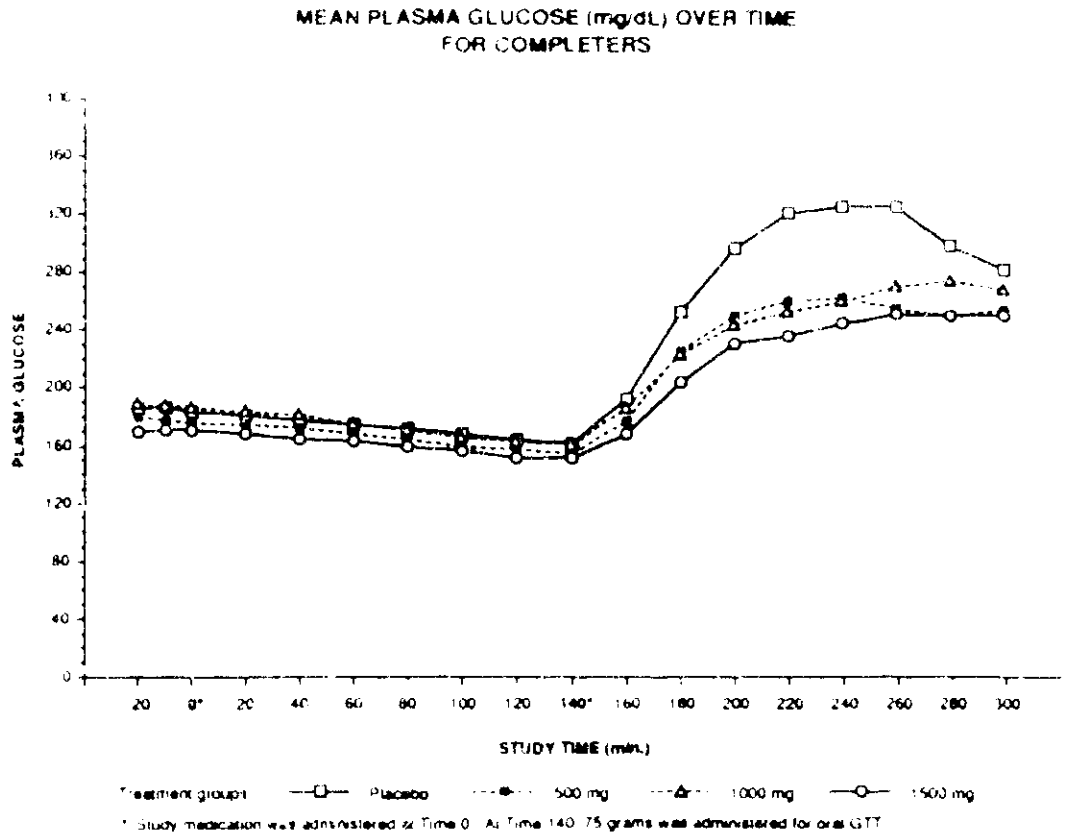
Summary of Pharmacodynamic Effects - Mean Values

Variables		Placebo	Treatment minus Placebo***		
			500 mg	1000 mg	1500 mg
Glucose (mg/dL)	Pre-Dosing	185.85	-7.93	1.54	-15.17
	Pre-Glucose	195.09	-7.89	-2.01	-11.61
	2-hour Post-GTT	327.35	-71.73**	-56.20**	-75.39**
Insulin (µIU/mL)	Pre-Dosing	19.83	-0.58	0.74	-2.17
	Pre-Glucose	16.38	0.57	0.68	-0.39
	2-hour Post-GTT	92.57	25.53	-26.17	-31.86
Lactate (mmol/L)	Pre-Dosing	1.40	0.14	0.11	0.04
	Pre-Glucose	1.15	0.11*	0.22**	0.09
	2-hour Post-GTT	1.49	0.35	0.49**	0.51**

* Corresponding p-values ≤0.05.

** Corresponding p-values ≤0.01

*** Within patient differences, calculated as active treatment minus placebo



CONCLUSIONS:

1. The $AUC_{(0-5)}$ increases for the 500, 1000, and 1500 mg doses were less than proportional which is similar to the dose proportionality results found in the previous study.

2. The single 500, 1000, and 1500 mg doses had no significant effect on basal plasma levels of glucose, insulin, or lactate in the studied NIDDM patients. However, 2-hour Post-GTT glucose plasma levels were significantly reduced compared to placebo for all metformin doses but the reductions were not proportional to metformin dose.

3. Plasma lactate was significantly increased for the 500 mg and 1000 mg doses before GTT and for the 1000 mg and 1500 mg doses for 2 hour Post-GTT.

TITLE: SINGLE DOSE STUDY OF METFORMIN IN PATIENTS WITH RENAL IMPAIRMENT AND IN HEALTHY ELDERLY AND YOUNG SUBJECTS (Study #90-13-6023; Volume 1.49 plus Amendment #13)

INVESTIGATOR:

DESIGN:

This was an open label, single dose study in 6 young, 3 middle-age and 12 elderly healthy adults and 15 adults with chronic renal impairment (CRI). The CRI subjects were broken into 3 groups based upon creatinine clearance that was corrected for body surface area ($corCL_{cr}$): mild (61-90 ml/min), moderate (31-60 ml/min), and severe (10-30 ml/min). A single metformin 850 mg tablet dose was administered to each subject after an overnight fast. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hr post-dose in healthy subjects plus at 72 hr in CRI patients. Urine samples were collected at -1-0, 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hr in healthy subjects plus at 48-72 hr in CRI patients.

ANALYTICAL:

RESULTS:

PARAMETER ESTIMATES RELATED TO PLASMA METFORMIN IN SUBJECTS AFTER A SINGLE 850 MG DOSE OF METFORMIN HCl
(DSD #90-13/EPIA #90-11-6023)

Parameter	Parameter Estimate (mean and SD)						Statistical Significance[1]
	Healthy Young (A)	Healthy Elderly (B)	Healthy Middle Age (C)	Mild CRI (D)	Moderate CRI (E)	Severe CRI (F)	
Sample Size (n)	6	12	3	5	4	6	
T_{max} (hr)	2.67 (0.82)	2.71 (1.05)	3.00 (1.00)	3.50 (0.45)	3.75 (0.50)	3.08 (1.09)	[illegible]
C_{max} (µg/ml)	1.89 (0.34)	2.45* (0.70)	1.64 (0.50)	1.86 (0.52)	1.12 (1.84)	1.13 (0.23)	[illegible]
AUC (µg h/ml)	9.81 (2.14)	15.72* (3.80)	10.92 (3.05)	12.83 (1.73)	57.55 (36.45)	51.97 (2[illegible]	[illegible]
AUCX (µg h/ml)	9.98 (2.12)	15.99* (3.80)	11.22 (3.19)	13.22 (2.00)	58.80 (36.58)	52.86 (3[illegible]	[illegible]
k (h^{-1})	0.123 (0.0348)	0.089 (0.0254)	0.074 (0.0041)	0.083 (0.0052)	0.048 (0.017)	[illegible]	[illegible]
t1/2 (h)	6.9 (4.2)	11.3 (7.3)	11.2 (5.2)	17.3 (21.2)	16.2 (7.6)	[illegible]	[illegible]
CL/f (ml/min)	1155 (273)	728* (186)	1081.7 (251.8)	852.4 (184.6)	238.3 (63.9)	[illegible]	[illegible]
V/f (l)	723 (588)	727 (503)	943.7 (524.3)	1350.2 (1259.6)	355.0 (248.8)	[illegible]	[illegible]
CLR (ml/min)	646 (84)	412* (98)	894.7 (83.8)	384.6 (122.3)	108.3 (57.2)	[illegible]	[illegible]

* Significant difference ($p \leq .05$) between Elderly (B) and Healthy Young (A).

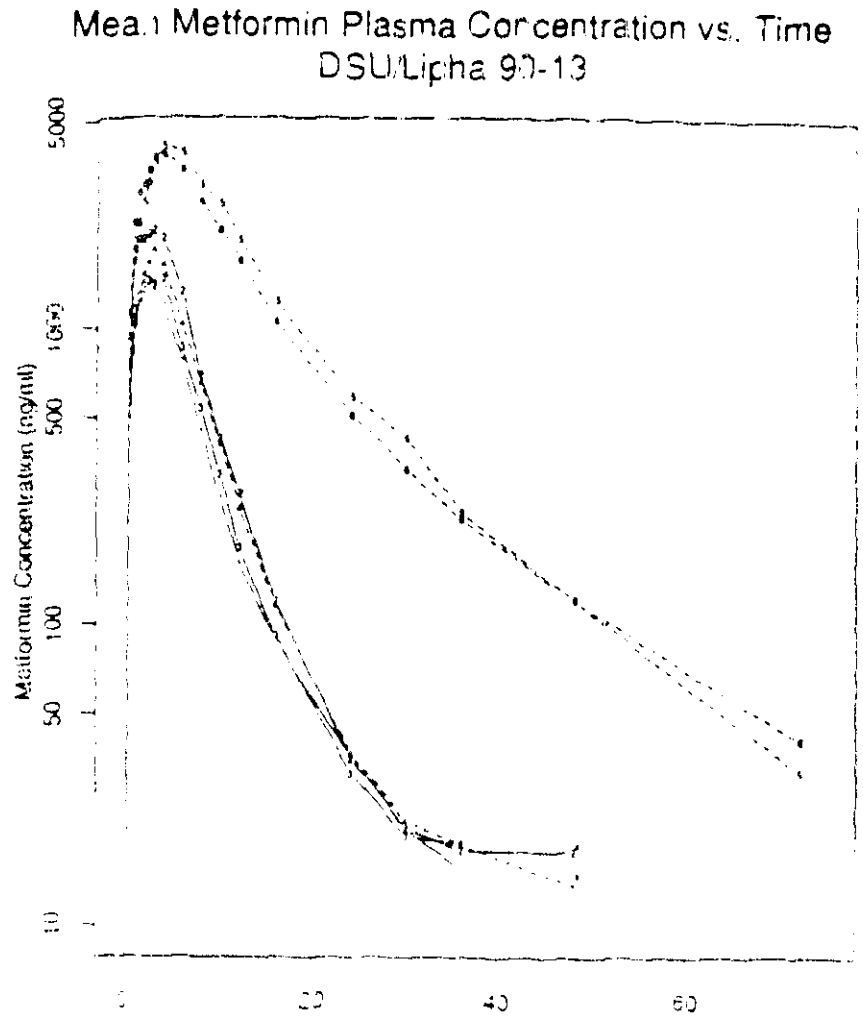
1 Groups under same line do not differ significantly ($p \leq .05$; ANOVA with Student Newman Keuls Test) [illegible] Young (A), Healthy Middle Age (C)

PARAMETER ESTIMATES RELATED TO BLOOD METFORMIN IN SUBJECTS AFTER A SINGLE 850 MG DOSE OF METFORMIN HCL (DSU/LIPHA 90-13 LIPHA 90-CC-6053)

Parameter	Healthy Young (A)	Healthy Elderly (B)	Healthy Middle Age (C)	Mild (4)	Moderate (5)	Severe (6)	Comparisons
Sample Size (n)	6	12	6	6	6	6	
t_{max} (h)	3.25 (0.88)	4.04 (1.06)	2.83 (1.36)	3.67 (1.25)	4.00 (1.55)	4.17 (1.47)	
C_{max} (µg/ml)	0.93 (0.22)	1.72* (0.54)	1.10 (0.43)	1.35 (0.28)	0.93 (0.50)	0.86 (0.55)	B > A, C, 4, 5, 6
AUC (µg h/ml)	10.63 (2.47)	17.44* (5.01)	12.21 (3.74)	14.93 (1.63)	55.21 (35.42)	53.64 (22.81)	B > A, C, 4, 5, 6
AUCX (µg h/ml)	12.63 (2.87)	21.53* (5.74)	16.88 (5.82)	19.92 (4.63)	59.00 (34.15)	57.28 (24.83)	B > A, C, 4, 5, 6
k_e (h^{-1})	0.031 (0.008)	0.024* (0.004)	0.018 (0.006)	0.030 (0.012)	0.031 (0.007)	0.031 (0.005)	B < A*
$t_{1/2}$ (h)	23.7 (5.8)	30.1* (5.1)	42.1 (17.0)	38.8 (25.7)	23.4 (4.8)	24.0 (4.0)	B > A*
CL/F (ml/min)	938 (233)	549* (155)	723.7 (304.0)	575.6 (118.1)	226.8 (102.0)	230.2 (76.4)	B < A, C, 4
V/F (l)	1890 (661)	1454 (557)	2496.0 (862.6)	1744.2 (682.7)	484.5 (268.8)	443.0 (163.5)	B < A*
CLR (ml/min)	644 (83)	428* (126)	439.0 (46.5)	401.0 (105.0)	138.3 (60.2)	133.0 (27.4)	B > A, C, 4, 5, 6

* significant difference ($p<.05$) between Elderly (B) and Healthy Young (A)

† Groups under same line do not differ significantly ($p<.05$, ANOVA with Student-Newman-Keuls Test) A: Healthy Young (A), Healthy Middle-Age (C)



CONCLUSIONS:

From the sponsors Amendment #13 that was submitted on 2/4/94 the following conclusions are given.

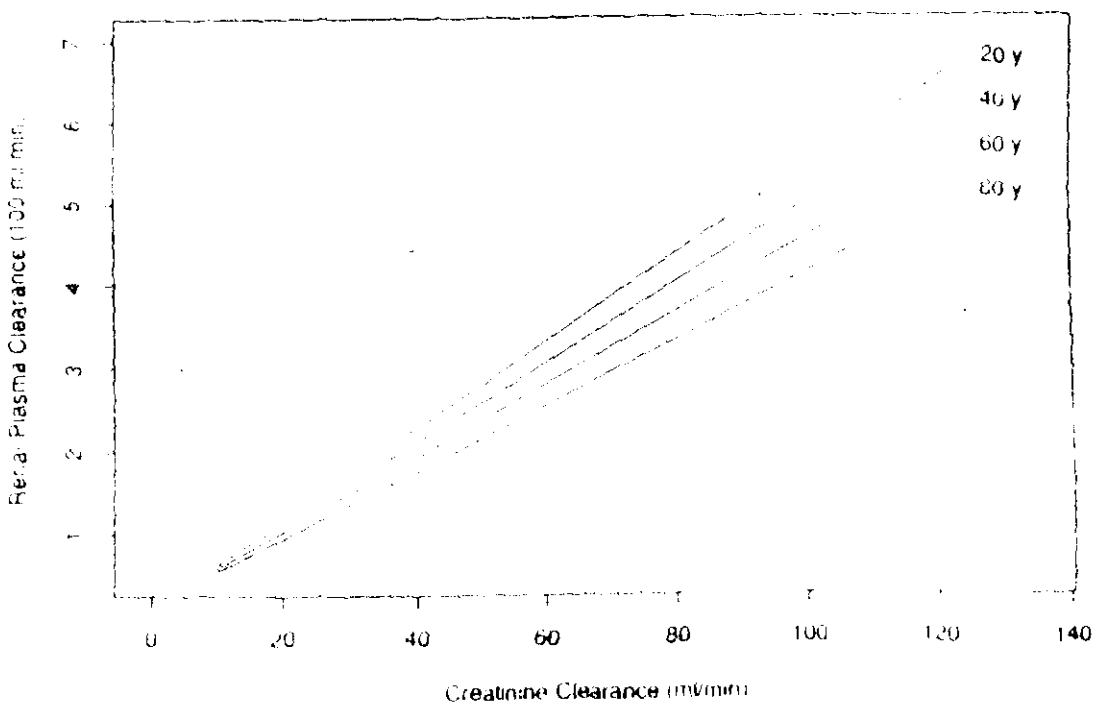
"Pharmacokinetic parameters of metformin in the mild CRI group were statistically comparable to those from the healthy elderly group

Multivariate regression analysis revealed that both renal function (as measured by corrected creatinine clearance) and age are predictors of *metformin clearance (both total and renal)* Whereas creatinine clearance as a single covariate was significant, age was only significant when *creatinine clearance* was considered and was not significant as a single covariate.

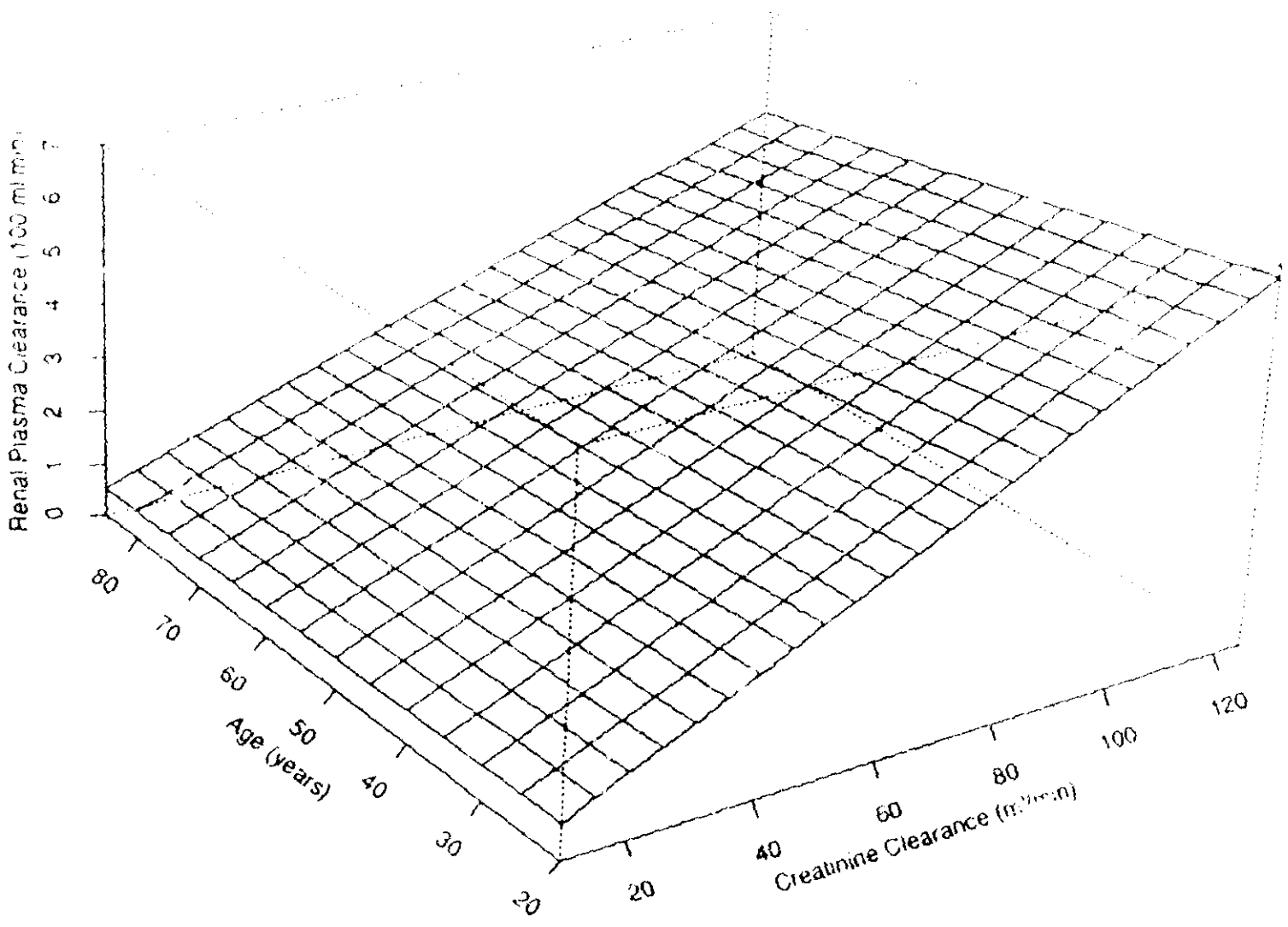
A model describing these relationships was developed, which indicates that, for individuals of the same age, *metformin clearance decreases linearly* as a function of (corrected) creatinine clearance For older individuals, the slope of the linear function is smaller, since they are already starting out at a lower clearance because their creatinine clearance is lower Thus, for individuals having the same creatinine clearance, *the older someone is, the lower the metformin clearance* will be However, for individuals with more severe degrees of renal impairment, the change in *metformin* clearance due to age is dampened These model-based relationships are shown graphically in Figures 4a, 4b, 5a, 5b, 6a, 6b, 7a and 7b of *the report (Pages 0064 through 0071* appended to this letter, for ease of review as **Item 2**) and in tabular form in Tables 8 through 11 *(Pages 0057 through 0060, appended to this letter, for ease of review, as* **Item 3**)

For example, according to the model, it is predicted that for a typical individual of ***30 years of age*** with a ***corrected creatinine clearance of 80 ml/min***, metformin total oral plasma clearance (CLF) will be 834 ml/min. In such an individual, according to the model, CLF is expected to decrease (increase) about 92 ml/min for every 10 ml/min decrease (increase) in corrected creatinine clearance In contrast, according to the model, for a typical individual ***70 years of age*** and with the same corrected creatinine clearance (i.e., 80 ml/min) CLF is predicted to be about 665 ml/min and is expected to decrease (increase) about 71 ml/min for every 10 ml/min decrease (increase) in corrected creatinine clearance."

Predicted Renal Plasma Clearance Based on Corrected Creatinine Clearance and Age
DSU/Lipha 90-13: Metformin



Predicted Renal Plasma Clearance vs. Corrected Creatinine Clearance and Age
Predicted Surface -- DSU/Lipha 90-13: Metformin



TITLE: A PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF THE ORAL METFORMIN AND GLYBURIDE IN NIDDM SUBJECTS (Study No. 89-2B-6023; Volume 1.51)

INVESTIGATOR:

DESIGN:

This was an open label, single dose, 3 way crossover study involving 15 mild to moderate NIDDM patients (6 M and 9 F; age range 40-67 years; weight range 74-110 kg) who had uncontrolled fasting plasma glucose values between 140-250 mg/dl after removal from their antidiabetic medication for 14 days. The female subjects were either postmenopausal or surgically sterile. Patients received the following treatments (washout between treatments = 7 days) after an overnight fast:

Trt A	1 X 850 mg metformin tablet
Trt B	1 X 5 mg glyburide tablet (Micronase®)
Trt C	1 X 850 mg metformin tablet **plus** 1 x 5 mg glyburide

Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hr post-dose. Plasma metformin and serum glyburide levels were determined as were serum glucose, insulin, and C-peptide levels. (Note: One patient had glyburide serum concentrations at each pre-dose zero time point of each treatment phase for which it was suspected that the subject never stopped taking her daily dose of glyburide. Therefore, only 14 patients' data were used.)

RESULTS:

Mean (± standard deviation) metformin pharmacokinetic parameters resulting from the oral administration of (A) one Glucophage Tablet 850 mg, and (C) one Glucophage Tablet 850 mg plus one MICRONASE Tablet 5 mg administered concurrently.

Parameter	Treatment A	Treatment C	ANOVA p Value
$AUC_{0-\infty}$ (mcg · hr/ml)	11.4 (3.4)	10.4 (2.1)	NS[a]
AUC_{0-4} (mcg · hr/ml)	3.94 (1.4)	3.49 (1.2)	NS
AUC_{4-8} (mcg · hr/ml)	3.58 (1.0)	3.37 (0.6)	NS
AUC_{8-24} (mcg · hr/ml)	7.52 (2.28)	6.87 (1.55)	NS
AUC_{0-24} (mcg · hr/ml)	10.9 (3.3)	10.1 (2.0)	NS
CL/F (L/hr)	79.8 (20.0)	84.6 (16.8)	NS
C_{max} (ng/ml)	1442 (432)	1342 (408)	NS
K_{term} (1/hr)	.135 (.027)	.150 (.015)	NS
$t_{1/2}$ (hr)[b]	5.13	4.62	–
T_{max} (hr)	3.36 (1.0)	3.21 (9)	NS
Vd/F (L)	612 (196)	568 (112)	NS

[a] No significant difference ($\alpha = .05$) between treatments using analysis of variance.
[b] Harmonic mean.

Mean (± standard deviation) glyburide pharmacokinetic parameters resulting from the oral administration of (B) one MICRONASE Tablet 5 mg and (C) one Glucophage Tablet 850 mg plus one MICRONASE Tablet 5 mg administered concurrently.

Parameter	Treatment B	Treatment C	ANOVA p Value
$AUC_{0-\infty}$ (ng · hr/ml)	1216 (696)	954 (362)	.0413
AUC_{0-4} (ng · hr/ml)	170 (199)	93.5 (80.9)	NS[a]
AUC_{4-8} (ng · hr/ml)	356 (240)	223 (158)	.0138
AUC_{8-8} (ng · hr/ml)	527 (411)	304 (219)	.0226
AUC_{0-24} (ng · hr/ml)	1014 (358)	787 (366)	NS
CL/F (L/hr	5.57 (3.19)	5.94 (2.08)	NS
C_{max} (ng/ml)	143 (88.5)	90.2 (44.9)	.0122
K_{term} (1/hr)	.093 (.036)	.114 (.081)	NS
$t_{1/2}$ (hr)[b]	7.45	6.08	–
T_{max} (hr)	6.43 (2.87)	7.79 (5.35)	NS
Vd/F (L)	81.1 (93.6)	79.2 (60.2)	NS

[a] No significant difference ($\alpha = .05$) between treatments using analysis of variance.
[b] Harmonic mean.

Mean (± standard deviation) serum glucose pharmacodynamic parameters resulting from the oral administration of (A) one Glucophage Tablet 850 mg and (B) one MICRONASE Tablet 5 mg, and (C) one Glucophage Tablet 850 mg plus one MICRONASE Tablet 5 mg administered concurrently.

Parameter	Treatment A	B	C	Statistics
$AUC_{(0-4)}$ (mg · hr/dl)	1009 (409)	1034 (408)	1034 (381)	NS*
$AUC_{(4-8)}$ (mg · hr/dl)	817 (404)	772 (397)	725 (378)	NS
$AUC_{(0-24)}$ (mg · hr/dl)	5671 (2295)	5519 (2097)	5216 (2300)	NS
C_{max} (mg/dl)	314 (107)	312 (103)	318 (91)	NS
T_{max} (hr)	6.4 (7.8)	5.6 (7.4)	5.5 (7.4)	NS

CONCLUSIONS:

1. The results of this single dose drug interaction study show that glyburide does not significantly effect the PK of metformin. On the other hand, for glyburide, AUC_{0-inf} and Cmax were reduced 22% and 37%, respectively.

2. The pharmacodynamic findings are summarized as follows:

Glucose:

There were no significant differences among treatments for serum glucose AUC_{0-4}, AUC_{4-8}, AUC_{0inf}, Cmax or Tmax.

Insulin:

There were no significant differences among treatments for serum insulin AUC, Cmax and Tmax except for AUC_{4-8}.

C-peptide:

There were no significant diferences among treatments for serum C-peptide AUC, Cmax and Tmax except for AUC_{0-4}.

TITLE: A SINGLE DOSE INTERACTION STUDY OF METFORMIN AND CIMETIDINE IN NORMAL HEALTHY VOLUNTEERS (Study No. 91-03-6023; Volume 1.54)

INVESTIGATOR:

DESIGN:

This was a randomized, single dose, 3-way crossover study involving 15 healthy male subjects (mean weight 79.3 kg ± 10.2) who received after an overnight fast (+4 hr post-dose fast) the following treatments (washout between treatments 7 days):

Trt A	1 X 850 mg metformin tablet
Trt B	1 X 400 mg cimetidine tablet (Tagamet®)
Trt C	1 X 850 mg metformin tablet **plus** 1 X 400 mg cimetidine tablet

Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 36 hr post-dose. Urine samples were collected at 0-4, 4-8, 8-12, 12-24, and 24-36 hr. Blood, plasma, and urine samples were assayed for metformin whereas plasma samples were only assayed for cimetidine All s that were acceptably validated.

RESULTS:

Table 1. The mean (±SD) metformin plasma PK parameters. (AUC=ng.h/ml)

	Metformin Treatment A	Met+Cimetidine Treatment C	p
Cmax(ng/ml)	1,707 ± 316	2,745 ± 842	S
AUC(0-24)	9,782 ± 2,021	13,698 ± 3,186	S
AUC(inf)	10,012 ± 2,045	14,052 ± 3,259	S
tmax (hr)	2.4 ± 0.7	2.8 ± 0.[illegible]	NS
$t_{½}$ (hr)	5.33 ± 1.5	5.37 ± 1.[illegible]	NS
Clp/F(ml/min)	1,142 ± 204	831 ± 218	S
Au (mg)	212 ± 80.2	211.3 ± 90.0	NS
Clr (ml/min)	349 ± 95.6	250 ± 93.1	S

Table 2. The mean (±SD) metformin blood PK parameters. (AUC=ng.h/ml)

	Metformin Treatment A	Met+Cimetidine Treatment C	p
Cmax(ng/ml)	986 ± 162	1,550 ± 408	S
AUC(0-24)	7,408 ± 1,465	10,396 ± 2,228	S
tmax (hr)	2.5 ± 0.8	2.9 ± 0.7	NS
$t_{½}$ (hr)	15.6 ± 2.2	14.5 ± 2.1	NS

Table 3. The mean (±SD) cimetidine PK parameters. (AUC=ng.h/ml)

	Cimetidine Treatment B	Cimetidine+Met Treatment C	p
Cmax(ng/ml)	2,071 ± 570	2,094 ± 417	NS
AUC(0-24)	8,610 ± 1,022	8,209 ± 1,305	NS
tmax (hr)	2.0 ± 0.9	2.5 ± 0.6	NS
$t_{½}$ (hr)	2.2 ± 0.2	2.5 ± 0.5	NS

CONCLUSIONS:

1. The sponsor makes reference to a multiple dose cimetidine study (Somogyi et.al) which found that cimetidine increased metformin AUC by 50% and decreased metformin renal clearance while not affecting the total metformin recovered in the urine. The conclusion was that the change in metformin kinetics was due to competition for proximal tubular secretion. Similar results were found in this single dose study. The co-administration of a single 400 mg cimetidine dose with a single 850 mg metformin dose resulted in an approximate 60% increase in plasma and whole blood Cmax and a 40% increase in metformin AUC. Metformin plasma clearance declined approximately 30%. The amount of metformin recovered over 36 hr in urine did not change and the elimination half-life did not change. It can be concluded that as in the multiple dose study the change in metformin kinetics can be due to competition between metformin and cimetidine for proximal tubular secretion.

2. Cimetidine kinetics were not altered in either this single dose study or the multiple dose study.

TITLE: SINGLE DOSE DRUG INTERACTION STUDY OF METFORMIN AND NIFEDIPINE IN NORMAL VOLUNTEERS (Study No. 91-04-C023; Volume 1,55)

INVESTIGATOR:

DESIGN:

This was a randomized, single dose, 3-way crossover study involving 18 healthy male subjects who received after an overnight fast (+4 hr post-dose fast) the following treatments (washout between treatments = 7 days):

Trt A	1 X 850 mg metformin tablet
Trt B	1 X 10 mg nifedipine tablet (Procardia^{R})
Trt C	1 X 850 mg metformin tablet **plus** 1 X 10 mg nifedipine tablet

Blood samples were obtained at 0, 15, 30, 45, and 60 min, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hr post-dose. Urine samples were collected at 0-4, 4-8, 8-12, and 12-24 hr. Blood, plasma and urine samples were assayed for metformin whereas plasma samples were only assayed for nifedipine

Acceptable validation data were provided for all methods.

RESULTS:

Table 1. The mean (±SD) metformin plasma PK parameters. (AUC=ng.h/ml)

	Metformin Treatment A	Met+Nifedipine Treatment C	p
Cmax(ng/ml)	1,866 ± 359	2,249 ± 388	<.01
AUC(0-24)	11,185 ± 2,464	12,990 ± 2,422	<.01
AUC(inf)	11,359 ± 2,493	13,149 ± 2,460	<.01
k (hr)	2.3 ± 0.82	2.1 ± 0.61	NS
(hr)	4.29 ± 0.89	4.05 ± 0.52	NS
(ml/min)	1,023 ± 252	875 ± 201	<.01
()	314 ± 88	450 ± 131	<.005
l/min)	474 ± 142	571 ± 131	<.05

Table 2. The mean (±SD) metformin blood PK parameters. (AUC=ng.h/ml)

	Metformin Treatment A	Met+Nifedipine Treatment C	p
Cmax(ng/ml)	1,130 ± 362	1,406 ± 321	NS
AUC(0-24)	8,777 ± 2628	9,601 ± 1931	<.05
tmax (hr)	2.7 ± 0.75	2.3 ± 0.73	NS
$t_{½}$ (hr)	10.0 ± 1.2	10.2 ± 1.9	NS

Table 3. The mean (±SD) nifedipine PK parameters. (AUC=ng.h/ml)

	Nifedipine Treatment B	Nifedipine+Met Treatment C	p
Cmax(ng/ml)	.10 ± 56.7	119 ± 39.4	NS
AUC(0-24)	206 ± 106.0	227 ± 120.2	<.05
tmax (hr)	0.67 ± 0.17	0.60 ± 0.12	NS
$t_{\frac{1}{2}}$ (hr)	3.6 ± 1.4	3.1 ± 1.4	NS

CONCLUSIONS:

1. The results of this single dose drug interaction study indicate that the co-administration of nifedipine with metformin caused an increase in plasma and whole blood metformin concentrations. The metformin plasma and whole blood Cmax values increased by 21% and 24%, respectively, while the plasma and whole blood AUC values increased by only 16 and 9%. Plasma clearance decreased 14% which was statistically significant.

2. For metformin urinary excretion, the mean amounts of metformin excreted increased from 314 mg (37%) to 450 mg (53%) after co-administration which reflected a 20% increase in Clr.

3. For nifedipine there was a statistically significant increase in AUC when nifedipine was co-administered with metformin but the increase was only 10%.

TITLE: SINGLE DOSE DRUG INTERACTION STUDY OF METFORMIN AND FUROSEMIDE IN NORMAL HEALTHY VOLUNTEERS (Study No. 91-05-6023; Volume 1.56)

INVESTIGATOR:

DESIGN:

This was a randomized, single dose, 3-way crossover study involving 18 healthy young male subjects who received after an overnight fast (+4 hr post-dose fast) the following treatments (washout between treatments = 7 days):

Trt A	1 X 850 mg metformin tablet
Trt B	1 X 40 mg furosemide tablet (Lasix®)
Trt C	1 X 850 mg metformin tablet **plus** 1 X 40 mg furosemide tablet

Blood samples were obtained at 0, 20, 40, 60 min, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hrs post dose. Urine samples were collected at 0-4, 4-8, 8-12, 12-24, and 24-36 hr. Blood, plasma, and urine samples were assayed for metformin and plasma and urine samples were also assayed for furosemide using H . All samples were assayed at and the methods were acceptably validated.

RESULTS:

Table 1. The mean (±SD) metformin plasma PK parameters. (AUC=μg.h/ml)

	Metformin Treatment A	Met+Furosemide Treatment C	STAT
Cmax(μg/ml)	1.62 ± 0.54	1.97 ± 0.64	S
AUC(0-36)	10.47 ± 3.12	11.48 ± 3.25	NS
AUC(inf)	10.64 ± 3.13	11.64 ± 3.26	NS
tmax (hr)	2.8 ± 1.02	2.4 ± 0.76	NS
$t_{½}$ (hr)	5.9 ± 1.8	5.7 ± 1.6	NS
Clp/F(ml/min)	1,119 ± 304	1,027 ± 309	NS
Au (mg)	347 ± 80	373 ± 124	NS
Clr (ml/min)	572 ± 142	562 ± 157	NS
V (L)	575 ± 248	511 ± 218	NS

Table 2. The mean (±SD) metformin blood PK parameters. (AUC=μg.h/ml)

	Metformin Treatment A	Met+Furosemide Treatment C	STAT
Cmax(μg/ml)	1.07 ± 0.35	1.31 ± 0.46	S
AUC(inf)	11.31 ± 3.07	12.98 ± 3.76	S
tmax (hr)	2.6 ± 1.06	2.5 ± 0.9	NS
$t_{½}$ (hr)	14.5 ± 3.4	14.5 ± 2.1	NS
Clb/f(ml/min)	1,046 ± 286	920 ± 258	S

Table 3. The mean (±SD) furosemide PK parameters. (AUC=ug.h/ml)

	Furosemide Treatment B	Furosemide+Met Treatment C	STAT
Cmax(μg/ml)	1.16 ± 0.57	0.80 ± 0.32	S
AUC(0-36)	2.32 ± 0.69	2.03 ± 0.46	S
AUC(inf)	2.39 ± 0.69	2.07 ± 0.46	S
tmax (hr)	1.28 ± 0.85	1.71 ± 1.26	NS
t½ (hr)	6.0 ± 2.3	4.1 ± 3.1	NS
Ae(mg)	11.2 ± 3.3	10.7 ± 2.6	NS
Clr (ml/min)	310 ± 90	320 ± 87	NS

CONCLUSIONS:

1. When co-administered with furosemide, metformin plasma Cmax, blood Cmax, and blood AUC(inf) were significantly increased when compared to be given alone by 22%, 22%, and 15% respectively.

2. When administered with metformin, furosemide Cmax, AUC(0-36) and AUC(inf) were significantly decreased by 31%, 13% and 13%, respectively, as compared to when furosemide was administered alone.

TITLE: SINGLE DOSE DRUG INTERACTION STUDY OF METFORMIN AND IBUPROFEN IN NORMAL HEALTHY VOLUNTEERS (Study No. 91-06-6023; Volume 1.58)

INVESTIGATOR:

DESIGN:

This was a randomized, single dose, 3-way crossover study enrolling 18 healthy volunteers but only 17 subjects' data was evaluable (8 males and 9 females). Each subject received after an overnight fast (+4 hr post-dose fast) the following treatments (washout between treatments = 7 days):

Trt A	1 X 850 mg metformin tablet
Trt B	1 X 400 mg ibuprofen tablet (Motrin®)
Trt C	1 X 850 mg metformin **plus** 1 X 400 mg ibuprofen tablet

Blood samples were obtained at 0, 30, 45, 60, 75 min, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hr post-dose. Urine samples were collected at 0-4, 4-8, 8-12, 12-24, and 24-36 hr. Blood, plasma, and urine samples were assayed for metformin and plasma was also assayed for ibuprofen . The samples were assayed at and all the methods were acceptably validated.

RESULTS:

Table 1. The mean (±SD) metformin plasma PK parameters. (AUC=μg.h/ml)

	Metformin Treatment A	Met+Ibuprofen Treatment C	
Cmax(μg/ml)	1.62 ± 0.4	1.73 ± 0.5	
AUC(0-36)	10.14 ± 2.4	10.71 ± 2.4	
AUC(inf)	10.45 ± 2.3	10.97 ± 2.4	
tmax (hr)	2.37 ± 0.8	1.99 ± 0.7	p<0.05
t½ (hr)	7.6 ± 2.8	7.4 ± 2.0	
Clp/F(ml/min)	1,111 ± 263	1,052 ± 220	
Au (mg)	280 ± 119	274 ± 76	
Clr (ml/min)	455 ± 143	431 ± 131	
V/F (L)	745 ± 393	684 ± 261	

Table 2. The mean (±SD) metformin blood PK parameters. (AUC=μg.h/ml)

	Metformin Treatment A	Met+Ibuprofen Treatment C
Cmax(μg/ml)	1.08 ± 0.3	1.16 ± 0.3
AUC(0-36)	9.23 ± 2.6	9.72 ± 2.3
AUC(inf)	10.95 ± 3.0	11.33 ± 2.7
tmax (hr)	2.34 ± 0.8	2.22 ± 0.8
$t_{\frac{1}{2}}$ (hr)	16 ± 4.3	15.4 ± 2.3
Clb/F(ml/min)	1,088 ± 314	1,030 ± 252
Clr,b(ml/min)	533 ± 153	509 ± 169

Table 3. The mean (±SD) ibuprofen PK parameters. (AUC=μg.h/ml)

	Ibuprofen Treatment B	Ibuprofen+Met Treatment C	
Cmax(μg/ml)	36.0 ± 11.8	36.3 ± 11.7	
AUC(0-36)	123.4 ± 27.6	120.8 ± 25.9	
AUC(inf)	126.6 ± 27.6	123.2 ± 26.0	
tmax (hr)	1.90 ± 1.2	1.37 ± 0.9	$p<0.05$
$t_{\frac{1}{2}}$ (hr)	1.9 ± 0.4	2.2 ± 1.5	
Cl/F(ml/min)	55.1 ± 12.2	56.2 ± 10.8	
V/F (L)	9.0 ± 2.4	10.9 ± 8.2	

CONCLUSIONS:

1. Following this single dose drug interaction study of metformin with ibuprofen, only metformin plasma tmax was significantly different when given together as compared to when it was given alone.

2. When administered with metformin, only tmax of ibuprofen was significantly different as compared to when it was given alone.

TITLE: SINGLE DOSE DRUG INTERACTION STUDY OF METFORMIN AND PROPRANOLOL IN NORMAL HEALTHY VOLUNTEERS (Study No. 92-01-6023; Volume 1.60)

INVESTIGATOR:

DESIGN:
This was a randomized, single dose, 3-way crossover study involving 18 healthy male subjects who received after an overnight fast (+4 hr post-dose fast) the following treatments (washout between treatments = 7 days):

Trt A	1 X 850 mg metformin tablet
Trt B	1 X 40 mg propranolol tablet (Inderal^{R})
Trt C	1 X 850 mg metformin **plus** 1 X 40 mg propranolol tablet

Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hr post-dose. Urine samples were collected at 0-4, 4-8, 8-12, and 12-24 hr. Blood, plasma, and urine samples were assayed for metformin and plasma samples were also assayed for propranolol and 4-hydroxypropranolol All the assay methods had acceptable validation data.

RESULTS:

Table 1. The mean (±SD) metformin plasma PK parameters. (AUC=ng.h/ml)

	Metformin Treatment A	Met+Propranolol Treatment C	Stat
Cmax(ng/ml)	1,684 ± 391	1,587 ± 378	NS
AUC(0-24)	10,123 ± 2,533	9,083 ± 2,026	S
AUC(inf)	10,287 ± 2,555	9,241 ± 2,051	S
tmax (hr)	2.2 ± 0.88	2.3 ± 0.52	NS
$t_{\frac{1}{2}}$ (hr)	4.56 ± 0.60	4.64 ± 0.67	NS
Clp/F(ml/min)	1,[illegible]5 ± 271	1,260 ± 314	S
Au (mg)	3[illegible]9 ± 77	299 ± 67	S
Clr (ml/ [illegible]r)	577 ± 135	549 ± 112	NS

Table 2. The mean (±SD) metformin blood PK parameters. (AUC=ng. [illegible]/ml)

	Metformin Treatment A	Metfromin+Propranolol Treatment C	STAT
Cmax(ng/ml	1,041 ± 248	953 ± 232	NS
AUC(0-24)	8,142 ± 2,009	7,302 ± 1,614	S
tmax (hr)	2.5 ± 0.89	2.2 ± 0.52	NS
$t_{\frac{1}{2}}$ (hr)	12.0 ± 1.80	12.2 ± 2.54	NS

Table 3. The mean (±SD) PK parameters. (AUC=ng.h/ml)

	Propranolol Treatment B	Propranolol+Metformin Treatment C	STAT
Cmax(ng/ml)	23.2 ± 13.1	23.6 ± 12.9	NS
AUC(0-24)	139 ± 77.4	141 ± 75.7	NS
tmax (hr)	2.2 ± 0.45	2.3 ± 0.49	NS
$t_{½}$ (hr)	4.18 ± 0.82	3.78 ± 0.59	S

CONCLUSIONS:

1. Following single dose co-administration of metformin with propranolol, metformin plasma AUC(0-24), plasma AUC(inf), blood AUC(0-24) and amount of metformin renally eliminated (AU) were decreased by 10%, 10%, 10% and 14%, respectively, which were statistically significant.

2. When administered with metformin, the kinetics of propranolol were not significantly different than when administered alone except for a statistically significant decrease of 10% in propranolol half-life. There were no statistically significant differences among the PK parameters for 4-hydroxypropranolol.

TITLE: A COMPARATIVE BIOEQUIVALENCE STUDY OF FOUR 500 MG METFORMIN FORMULATIONS (Study No. RD298/17142; Volume 1.61)

INVESTIGATOR:

OBJECTIVES: To compare the relative bioavailability of 4 different metformin formulations.

DESIGN:

This was a single blind, single dose, randomized, 4 period crossover study with a 7 day washout period between treatments which were administered fasting. Twenty healthy, adult male volunteers between 18-45 years and within 15% of their IDBW participated. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 18, and 24 hr post-dose.

TREATMENTS:

500 mg tablet manufactured in France
500 mg tablet manufactured in UK
500 mg tablet manufactured in Austria
500 mg tablet manufactured in Holland

RESULTS:

Table 1. The mean metformin PK parameters (N=20).
Cmax = ng/ml; tmax = hr; AUC = ng.h/ml; K = 1/hr

	Austria	France	Holland	UK	STAT
Cmax	996 ± 292	1124 ± 330	1128 ± 222	1110 ± 298	NS
Tmax	3	3	3	2.5	
AUC	7215 ± 2404	7532 ± 1817	7529 ± 1837	7769 ± 2000	NS
K	0.22 ± 0.04	0.25 ± 0.05	0.23 ± 0.05	0.24 ± 0.05	
$T_{1/2}$	3.3 ± 0.64	2.8 ± 0.53	3.1 ± 0.74	3.0 ± 0.64	

Table 2. The relative bioavailabilities of Austria, France, and Holland tablets to the UK tablet.

Austria/UK =
France/UK =
Holland/UK =

CONCLUSIONS:

1. There appear to be no bioavailability differences in metformin tablets made in different countries.

GENDER PK ANALYSES (1/11/94 submission)

Upon request, Lipha carried out gender analyses on PK parameters from the following single dose studies.

1. Study No. 89-12-6023: 1 X 850 mg metformin tablet (fasting)
   9 Healthy Subjects plus 9 NIDDM Patients
   11 Males plus 7 Females

RESULTS:

Table 1 Data Characteristic

PK Parameter		Mean Male	Mean Female	Estimated Difference	95% CI* of Difference
Weight	kg	76.29	62.47	13.82	(-0.74, 28.34)
Age	(y)	42.91	53.14	-10.23	(-18.89, -1.57)
corCLcr*	ml/min	97.82	83.00	14.82	(-9.50, 39.14)

* confidence interval

* creatinine clearance corrected for body surface area

Table 2 Regression: metformin clearance vs. weight

Clearance	Slope	S.E.	p-Value	r^2
Plasma	-0.14	0.12	0.23	0.05
Blood	-0.11	0.13	0.41	0.04
Renal	-0.17	0.22	0.44	0.04
Renal (blood)	-0.12	0.21	0.60	0.02

Table 3 Regression: metformin clearance vs. age

Clearance	Slope	S.E.	p-Value	r^2
Plasma	0.11	0.24	0.66	0.01
Blood	-0.01	0.26	0.97	0.00
Renal	-0.07	0.44	0.87	0.00
Renal (blood)	-0.15	0.42	0.90	0.00

Table 4 Gender effect in plasma PK parameters of metformin

PK Parameter		Mean Male	Mean Female	Estimated Difference	95% CI* of Difference
t_{max}	(h)	2.96	2.93	0.036	(-1.00, 1.07)
C_{max}	(mcg/ml)	1.58	1.58	0.01	(-0.28, 0.30)
AUC	(mcg·h/ml)	11.52	12.00	-0.48	(-4.08, 3.12)
AUCX	(mcg·h/ml)	11.72	12.29	-0.57	(-4.24, 3.09)
k	(h^{-1})	0.164	0.143	0.022	(-0.040, 0.083)
$t_{1/2}$	(h)	5.21	6.94	-1.73	(-6.25, 2.79)
CL/F	(l/h)	61.24	58.11	3.13	(-14.64, 20.90)
V/F	(l)	753.93	941.56	-187.60	(-819, 444)
CLe	(l/h)	32.02	27.27	4.75	(-4.60, 14.10)

Table 5 Gender effect in blood PK parameters of metformin

PK Parameter		Mean Male	Mean Female	Estimated Difference	0.95 CI* of Difference
t_{max_b}	(h)	3.41	2.71	0.70	(-0.15, 1.55)
C_{max_b}	(mcg/ml)	1.14	1.32	-0.18	(-0.60, 0.25)
C_b	(mcg·h/ml)	12.64	13.08	-0.44	(-4.87, 3.10)
$AUCX_b$	(mcg·h/ml)	13.80	15.24	-0.45	(-5.71, 4.81)
k_b	(h^{-1})	0.038	0.038	-0.001	(-0.011, 0.009)
$t_{1/2_b}$	(h)	19.75	19.13	0.62	(-4.38, 5.12)
CL/F_b	(l/h)	49.29	49.13	0.16	(-17.02, 17.33)
V/F_b		2253.13	2169.14	80.99	(-599.53, 761.51)
CLe_b	(l/h)	33.66	28.86	4.81	(-5.62, 15.24)

* confidence interval

CONCLUSION:

The disposition of metformin does not differ significantly between men and women.

2. Study No. 91-06-6023: 1 X 850 mg metformin tablet (fasting)
17 Healthy Subjects
8 Males and 9 Females

RESULTS:

Table 1 Demographic Characteristics

PK Parameter	Mean Male	Mean Female	Estimated Difference	0.95 CI* of Difference
Weight (kg)	76.89	64.54	12.34	(0.52, 24.08)
Age (yr)	27.63	29.78	-2.15	(-6.92, 2.62)

* confidence interval

Table 2 Regression: metformin clearance vs. weight

Clearance	Slope	S.E.	p-Value	r^2
Plasma	0.16	0.48	0.74	0.01
Blood	-0.54	0.55	0.34	0.06
Renal	-0.29	0.16	0.08	0.19
Renal (blood)	-0.27	0.17	0.15	0.13

Table 3 Regression: metformin clearance vs. age

Clearance	Slope	S.E.	p-Value	r^2
Plasma	1.47	1.27	0.26	0.08
Blood	-0.90	1.57	0.76	0.01
Renal	0.16	0.48	0.74	0.01
Renal (blood)	0.26	0.51	0.62	0.02

Table 4 Gender effect in plasma PK parameters of metformin

PK Parameter	Mean Male	Mean Female	Estimated Difference	0.95 CI* of Difference
t_{max} (h)	2.41	2.33	0.07	(-0.82, 0.97)
C_{max} (mcg/ml)	1.75	1.51	0.24	(-0.16, 0.65)
AUC (mcg h/ml)	10.81	9.56	1.27	(-1.18, 3.72)
AUCX (mcg h/ml)	11.06	9.90	1.16	(-1.23, 3.72)
K (h^{-1})	0.096	0.116	-0.021	(-0.056, 0.035)
$t_{1/2}$ (h)	7.44	7.74	-0.31	(-3.27, 2.65)
CL/F (l/h)	62.24	70.23	-8.38	(-24.57, 7.81)
V/F (l)	676.00	805.67	-129.69	(-542.92, 283.52)
CL_R (l/h)	25.79	28.66	-2.87	(-11.92, 6.18)

* confidence interval

Table 5 Gender effect in blood PK parameters of metformin

PK Parameter	Mean Male	Mean Female	Estimated Difference	0.95 CI* of Difference
t_{max} (h)	2.41	2.28	0.13	(-0.70, 0.96)
C_{max} (mcg/ml)	1.16	1.02	0.13	(-0.16, 0.43)
AUC (mcg h/ml)	9.77	8.75	1.02	(-1.73, 3.77)
AUCX (mcg h/ml)	11.42	10.52	0.90	(-2.27, 4.07)
K (h^{-1})	0.047	0.045	0.002	(-0.009, 0.012)
$t_{1/2}$ (h)	14.98	16.97	-1.99	(-6.51, 2.53)
CL/F (l/h)	61.93	68.21	-6.28	(-26.11, 13.55)
V/F (l)	1311.63	1633.67	-322.04	(-786.28, 142.34)
CL_R (l/h)	30.80	33.01	-2.20	(-11.96, 7.56)

CONCLUSION:

The disposition of metformin does not differ significantly between men and women.

APPENDIX II

3 pages
PURGED

Mean Concentration for METFORMIN PLASMA
Treatment A: 500 mg Metformin Tablet, Fasting
Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	212.	108.	50.7
0.40	24	558.	184.	32.9
1.00	24	733.	215.	29.3
1.50	24	876.	357.	40.7
2.00	24	903.	259.	28.7
2.50	24	933.	298.	32.0
3.00	24	953.	277.	29.1
4.00	24	889.	221.	24.9
6.00	24	523.	166.	31.8
8.00	24	304.	69.4	22.8
10.00	24	204.	101.	49.3
12.00	24	107.	43.8	40.8
16.00	24	46.6	18.3	39.2
24.00	24	17.6	12.5	70.8
48.00	24	0.00	0.00	

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Mean Concentration for METFORMIN PLASMA

Treatment B: 850 mg Metformin Tablet, Fasting

Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	415.	239	57.4
0.40	24	920.	355.	38.6
1.00	24	1190.	385.	32.5
1.50	24	1260.	344.	27.3
2.00	24	1340.	335.	25.0
2.50	24	1440.	364.	25.3
3.00	24	1480.	418.	28.2
4.00	24	1340.	389.	29.1
6.00	24	716.	234.	32.7
8.00	24	448.	173.	38.6
10.00	24	262.	118.	45.1
12.00	24	154.	72.8	47.4
16.00	24	73.1	32.3	44.2
24.00	24	30.8	19.9	64.6
48.00	23	1.13	3.75	332.

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Mean Concentration for METFORMIN PLASMA
Treatment C: 850 mg Metformin Solution, Fasting
Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	466.	249.	53.4
0.40	24	871.	254.	29.2
1.00	24	1070.	271.	25.3
1.50	24	1220.	371.	30.4
2.00	24	1320.	408.	30.9
2.50	24	1380.	374.	27.1
3.00	24	1340.	346.	25.8
4.00	24	1230.	354.	28.7
6.00	24	696.	271.	38.9
8.00	24	405.	183.	45.1
10.00	24	267.	143.	53.4
12.00	24	160.	93.7	58.6
16.00	23	75.8	37.8	49.9
24.00	24	30.0	22.0	73.1
48.00	23	0.00	0.00	

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Mean Concentration for METFORMIN PLASMA
Treatment D: 850 mg Metformin Tablet, Breakfast
Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	161.	137.	85.5
0.40	24	418.	243.	58.1
1.00	24	601.	247.	41.0
1.50	23	707.	212.	29.9
2.00	24	787.	224.	28.4
2.50	24	821.	200.	24.4
3.00	24	863.	206.	23.9
4.00	24	913.	206.	22.6
6.00	24	679.	189.	27.9
8.00	24	442.	136.	30.8
10.00	24	286.	95.5	33.4
12.00	24	170.	66.4	39.0
16.00	24	79.6	28.8	36.2
24.00	24	29.1	13.2	45.3
48.00	24	0.567	2.78	490.

Mean Concentration for METFORMIN BLOOD

Treatment A: METFORMIN 500MG/TAB FASTING

Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	23	142.	69.9	49.4
0.40	24	380.	118.	31.0
1.00	23	490.	146.	29.8
1.50	24	578.	178.	30.9
2.00	24	607.	181.	29.7
2.50	24	639.	188.	29.4
3.00	24	642.	160.	24.9
4.00	24	604.	144.	23.8
6.00	24	398.	116.	29.2
8.00	24	267.	70.8	26.5
10.00	24	188.	57.7	30.7
12.00	24	146.	43.0	29.4
16.00	23	102.	27.9	27.3
24.00	24	71.3	25.1	35.2
48.00	19	16.7	15.9	95.6

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Mean Concentration for METFORMIN BLOOD

Treatment B: METFORMIN 850MG/TAB FASTING

Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	258.	154.	59.7
0.40	24	570.	216.	37.8
1.00	24	745.	217.	29.1
1.50	24	810.	224.	27.7
2.00	24	904.	248.	27.5
2.50	24	924.	249.	27.0
3.00	24	951.	237.	25.0
4.00	24	869.	225.	25.8
6.00	24	538.	161.	30.0
8.00	23	373.	140.	37.6
10.00	24	270.	96.4	35.7
12.00	24	205.	81.4	39.7
16.00	24	154.	40.5	26.4
24.00	19	96.2	36.0	37.4
48.00	19	35.1	28.7	81.8

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Mean Concentration for METFORMIN BLOOD
Treatment C: METFORMIN 850MG/SOL FASTING
Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	274.	125.	45.8
0.40	24	556.	154.	27.7
1.00	24	692.	198.	28.6
1.50	24	814.	272.	33.4
2.00	24	380.	279.	31.7
2.50	23	884.	238.	26.9
3.00	24	901.	228.	25.3
4.00	24	343.	283.	33.5
6.00	21	526.	220.	41.8
8.00	24	363.	152.	41.9
10.00	23	267.	111.	41.6
12.00	23	196.	84.0	42.8
16.00	24	148.	54.9	37.2
24.00	23	104.	38.9	37.3
48.00	17	40.7	34.5	84.9

Mean Concentration for METFORMIN BLOOD

Treatment D: METFORMIN 850MG/TAB BREAKFAST

Study # 89-011

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	24	0.00	0.00	
0.20	24	101.	92.3	91.2
0.40	24	275.	162.	59.1
1.00	24	391.	168.	42.8
1.50	24	481.	162.	33.6
2.00	24	521.	160.	30.7
2.50	23	557.	161.	28.9
3.00	23	600.	166.	27.7
4.00	24	615.	166.	27.0
6.00	24	501.	159.	31.8
8.00	23	360.	126.	34.8
10.00	24	253.	86.4	34.1
12.00	23	185.	57.9	31.2
16.00	24	124.	38.6	31.1
24.00	22	87.7	28.5	32.5
48.00	20	30.5	25.1	82.3

METFORMIN STUDY DSU#89-011

MEAN Blood to Plasma Ratio
Treatment A: 500 mg Metformin Tablet, Fasting

TIME	n	MEAN	ST DEV	CV%
0.0	24	*	*	*
0.2	23	0.685	0.160	23.32
0.4	24	0.702	0.169	24.09
1.0	23	0.661	0.114	17.23
1.5	24	0.680	0.114	16.73
2.0	24	0.672	0.094	14.02
2.5	23	0.697	0.122	17.51
3.0	24	0.685	0.093	13.61
4.0	24	0.690	0.112	16.23
6.0	24	0.773	0.123	15.90
8.0	24	0.881	0.129	14.60
10.0	24	0.975	0.229	23.50
12.0	24	1.45	0.41	28.27
16.0	23	2.32	0.66	28.33
24.0	18	3.42	1.20	35.08

METFORMIN STUDY DSU#89-011

MEAN Blood to Plasma Ratio
Treatment B: 850 mg Metformin Tablet, Fasting

TIME	n	MEAN	ST DEV	CV%
0.0	24	*	*	*
0.2	24	0.638	0.115	17.99
0.4	24	0.620	0.054	8.75
1.0	24	0.637	0.065	10.13
1.5	24	0.647	0.082	12.72
2.0	24	0.677	0.113	16.74
2.5	24	0.644	0.068	10.50
3.0	24	0.650	0.083	12.76
4.0	24	0.660	0.072	10.90
6.0	24	0.766	0.112	14.68
8.0	23	0.854	0.162	19.02
10.0	24	1.08	0.20	18.86
12.0	24	1.42	0.34	24.27
16.0	24	2.32	0.69	29.90
24.0	17	3.84	2.07	53.80

METFORMIN STUDY DSU#89-011

MEAN Blood to Plasma Ratio
Treatment C: 850 mg Metformin Solution, Fasting

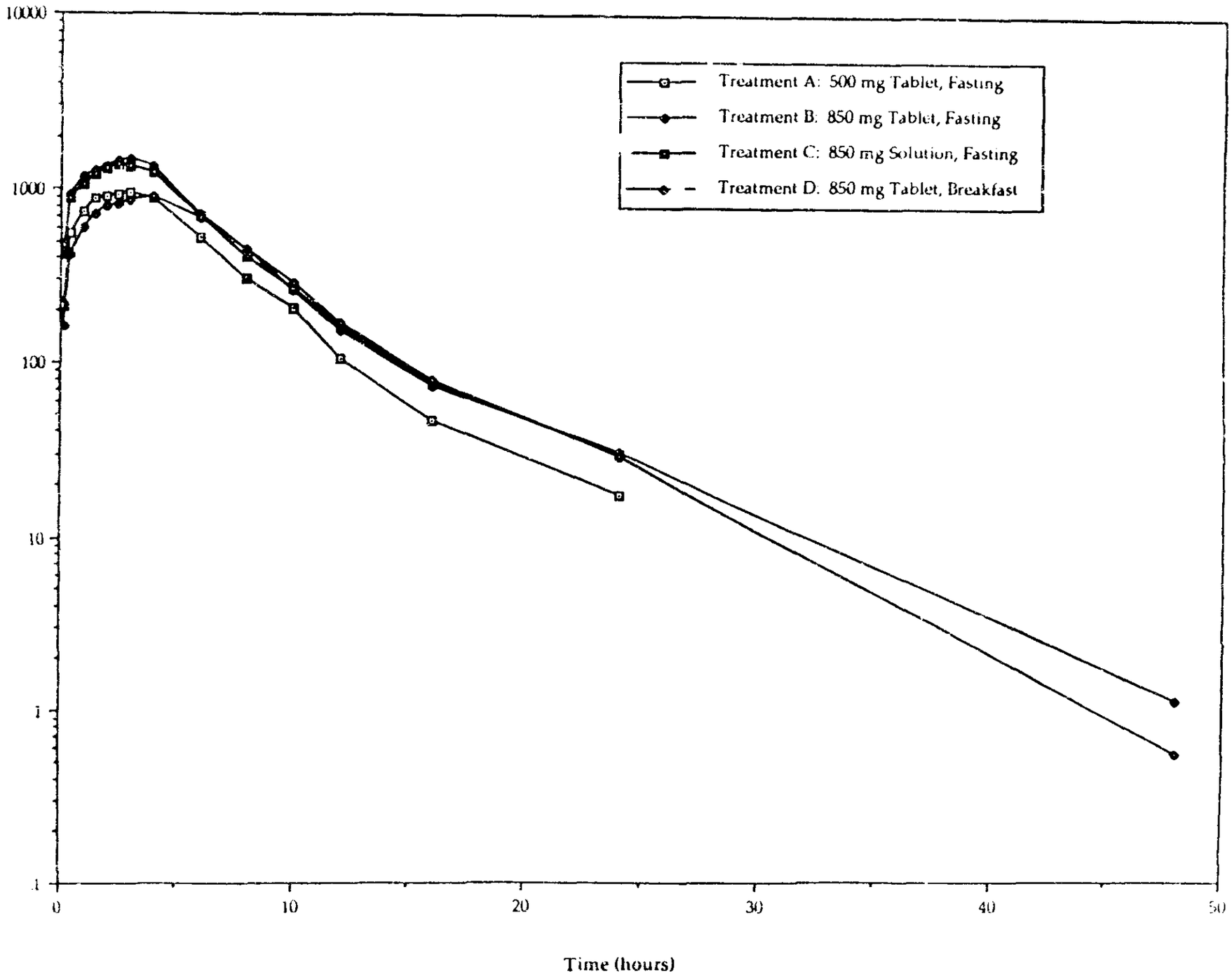
TIME	n	MEAN	ST DEV	CV%
0.0	24	*	*	*
0.2	23	0.604	0.096	15.84
0.4	24	0.644	0.086	13.29
1.0	24	0.645	0.081	12.57
1.5	24	0.667	0.070	10.52
2.0	24	0.673	0.093	13.85
2.5	23	0.657	0.063	9.54
3.0	24	0.678	0.079	11.69
4.0	24	0.682	0.088	12.95
6.0	24	0.760	0.077	10.13
8.0	24	0.909	0.140	15.45
10.0	23	1.03	0.18	17.04
12.0	23	1.33	0.36	26.94
16.0	23	2.18	0.80	36.65
24.0	20	3.72	1.53	41.26

METFORMIN STUDY DSU#89-011

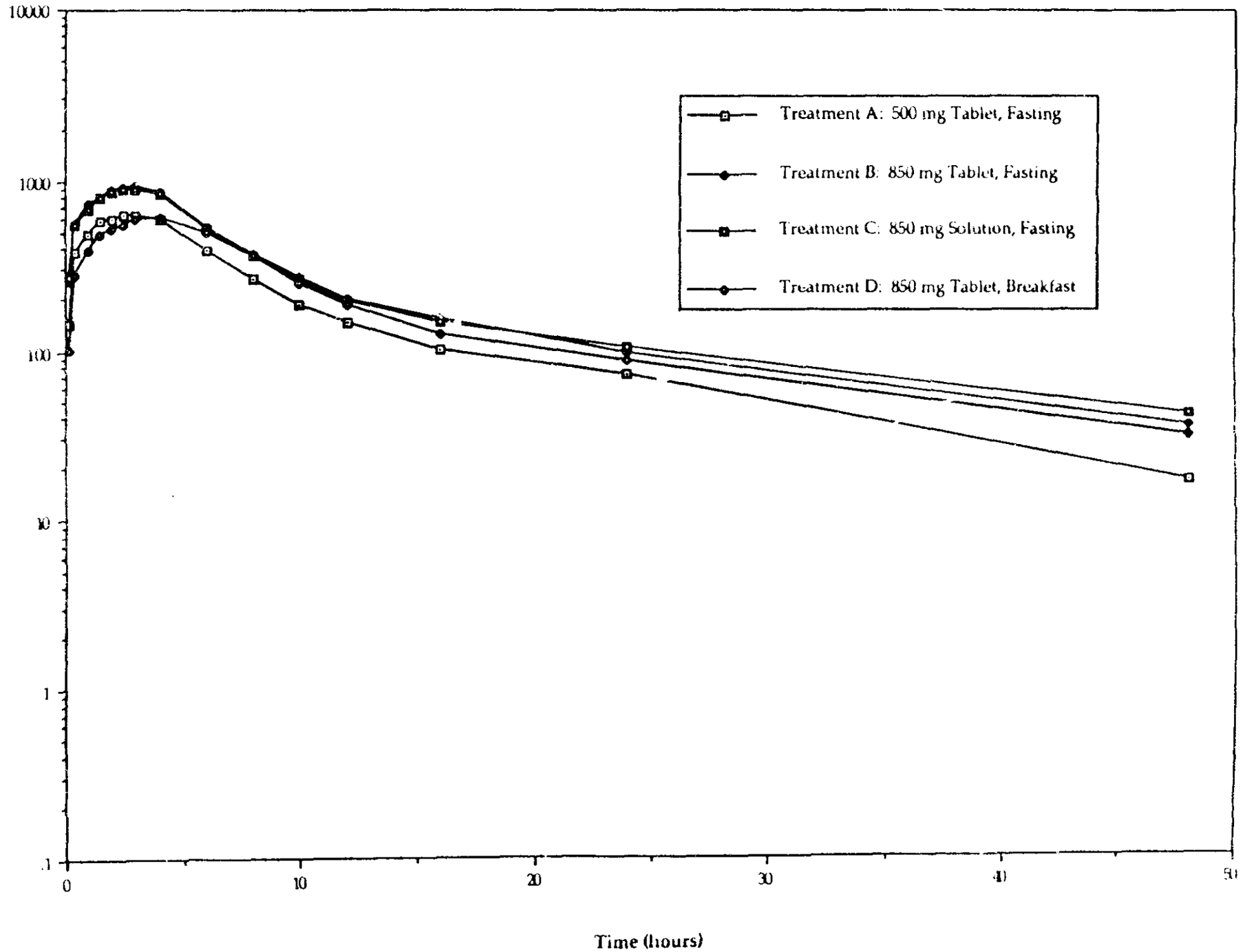
MEAN Blood to Plasma Ratio
Treatment D: 850 mg Metformin Tablet, Breakfast

TIME	n	MEAN	ST DEV	CV%
0.0	24	*	*	*
0.2	21	0.651	0.298	45.77
0.4	23	0.657	0.076	11.61
1.0	24	0.656	0.108	16.51
1.5	23	0.685	0.114	16.66
2.0	24	0.668	0.075	11.15
2.5	23	0.677	0.088	13.03
3.0	23	0.692	0.091	13.21
4.0	24	0.671	0.093	13.87
6.0	24	0.737	0.088	11.87
8.0	23	0.807	0.107	13.31
10.0	24	0.897	0.142	15.84
12.0	23	1.14	0.24	20.90
16.0	24	1.65	0.49	29.67
24.0	21	3.14	1.35	43.06

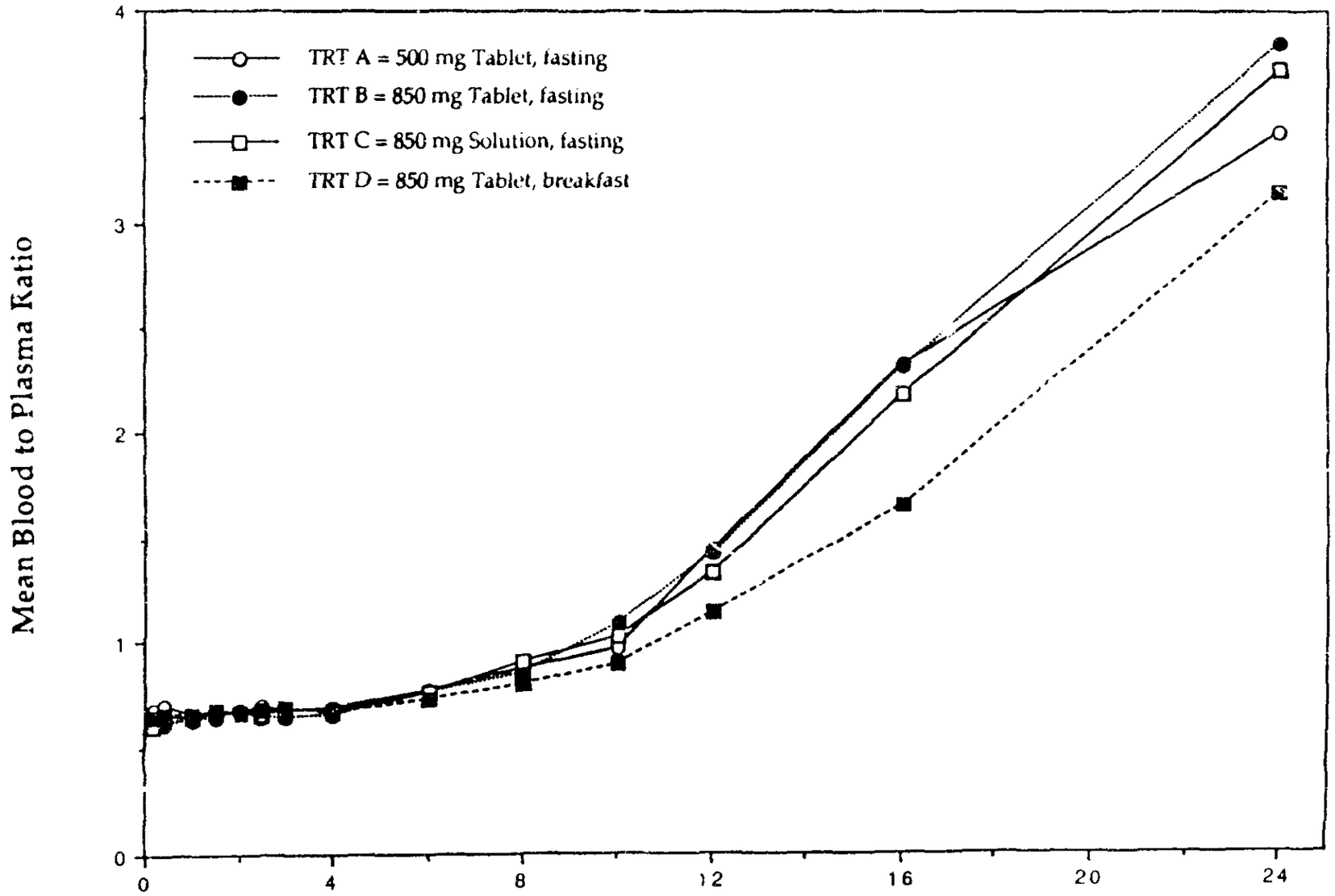
MEAN CONCENTRATION OF METFORMIN IN PLASMA



MEAN CONCENTRATION OF METFORMIN IN BLOOD



METFORMIN STUDY DSU #89-011
MEAN Blood to Plasma Concentration Ratios



DSU STUDY 89-011

URINARY EXCRETION AMOUNT AND PEAK EXCRETION RATE OF METFORMIN

Treatment A: 500 mg Metformin Tablet, Fasting

Subject Number	T_{mid} (hr.)	Peak Excretion Rate (mg/hr)	Urinary Excretion Amount (mg)
1	6		
2	2		
3	2		
4	2		
5	2		
6	2		
7	2		
8	2		
9	6		
10	6		
11	2		
12	2		
13	6		
14	2		
15	2		
16	2		
17	2		
18	2		
19	2		
20	2		
21	2		
22	2		
23	2		
24	2		
Mean	2.67	27.7	226.50
S.D.	1.52	6.20	36.1
%C.V.	57.1	22.4	15.9

[a] Excluded from the calculations due to incomplete urine collection.

DSU STUDY 89-011

URINARY EXCRETION AMOUNT AND PEAK EXCRETION RATE OF METFORMIN

Treatment B: 850 mg Metformin Tablet, Fasting

Subject Number	T_{mid} (hr.)	Peak Excretion Rate (mg/hr)	Urinary Excretion Amount (mg)
1	2		
2	6		
3	2		
4	2		
5	6		
6	2		
7	6		
8	2		
9	2		
10	NA		
11	2		
12	2		
13	2		
14	6		
15	2		
16	NA		
17	2		
18	2		
19	2		
20	2		
21	2		
22	6		
23	6		
24	6		
Mean	3.17	41.5	328.42
S.D.	1.86	9.84	84.4
%C.V.	58.6	23.7	25.7

[a] Excluded from the calculations due to incomplete urine collection.

NA - Not applicable due to missing urine sample.

DSU STUDY 89-011

URINARY EXCRETION AMOUNT AND PEAK EXCRETION RATE OF METFORMIN

Treatment C: 850 mg Metformin Solution, Fasting

Subject Number	T_{mid} (hr.)	Peak Excretion Rate (mg/hr)	Urinary Excretion Amount (mg)
1	6		
2	2		
3	2		
4	2		
5	2		
6	6		
7	2		
8	6		
9	2		
10	2		
11	2		
12	6		
13	2		
14	2		
15	NA		
16	6		
17	2		
18	2		
19	2		
20	2		
21	2		
22	2		
23	6		
24	2	[illegible]	
Mean	3.00	41.8	329.69
S.D.	1.77	9.20	77.9
%C.V.	59.0	22.0	23.6

[a] Excluded from the calculations due to incomplete urine collection.

NA - Not applicable due to missing urine sample.

DSU STUDY 89-011

URINARY EXCRETION AMOUNT AND PEAK EXCRETION RATE OF METFORMIN

Treatment D: 850 mg Metformin Tablet, Breakfast

Subject Number	T_{mid} (hr.)	Peak Excretion Rate (mg/hr)	Urinary Excretion Amount (mg)
1	10		
2	6		
3	6		
4	2		
5	2		
6	6		
7	2		
8	6		
9	10		
10	6		
11	6		
12	2		
13	2		
14	6		
15	6		
16	2		
17	2		
18	2		
19	6		
20	2		
21	2		
22	NA		
23	6		
24	NA		
Mean	4.67	30.0	276.08
S.D.	2.81	9.13	54.5
%C.V.	60.2	30.4	19.7

[a] Excluded from the calculations due to incomplete urine collection.

NA - Not applicable due to missing urine sample.

TABLE 7

PARAMETER ESTIMATES RELATED TO BLOOD METFORMIN IN 9 SUBJECTS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS AFTER METFORMIN HCL SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E)
(DSU #89-12/LIPHA 89-12-6023)

Parameter	Estimate (mean ± SD)				ANOVA/POSTHOC*	
	850 mg x 1 (Tx A)	850 mg x 2 (Tx B)	850 mg x 3 (Tx C)	850 mg MD† (Tx E)	Tx A vs Tx B vs Tx C	Tx A vs Tx E
$t_{max,b}$ (h)	3.49 (1.18)	3.28 (1.03)	2.54 (1.08)	2.28 (1.15)	C B A	NA
$C_{max,b}$ (µg/ml)	1.04 (0.30)	1.81 (0.32)	2.26 (0.64)	1.73 (0.41)	NA	NA
Norm $C_{max,b}$• (µg/ml)	1.04 (0.30)	0.91 (0.16)	0.75 (0.21)	1.73 (0.41)	C B A	NA
AUC_b (µg·h/ml)	11.51¶ (4.03)	19.32 (3.43)	24.09 (8.07)	NA	NA	NA
Norm AUC_b• (µg·h/ml)	11.51¶ (4.03)	9.66 (1.72)	8.03 (2.69)	NA	C B A	NA
AUCX§ (µg·h/ml)	13.80 (4.96)	22.41 (3.78)	28.36 (8.26)	11.17 (2.97)	NA	NA
Norm $AUCX_b$• (µg·h/ml)	13.80 (4.96)	11.20 (1.89)	9.45 (2.75)	11.17 (2.97)	C B A	E A
k_b (h^{-1})	0.040 (0.015)	0.034 (0.007)	0.034 (0.005)	0.028 (0.004)	C B A	E A
$t_{1/2,b}$ (h)	19.0 (6.2)	20.9 (4.2)	20.5 (12.3)	25.4 (3.8)	A C B	A E
CL/F_b (L/h)	53.1 (16.3)	60.5 (9.1)	76.4 (26.6)	62.9 (15.8)	A B C	A E
$CL_{R,b}$ (L/h)	31.2 (8.5)	28.4 (7.7)	40.9 (28.8)	31.1 (7.8)	B A C	E A

* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.
• Normalized to 850 mg.
§ $AUC_{0-\infty}$ for single doses and $AUC_{0-8\ h}$ for Treatment E.
¶ $AUC_{0-8\ h}$ for Treatment A = 5.87 ± 1.63 µg/ml.
NA=Not Applicable

TABLE 9

PARAMETER ESTIMATES RELATED TO BLOOD METFORMIN IN 9 HEALTHY SUBJECTS AFTER METFORMIN HCL SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E) *(DSU #89-12/LIPHA #89-12-6023)*

Parameter	Estimate (mean ± SD)				ANOVA/POSTHOC*	
	850 mg x1 (Tx A)	850 mg x 2 (Tx B)	850 mg x 3 (Tx C)	850 mg MD† (Tx E)	Tx A vs Tx B vs Tx C	Tx A vs Tx E
$t_{max,b}$ (h)	2.78 (0.79)	2.71 (0.86)	2.09 (0.47)	2.00 (1.20)	C B A	NA
$C_{max,b}$ (µg/ml)	1.38 (0.46)	1.92 (0.44)	2.80 (1.15)	2.06 (0.78)	NA	NA
Norm $C_{max,b}$• (µg/ml)	1.38 (0.46)	0.96 (0.22)	0.93 (0.38)	2.06 (0.78)	C B A	NA
AUC_b (µg·h/ml)	14.11¶ (4.16)	19.87 (4.34)	27.34 (9.85)	NA	NA	NA
Norm AUC_b• (µg·h/ml)	14.11¶ (4.16)	9.94 (2.17)	9.11 (3.28)	NA	C B A	NA
AUCX§ (µg·h/ml)	16.14 (5.00)	23.78 (4.88)	31.94 (10.41)	11.72 (4.22)	NA	NA
NormAUCX$_b$• (µg·h/ml)	16.14 (5.00)	11.89 (2.44)	10.65 (3.47)	11.72 (4.22)	C B A	E A
k_b (h^{-1})	0.035 (0.005)	0.031 (0.008)	0.031 (0.005)	0.029 (0.003)	C B A	E A
$t_{1/2,b}$ (h)	20.0 (2.9)	24.1 (7.7)	23.2 (4.8)	24.6 (3.1)	A C B	A E
CL/F_b (L/h)	45.3 (16.2)	58.5 (15.5)	68.3 (21.7)	63.4 (23.0)	A B C	A E
$CL_{R,b}$ (L/h)	32.4 (12.1)	27.6 (9.5)	23.2 (7.0)	36.9 (11.0)	C B A	A E

* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.
• Normalized to 850 mg.
§ $AUC_{0-\infty}$ for single doses and $AUC_{0-8\ h}$ for Treatment E.
¶ $AUC_{0-8\ h}$ for Treatment A = 7.46 ± 2.23 µg/ml.
NA=Not Applicable

TABLE 9

PARAMETER ESTIMATES RELATED TO URINE METFORMIN IN 9 SUBJECTS WITH NONINSULIN-DEPENDENT DIABETES AND 9 HEALTHY SUBJECTS AFTER METFORMIN HCl SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E) *(DSU #89-12/LIPHA #89-12-6023)*

Parameter	Estimate (mean ± SD)				ANOVA/POSTHOC*	
	850 mg x1 (Tx A)	850 mg x 2 (Tx B)	850 mg x 3 (Tx C)	850 mg MD† (Tx E)	Tx A vs Tx B vs Tx C	Tx A vs Tx E
Subjects with Non-Insulin-Dependent Diabetes Mellitus						
time of Peak Excr Rate (h)	3.00 (1.85)	3.78 (2.91)	3.33 (2.00)	3.33 (2.00)	$\overline{A\ C\ B}$	NA
Peak Excr Rate (mg/h)	36.85 (6.07)	57.49 (19.57)	56.91 (23.25)	53.69 (19.73)	NA	NA
Normalized Peak Excr Rate• (mg/h)	36.85 (6.07)	28.74 (9.79)	28.45 (11.63)	53.69 (19.73)	$\overline{C\ B\ A}$	NA
Total Amt Excr in Urine (mg)	308.6 (46.7)	490.0 (125.1)	736.6 (248.5)	339.6§ (102.4)	NA	NA
Normalized Total Amt Excr in Urine• (mg)	308.6 (46.7)	245.0 (62.5)	245.5 (82.8)	339.6§ (102.4)	$\overline{B\ C\ A}$	$\overline{A\ E}$
Healthy Subjects						
time of Peak Excr Rate (h)	3.33 (2.00)	2.44 (1.33)	2.44 (1.33)	2.44 (1.33)	$\overline{C\ B\ A}$	NA
Peak Excr Rate (mg/h)	43.82 (11.84)	61.30 (19.13)	53.46 (12.75)	57.80 (14.77)	NA	NA
Normalized Peak Excr Rate• (mg/h)	43.82 (11.84)	30.65 (9.56)	26.73 (6.38)	57.80 (14.77)	$\overline{C\ B}\ \overline{A}$	NA
Total Amt Excr in Urine (mg)	362.8 (88.3)	485.6 (145.5)	632.2 (126.3)	391.8§ (82.9)	NA	NA
Normalized Total Amt Excr in Urine• (mg)	362.8 (88.3)	242.8 (72.7)	210.7 (42.1)	391.8§ (82.9)	$\overline{C\ B}\ \overline{A}$	$\overline{A\ E}$

* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.
• Normalized to 850 mg.
§ 0-8 h only.
NA=Not Applicable

TABLE 10

AVERAGE PLASMA GLUCOSE, LACTATE AND INSULIN CONCENTRATIONS IN 9 SUBJECTS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS AFTER METFORMIN HCL SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E) *(DSU #89-12/LIPHA #89-12-6023)*

Parameter		Estimate (mean ± SD)					ANOVA/POSTHOC*	
		Placebo (Tx D)	850 mg x1 (Tx A)	850 mg x 2 (Tx B)	850 mg x 3 (Tx C)	850 mg MD† (Tx E)	A vs. B vs. C vs. D	E vs. D
Subjects with Non-Insulin-Dependent Diabetes Mellitus								
average $C_{glucose}$ (mg/dl)	0-4 h*	171.6 (41.6)	169.9 (38.1)	164.8 (38.9)	170.7 (40.4)	130.7 (27.1)	B A C D	E D
	4-10 h	187.7 (44.9)	177.2 (35.0)	166.4 (40.6)	169.6 (46.9)	136.0 (27.5)	B C A D	E D
	4-6 h	200.4 (41.5)	184.4 (33.5)	172.3 (44.2)	186.3 (55.2)	143.4 (31.4)	D C A B	E D
	0-10 h	181.3 (43.0)	174.3 (34.8)	165.7 (39.6)	170.0 (43.9)	133.9 (27.1)	B C A D	E D
average $C_{lactate}$ (mg/dl)	0-4 h	9.9 (2.6)	11.3 (2.3)	11.5 (2.3)	11.8 (2.6)	14.1 (4.3)	D A B C	D E
	4-10 h	11.9 (2.6)	15.0 (4.8)	13.8 (3.5)	15.5 (3.2)	15.9 (3.3)	D B A C	D E
	0-10 h	11.1 (2.4)	13.5 (3.6)	12.9 (2.8)	14.0 (2.9)	15.2 (3.6)	D B A C	D E
average $C_{insulin}$ (μU/ml)	0-4 h	35.3 (10.1)	33.8 (9.6)	34.5 (14.5)	34.2 (11.1)	28.5 (7.9)	A C B D	E D
	4-10 h	53.3 (16.3)	59.7 (21.2)	49.4 (22.3)	52.3 (20.9)	44.9 (19.4)	B C D A	E D
	4-6 h	60.4 (25.9)	62.7 (24.2)	52.2 (31.1)	58.9 (26.2)	48.7 (26.8)	B C D A	E D
	0-10 h	46.1 (12.7)	49.3 (15.1)	43.5 (19.0)	45.0 (16.1)	38.3 (14.5)	B C D A	E D

* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.

TABLE 11

AVERAGE PLASMA GLUCOSE, LACTATE AND INSULIN CONCENTRATIONS IN 9 HEALTHY SUBJECTS AFTER METFORMIN HCL SINGLE DOSES OF 850 MG X 1 (TREATMENT A), 850 MG X 2 (TREATMENT B), 850 MG X 3 (TREATMENT C) AND AFTER THE FINAL DOSE OF 850 MG THREE TIMES DAILY X 19 (TREATMENT E) *(DSU #89-12/LIPHA #89-12-6023)*

Parameter		Estimate (mean ± SD)					ANOVA/POSTHOC*	
		Placebo (Tx D)	850 mg x1 (Tx A)	850 mg x 2 (Tx B)	850 mg x 3 (Tx C)	850 mg MD† (Tx E)	A vs. B vs. C vs. D	E vs. D
Healthy Subjects								
average $C_{glucose}$ (mg/dl)	0-4 h	87.5 (8.0)	89.4 (7.0)	85.7 (5.6)	85.7 (6.9)	88.2 (8.7)	C B D A	D E
	4-10 h	87.4 (10.8)	89.3 (10.3)	88.5 (9.3)	91.3 (8.2)	92.2 (8.9)	D B A C	D E
	4-6 h	95.9 (15.3)	94.8 (15.5)	91.8 (17.8)	94.7 (12.8)	99.9 (15.3)	B C A D	D E
	0-10 h	87.4 (9.0)	89.3 (7.9)	87.4 (7.3)	89.1 (6.6)	90.6 (8.5)	B D C A	D E
average $C_{lactate}$ (mg/dl)	0-4 h	8.7 (2.0)	9.1 (2.1)	9.3 (1.8)	11.3 (3.8)	10.3 (1.6)	D A B C	D E
	4-10 h	9.0 (2.1)	10.1 (2.0)	10.9 (2.3)	11.3 (1.6)	11.0 (1.9)	D A B C	D E
	0-10 h	8.9 (2.0)	9.7 (1.9)	10.3 (1.9)	11.3 (2.1)	10.7 (1.5)	D A B C	D E
average $C_{insulin}$ (μU/ml)	0-4 h	22.5 (4.0)	22.2 (4.8)	22.0 (5.9)	21.7 (4.9)	21.8 (6.3)	C B A D	E D
	4-10 h	35.7 (10.5)	32.9 (8.5)	34.7 (9.7)	33.9 (11.1)	32.1 (13.5)	C B D A	E D
	4-6 h	52.7 (19.7)	41.3 (15.2)	44.6 (20.3)	40.5 (16.3)	39.4 (20.5)	C A B D	E D
	0-10 h	30.4 (7.6)	28.6 (6.4)	29.6 (7.7)	29.0 (8.3)	28.0 (10.2)	A C B D	E D

* Treatments under same line do not differ significantly.
† MD=after multiple (19) doses.

Figure 2

DSU/Lipha 89-12: Mean Plasma Concentration
Normalized to 850 mg Dose, NIDDM

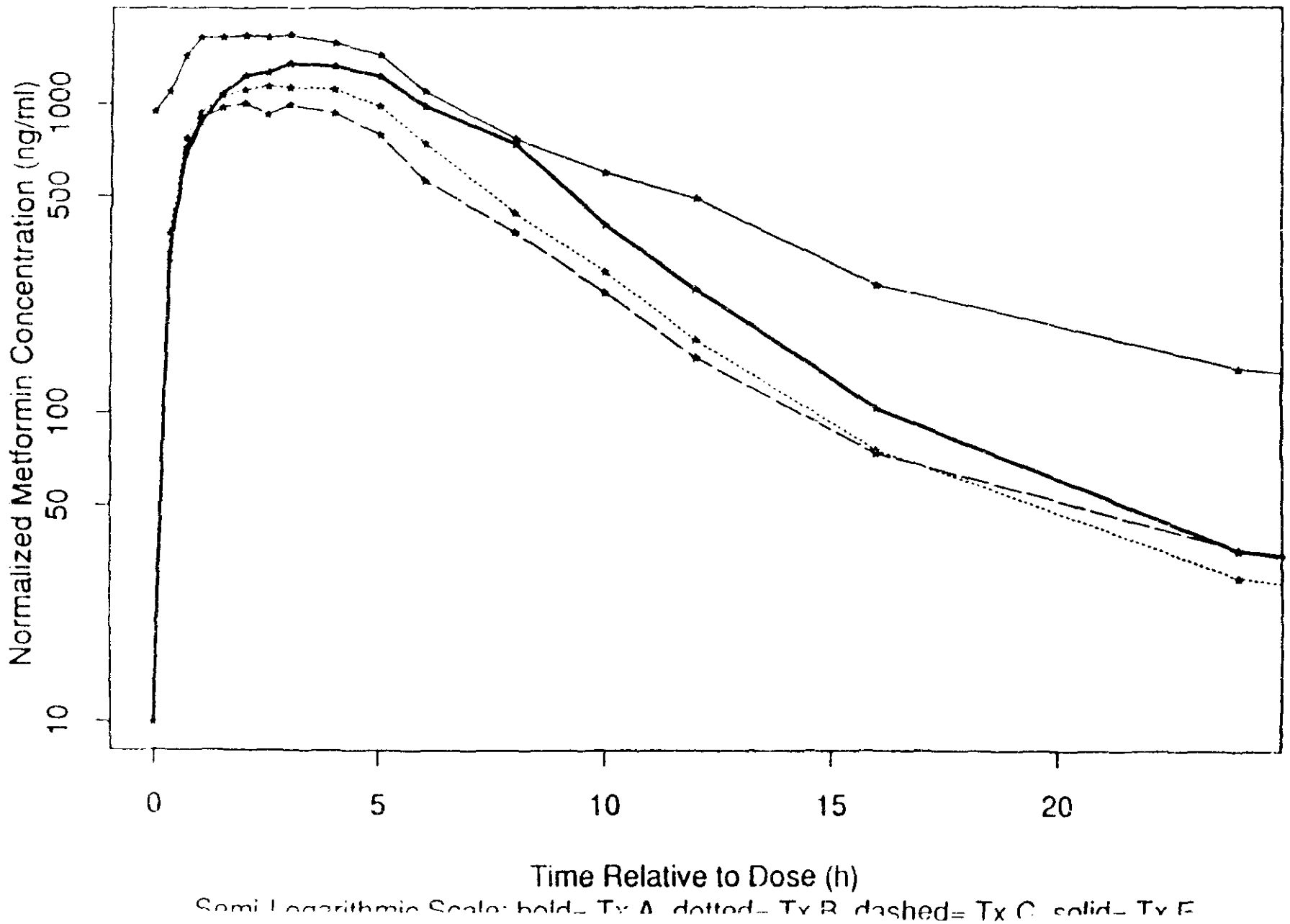


Figure 3

DSU/Lipha 89-12: Mean Plasma Concentration
Normalized to 850 mg Dose, Healthy

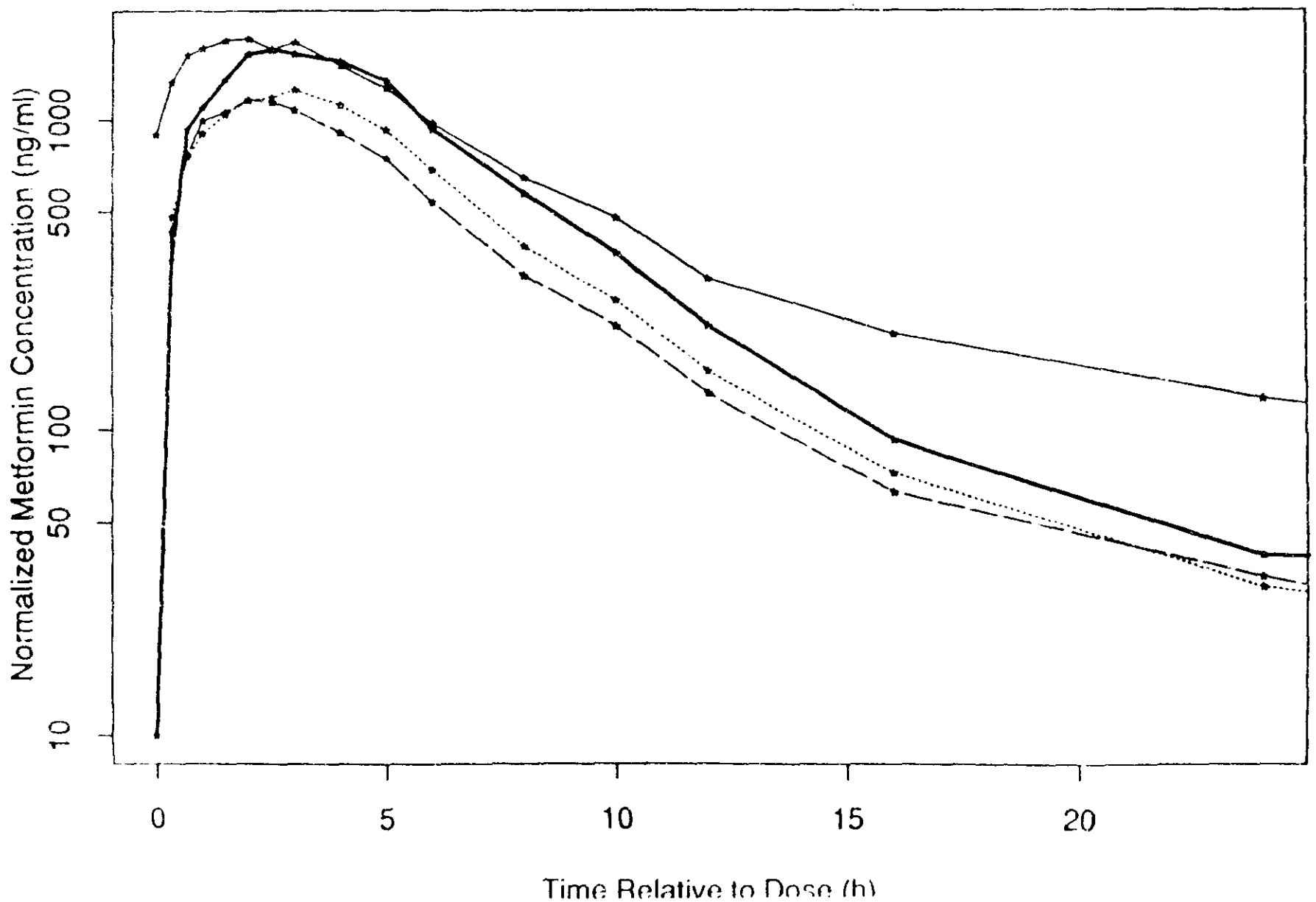
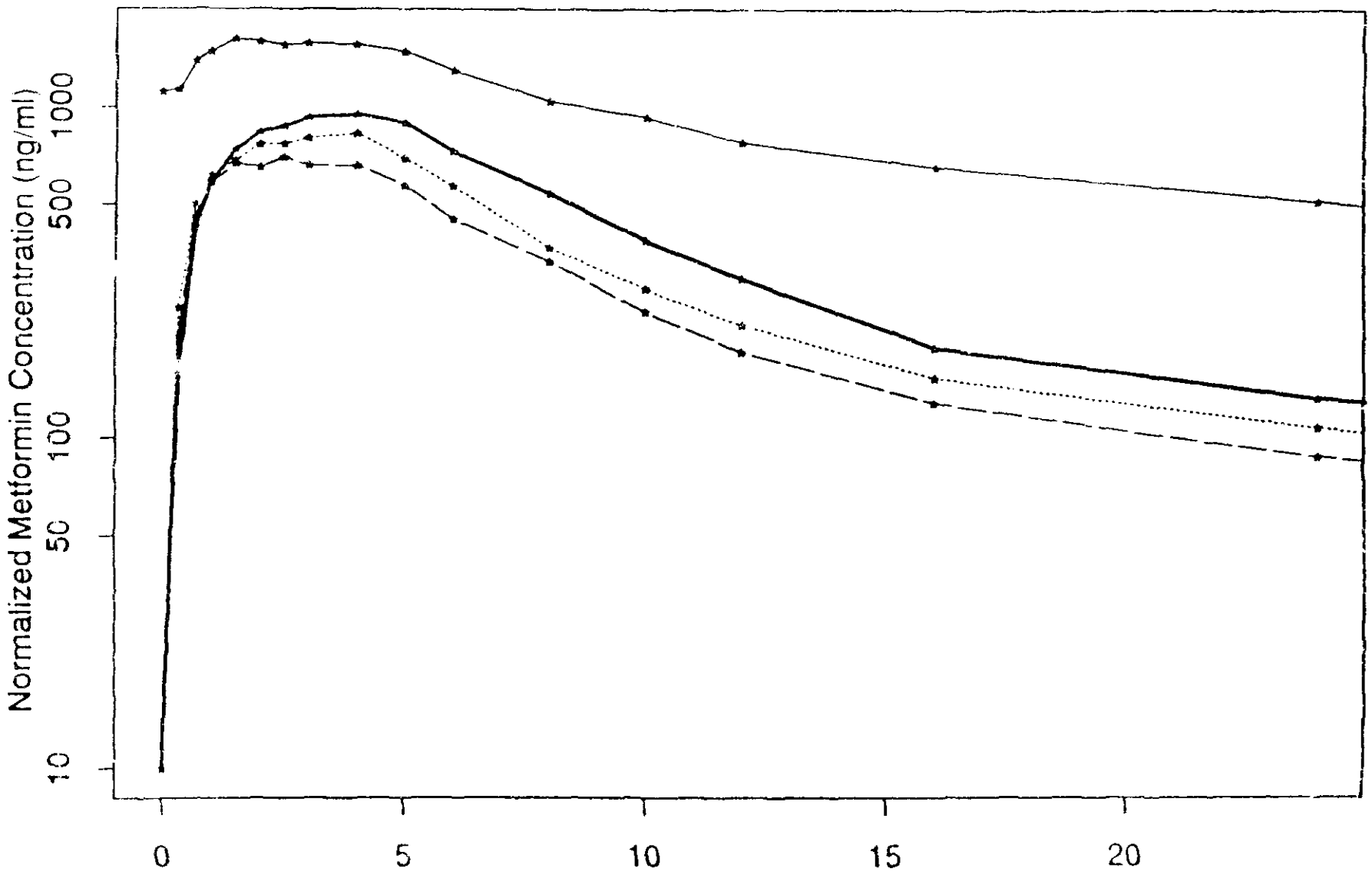


Figure 6

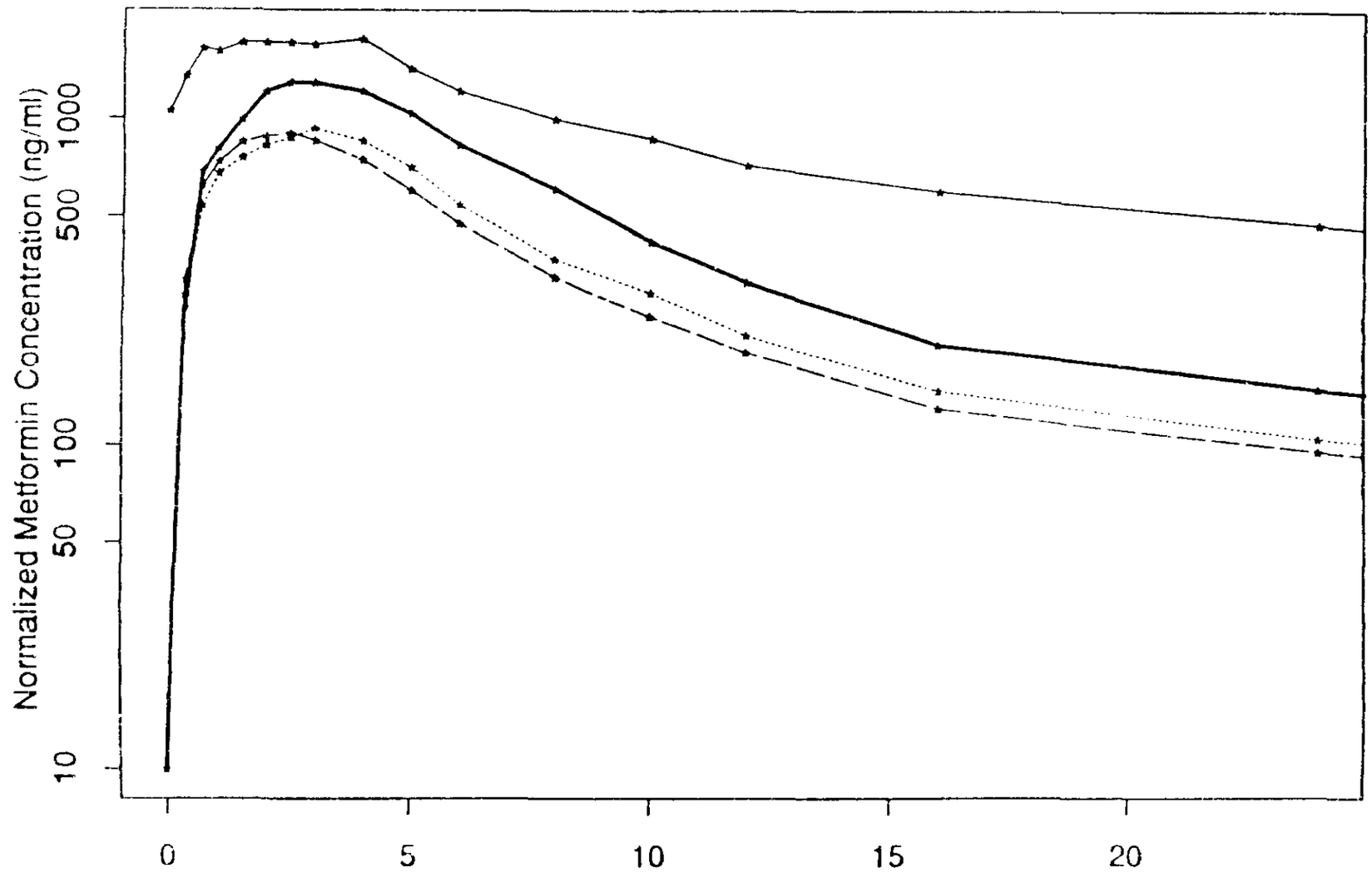
DSU/Lipha 89-12: Mean Blood Concentration
Normalized to 850 mg Dose, NIDDM



Semi-Logarithmic Scale: bold= Tx A, dotted= Tx B, dashed= Tx C, solid= Tx E

Figure 7

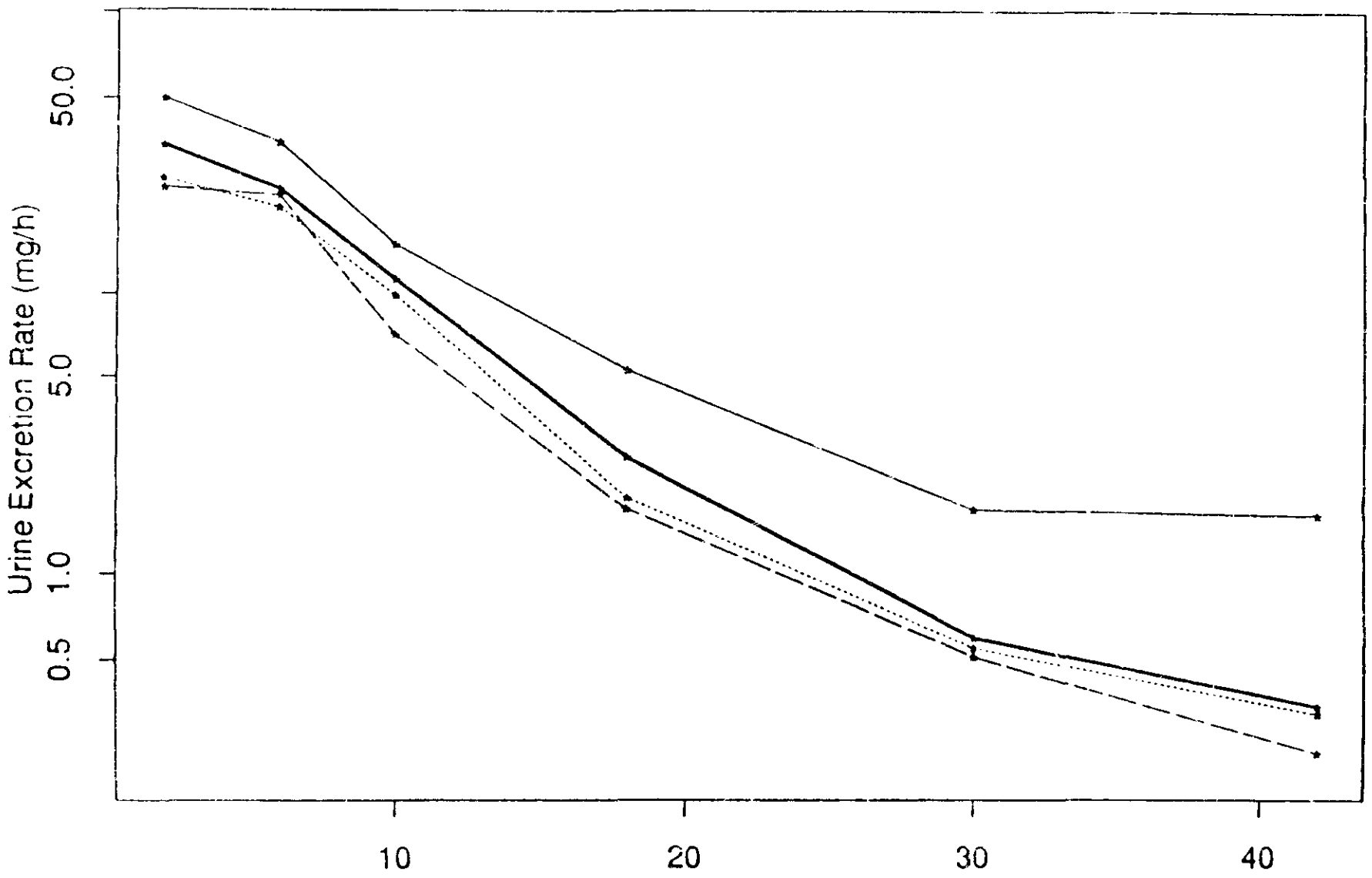
DSU/Lipha 89-12: Mean Blood Concentration
Normalized to 850 mg Dose, Healthy



Semi-Logarithmic Scale: bold= Tx A, dotted= Tx B, dashed= Tx C, solid= Tx E

Figure 9

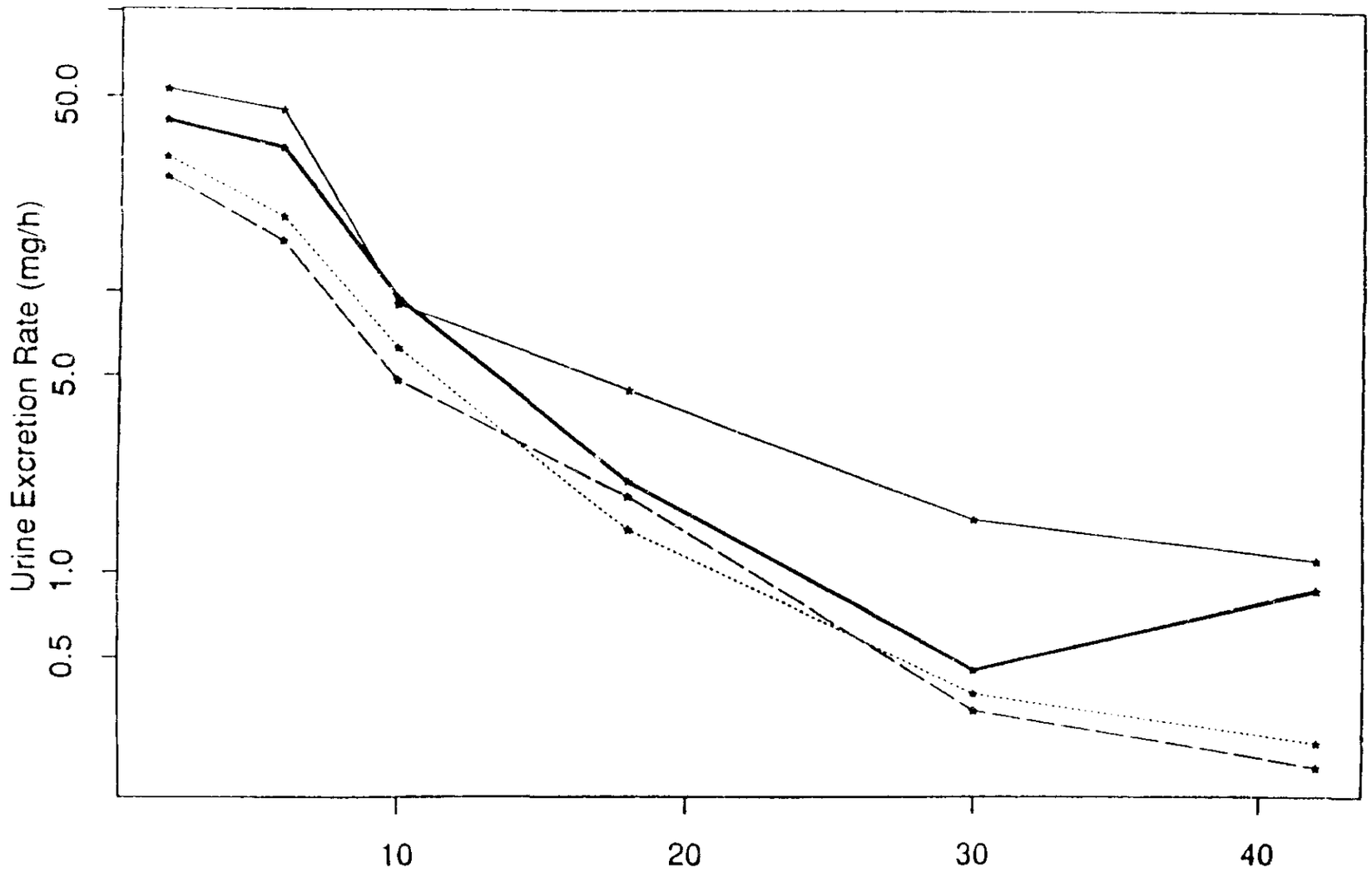
DSU/Lipha 89-12: Mean Urine Excretion Rate
Normalized to 850 mg Dose, NIDDM



Semi-Logarithmic Scale: bold= Tx A, dotted= Tx B, dashed= Tx C, solid= Tx E

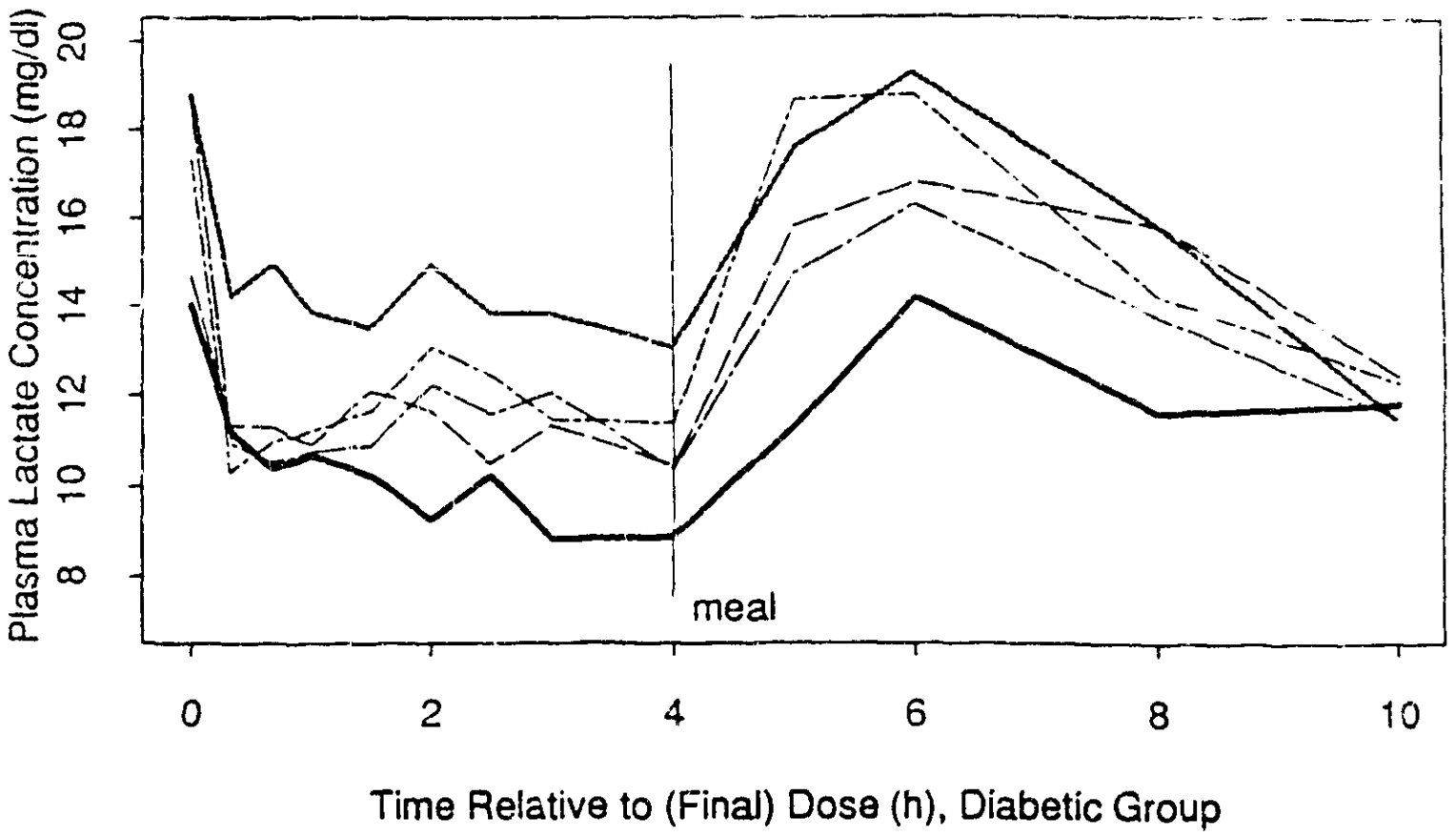
Figure 10

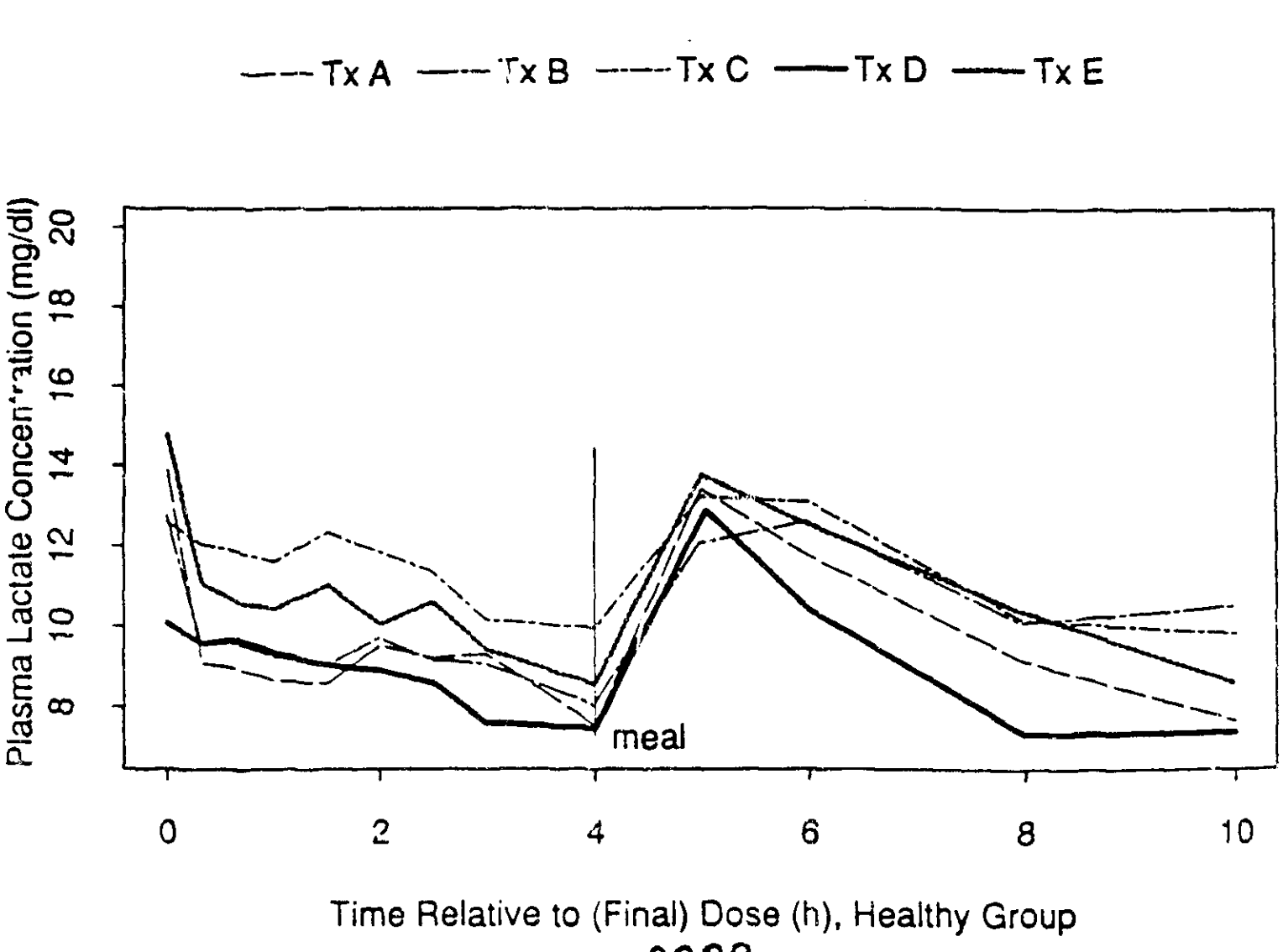
DSU/Lipha 89-12: Mean Urine Excretion Rate
Normalized to 850 mg Dose, Healthy



Semi-Logarithmic Scale: bold= Tx A, dotted= Tx B, dashed= Tx C, solid= Tx E

Fig. 13 Metformin Study 89-12, Comparison of Treatment Mean Plasma Lactate Concentration vs Time





0088

06 000806

Fig. 14 Metformin Study 89-12, Comparison of Treatment
Mean Plasma Insulin Concentration vs Time

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment A (1 x 850 mg Single Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.329	0.376	114.5
0.67	8	0.684	0.418	61.1
1.00	9	0.868	0.370	42.6
1.50	9	1.082	0.411	38.0
2.00	9	1.241	0.467	37.6
2.50	9	1.272	0.410	32.3
3.00	9	1.358	0.433	31.9
4.00	9	1.328	0.393	29.6
5.00	9	1.231	0.416	33.8
6.00	9	0.985	0.354	35.9
8.00	9	0.741	0.444	59.8
10.00	9	0.407	0.216	53.1
12.00	9	0.252	0.152	60.1
16.00	9	0.104	0.068	65.7
24.00	9	0.036	0.017	47.9
48.00	3	0.016	0.006	35.8

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment B (2 x 850 mg Single Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.762	0.538	70.6
0.67	9	1.551	0.546	35.2
1.00	9	1.880	0.662	35.2
1.50	9	2.131	0.622	29.2
2.00	9	2.231	0.614	27.5
2.50	9	2.293	0.545	23.8
3.00	9	2.277	0.501	22.0
4.00	9	2.241	0.485	21.6
5.00	9	1.967	0.350	17.8
6.00	9	1.488	0.408	27.4
8.00	9	0.883	0.354	40.1
10.00	9	0.576	0.220	38.1
12.00	9	0.344	0.161	46.9
16.00	9	0.153	0.071	46.0
24.00	9	0.060	0.026	43.5
48.00	6	0.022	0.009	42.3

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment C (3 x 850 mg Single Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.926	0.459	49.6
0.67	9	2.168	0.576	26.6
1.00	9	2.677	0.728	27.2
1.50	9	2.927	0.941	32.2
2.00	9	3.038	0.998	32.9
2.50	9	2.776	0.806	29.0
3.00	9	2.983	0.917	30.7
4.00	9	2.806	0.968	34.5
5.00	9	2.381	0.853	35.8
6.00	9	1.683	0.619	36.7
8.00	9	1.152	0.576	50.0
10.00	9	0.739	0.344	46.5
12.00	9	0.451	0.209	46.4
16.00	9	0.224	0.156	70.0
24.00	9	0.109	0.069	63.0
48.00	5	0.024	0.010	40.7

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment E (Multiple Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	8	0.948	0.414	43.7
0.33	9	1.098	0.333	30.4
0.67	9	1.436	0.464	32.3
1.00	9	1.646	0.701	42.6
1.50	9	1.647	0.540	32.8
2.00	9	1.672	0.581	34.8
2.50	9	1.646	0.498	30.3
3.00	9	1.674	0.676	40.4
4.00	9	1.582	0.648	41.0
5.00	9	1.444	0.536	37.1
6.00	9	1.100	0.475	43.2
8.00	9	0.769	0.377	49.0
10.00	9	0.596	0.365	61.3
12.00	9	0.492	0.226	45.9
16.00	9	0.260	0.113	43.3
24.00	9	0.139	0.069	49.8
48.00	9	0.070	0.061	87.1

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment A (1 x 850 mg Single Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.349	0.141	40.3
0.67	9	0.933	0.239	25.6
1.00	9	1.098	0.247	22.5
1.50	9	1.365	0.449	32.9
2.00	9	1.644	0.630	38.3
2.50	9	1.699	0.651	38.3
3.00	9	1.645	0.521	31.7
4.00	9	1.556	0.423	27.2
5.00	9	1.342	0.374	27.9
6.00	9	0.928	0.249	26.8
8.00	9	0.570	0.158	27.8
10.00	9	0.368	0.101	27.4
12.00	9	0.214	0.058	27.1
16.00	9	0.093	0.036	38.4
24.00	9	0.039	0.025	63.7
48.00	1	0.032		NA

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment B (2 x 850 mg Single Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.965	0.598	62.0
0.67	9	1.509	0.390	25.9
1.00	9	1.806	0.545	30.2
1.50	9	2.086	0.622	29.8
2.00	9	2.321	0.539	23.2
2.50	9	2.378	0.521	21.9
3.00	9	2.517	0.544	21.6
4.00	9	2.230	0.538	24.1
5.00	9	1.844	0.426	23.1
6.00	9	1.355	0.372	27.4
8.00	9	0.774	0.211	27.2
10.00	9	0.516	0.131	25.4
12.00	9	0.306	0.105	34.1
16.00	9	0.145	0.043	29.4
24.00	9	0.062	0.024	38.0
48.00	4	0.023	0.010	42.7

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment C (3 x 850 mg Single Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	1.300	0.656	50.5
0.67	9	2.312	1.039	44.9
1.00	9	2.992	0.976	32.6
1.50	9	3.179	0.960	30.2
2.00	9	3.493	1.052	30.1
2.50	9	3.441	1.155	33.6
3.00	9	3.231	1.111	34.4
4.00	9	2.724	0.874	32.1
5.00	9	2.217	0.740	33.4
6.00	9	1.602	0.545	34.0
8.00	9	0.937	0.401	42.8
10.00	9	0.641	0.293	45.7
12.00	9	0.389	0.179	45.9
16.00	9	0.189	0.082	43.4
24.00	9	0.100	0.048	48.1
48	8	0.023	0.009	40.0

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Plasma

Treatment E (Multiple Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	7	0.897	0.221	24.7
0.33	9	1.340	0.400	29.8
0.67	9	1.626	0.313	19.3
1.00	9	1.718	0.436	25.4
1.50	9	1.823	0.474	26.0
2.00	9	1.843	0.485	26.3
2.50	9	1.706	0.518	30.4
3.00	9	1.791	0.478	26.7
4.00	9	1.509	0.505	33.5
5.00	9	1.269	0.415	32.7
6.00	9	0.969	0.307	31.6
8.00	9	0.641	0.196	30.6
10.00	9	0.476	0.156	32.8
12.00	9	0.305	0.120	39.3
16.00	9	0.202	0.081	40.3
24.00	9	0.126	0.059	46.4
48.00	7	0.054	0.050	93.4

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment A (1 x 850 mg Single Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.154	0.108	69.7
0.67	9	0.428	0.205	47.9
1.00	9	0.594	0.234	39.4
1.50	9	0.742	0.242	32.6
2.00	9	0.837	0.277	33.2
2.50	9	0.876	0.275	31.4
3.00	9	0.931	0.280	30.0
4.00	9	0.954	0.276	28.9
5.00	9	0.897	0.265	29.5
6.00	9	0.731	0.279	38.2
8.00	9	0.542	0.236	43.6
10.00	9	0.391	0.155	39.8
12.00	9	0.301	0.132	44.0
16.00	9	0.186	0.079	42.8
24.00	9	0.131	0.037	27.8
48.00	7	0.073	0.034	46.5

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment B (2 x 850 mg Single Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.491	0.361	73.5
0.67	9	1.010	0.339	33.6
1.00	9	1.240	0.459	37.0
1.50	9	1.374	0.332	24.1
2.00	9	1.534	0.314	20.5
2.50	9	1.542	0.290	18.8
3.00	9	1.609	0.284	17.6
4.00	9	1.666	0.280	16.8
5.00	9	1.390	0.260	18.7
6.00	9	1.139	0.247	21.7
8.00	9	0.747	0.187	25.0
10.00	9	0.560	0.136	24.3
12.00	9	0.434	0.132	30.5
16.00	9	0.302	0.074	24.4
24.00	9	0.215	0.037	17.3
48.00	9	0.102	0.021	20.1

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment C (3 x 850 mg Single Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.600	0.300	50.0
0.67	9	1.388	0.579	41.7
1.00	9	1.755	0.476	27.1
1.50	9	2.021	0.615	30.4
2.00	9	1.956	0.540	27.6
2.50	9	2.097	0.673	32.1
3.00	9	1.989	0.642	32.3
4.00	9	1.987	0.671	33.8
5.00	9	1.724	0.607	35.2
6.00	9	1.361	0.561	41.2
8.00	9	1.019	0.444	43.6
10.00	9	0.714	0.274	38.4
12.00	9	0.541	0.179	33.1
16.00	9	0.382	0.136	35.7
24.00	9	0.263	0.098	37.4
48.00	8	0.135	0.039	28.5

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment E (Multiple Dose), NIDDM

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	8	1.117	0.281	25.2
0.33	9	1.137	0.273	24.1
0.67	9	1.379	0.319	23.2
1.00	9	1.470	0.366	24.9
1.50	9	1.614	0.433	26.8
2.00	9	1.577	0.444	28.2
2.50	9	1.538	0.415	27.0
3.00	9	1.558	0.430	27.6
4.00	9	1.549	0.459	29.6
5.00	9	1.472	0.436	29.6
6.00	9	1.297	0.373	28.7
8.00	9	1.047	0.288	27.5
10.00	9	0.930	0.244	26.2
12.00	9	0.779	0.226	29.0
16.00	9	0.638	0.196	30.6
24.00	9	0.498	0.133	26.6
48.00	7	0.268	0.061	22.6

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment A (1 x 850 mg Single Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.262	0.114	43.5
0.67	9	0.684	0.205	29.9
1.00	9	0.806	0.222	27.6
1.50	9	0.995	0.318	31.9
2.00	9	1.221	0.455	37.3
2.50	9	1.296	0.474	36.6
3.00	9	1.296	0.443	34.2
4.00	9	1.221	0.373	30.5
5.00	9	1.036	0.399	38.5
6.00	9	0.829	0.273	33.0
8.00	9	0.608	0.188	30.9
10.00	9	0.422	0.138	32.6
12.00	9	0.317	0.114	35.9
16.00	9	0.203	0.061	30.2
24.00	9	0.148	0.043	28.8
48.00	9	0.069	0.027	39.2

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment B (2 x 850 mg Single Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.577	0.240	41.7
0.67	9	1.073	0.335	31.2
1.00	9	1.351	0.435	32.2
1.50	9	1.521	0.501	32.9
2.00	9	1.656	0.434	26.2
2.50	9	1.743	0.453	26.0
3.00	9	1.861	0.471	25.3
4.00	9	1.707	0.400	23.5
5.00	9	1.416	0.323	22.8
6.00	9	1.086	0.309	28.5
8.00	9	0.741	0.192	25.9
10.00	9	0.590	0.137	23.1
12.00	9	0.433	0.104	24.1
16.00	9	0.292	0.072	24.6
24.00	9	0.209	0.048	23.2
48.00	9	0.108	0.025	23.5

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment C (3 x 850 mg Single Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	9	0.000	0.000	NA
0.33	9	0.962	0.524	54.5
0.67	9	1.854	0.742	40.0
1.00	9	2.197	0.760	34.6
1.50	9	2.532	0.976	38.5
2.00	9	2.638	1.057	40.1
2.50	9	2.698	1.126	41.7
3.00	9	2.561	1.013	39.6
4.00	9	2.244	0.858	38.2
5.00	9	1.804	0.679	37.6
6.00	9	1.430	0.536	37.5
8.00	9	0.984	0.394	40.0
10.00	9	0.743	0.292	39.4
12.00	9	0.577	0.224	38.8
16.00	9	0.388	0.149	38.4
24.00	9	0.287	0.103	35.9
48.00	9	0.139	0.037	26.8

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin: Blood

Treatment E (Multiple Dose), Healthy

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	8	1.057	0.244	23.1
0.33	9	1.446	0.423	29.3
0.67	9	1.637	0.419	25.6
1.00	9	1.607	0.372	23.1
1.50	9	1.712	0.497	29.0
2.00	9	1.716	0.511	29.8
2.50	9	1.710	0.567	33.1
3.00	9	1.692	0.696	41.1
4.00	9	1.758	0.887	50.4
5.00	9	1.429	0.626	43.8
6.00	9	1.223	0.518	42.3
8.00	9	0.998	0.408	40.9
10.00	9	0.868	0.344	39.6
12.00	9	0.720	0.283	39.3
16.00	9	0.599	0.220	36.7
24.00	9	0.472	0.165	34.9
48.00	9	0.245	0.086	35.4

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment A: 1 x 850 mg Metformin, NIDDM

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	8	9	9	9	6	4
mean	34.27	23.75	11.32	2.61	0.60	0.34
s.d.	9.54	7.38	5.01	1.21	0.24	0.11
CV (%)	27.8	31.1	44.3	46.4	60.0	32.4

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment B: 2 x 850 mg Metformin, NIDDM

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	8	9	9	9	9	6
mean	51.88	40.74	19.80	3.75	1.10	0.64
s.d.	20.55	19.33	18.00	1.02	0.47	0.18
CV (%)	39.6	47.4	90.9	27.2	42.7	28.1

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment C: 3 x 850 mg Metformin, NIDDM

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	9	9	8	9	9	6
mean	72.09	67.49	21.35	5.13	1.54	0.69
s.d.	24.58	40.12	11.78	2.30	0.62	0.29
CV (%)	34.1	59.4	55.2	44.8	40.3	42.0

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment E: Multiple Dose Metformin, NIDDM

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	9	9	9	9	9	8
mean	50.11	34.79	15.10	5.30	1.70	1.62
s.d.	22.44	9.80	11.72	2.43	1.00	1.20
CV (%)	44.8	28.2	77.6	45.8	58.8	74.1

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment A: 1 x 850 mg Metformin, Healthy

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	9	9	9	9	6	1
mean	41.07	32.57	9.48	2.13	0.45	0.86
s.d.	10.37	14.07	4.36	0.71	0.21	NA
CV (%)	25.2	43.2	46.0	33.3	46.7	NA

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment B: 2 x 850 mg Metformin, Healthy

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	9	9	9	9	8	5
mean	60.56	36.87	12.63	2.85	0.74	0.49
s.d.	19.56	14.56	5.43	1.23	0.31	0.36
CV (%)	32.3	39.5	43.0	43.2	41.9	73.5

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

Treatment C: 3 x 850 mg Metformin, Healthy

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	9	9	9	9	9	8
mean	76.82	45.23	14.52	5.64	0.97	0.60
s.d.	25.91	15.43	7.92	4.13	0.43	0.30
CV (%)	33.7	34.1	54.5	73.2	44.3	50.0

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 89-12

Metformin, Urine Excretion Rate

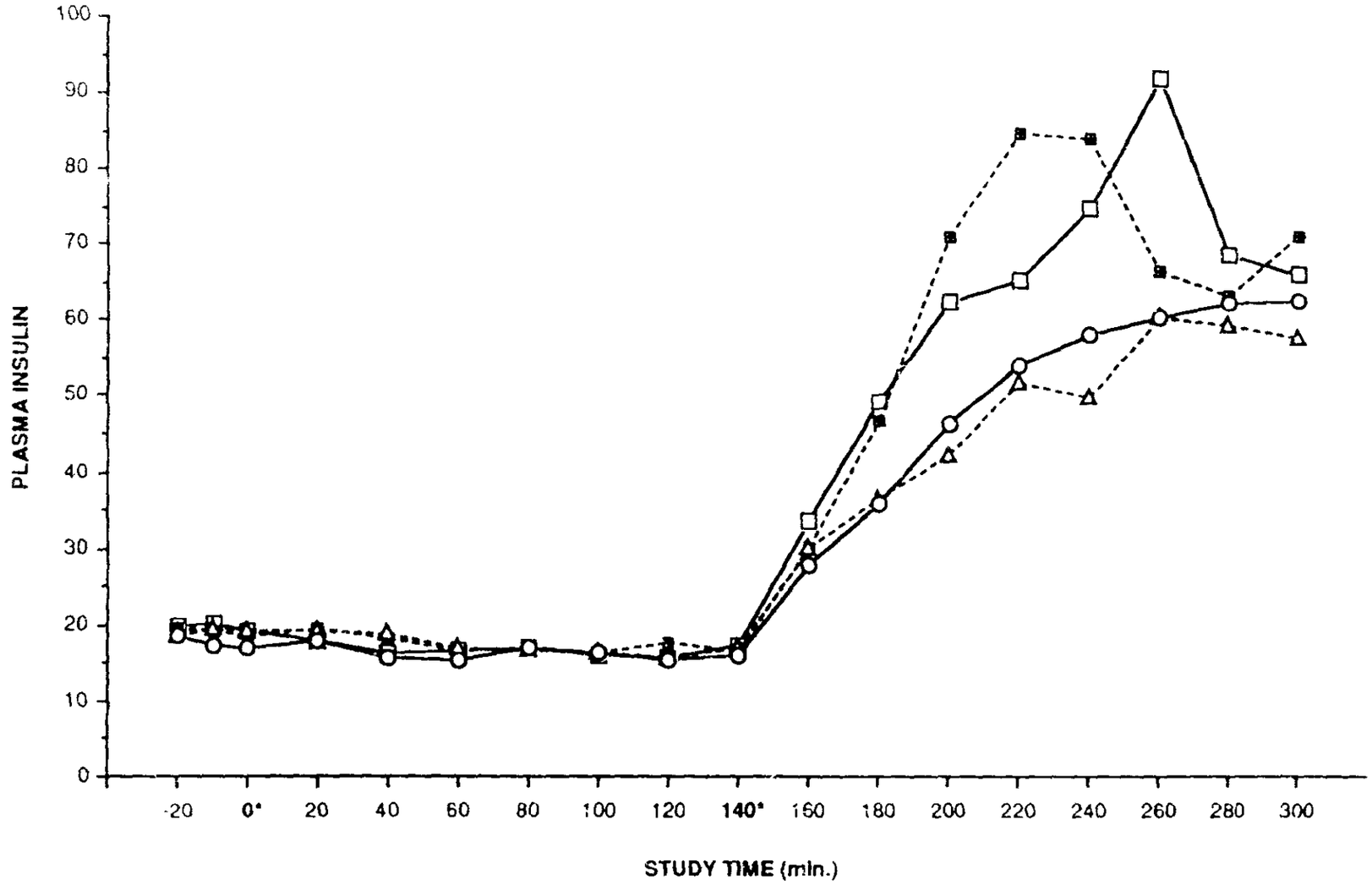
Treatment E: Multiple Dose Metformin, Healthy

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
7						
8						
9						
n	9	9	9	9	9	9
mean	53.35	44.60	9.03	4.49	1.55	1.10
s.d.	6.13	19.10	4.88	1.92	0.76	0.86
CV (%)	11.5	42.8	54.0	42.8	49.0	78.2

NA: not applicable

FIGURE 2

MEAN PLASMA INSULIN (μIU/mL) OVER TIME FOR COMPLETERS



* Study medication was administered at Time 0. At Time 140, 75 grams was administered for oral GTT.

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin: Plasma

1 x 850 mg Single Dose, Young

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	6	0.000	0.000	NA
0.50	6	0.597	0.178	29.8
1.00	6	1.178	0.296	25.1
1.50	6	1.290	0.349	27.1
2.00	6	1.308	0.313	23.9
2.50	6	1.286	0.398	30.9
3.00	6	1.348	0.319	23.7
4.00	6	1.202	0.258	21.5
6.00	6	0.776	0.267	34.4
8.00	6	0.452	0.104	23.0
10.00	6	0.267	0.089	33.3
12.00	6	0.163	0.049	30.1
16.00	6	0.090	0.053	58.9
24.00	6	0.036	0.023	63.9
30.00	4	0.021	0.006	28.6
36.00	2	0.016	0.005	31.2
48.00	0	NA	NA	NA

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin: Plasma

1 x 850 mg Single Dose, Elderly

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	12	0.000	0.000	NA
0.50	12	0.936	0.509	54.4
1.00	12	1.695	0.677	39.9
1.50	12	2.017	0.860	42.6
2.00	12	2.023	0.765	37.8
2.50	12	2.097	0.724	34.5
3.00	12	2.158	0.554	25.7
4.00	12	2.034	0.618	30.4
6.00	12	1.334	0.368	27.6
8.00	12	0.700	0.169	24.1
10.00	12	0.424	0.121	28.5
12.00	12	0.278	0.080	28.8
16.00	12	0.122	0.035	28.7
24.00	12	0.036	0.008	22.2
30.00	12	0.021	0.006	28.6
36.00	8	0.018	0.004	22.2
48.00	4	0.018	0.003	16.7

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin: Plasma

1 x 850 mg Single Dose, Middle-Age

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	3	0.000	0.000	NA
0.50	3	0.565	0.119	21.0
1.00	3	1.070	0.245	22.9
1.50	3	1.265	0.273	21.6
2.00	3	1.413	0.244	17.2
2.50	3	1.453	0.268	18.4
3.00	3	1.420	0.332	23.4
4.00	3	1.483	0.636	42.9
6.00	3	0.863	0.293	34.0
8.00	3	0.541	0.190	35.1
10.00	3	0.322	0.109	33.8
12.00	3	0.183	0.061	33.2
16.00	3	0.093	0.036	39.1
24.00	3	0.032	0.004	13.2
30.00	3	0.020	0.005	26.0
36.00	2	0.019	0.001	7.5
48.00	NA	NA	NA	
72.00	NA	NA	NA	

NA = Not Applicable

bp

Pharmacokinetic Summary

DSU Lipha 90-13

0445

Pharmacokinetic Summary

DSU Lipha 90-13

Metformin: Plasma

1 x 850 mg Single Dose, Mild Impaired

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	5	0.000	0.000	NA
0.50	5	0.507	0.232	45.8
1.00	5	1.037	0.301	29.1
1.50	5	1.319	0.433	32.9
2.00	5	1.538	0.567	36.9
2.50	5	1.682	0.559	33.2
3.00	5	1.864	0.515	27.6
4.00	5	1.654	0.259	15.6
6.00	5	1.040	0.157	15.1
8.00	5	0.659	0.053	8.1
10.00	5	0.409	0.085	20.7
12.00	5	0.248	0.063	25.4
16.00	5	0.117	0.031	26.7
24.00	5	0.037	0.009	24.5
30.00	5	0.022	0.008	33.6
36.00	3	0.019	0.002	12.5
48.00	1	0.014	NA	NA
72.00	NA	NA	NA	

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin: Plasma

1 x 850 mg Single Dose, Moderate Impaired

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	4	0.000	0.000	NA
0.50	4	1.125	0.526	46.8
1.00	4	1.853	0.650	35.1
1.50	4	2.280	0.741	32.5
2.00	4	2.695	0.882	32.7
2.50	4	3.140	1.161	37.0
3.00	4	3.652	1.772	48.5
4.00	4	4.115	1.835	44.6
6.00	4	3.892	1.826	46.9
8.00	4	3.045	1.596	52.4
10.00	4	2.615	1.620	61.9
12.00	4	1.998	1.385	69.3
16.00	4	1.241	0.978	78.8
24.00	4	0.594	0.569	95.8
30.00	4	0.429	0.487	113.6
36.00	4	0.241	0.280	116.1
48.00	4	0.123	0.130	105.9
72.00	4	0.033	0.022	67.8

NA = Not Applicable

Pharmacokinetic Summary

DSU Lipha 90-13

Metformin: Plasma

1 x 850 mg Single Dose, Severe Impaired

Mean Concentration (µg/ml)

Time (h)	n	mean	S.D.	C.V. (%)
0.00	6	0.000	0.000	NA
0.50	6	1.141	0.738	64.7
1.00	6	2.282	1.087	47.7
1.50	6	2.900	0.687	23.7
2.00	6	3.088	0.657	21.3
2.50	6	3.412	0.870	25.5
3.00	6	3.762	0.968	25.7
4.00	6	3.867	0.958	24.8
6.00	6	3.413	1.067	31.2
8.00	6	2.680	0.954	35.6
10.00	6	2.140	0.877	41.0
12.00	6	1.701	0.856	50.3
16.00	6	1.058	0.842	79.6
24.00	6	0.514	0.586	114.1
30.00	6	0.337	0.495	146.9
36.00	6	0.228	0.327	143.5
48.00	6	0.123	0.204	166.5
72.00	4	0.042	0.031	73.6

NA = Not Applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin, Urine Excretion Rate

Treatment: 1 x 850 mg Metformin, Young

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
1						
2						
3						
4						
5						
6						
n	6	6	6	6	4	2
mean	41.90	31.89	10.88	2.27	0.51	0.23
s.d.	9.63	8.67	4.21	0.60	0.13	0.08
CV (%)	23.0	27.2	38.7	26.4	25.5	34.8

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin, Urine Excretion Rate

Treatment: 1 x 850 mg Metformin, Elderly

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
n	12	12	12	12	6	1
mean	42.79	32.66	9.87	2.20	0.50	0.67
s.d.	11.07	10.09	2.52	0.58	0.16	NA
CV (%)	25.9	30.9	25.5	26.4	32.0	NA

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin, Urine Excretion Rate

Treatment: 1 x 850 mg Metformin, Middle-Age

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
R001-1						
R002-1						
R004-2						
n	3	3	3	3	2	1
mean	26.4	22.6	9.0	2.1	0.5	0.4
s.d.	7.6	9.9	6.1	1.1	0.2	NA
CV (%)	28.9	43.9	67.7	51.6	42.7	NA

NA: not applicable

Pharmacokinetic Summary

DSU Lipha 90-13

Metformin, Urine Excretion Rate

Treatment: 1 x 850 mg Metformin, Mild Impaired

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)						
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)	(48, 72)
R003-1							
R004-1							
R005-1							
R006-1							
R00[illegible]							
n	5	5	5	5	4	4	0
mean	30.0	23.2	7.3	3.4	0.5	0.2	NA
s.d.	10.0	6.9	3.3	3.4	0.2	0.0	NA
CV (%)	33.4	29.6	44.7	99.4	30.4	18.6	NA

NA: not applicable

Pharmacokinetic Summary

DSU/Lipha 90-13

Metformin, Urine Excretion Rate

Treatment: 1 x 850 mg Metformin, Moderate Impaired

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)					
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)
R002-2						
R003-2						
R004-2						
R005-2						
n	4	4	3	4	4	3
mean	14.5	19.8	10.2	5.5	1.6	0.6
s.d.	10.7	13.1	10.1	2.4	1.9	1.3
CV (%)	74.1	66	98.8	43.0	117.6	200.0

NA: not applicable

Pharmacokinetic Summary

DSU Lipha 90-13

Metformin, Urine Excretion Rate

Treatment: 1 x 850 mg Metformin, Severe Impaired

Subject ID	Urine Excretion Rate (*mg/h*), by Time Interval (*h*)						
	(0, 4)	(4, 8)	(8, 12)	(12, 24)	(24, 36)	(36, 48)	(48, 72)
R001-3							
R002-3							
R003-3							
R004-3							
R005-3							
R006-3							
n	6	6	6	6	6	5	2
mean	19.2	21.9	13.6	4.6	1.8	0.7	0.4
s.d.	9.4	10.0	3.1	1.5	1.4	0.5	0.2
CV (%)	48.7	45.8	22.6	32.2	73.9	81.6	45.2

NA: not applicable

Figure 1
DSU/Lipha #90-13
Metformin Plasma Concentration vs. Time, Mean Plots

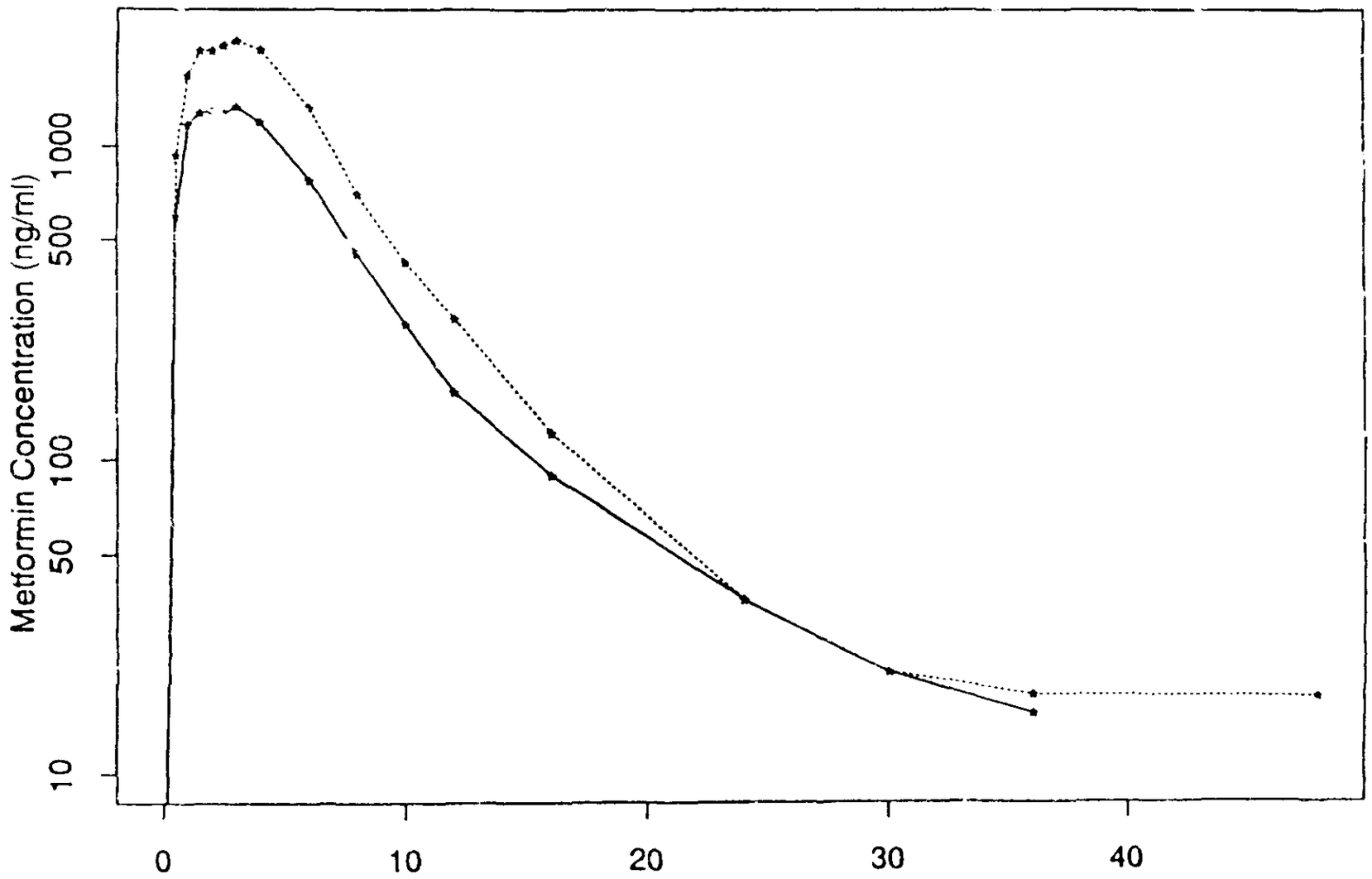


Figure 2
DSU/Lipha #90-13
Metformin Blood Concentration vs. Time, Mean Plots

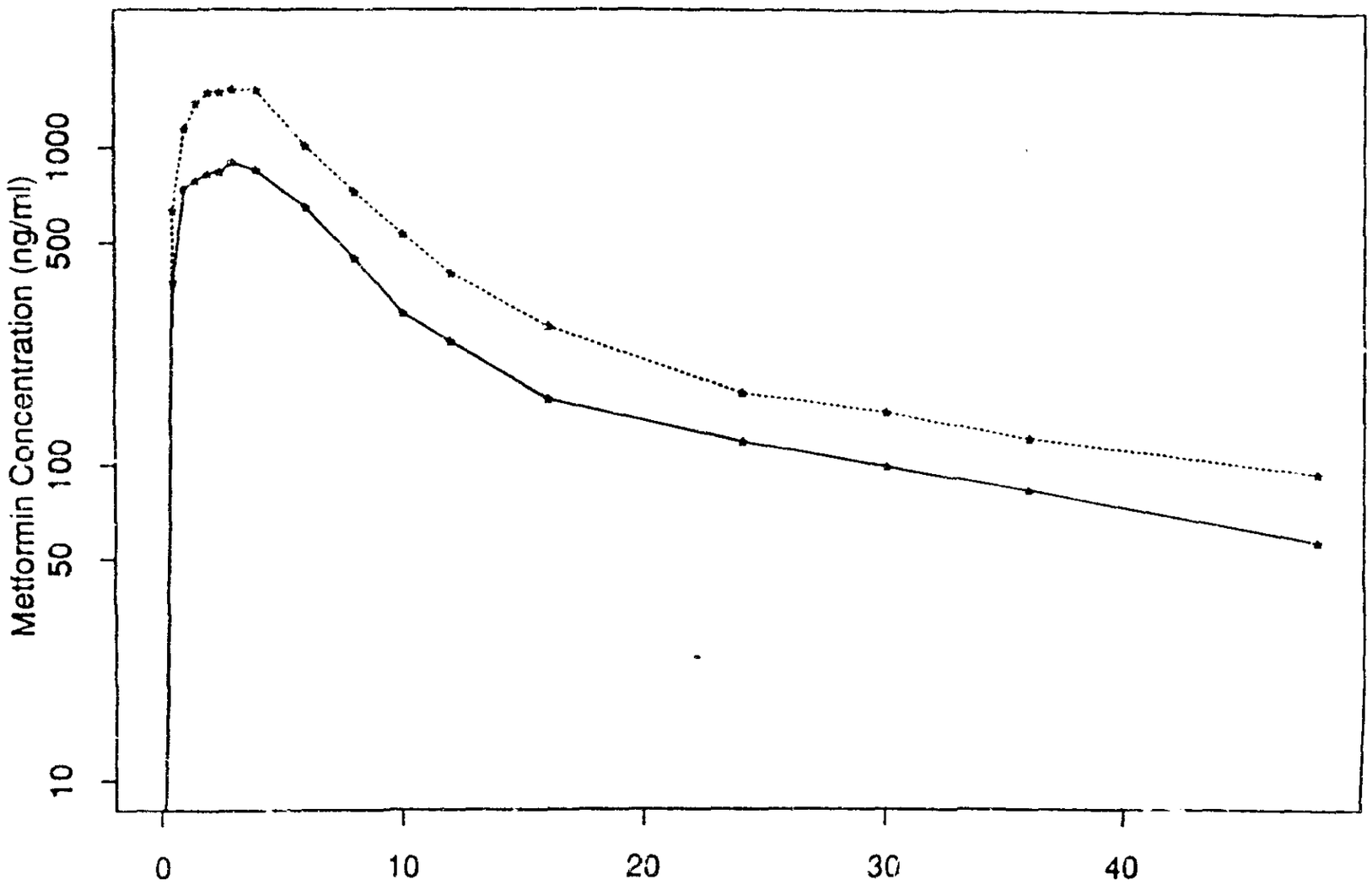
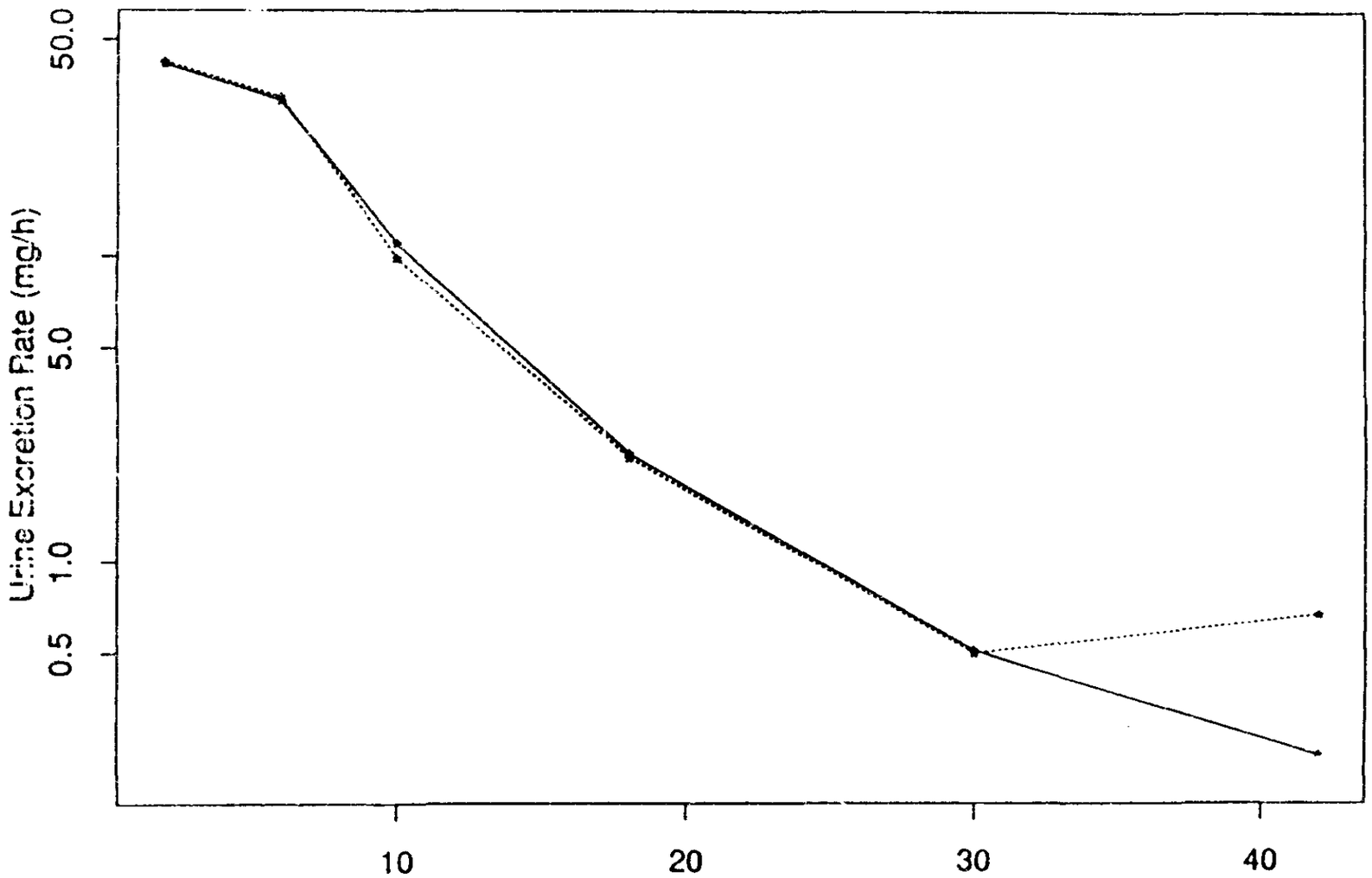
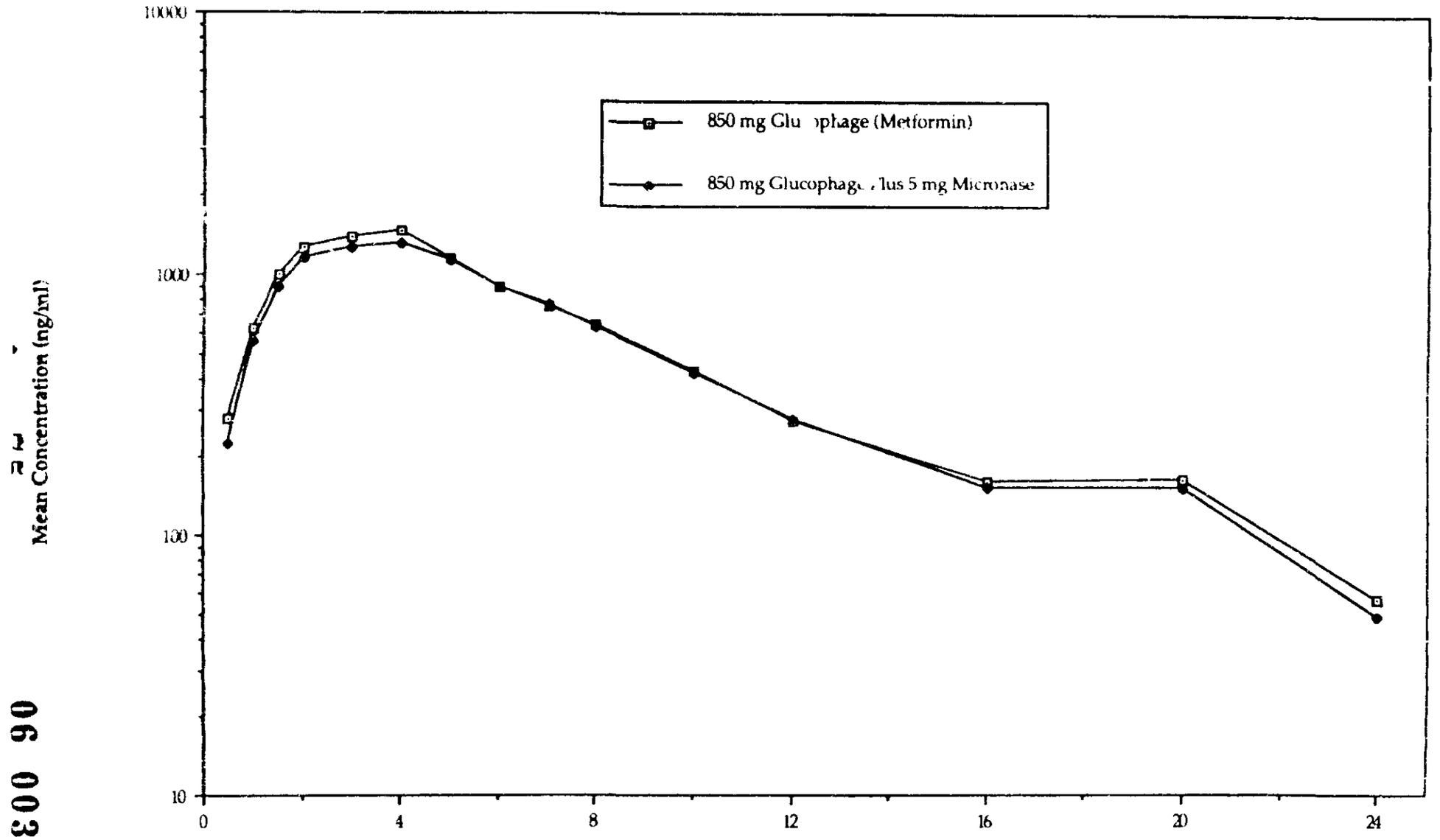


Figure 3
DSU/Lipha #90-13
Metformin Urine Excretion Rate vs. Time, Mean Plots



Mean Metformin Concentration

DSU 89-019



Mean Concentration for METFORMIN

Treatment A: 850 mg GLUCOPHAGE (METFORMIN)

Study # 89-019

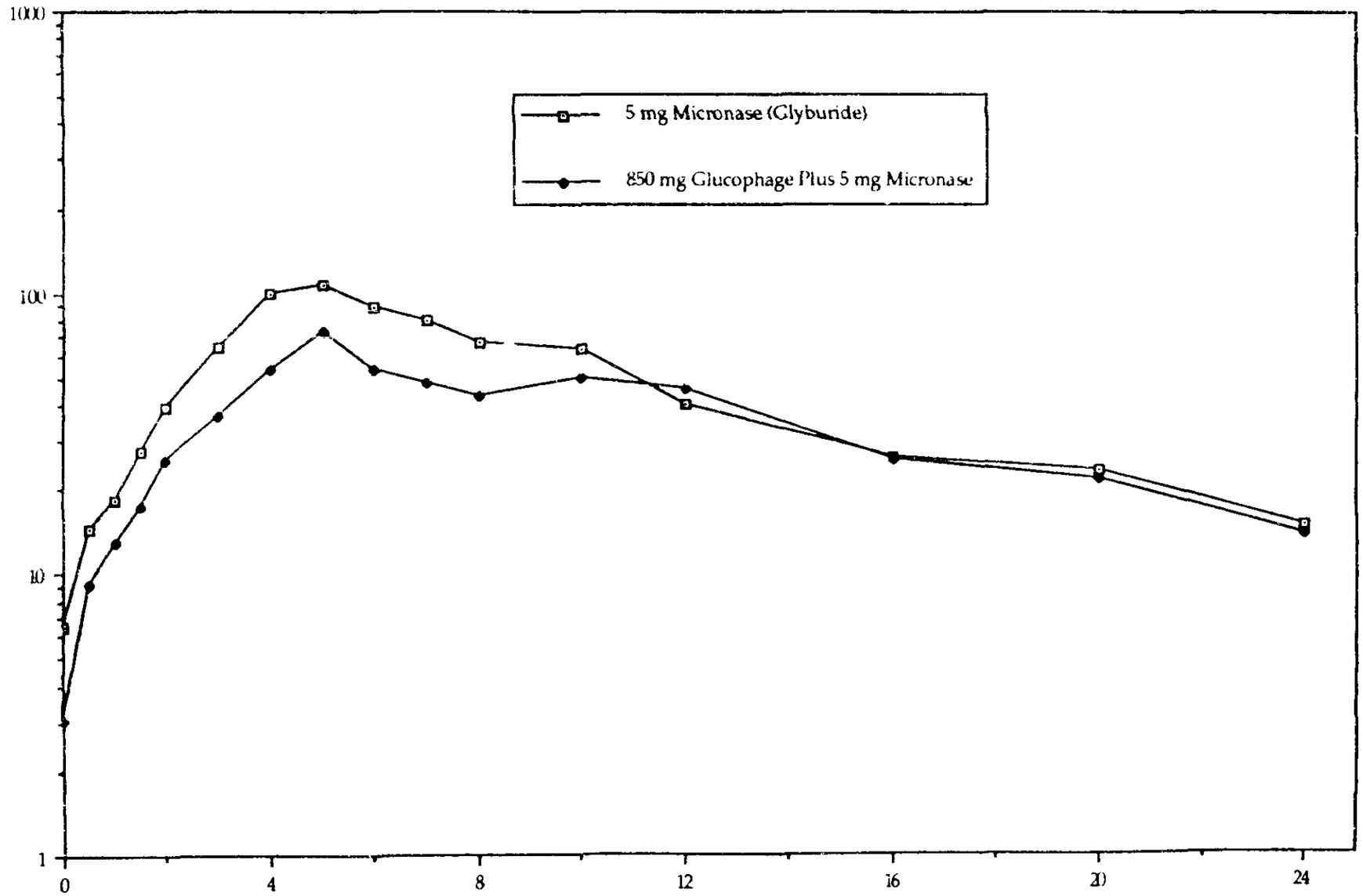
Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	15	0.00	0.00	
0.50	15	281.	248.	88.5
1.00	15	615.	369.	60.0
1.50	15	1000.	536.	53.4
2.00	15	1260.	466.	36.9
3.00	15	1390.	403.	29.1
4.00	15	1460.	490.	33.7
5.00	15	1150.	381.	33.1
6.00	15	888.	333.	37.5
7.00	15	764.	305.	40.0
8.00	15	638.	271.	42.5
10.00	15	426.	171.	40.2
12.00	15	27[illegible].	139.	50.4
16.00	15	161.	73.4	45.4
20.00	15	165.	79.9	48.5
24.00	15	56.8	34.1	60.0

Mean Concentration for METFORMIN
Treatment C: 850 mg GLUCOPHAGE PLUS 5 mg MICRONASE
Study # 89-019

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	15	0.00	0.00	
0.50	15	224.	163.	72.8
1.00	15	555.	303.	54.6
1.50	15	901.	403.	44.7
2.00	15	1150.	480.	41.6
3.00	15	1280.	424.	33.2
4.00	15	1320.	564.	42.9
5.00	15	1140.	514.	45.0
6.00	15	900.	422.	46.9
7.00	15	773.	353.	45.6
8.00	15	631.	307.	48.6
10.00	15	421.	169.	40.1
12.00	15	279.	150.	54.0
16.00	15	153.	88.1	57.7
20.00	15	153.	86.6	56.7
24.00	15	48.7	34.7	71.2

Mean Glyburide Concentration

DSU 89-019



Mean Concentration for Glyburide

Treatment B: 5mg. Micronase (Glyburide)

Study # 89-19

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	15	6.48	14.4	223.
0.50	15	14.4	25.1	174.
1.00	15	18.2	28.1	155.
1.50	15	27.4	38.1	139.
2.00	15	39.0	51.9	133.
3.00	15	64.2	65.3	102.
4.00	15	98.7	93.8	95.0
5.00	15	107.	69.1	64.7
6.00	15	88.9	62.5	70.4
7.00	15	79.5	56.8	71 5
8.00	15	67.2	37.7	56.1
10.00	15	63.0	44.1	70.0
12.00	15	40.4	26.4	65.3
16.00	15	25.9	17.4	67.2
20.00	15	23.4	16.9	72.2
24.00	15	14.7	16.7	113.

Mean Concentration for Glyburide
Treatment C: 850mg. Glucophage plus 5 mg. Micronase
Study # 89-19

Time (hrs.)	n	Mean Conc. (ng/ml)	Standard Deviation	C.V. %
0.00	15	3.01	5.96	198.
0.50	15	9.25	16.2	175.
1.00	15	13.0	20.1	154.
1.50	15	17.5	19.9	114.
2.00	15	25.4	28.7	113.
3.00	15	36.9	33.2	90.0
4.00	14	53.8	39.9	74.2
5.00	15	73.0	48.7	66.6
6.00	15	54.0	43.6	80.9
7.00	15	47.8	37.5	78.3
8.00	15	43.0	24.7	57.4
10.00	15	49.4	28.8	58.3
12.00	15	45.1	35.0	77.5
16.00	15	25.6	14.8	58.0
20.00	15	21.6	12.7	58.8
24.00	15	13.6	14.5	107.

Figure 1

GLYBURIDE/METFORMIN STUDY M/5200/0146

PLASMA METFORMIN LEVELS FOLLOWING THE ADMINISTRATION OF ONE GLUCOPHAGE TABLET 850 MG, ALONE OR IN COMBINATION WITH ONE MICRONASE TABLET 5 MG

AVERAGE RESULTS FOR FOURTEEN (14) SUBJECTS

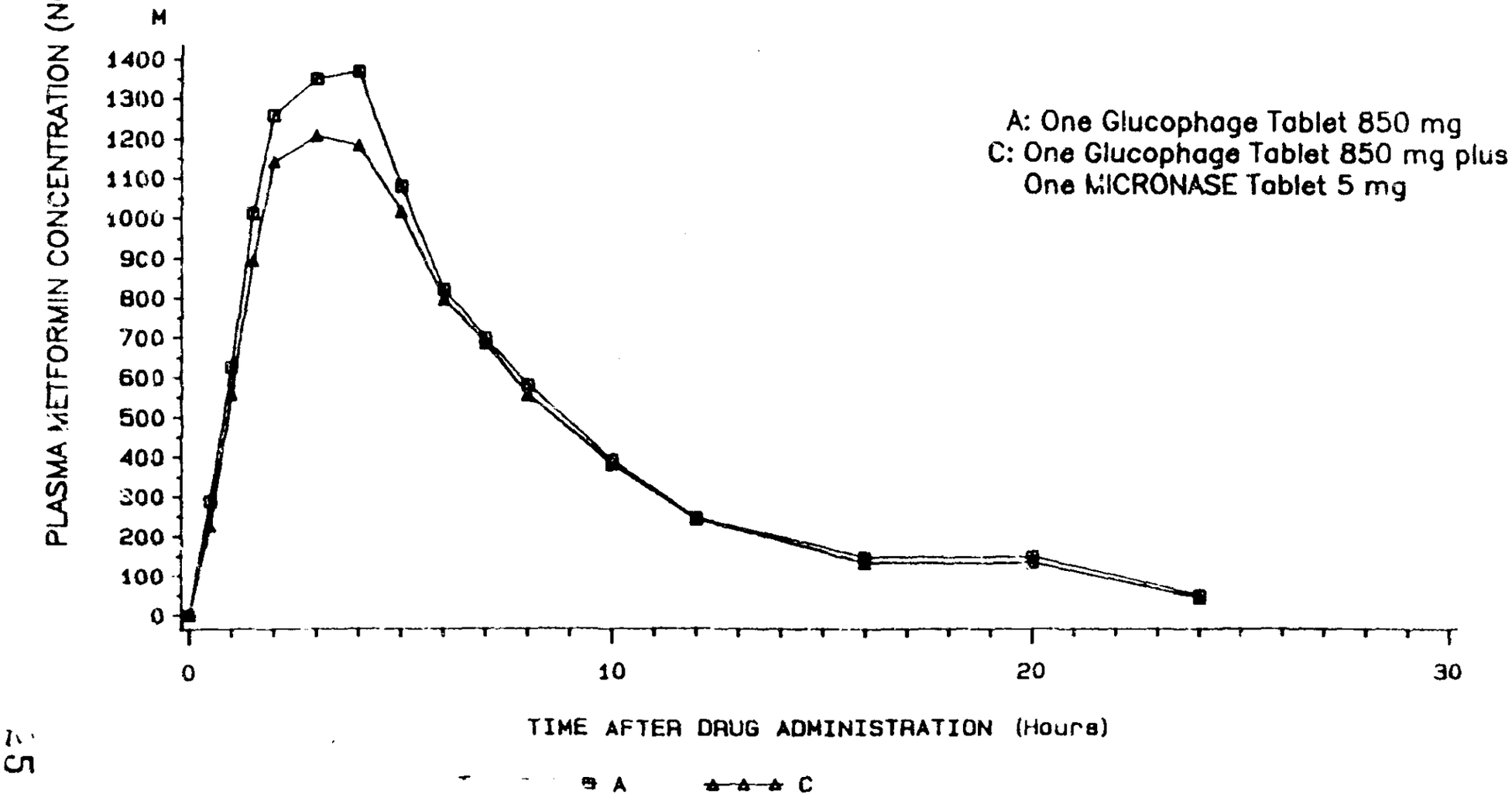


Figure 2

GLYBURIDE/METFORMIN STUDY M/5200/0146

SERUM GLYBURIDE LEVELS FOLLOWING THE ADMINISTRATION
OF ONE MICRONASE TABLET 5 MG, ALONE OR IN
COMBINATION WITH ONE GLUCOPHAGE TABLET 850 MG

AVERAGE RESULTS FOR FOURTEEN (14) SUBJECTS

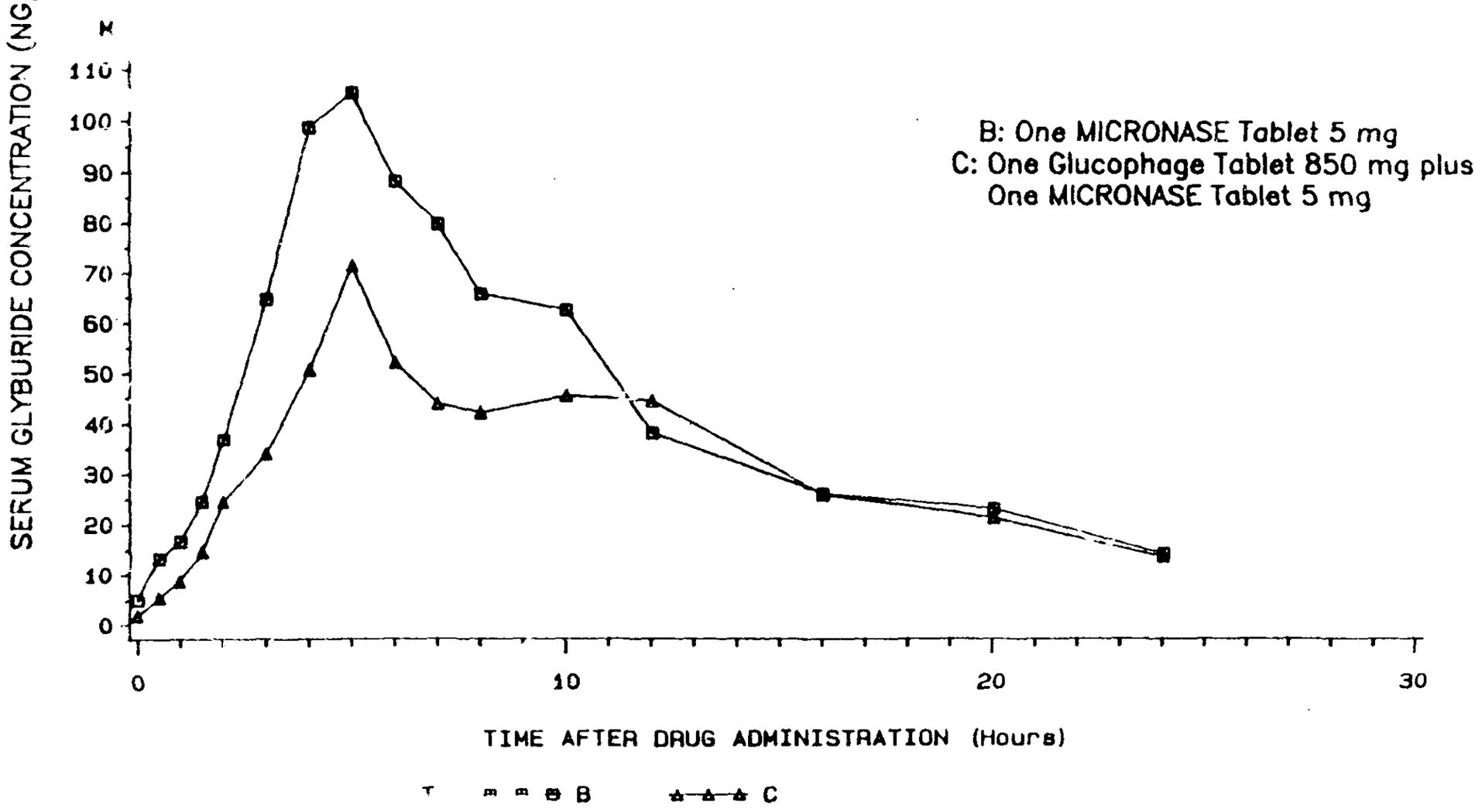


Table 6. Mean (± standard deviation) serum concentrations of glucose (mg/dl)

Hr	Treatments[a] A	B	C	Pairwise Comparisons
0	220 (93.2)	222 (86.8)	230 (77.6)	NS[b]
0.5	269 (91.3)	270 (87.1)	379 (87.4)	NS
1.0	297 (98.9)	294 (103)	306 (95.9)	NS
1.5	294 (112)	299 (109)	298 (103)	NS
2.0	272 (110)	280 (110)	284 (103)	NS
3.0	225 (109)	237 (110)	228 (98.7)	NS
4.0	190 (99.8)	200 (97.6)	188 (96.7)	NS
5.0	225 (106)	230 (108)	198 (100)	$\overline{\text{BA}}$ $\overline{\text{C}}$ [c]
6.0	217 (105)	197 (106)	199 (105)	NS
7.0	195 (101)	170 (101)	173 (101)	NS
8.0	170 (91.8)	149 (94.8)	150 (86.1)	NS
10.0	162 (77.5)	149 (81.3)	145 (72.1)	NS
12.0	259 (87.7)	244 (86.1)	219 (100)	$\overline{\text{A B C}}$
16.0	266 (108)	252 (92.9)	237 (120)	NS
20.0	265 (107)	257 (92.1)	234 (116)	NS
24.0	227 (94.2)	250 (82.7)	228 (86.5)	NS

[a] Treatment A: One Glucophage Tablet 850 mg (metformin)
Treatment B: One MICRONASE Tablet 5 mg (glyburide)
Treatment C: One Glucophage Tablet 850 mg plus one MICRONASE Tablet 5 mg administered concurrently.

[b] NS = no significant difference among treatments (α=.05) using analysis of variance.

[c] Treatments connected by a line are not significantly different at p=0.05.

Table 7. Mean (± standard deviation) serum concentrations of insulin (mcU/ml)

Hr	Treatments[a] A	B	C	Pairwise Comparisons
0	17.8 (10.6)	14.3 (10.1)	13.1 (8.58)	NS[b]
0.5	48.3 (25.5)	50 (35.3)	39.2 (20.9)	NS
1.0	69.7 (47.3)	59.6 (58.9)	57.7 (33.9)	NS
1.5	58.9 (51.5)	55.9 (41.4)	52.8 (29)	NS
2.0	48.4 (27.8)	44.5 (29.7)	40.9 (32.1)	NS
3.0	31.3 (17.1)	36.4 (26.9)	34.1 (21.7)	NS
4.0	25.3 (11.6)	31.7 (21.9)	29.1 (15.7)	NS
5.0	46.4 (28.6)	91.8 (55.7)	64.2 (38.9)	B CA[c]
6.0	37.3 (18.3)	55.7 (29)	45 (20.8)	B CA
7.0	26.4 (14.5)	43.3 (21.3)	34.9 (12.2)	B CA
8.0	23.1 (8.64)	32.4 (12.6)	27.3 (11.6)	B CA
10.0	19.9 (7)	24.1 (9.15)	21.6 (6.2)	NS
12.0	51 (36.2)	57.8 (45)	50.9 (34.5)	NS
16.0	60.8 (35.4)	51.3 (39.1)	47.7 (44.8)	NS
20.0	55 (42)	45.8 (28.8)	43.9 (32.5)	NS
24.0	19.1 (12.2)	22.4 (15.2)	19.4 (10.3)	NS

[a] Treatment A: One Glucophage Tablet 850 mg (metformin)
Treatment B: One MICRONASE Tablet 5 mg (glyburide)
Treatment C: One Glucophage Tablet 850 mg plus one MICRONASE Tablet 5 mg administered concurrently.

[b] NS = no significant difference among treatments (α=.05) using analysis of variance.

[c] Treatments connected by a line are not significantly different at p=0.05.

Table 8. Mean (± standard deviation) serum concentrations of C-peptide (ng/ml)

Hr	Treatments[a] A	B	C	Pairwise Comparisons
0	2.71 (1.28)	2.68 (0.97)	2.8 (0.98)	NS[b]
0.5	4.51 (1.92)	4.64 (2.08)	4.49 (1.58)	NS
1.0	5.49 (2.92)	5.52 (2.98)	5.65 (1.99)	NS
1.5	5.79 (3.51)	5.72 (2.71)	5.89 (2.19)	NS
2.0	5.47 (2.94)	5.69 (2.49)	5.64 (2.34)	NS
3.0	4.71 (2.01)	5.09 (1.61)	5.44 (2.29)	NS
4.0	3.81 (1.36)	4.86 (1.56)	4.99 (1.97)	$\overline{CB}$ A[c]
5.0	5.42 (1.88)	7.52 (2.95)	6.99 (2.23)	$\overline{CB}$ A
6.0	5.11 (1.72)	6.62 (2.14)	6.58 (2.16)	$\overline{CB}$ A
7.0	4.48 (1.53)	5.98 (2.18)	5.69 (1.7)	$\overline{CB}$ A
8.0	3.62 (1.29)	4.79 (1.69)	4.79 (1.64)	$\overline{CB}$ A
10.0	3.06 (1.0)	4.08 (1.28)	4.14 (1.25)	$\overline{CB}$ A
12.0	6.05 (2.86)	6.49 (3.46)	6.67 (2.19)	NS
16.0	6.11 (3.62)	6.32 (3.01)	6.34 (2.71)	NS
20.0	5.53 (2.67)	6.27 (2.96)	6.23 (2.73)	NS
24.0	2.95 (1.29)	4.1 (1.89)	3.71 (1.41)	$\overline{CB}$ A

[a] Treatment A: One Glucophage Tablet 850 mg (metformin)
Treatment B: One MICRONASE Tablet 5 mg (glyburide)
Treatment C: One Glucophage Tablet 850 mg plus one MICRONASE Tablet 5 mg administered concurrently.

[b] NS = no significant difference among treatments (α=.05) using analysis of variance.

[c] Treatments connected by a line are not significantly different at p=0.05.

Table 1

Plasma Metformin Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin: Treatment A

	Time After Dosing (Hours)														
Subject	0.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10.0	12.0	16.0	24.0	36.0
1															
2															
103															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															
14															
15															
Mean	0	548	1167	1422	1573	1571	1527	1320	657	389	240	144	67.0	27.4	3.92
SD	0	224.7	304	412	387	292	283	317	167.6	108.1	77.0	48.5	26.14	7.03	6.811
RSD (%	NA	41.0	26.1	29.0	24.6	18.6	18.5	24.0	25.5	27.8	32.2	33.7	30.1	25.7	174

a Outlier value excluded from all statistical and pharmacokinetic evaluations.

Table 2

Plasma Metformin Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin and 400 mg of Cimetidine: Treatment C

	Time After Dosing (Hours)														
Subject	0.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10.0	12.0	16.0	24.0	36.0
1															
2															
103															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															
14															
15															
Mean	0	654	1213	1720	2115	2561	2424	2031	781	469	360	216	114	37.5	8.58
SD	0	232.4	343	472	783	870	877	698	255.9	136.5	72.6	43.2	55.1	12.68	8.882
RSD (%	NA	35.5	28.3	27.5	37.0	34.0	36.2	34.4	32.8	29.1	20.2	20.0	48.?	33.8	104

Table 12

Plasma Cimetidine Concentrations (ng/mL) in Healthy Subjects
Following Administration of 400 mg of Cimetidine: Treatment B

	Time After Dosing (hours)														
Subject	0.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10.0	12.0	16.0	24.0	36.0
1															
2															
103															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															
14															
15															
Mean	0	561	1391	1348	1530	1657	1595	1117	607	326	168	88.6	4.59	0	0
SD	0	505.6	726	437	526	567	402	196	180.7	99.4	50.8	26.01	17.764	0	0
RSD (%	NA	90.1	52.2	32.5	34.4	34.2	25.2	17.6	29.8	30.5	30.2	29.3	387	NA	NA

Table 13

Plasma Cimetidine Concentrations (ng/mL) in Healthy Subjects Following Administration of 400 mg of Metformin and 400 mg of Cimetidine. Treatment C

	Time After Dosing (hours)														
Subject	0.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10.0	12.0	16.0	24.0	36.0
1															
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103															
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13															
14															
15															
Mean	0	337	777	1312	1803	1738	1580	1085	536	303	174	96.9	16.1	0	0
SD	0	266.4	523.8	632	540	409	449	274	107.8	55.7	42.2	26.81	27.92	0	0
%SD (%	NA	79.0	67.5	48.2	29.9	23.5	28.4	25.2	20.1	18.4	24.2	27.7	173	NA	NA

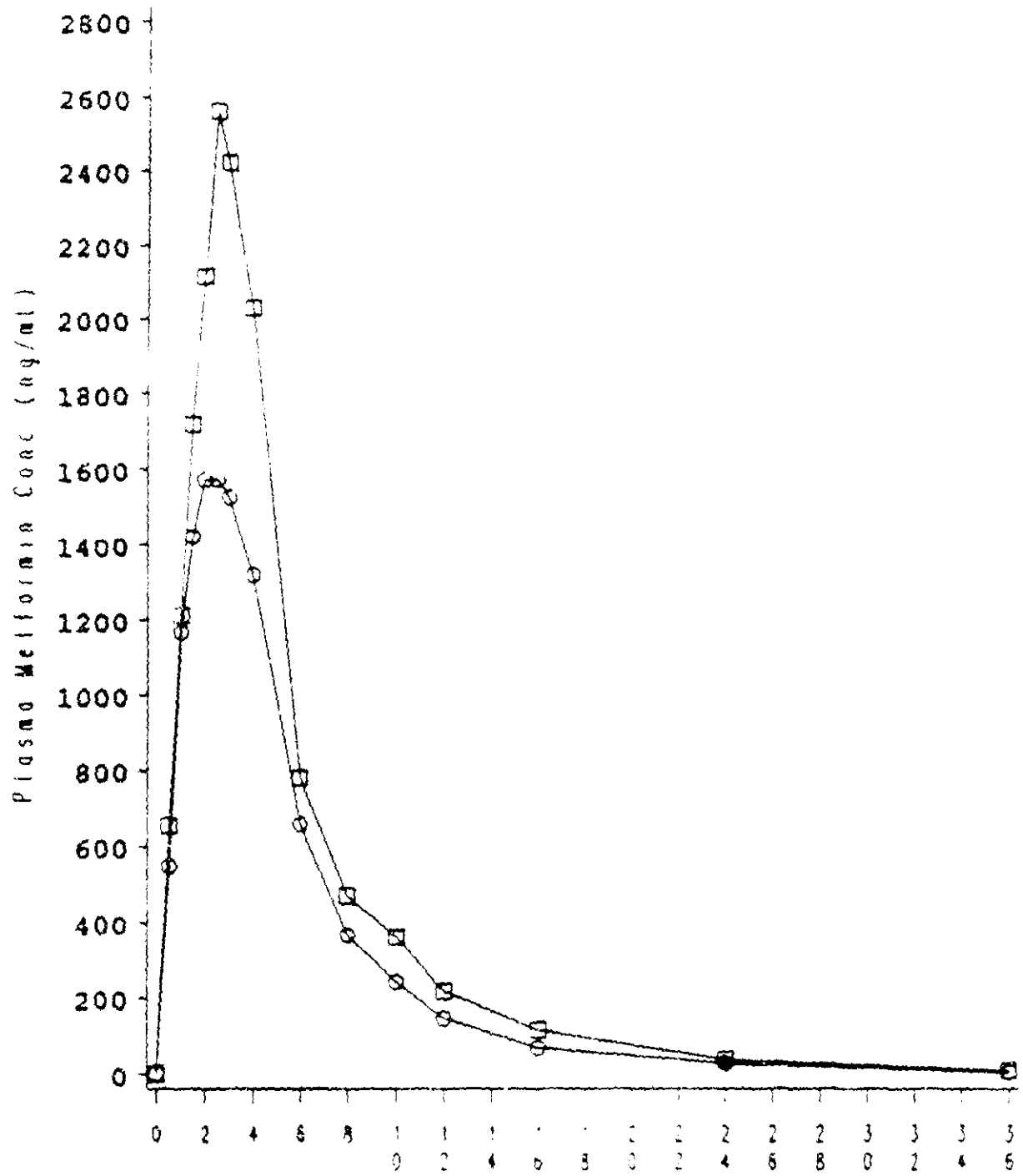

Figure 1. Mean Plasma Metformin Concentration-Time Profiles Following Dosing with 850 mg of Metformin or 850 mg of Metformin Plus 400 mg of Cimetidine.

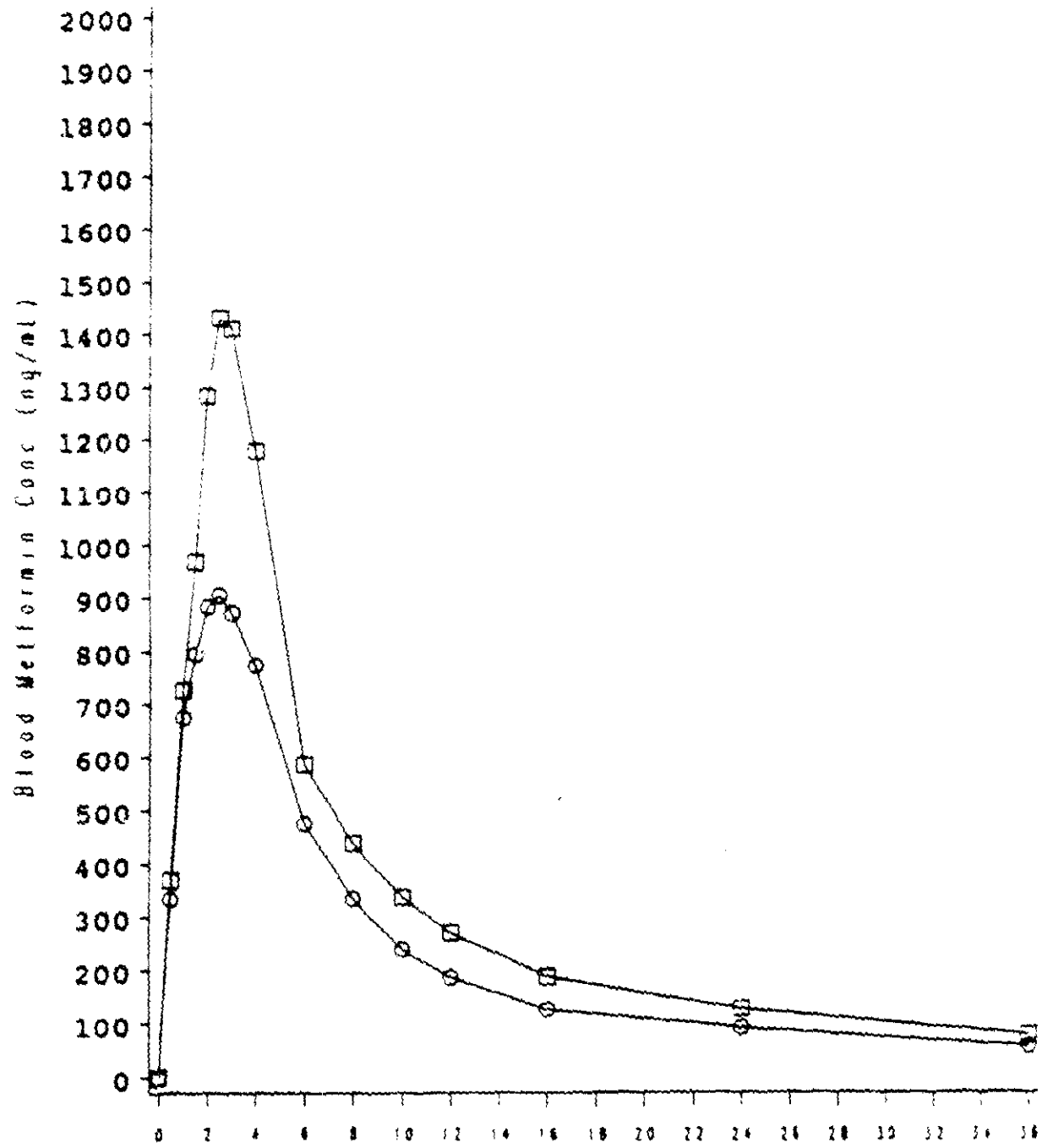

Figure 2. Mean Whole Blood Metformin Concentration-Time Profiles Following Dosing with 850 mg of Metformin or 850 mg of Metformin Plus 400 mg of Cimetidine.

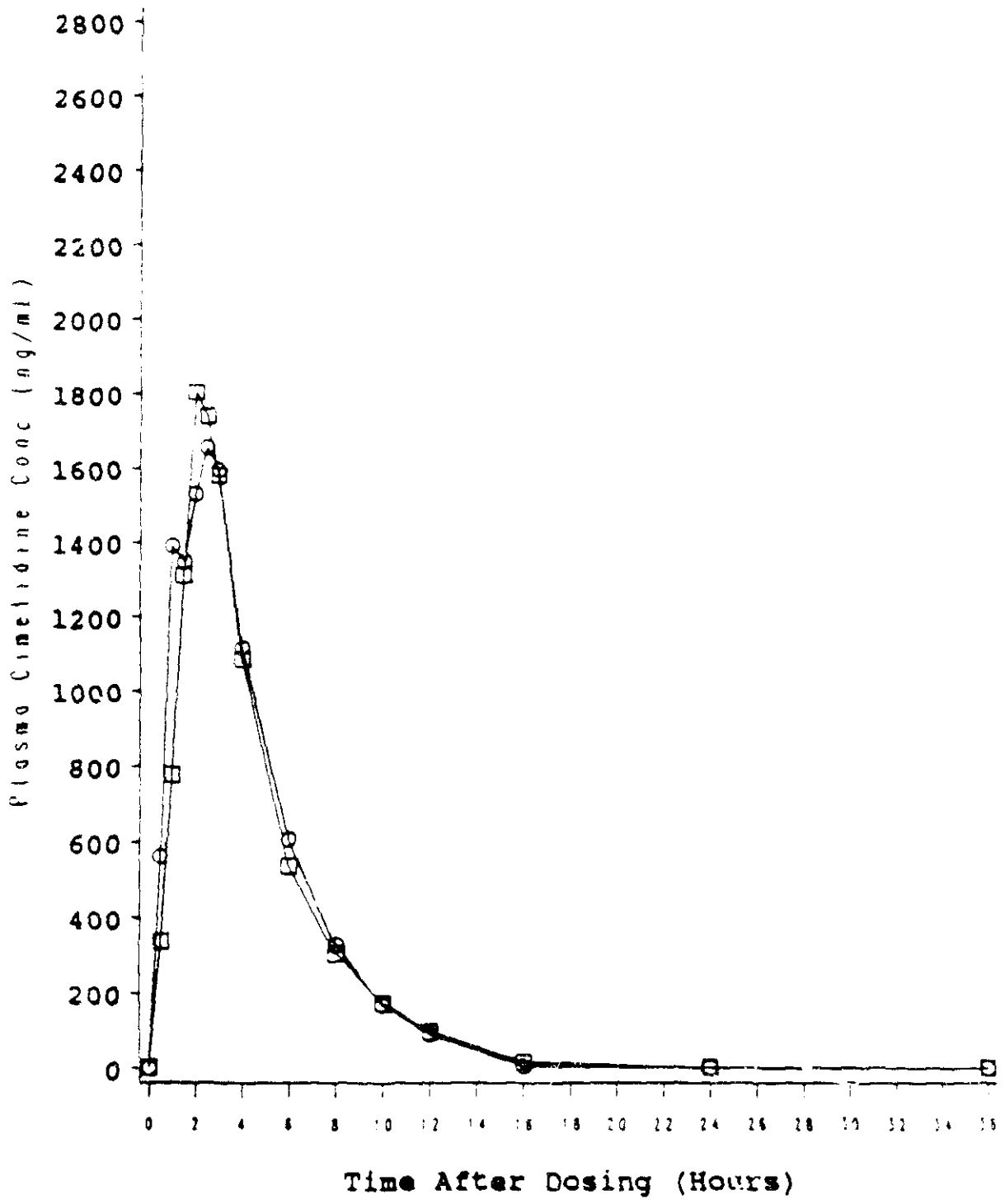

Figure 4. Mean Plasma Cimetidine Concentration-Time Profiles Following Dosing with 400 mg of Cimetidine or 400 mg of Cimetidine Plus 850 mg of Metformin.

Table 1

Plasma Metformin Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin: Treatment A

Subject No.	Time after Dosing (Hours)															
	0	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
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17																
18																
Mean	0	215	809	1202	1394	1692	1738	1683	1724	1492	753	451	290	162	73.5	27.1
SD	0	131	283	291	297	367	329	325	373	430	208	137	100	53.2	53.2	53.2
RSD (%)	NA	61.0	34.9	24.2	21.3	21.7	19.0	19.2	21.7	28.8	27.7	30.3	34.6	32.8	31.1	39.0

a No sample for analysis.

Table 2

Plasma Metformin Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin and 10 mg of Nifedipine: Treatment C

Subject No.	Time after Dosing (Hours)															
	0	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
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Mean	0	231	933	1444	1688	2095	2158	2016	2028	1761	851	512	313	175	74.5	26.3
SD	0	185	381	344	370	377	403	383	405	391	198	130	70.1	52.2	20.5	9.77
RSD (%)	NA	79.9	40.8	23.8	21.9	18.0	18.7	19.0	19.9	22.2	23.3	25.4	22.4	29.8	27.5	37.1

Table 5

Metformin Urinary Excretion (A_u^{24}) and Renal Clearance (Cl_r) Values for Normal Healthy Subjects Dosed with 850 mg of Metformin or 850 mg of Metformin Plus 10 mg of Nifedipine

Subject No.	----Treatment A--- D_u^{24} (mg)	Cl_r (mL/min)	----Treatment C--- D_u^{24} (mg)	Cl_r (mL/min)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
Mean	314	474	450	571
SD	87.7	141.5	130.8	131.2
RSD (%)	27.9	29.9	29.1	23.0

Table 12

Plasma Nifedipine Concentrations (ng/mL) in Healthy Subjects following Administration of 10 mg of Nifedipine: Treatment B

Subject No.	Time After Dosing (Hours)															
	0	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1																
2																
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5																
6																
7																
8																
9																
10																
11																
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14																
15																
16																
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18																
Mean	0	20.9	106	82.3	64.5	44.9	31.1	24.9	19.9	14.0	7.92	4.80	3.33	2.28	0.68	0
SD	0	35.3	62.0	41.3	31.8	23.5	14.9	11.2	9.11	7.05	4.52	3.05	2.33	2.24	1.35	0
RSD (%)	NA	169	59	50.2	49.3	52.3	48.0	44.9	45.7	50.2	57.1	63.6	70.1	98.6	200	NA

a Sample exceeded standard curve range. Insufficient sample for further analysis.

Table 13

Plasma Nifedipine Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin and 10 mg of Nifedipine: Treatment C

Subject No.	Time After Dosing (Hours)														
	0	0.25	0.50	0.75	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1																
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7																
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9																
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Mean	0	16.6	102	97.4	79.1	55.3	38.0	27.9	22.0	14.8	7.91	4.83	3.14	2.11	0.38	0.15
SD	0	33.1	58.7	29.7	25.6	20.4	17.2	14.2	12.4	9.04	5.64	4.29	3.47	3.43	2.05	0.62
RSD (%)	NA	199	57.5	30.5	32.3	36.9	45.3	50.9	56.2	61.1	71.3	88.8	111	163	233	424

Protocol 91-04-6023
HWI 62C1-107

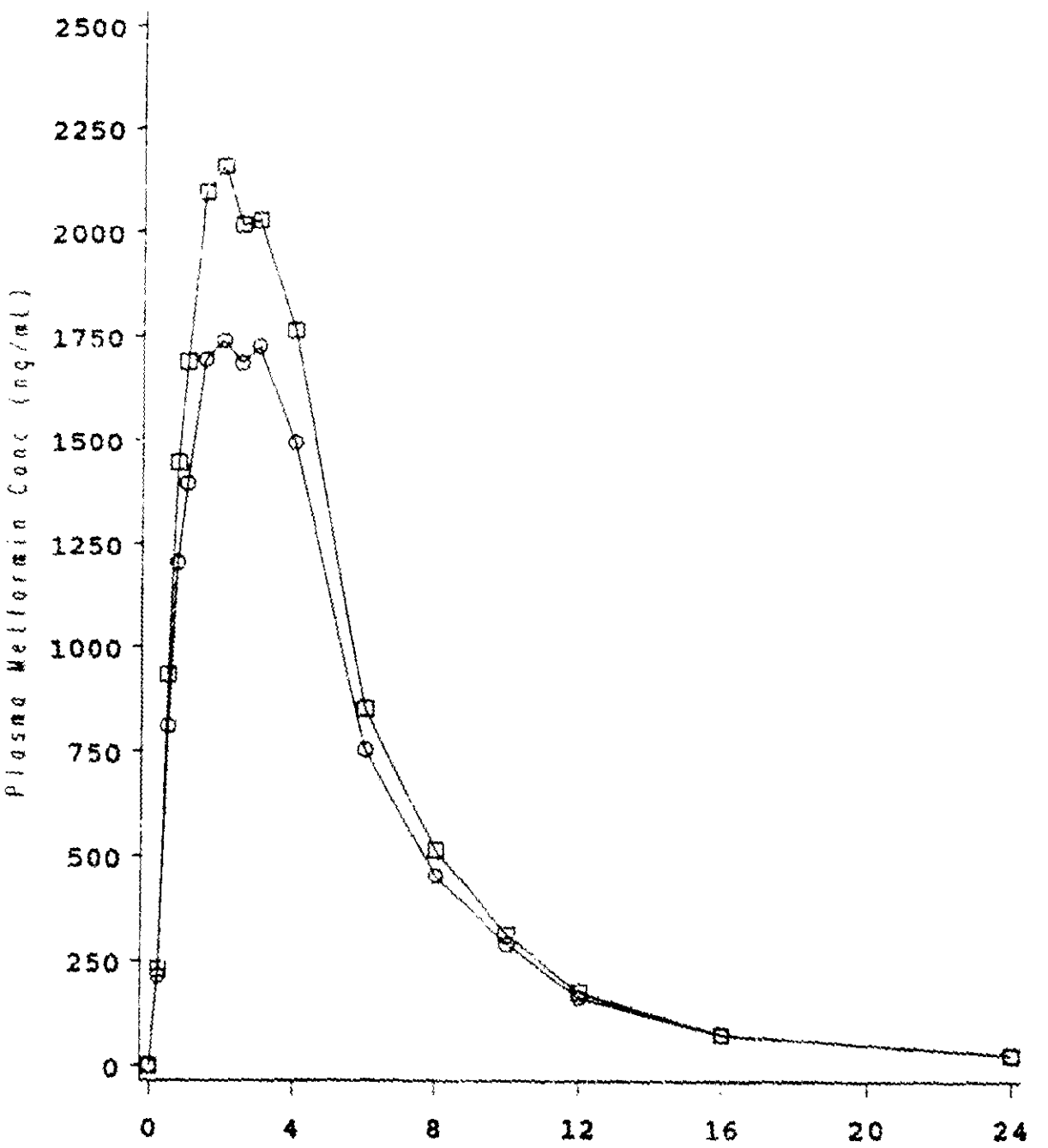


Figure 1. Mean Plasma Metformin Concentration-Time Profiles Following Dosing with 850 mg of Metformin or 850 mg of Metformin Plus 10 mg of Nifedipine

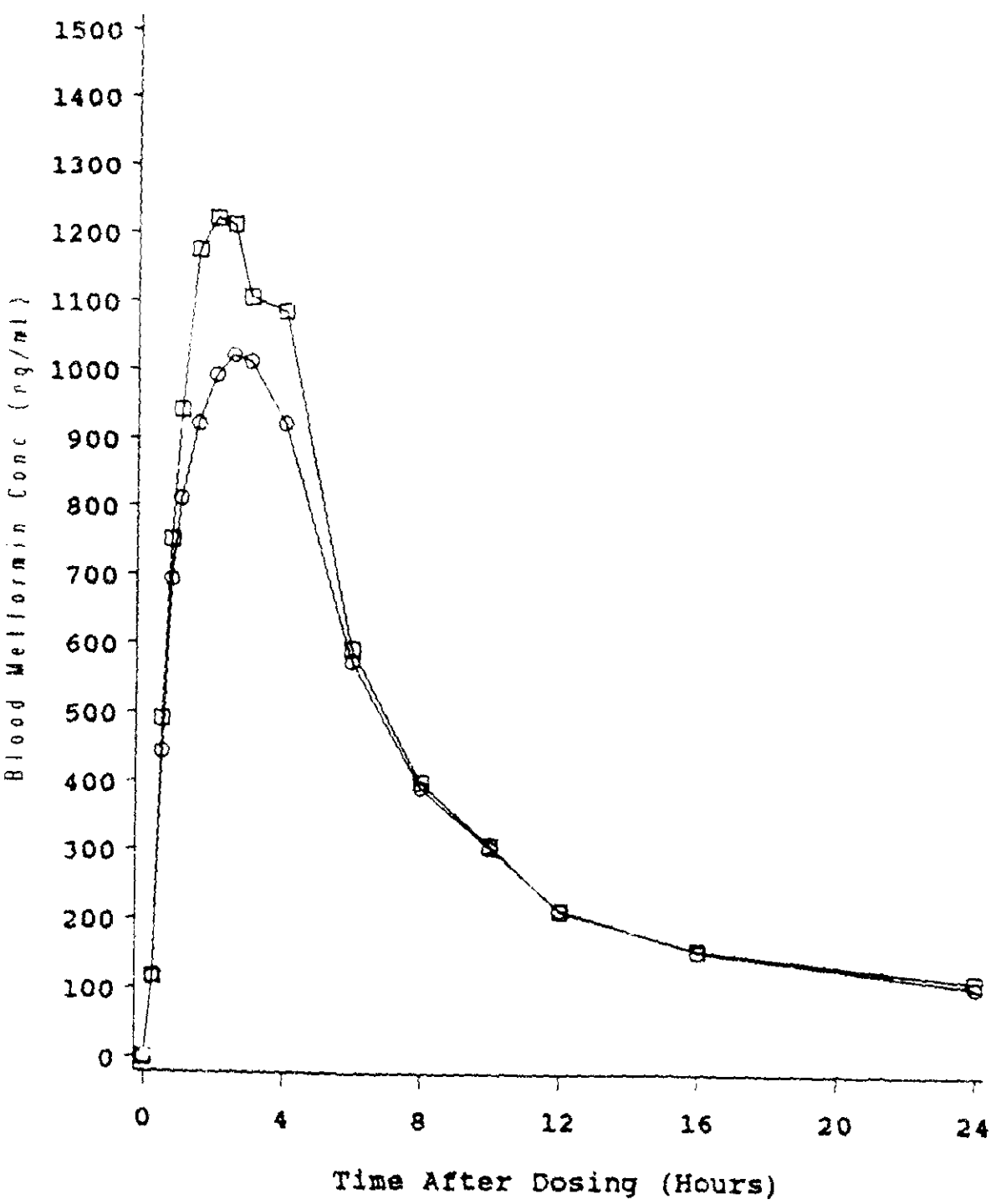


Figure 2. Mean Whole Blood Metformin Concentration-Time Profiles Following Dosing with 850 mg of Metformin or 850 mg of Metformin Plus 10 mg of Nifedipine

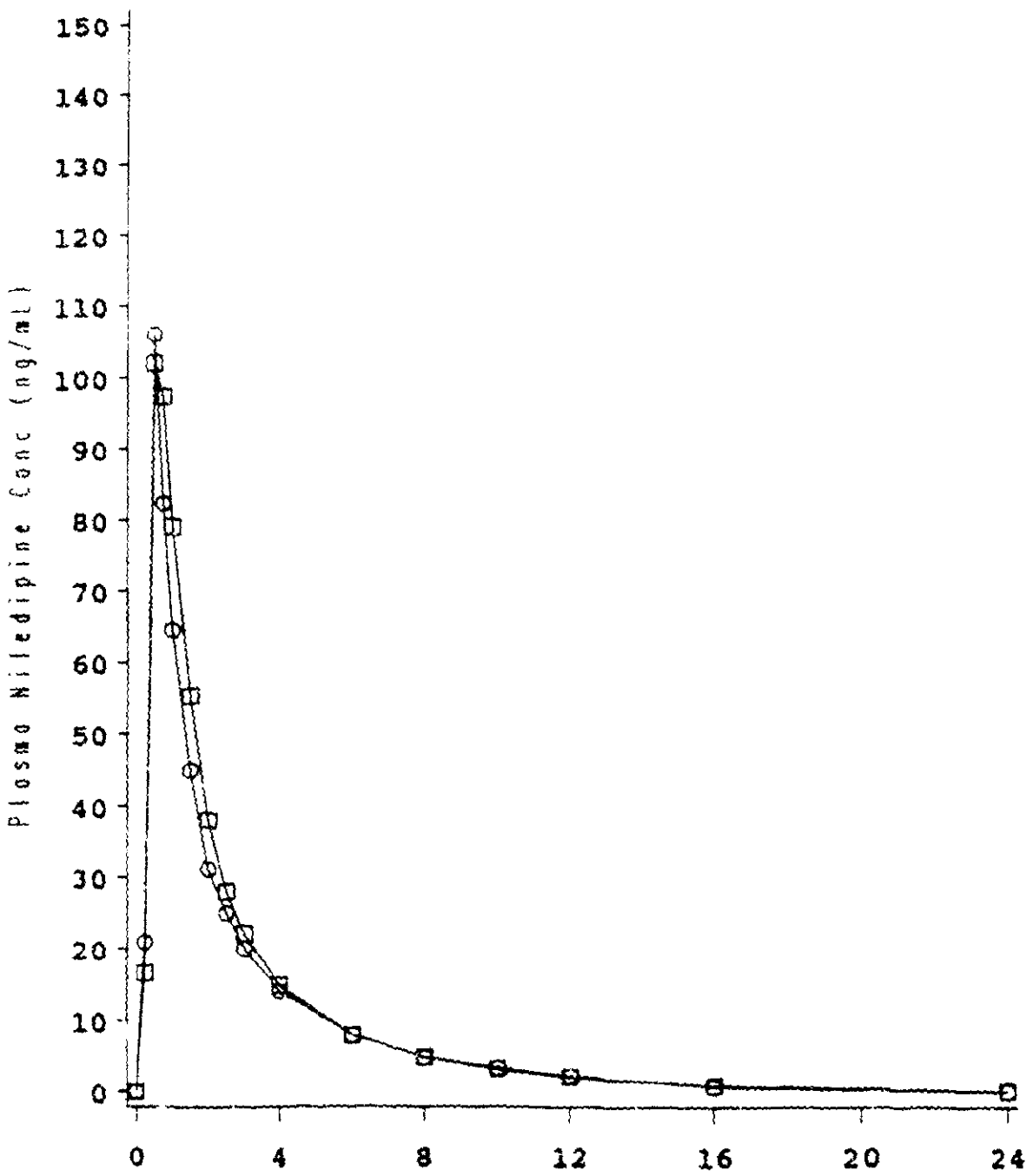


Figure 4. Mean Plasma Nifedipine Concentration-Time Profiles Following Dosing with 10 mg of Nifedipine or 10 mg of Nifedipine Plus 850 mg of Metformin

MEAN CONCENTRATION OF METFORMIN PLASMA
DSU 91-049

TREATMENT A: 850 mg Metformin

Time (hrs.)	n	Mean Conc. (ng/ml)	S.D.	%C.V.
0	18	*	-	-
0.33	18	359	208	58.0
0.66	18	823	364	44.2
1.00	18	1090	464	42.4
1.50	18	1340	548	41.0
2.00	18	1510	574	38.1
2.50	18	1490	551	37.0
3.00	18	1450	505	34.9
4.00	18	1330	516	38.7
6.00	18	710	213	30.0
8.00	18	458	150	32.9
10.0	18	284	104	36.8
12.0	18	177	72.0	40.8
16.0	18	121	48.4	40.1
24.0	18	43.6	44.1	101
36.0	18	11.6	10.6	91.2

* Below Assay Sensitivity - 10.0 ng/ml

MEAN CONCENTRATION OF METFORMIN PLASMA
DSU 91-049

TREATMENT C: 850 mg Metformin and 40 mg Furosemide

Time (hrs.)	n	Mean Conc. (ng/ml)	S.D.	%C.V.
0	18	*	-	-
0.33	18	394	233	59.3
0.66	18	934	433	46.4
1.00	18	1310	491	37.4
1.50	18	1580	635	40.1
2.00	18	1760	665	37.8
2.50	18	1770	631	35.6
3.00	18	1720	523	30.4
4.00	18	1450	595	41.0
6.00	18	867	322	37.1
8.00	18	458	163	35.7
10.0	18	281	89.6	31.9
12.0	18	176	48.1	27.3
16.0	18	114	31.7	27.8
24.0	18	29.3	8.44	28.8
36.0	18	10.0	9.82	98.1

* Below Assay Sensitivity - 10.0 ng/ml

MEAN CONCENTRATION OF FUROSEMIDE PLASMA
DSU 91-049

TREATMENT B: 40 mg Furosemide

Time (hrs.)	n	Mean Conc. (ng/ml)	S.D.	%C.V.
0	18	*	-	-
0.33	18	315	585	186
0.66	18	793	694	87.5
1.00	18	776	599	77.2
1.50	18	588	439	74.7
2.00	18	494	233	47.2
2.50	18	449	246	54.7
3.00	18	341	167	49.1
4.00	18	220	116	52.9
6.00	18	71.1	35.9	50.6
8.00	18	36.0	17.0	47.1
10.0	18	19.4	6.61	34.0
12.0	18	12.6	4.52	35.8
16.0	18	9.54	3.80	39.8
24.0	18	*	-	-
36.0	18	*	-	-

* Below Assay Sensitivity - 5.00 ng/ml

MEAN CONCENTRATION OF FUROSEMIDE PLASMA
DSU 91-049

TREATMENT C: 850 mg Metformin and 40 mg Furosemide

Time (hrs.)	n	Mean Conc. (ng/ml)	S.D.	%C.V.
0	18	*	-	-
0.33	18	240	219	91.1
0.66	18	475	374	78.7
1.00	18	575	428	74.5
1.50	18	581	255	43.9
2.00	18	526	248	47.2
2.50	18	439	154	35.1
3.00	18	332	123	37.0
4.00	18	209	97.4	46.6
6.00	18	75.7	65.8	86.9
8.00	18	26.1	16.9	64.8
10.0	18	15.2	9.89	65.2
12.0	18	7.46	8.55	115
16.0	18	*	-	-
24.0	18	*	-	-
36.0	18	*	-	-

* Below Assay Sensitivity - 5.00 ng/ml

Figure 1

Mean Concentration for Metformin Plasma (DSU 91-049)

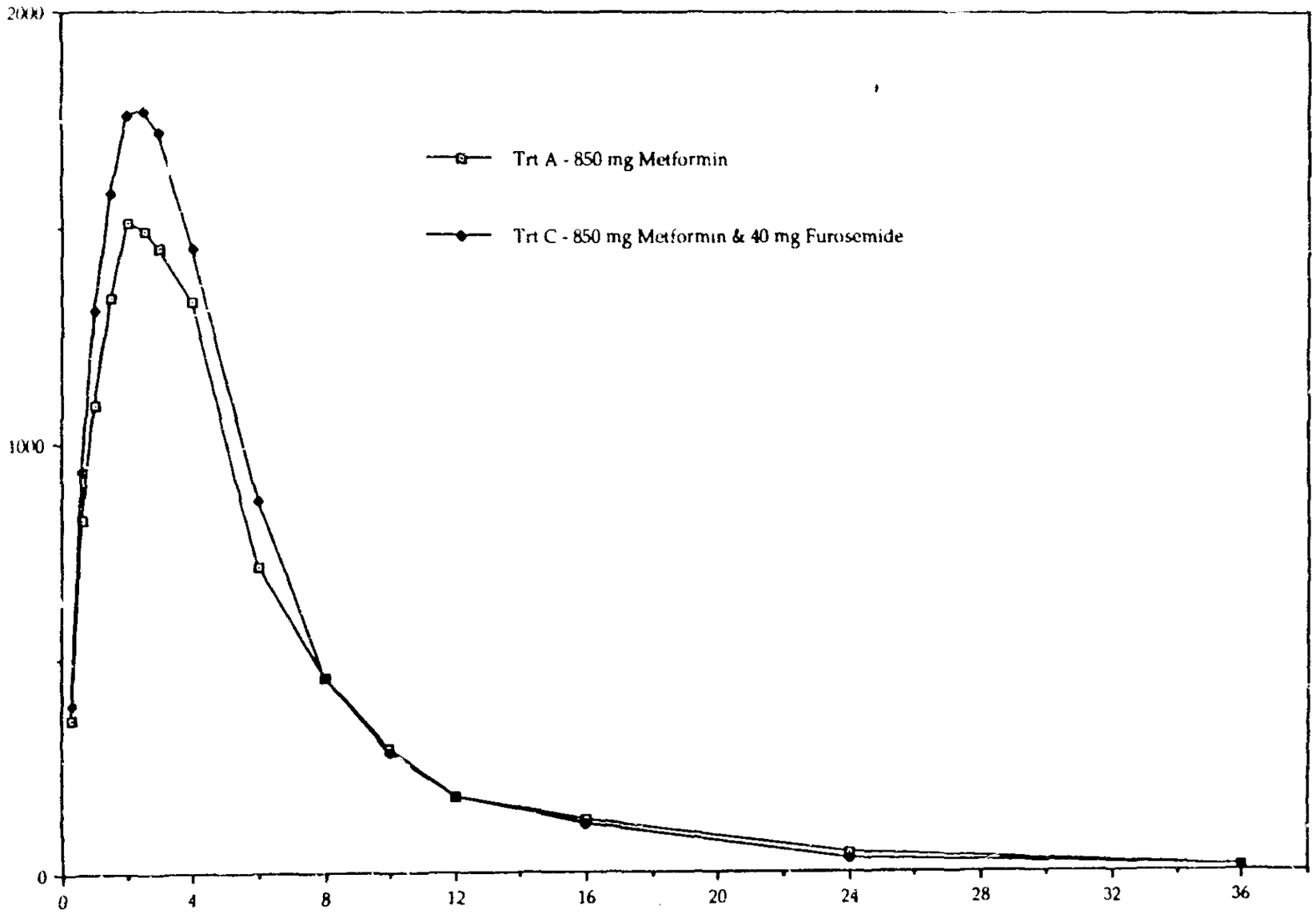


Figure 2

Mean Concentration for Metformin Blood (DSU 91-04°)

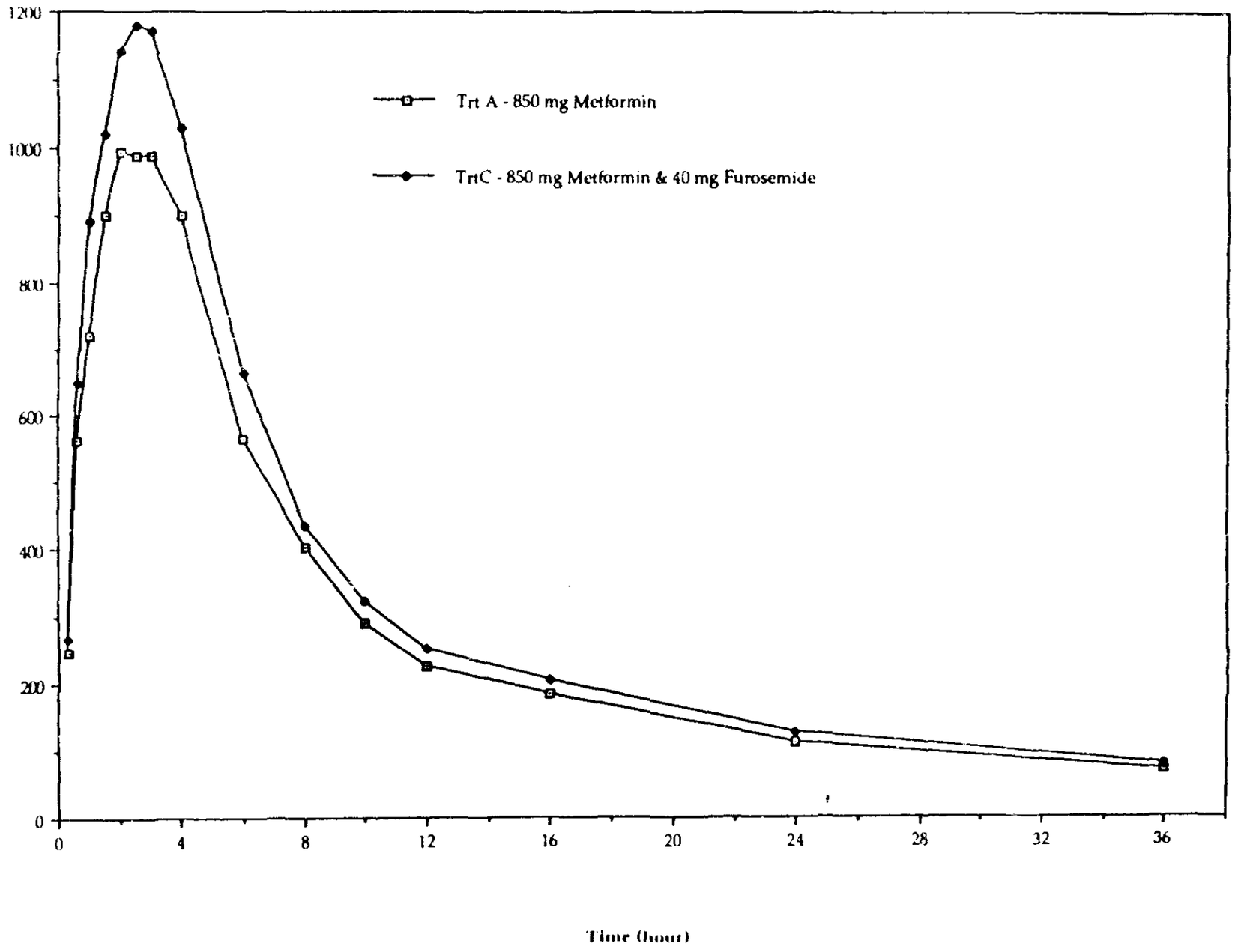
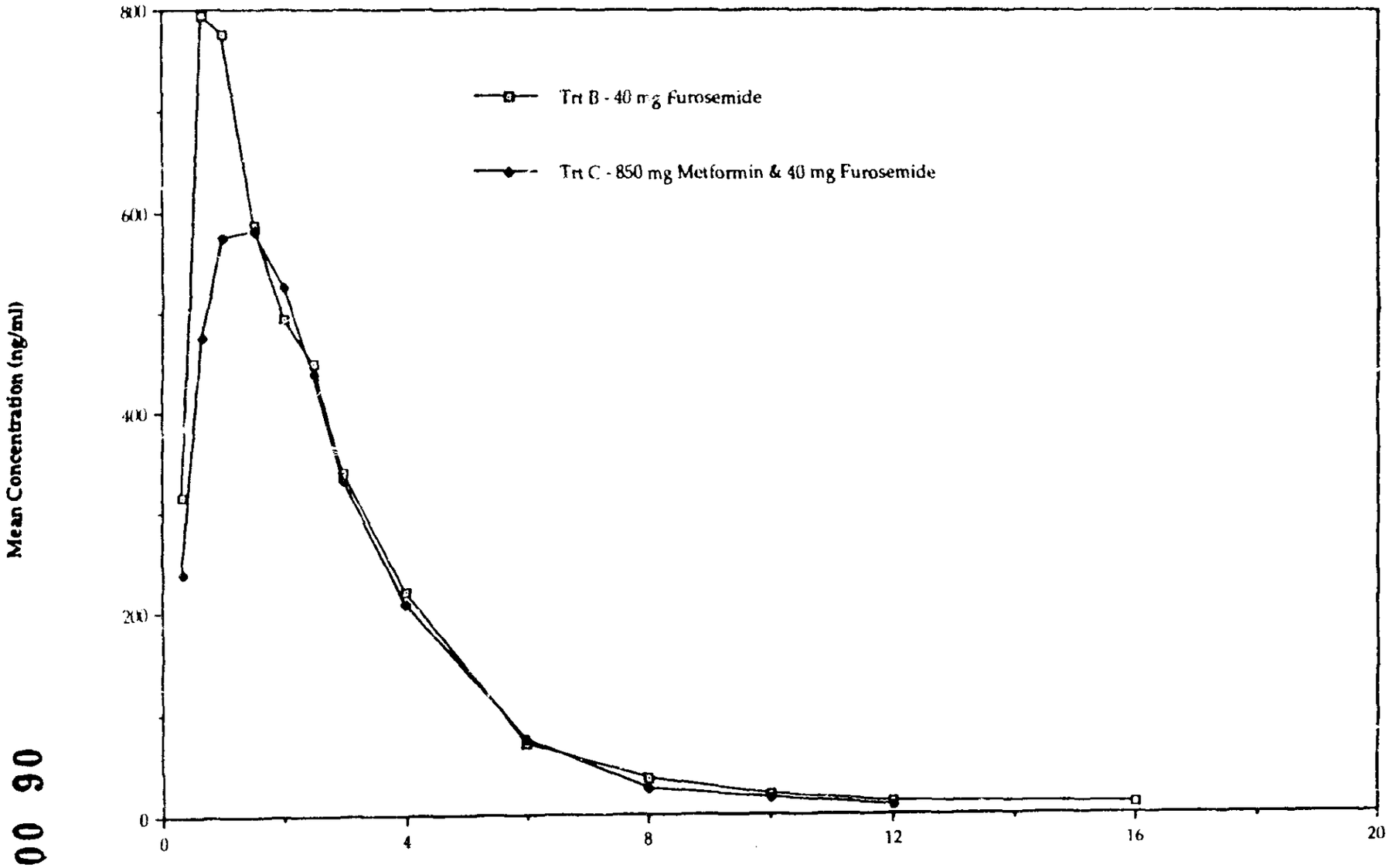


Figure 3

Mean Concentration for Furosemide Plasma (DSU 91-049)



MEAN CONCENTRATION OF METFORMIN PLASMA
DSU 91-061

TREATMENT A: 850 mg Metformin

Time (hrs.)	n	Mean Conc. (ng/ml)	S.D.	%C.V.
0	18	*	-	-
0.50	18	651	342	52.5
0.75	18	1030	328	31.9
1.00	18	1200	339	28.2
1.25	18	1260	336	26.7
1.50	18	1340	371	27.7
2.00	18	1420	359	25.2
3.00	18	1500	404	27.0
4.00	18	1250	371	29.8
6.00	18	691	202	29.2
8.00	18	412	117	28.4
10.0	18	251	68.6	27.3
12.0	18	163	44.9	27.5
24.0	18	41.3	17.6	42.5
36.0	18	21.6	11.8	54.5

* Below Assay Sensitivity - 10.0 ng/ml

MEAN CONCENTRATION OF METFORMIN PLASMA
DSU 91-06

TREATMENT C: 850 mg Metformin and 400 mg Ibuprofen

Time (hrs.)	n	Mean Conc. (ng/ml)	S.D.	%C.V.
0	17	*	-	-
0.50	17	802	329	41.0
0.75	17	1230	445	36.2
1.00	17	1260	547	43.3
1.25	17	1430	542	37.9
1.50	17	1460	442	30.3
2.00	17	1560	434	27.9
3.00	17	1510	436	29.0
4.00	17	1300	348	26.8
6.00	17	703	187	26.6
8.00	17	433	134	30.9
10.0	17	254	79.2	31.2
12.0	17	167	43.3	25.9
24.0	17	42.9	15.5	36.2
36.0	17	20.2	11.1	55.2

* Below Assay Sensitivity - 10.0 ng/ml

Subject 6C was not included in the mean data.

MEAN CONCENTRATION OF IBUPROFEN PLASMA
DSU 91-061

TREATMENT B: 400 mg Ibuprofen

Time (hrs.)	n	Mean Conc. (µg/ml)	S.D.	%C.V.
0	18	*	-	-
0.50	18	14.2	10.4	73.4
0.75	18	24.3	15.5	63.7
1.00	18	27.3	16.5	60.5
1.25	18	26.8	14.9	55.4
1.50	18	24.6	12.2	49 6
2.00	18	23.8	9.29	39.1
3.00	18	17.9	5.85	32.6
4.00	18	17.4	7.21	41.3
6.00	18	7.67	3.28	42.7
8.00	18	4.03	1.72	42.6
10.0	18	2.02	1.13	56.0
12.0	18	0.979	0.703	71.8
24.0	18	*	-	-
36.0	18	*	-	-

* Below Assay Sensitivity - 0.250 µg/ml

MEAN CONCENTRATION OF IBUPROFEN PLASMA
DSU 91-061

TREATMENT C: 850 mg Metformin and 400 mg Ibuprofen

Time (hrs.)	n	Mean Conc. (µg/ml)	S.D.	%C.V.
0	17	*	-	-
0.50	17	23.8	14.4	60.5
0.75	17	30.1	12.1	40.3
1.00	17	28.8	14.1	48.9
1.25	17	30.3	12.4	40.8
1.50	17	27.5	10.2	37.2
2.00	17	23.4	7.84	33.6
3.00	17	19.0	5.64	29.7
4.00	17	13.9	4.85	34.8
6.00	17	5.96	2.15	36.0
8.00	17	3.38	1.61	47.5
10.0	17	1.60	0.978	61.2
12.0	17	0.806	0.748	92.8
24.0	17	*	-	-
36.0	17	*	-	-

* Below Assay Sensitivity - 0.250 µg/ml
Subject 6C was not included in the mean data.

Figure 1

Mean Concentration fo. Metformin Plasma (DSU 91-061)

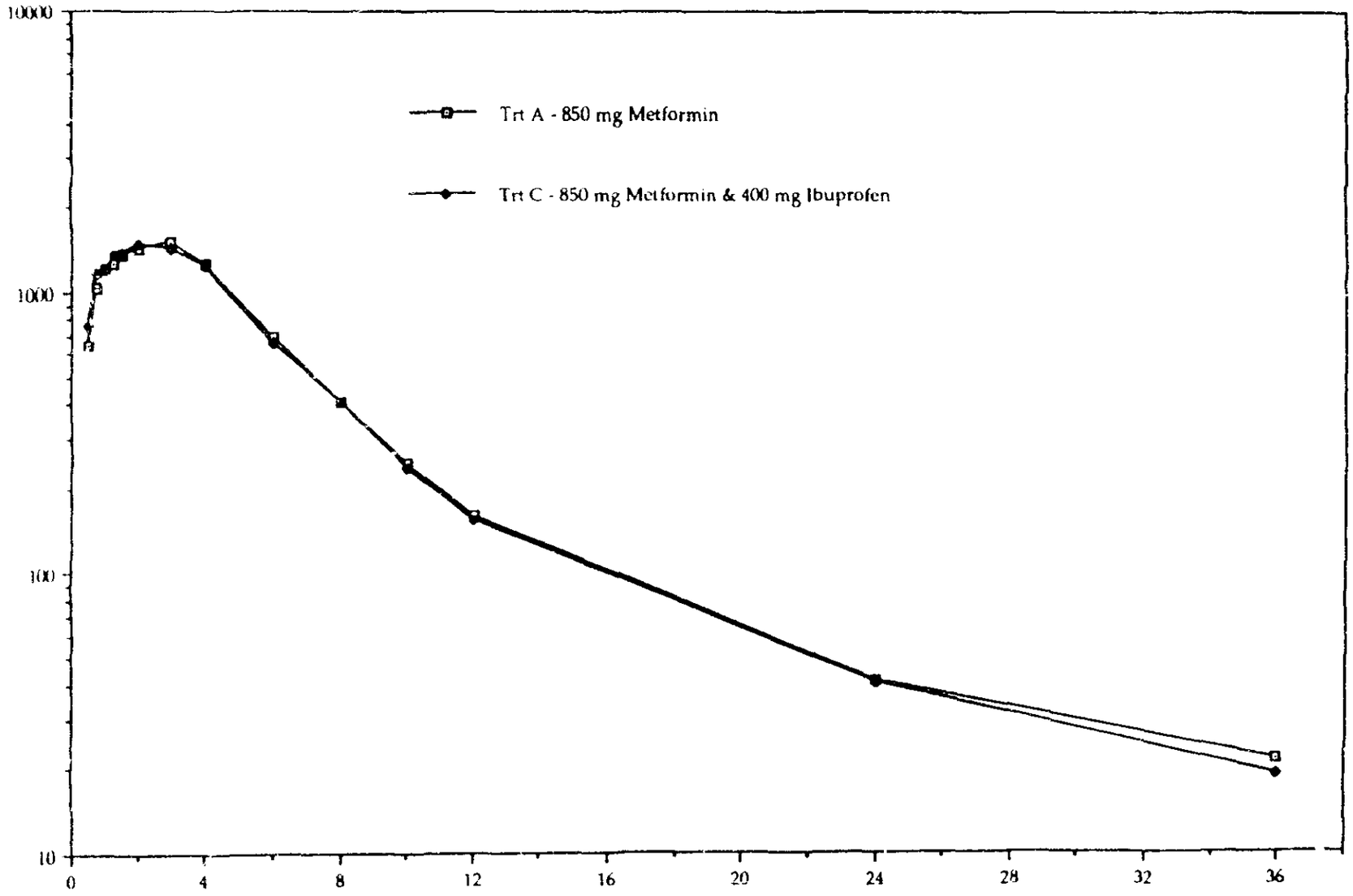


Figure 2

Mean Concentration for Metformin Blood (DSU 91-061)

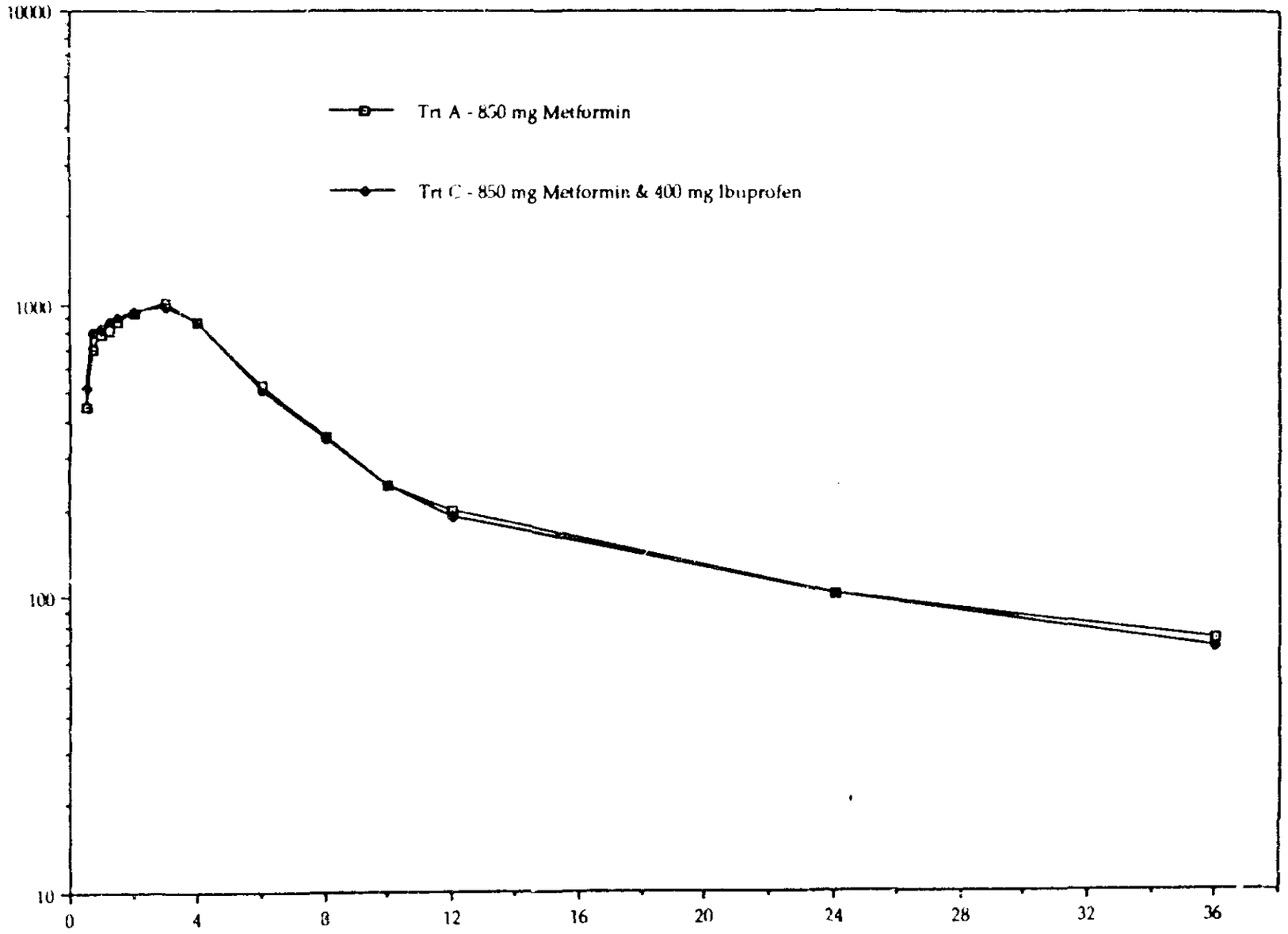


Figure 3

Mean Concentration . Ibuprofen Plasma (DSU 91-061)

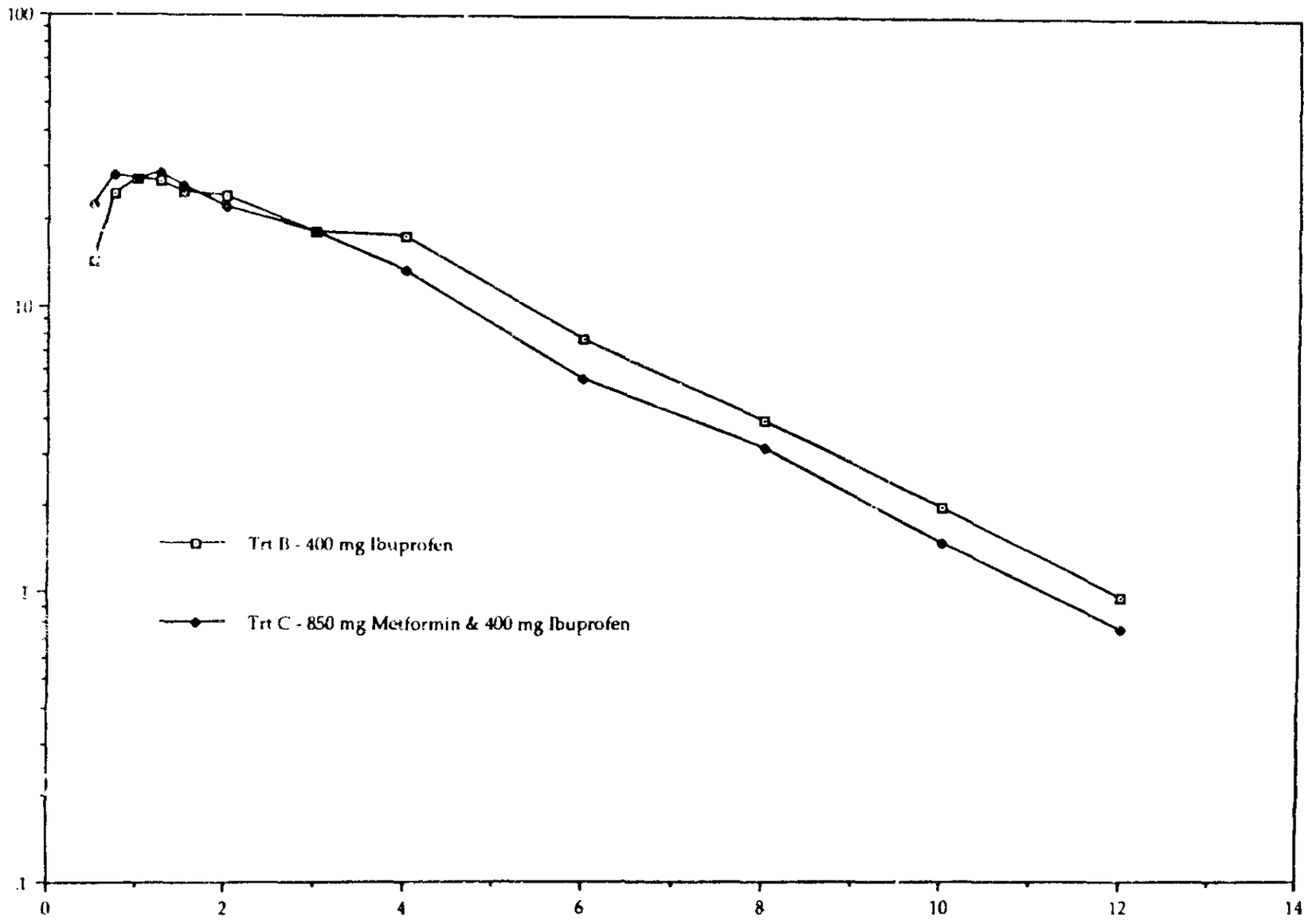


Table 1

Plasma Metformin Concentrations (ng/mL) in Healthy Subjects
Following Administration of 850 mg of Metformin: Treatment A

Subject No.	Time After Dosing (Hours) 0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
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17														
18														
Mean	0	708	1216	1470	1585	1543	1511	1385	741	417	235	131	62.3	24.7
SD	0	244.4	270.6	389.2	417.3	395.4	365.5	417.8	224.6	138.5	76.5	43 5	18.83	8.08
RSD (%)	-	34.5	22.3	26.5	26.3	25.6	24.2	30.2	30.3	33.2	32.6	33.1	30.2	32.7

Table 2

Plasma Metformin Concentrations (ng/mL) in Healthy Subjects
Following Administration of 850 mg of Metformin and
40 mg of Propranolol: Treatment C

Subject No.	Time After Dosing (Hours) 0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1														
2														
3														
4														
5														
6														
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9														
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16														
17														
18														
Mean	0	688	1168	1411	1498	1471	1402	1192	624	353	200	116	55.4	23.4
SD	0	290.0	315.9	431.5	406.9	343.0	262.4	251.2	158.1	109.2	65.2	40.3	18.73	7.00
RSD (%)	-	42.2	27.1	30.6	27.2	23.3	18.7	21.1	25.3	30.9	32.6	34.9	33.8	29.9

Table 12

Plasma Propranolol Concentrations (ng/mL) in Healthy Subjects
Following Administration of 40 mg of Propranolol: Treatment B

Subject No.	Time After Dosing (Hours)													
	0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														
17														
18														
Mean	0	1.64	12.3	19.8	22.0	21.7	20.7	17.1	10.2	6.30	4.14	2.85	1.44	0
SD	0	2.350	7.93	11.87	13.50	12.45	11.82	9.95	5.40	3.179	2.232	1.511	0.997	0.440
RSD (%)	-	143.1	64.6	60.1	61.5	57.3	57.2	58.1	53.1	50.4	53.9	53.0	69.3	-

Table 13

Plasma Propranolol Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin and 40 mg of Propranolol: Treatment C

Subject No.	Time After Dosing (Hours) 0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														
17														
18														
Mean	0	1.20	10.2	19.5	22.4	23.0	21.7	18.3	10.7	6.54	4.19	2.79	1.34	0
SD	0	1.469	6.74	11.64	12.47	12.57	11.92	9.83	5.44	3.137	2.136	1.530	1.000	0.257
RSD (%)	-	122.0	66.3	59.6	55.7	54.7	55.0	53.7	50.7	48.0	51.0	54.8	74.9	-

Table 16

Plasma 4-Hydroxypropranolol Concentrations (ng/mL) in Healthy Subjects Following Administration of 40 mg of Propranolol: Treatment B

Subject No.	Time After Dosing (Hours) 0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														
17														
18														
Mean	0	1.80	5.62	5.42	4.31	3.48	2.70	1.48	<1.0	0	0	0	0	0
SD	0	1.631	2.348	2.071	1.722	1.375	1.138	1.091	0.71	0.33	0.00	0.00	0.00	0.00
RSD (%)	-	90.5	41.7	38.2	40.0	39.5	42.1	73.6	-	-	-	-	-	-

Table 17

Plasma 4-Hydroxypropranolol Concentrations (ng/mL) in Healthy Subjects Following Administration of 850 mg of Metformin and 40 mg of Propranolol: Treatment C

Subject No.	Time After Dosing (Hours) 0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	10	12	16	24
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														
17														
18														
Mean	0	1.88	5.34	5.88	4.60	3.68	2.94	1.76	<1.0	0	0	0	0	0
SD	0	1.387	1.748	2.064	1.743	1.345	1.168	0.942	0.80	0.52	0.00	0.00	0.00	0.00
RSD (%)	-	74.0	32.7	35.1	37.9	36.6	39.7	53.5	-	-	-	-	-	-

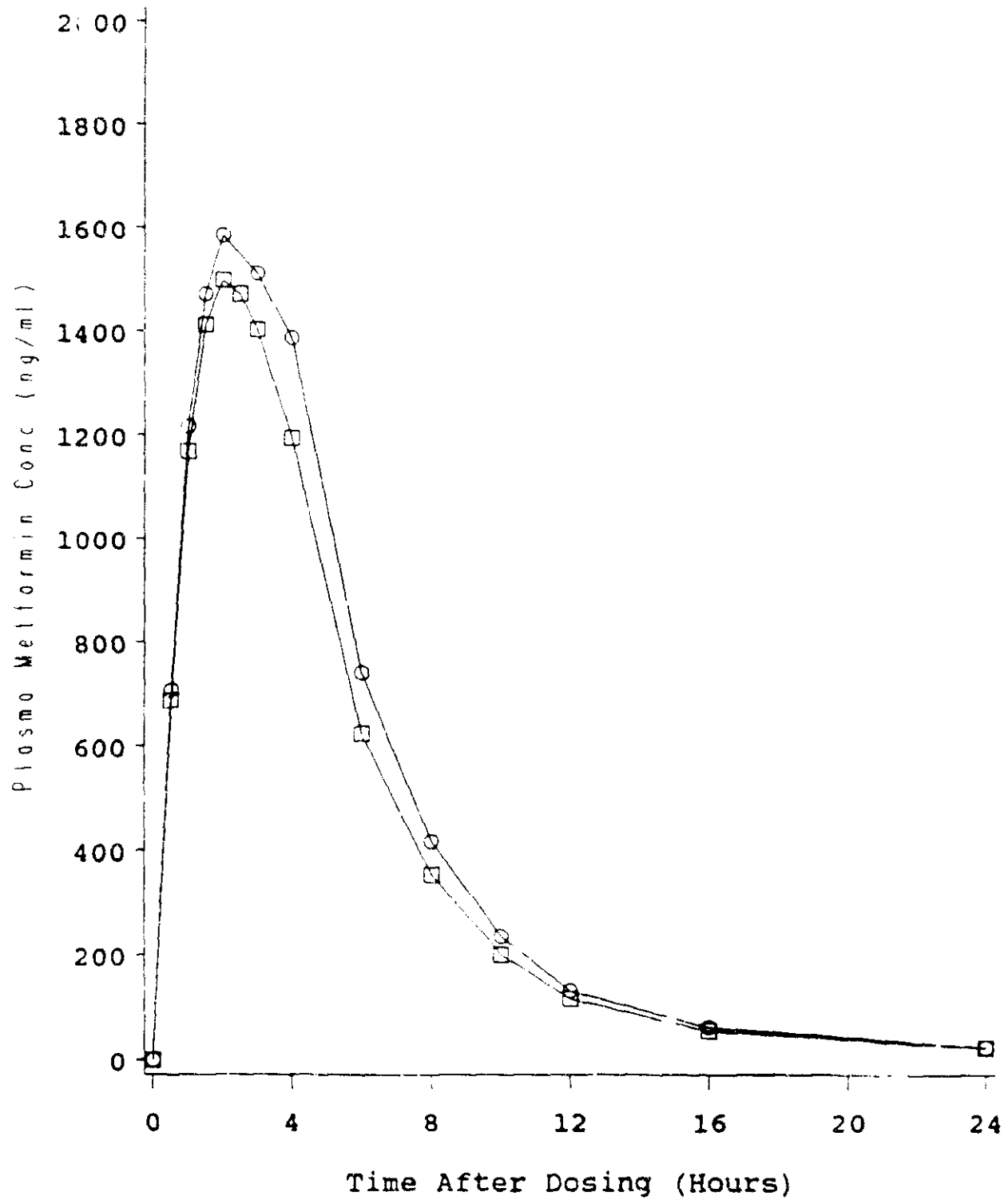


Figure 1. Mean Plasma Metformin Concentration-Time Profiles Following Dosing with 850 mg of Metformin (Treatment A) or 850 mg of Metformin Plus 40 mg of Propranolol (Treatment C)

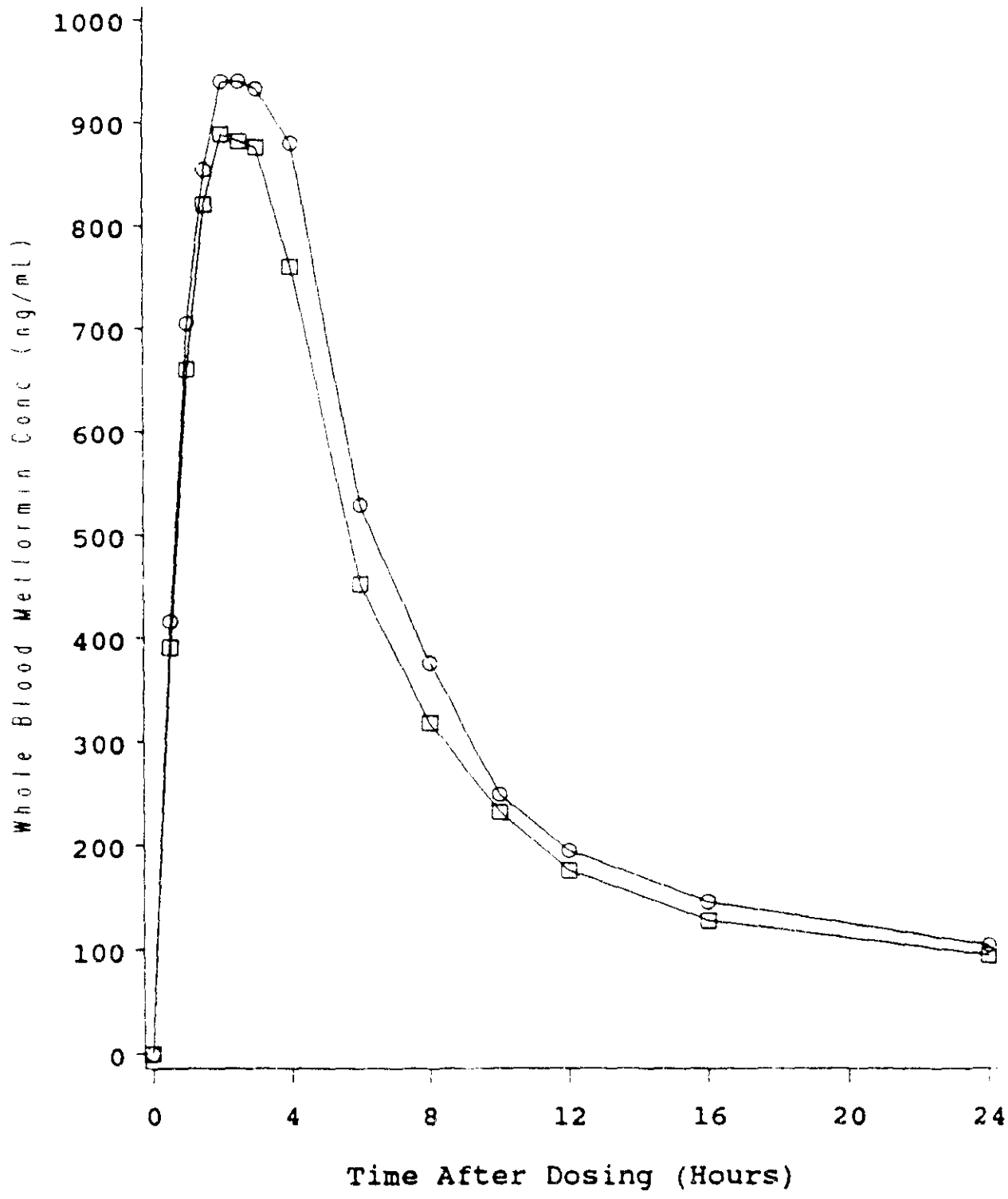


Figure 2. Mean Whole Blood Metformin Concentration-Time Profiles Following Dosing with 850 mg of Metformin (Treatment A) or 850 mg of Metformin Plus 40 mg of Propranolol (Treatment C)

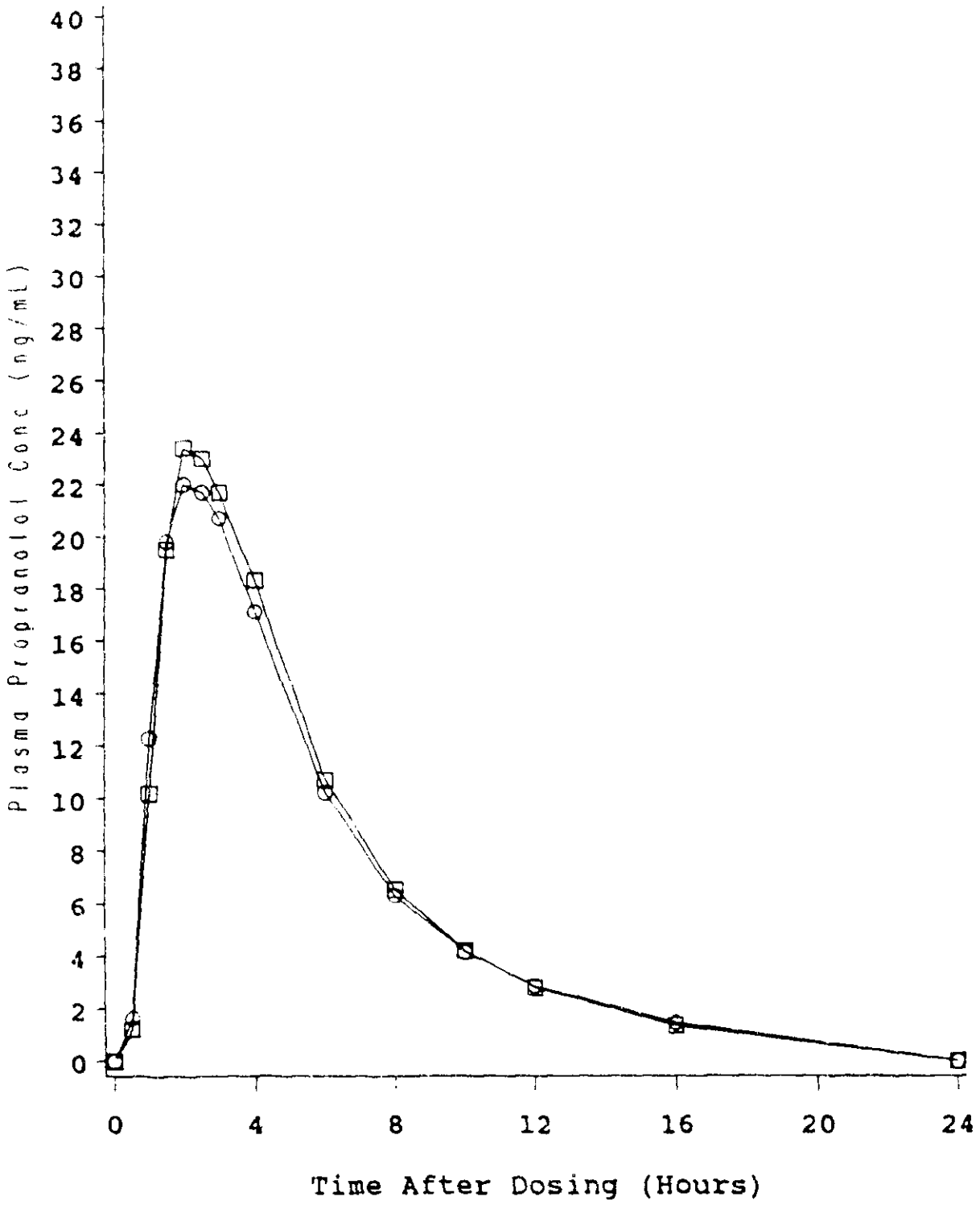


Figure 4. Mean Plasma Propranolol Concentration-Time Profiles Following Dosing with 40 mg of Propranolol (Treatment B) or 40 mg of Propranolol Plus 850 mg of Metformin (Treatment C)

TREATMNT Propranolol Only Propranolol+Met

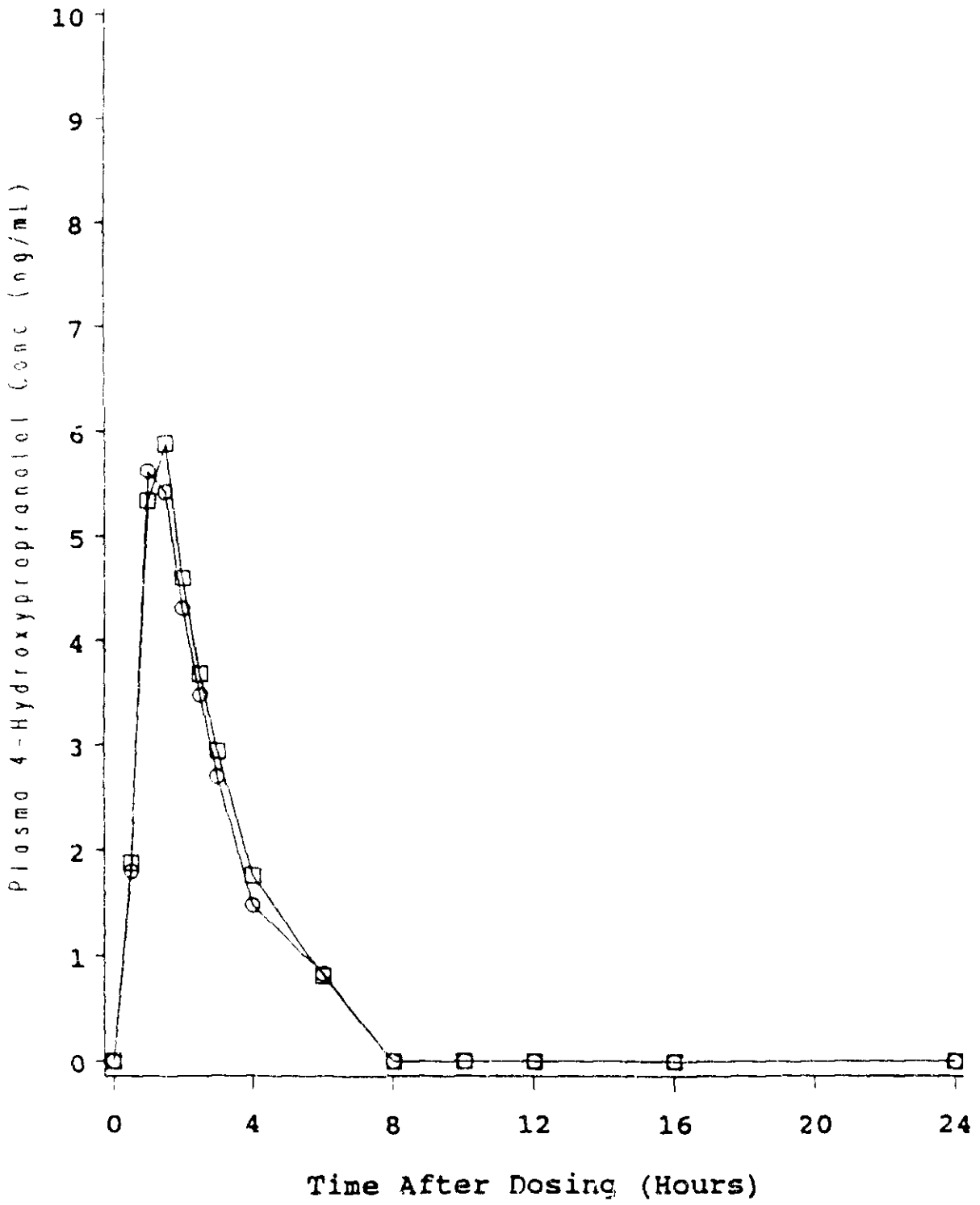


Figure 5. Mean Plasma 4-Hydroxypropranolol Concentration-Time Profiles Following Dosing with 40 mg of Propranolol (Treatment B) or 40 mg of Propranolol Plus 850 mg of Metformin (Treatment C)

DEC 22 1994

NDA 20-357 Submission Date: 10/19/94
11/29/94

Metformin (500 & 850 mg Tablets)
Glucophage® **Reviewer:** John Hunt

Sponsor: Lipha Pharmaceuticals, Inc.
New York, New York

Type of Submission: Amendments to NDA

Background:

NDA 20-357 for metformin HCl 500 and 850 mg tablets was previously evaluated by the Division of Biopharmaceutics (HFD-420) in a bio-review dated 7/13/94. In that bio-review a comment related to the proposed *in vitro* dissolution method and specification, as well as eight comments related to the product's proposed package insert (PI), was raised which needed to be addressed by the sponsor (see Appendix I).

In NDA Amendment No. 30 submitted on 10/19/94, the sponsor provided a revision of the PI (i.e., updated on 10/18/94) that incorporated FDA's initial recommendations (see Appendix II). Appendix II contains:

1. A cover letter for Amendment No. 30.
2. The updated version of the PI.
3. A summary table of pharmacokinetic parameters.
4. Literature references for studies of metformin with various sulfonylureas.

Following a meeting that was held within HFD-510 on 11/28/94, further comments related to the updated PI were communicated to the sponsor. [Note: Comment No. 1 below indicates the information that was covered by HFD-420 at the 11/28/94 meeting as related to the initial revised PI.] On 11/29/94 a new version of the PI (Amendment No. 35) was submitted by the sponsor (see Appendix III). The 11/29/94 version of the PI was discussed with the group leader medical officer on 12/20/94 and the information covered under Comment No. 2 below was recommended to be included in the PI.

Comments:

[Note: The input from HFD-510's medical staff who were present at the 11/28/94 meeting, as related to each item covered under Comment No. 1 , is given in parentheses.]

1. For the 10/18/94 version of the package insert for Glucophage®, the following changes were recommended to be made under the Clinical Pharmacology section.

a. Under the "Absorption and Bioavailability" subsection (page 7) of the Pharmacokinetics section, the first sentence should be changed to state: "The absolute bioavailability of a 500 mg metformin HCl tablet given under fasting conditions is 50-60%." (HFD-510's medical staff concurred with this.)

b. Under the "NIDDM Subjects" subsection (page 9) of the Special Populations section, the first and last sentences appear to be redundant. Therefore, the last sentence should be deleted. (HFD-510's medical staff concurred with this.)

c. On page 11, replace Table 4 with the table of summary pharmacokinetic parameters that is found under Appendix 1 of the 10/19/94 Amendment submission. (HFD-510's medical staff felt that only Cmax values should be added to Table 4. It was felt that other pharmacokinetic parameters were not needed e.g., t1/2, etc. Therefore, on page 9 under the subsection Renal Insufficiency of the Special Populations section, the part, "(see Table 4)", at the end of the sentence should be dropped.)

d. Under the "Drug Interactions" section (page 26) following "Cationic drugs" in the first sentence of the second paragraph incorporate, "(e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, etc.)". (HFD-510's medical staff felt that the statement as presented in the revised PI was sufficient and should not be changed. Additionally, it was recommended that the second paragraph of this section be moved to page 28 before the paragraph that started with "Certain drugs...")

2. For the 11/29/94 version of the package insert for Glucophage®, the following changes should be incorporated

a. Table 4 on page 11 should delete AUCX along with footnote c. Included should be Tmax and half-life in addition to Cmax and renal clearance.

b. Under the "Drug Interactions" section (page 27) following "Cationic drugs" in the first sentence of the fifth paragraph, incorporate "(e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, etc.)".

Recommendation:

The Division of Biopharmaceutics has evaluated the information that was submitted on 10/19/94 under NDA 20-357 Amendment No. 30 and the information that was submitted on 11/29/94 under NDA 20-357 Amendment No. 35. Comment No. 2 should be communicated to the sponsor in order to further update its package insert for Glucophage®.

[Note: Still outstanding is an issue related to the *in vitro* dissolution method and specification for Glucophage® which was previously raised in a bio-review dated 7/13/94 for NDA 20-357 (i.e, General Comment No. 1). HFD-510 is requested to determine the status of this outstanding issue.]

John Hunt
Pharmacokinetics Evaluation Branch II

RD/FT Initialed by M. Chen, Ph.D.

cc: NDA 20-357, HFD-510, HFD-426 (Fleischer), HFD-427 (M. Chen, Hunt), HFD-19 (FOI), HFD-340 (Vish), Drug, Chron, Reviewer

NDA 20-357

GLUCOPHAGE

APPROVAL LETTER

NDA 20-357

DEC 29 1994

Lipha Pharmaceuticals Inc.
Attention: Gerard L. Daniel, M.D.
Chairman, President & Chief Executive Officer
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Dr. Daniel:

Please refer to your September 29, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage (metformin hydrochloride tablets) 500 and 850 mg Tablets.

We acknowledge receipt of your amendments dated September 29, November 12, 16, 18, 19, and 23, and December 1, 6, 13, and 15, 1993; and January 11 (2), February 2, 3, 4, 7, 11, 15, and 23, March 4, 7, 11, and 12 (2), May 12, 13, 19, 20, and 27, June 15 and 22, August 19, 30, and 31, October 19 and 28, November 8, 11, 21, 22, and 29, and December 28 and 29 (2), 1994. Your major amendment of August 19, 1994, extended the Goal Date for this NDA to December 29, 1994.

This new drug application provides for the use of Glucophage as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II diabetes), whose hyperglycemia cannot be satisfactorily managed on diet alone.

We have completed the review of this application as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted September 29, 1993 (bottle labels), November 11 (blister packaging), and December 29, 1994 (package insert). Accordingly, the application is approved, effective on the date of this letter.

Please submit 15 copies of the final printed labeling (FPL) as soon as available, in no case more than 30 days after it is printed. The FPL must be identical to the draft labeling submitted September 29, 1993 (bottle labels), November 11 (blister packaging), and December 29, 1994 (package insert). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. Please individually mount 10 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-357. Approval of this labeling by FDA is not required before it is used.

We refer to your communication dated December 28, 1994, proposing a patient package insert (PPI). Although we have not completed our review of the PPI, we will do so in the near future. We also refer to your communication of December 29, 1994, in which you committed not to market Glucophage without an accompanying PPI containing mutually agreeable language. You also stated in the latter submission that each bottle of 100 tablets will include a

copy of the approved PPI, and if larger bulk containers are proposed in the future, an appropriate mechanism for distributing the PPI to each patient will be developed in consultation with FDA.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please include the MedWatch telephone number in all your advertising and promotional materials (1-800-FDA-~~0178~~ 1088). Not corrected in original letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Your communications of May 27 and August 31, 1994, commit to performing Phase 4 studies as follows:

1) Your May 27 submission contains a draft of a dose-ranging protocol (No. 94-02-6023) entitled "Dose-Response Study of Various Dose Levels of Metformin v. Placebo in Non-Insulin-Dependent Diabetic Outpatients." A final protocol should be submitted to your IND to conduct this study.

2) Your August 31 submission includes a draft proposal (in response to our letter dated June 29, 1994) for a prospective, randomized, controlled clinical trial involving 10,000 patients with NIDDM to focus on detection, confirmation, and evaluation of the incidence of lactic acidosis while taking Glucophage. Further, you have submitted a detailed protocol to IND on December 8, 1994. We will now solicit a written review of the protocol by several consultants. Their comments will be provided to you so that you can refine the protocol and submit a final version to the IND prior to initiation of the study.

Prominently identify all communications regarding these Phase 4 studies as such.

Your communication of August 31 also provides an overview of the type of medical education program to be conducted by Bristol-Myers Squibb for various health professionals. You indicate that it will primarily emphasize preventing the occurrence of lactic acidosis with proper Glucophage usage.

Please note that we will very likely convene an Endocrinologic and Metabolic Drugs Advisory Committee meeting after Glucophage has been marketed for one year to assess the implementation of the Phase 4 commitment in regard to the large cohort study and the completion of the Phase 4 commitment of the dose-response study.

Regarding the carton and blister-pack labels used for Glucophage Tablets, the "tablet" designation should appear as part of the established name, i.e., "metformin hydrochloride tablets" rather than "metformin hydrochloride." This change can be made some time after introduction of the drug and reported in the first annual report.

Please submit one market package of the drug product when it is available.

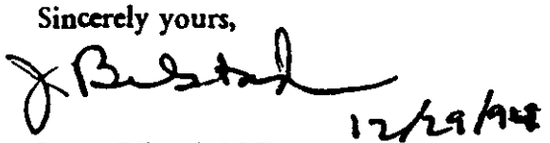
Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. John R. Short
Consumer Safety Officer
(301) 443-3510

Sincerely yours,



12/29/94

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

49

ODE I/II ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 20-357 Drug Glucophage (metformin) Tablets

Applicant Lipha Pharmaceuticals CSO Short /phone X33570

		Check or Comment
Arrange package in the following order:		
1.	ACTION LETTER with supervisory signatures	AP ✓ AE ___ NA ___
2.	~~ACTION PACKAGE TRACKING FORM~~ No Longer Used	
3.	Completed copy of this CHECKLIST in package	Chem/Ther Types IP
4.	LABELING (package insert and labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx PI and HFD-210 review of OTC insert.)	Draft X Final ___ Revised Draft ___
5.	SUMMARY BASIS OF APPROVAL. (Copy of previous version with ODE's comment as well as disk, FPL and sign-off sheet must accompany revised or final version. If no SBA, include memo stating what reviews will be used as SBA equivalent.)	SBA ___ Revised SBA ___ SBA Equivalent X
6.	PATENT INFORMATION ✓	EXCLUSIVITY CHECKLIST ✓
7.	Debarment Certification (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992)	✓
8.	DIVISION DIRECTOR'S MEMO (If more than 1 review for any 1 discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented.)	✓
	GROUP LEADER'S MEMO	✓
	PEDIATRIC PAGE	✓
	MEDICAL REVIEW	✓
	SAFETY UPDATE REVIEW	✓
	STATISTICAL REVIEW	✓
	BIOPHARMACEUTICS REVIEW	✓
	PHARMACOLOGY REVIEW (Include pertinent IND reviews)	✓
	Statistical Review of Carcinogenicity Study(ies)	✓
	CHEMISTRY REVIEW	✓
	Date EER completed 12/7/94 (attach signed form or CIRTS printout); FUR needed ___ requested ✓ 11/17	OK ✓ No ___
	Have the methods been validated?	Yes (attach) ___ No ✓
	Environmental Assessment Review	✓
	MICROBIOLOGY REVIEW	N/A
	Has the monograph been approved?	Yes ___ No ___
9.	Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES. If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.	See COMIS Printout ✓
10.	CORRESPONDENCE and MEMOS OF TELECONS	✓
11.	MINUTES OF MEETINGS	✓
	Date of End-of-Phase II Meeting ✓ 12/4/87	
	Date of pre-NDA Meeting ✓ 7/9/92	
12.	ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript	Minutes ✓ 10/15/81 5/18/94 Info Alert ___ Transcript ___ No mtg ___
13.	FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	N/A
14.	If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ___ No X Yes, documentation attached ___ No, included in AP ltr X
15.	Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes X No ___
16.	Integrated Summary of Safety	✓ 11 Volumes in Lot (available)
17.	NDA (especially Medical/Statistical) Summary	✓

9/9/92

NDA 20-357

SBA EQUIVALENT

Medical Officer Reviews/Memos dated:

1/27/94 (Dr. Stadel)
3/22/94 (Dr. Gueriguian)
5/17/94 (Dr. Innerfield)
5/18/94 (Dr. Stadel)
5/20/94 (Dr. Innerfield)
7/18/94 (Dr. Innerfield)
9/9/94 (Dr. Stadel)
11/29/94 (Dr. Gueriguian)
11/29/94 (Div. Dir.'s Memo)
12/16/94 (Group Leader's Memo)
12/29/94 (Dr. O'Neill's Memo)

Statistical Review dated:

3/1/94

Biopharmaceutics Review dated:

7/3/94
12/22/94

Pharmacology Reviews dated:

5/3/94 (Mr. Hertig)
6/2/94 (Dr. Lin/Statistical Review of Carcinogenicity Studies)

LABELING

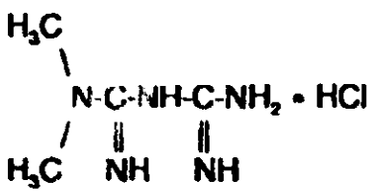
12/29/94 Submission

REVISED PACKAGE INSERT

GLUCOPHAGE® (metformin hydrochloride tablets) — 500 mg and 850 mg

DESCRIPTION

GLUCOPHAGE (metformin hydrochloride tablets) is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to the oral sulfonylureas. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE Tablets contain 500 mg and 850 mg of metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate and hydroxypropyl methylcellulose (hypromellose) coating.

REVISED PACKAGE INSERT

GLUCOPHAGE® (metformin hydrochloride tablets) — 500 mg and 850 mg

CLINICAL PHARMACOLOGY:

Antidiabetic Activity

GLUCOPHAGE is an antihyperglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from those of sulfonylureas. GLUCOPHAGE decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, GLUCOPHAGE does not produce hypoglycemia in either diabetic or nondiabetic subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese NIDDM patients whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with GLUCOPHAGE (up to 2.55 g/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and HbA_{1c} of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to placebo group (see Table 1).

Table 1. GLUCOPHAGE vs Placebo
Summary of Mean Changes from Baseline* in Plasma Glucose
HbA_{1c} and Body Weight, at Final Visit (29-week study)

	GLUCOPHAGE (n = 141)	Placebo (n = 145)	P-Value
FPG (mg/dL)			
Baseline	241.5	237.7	NS
Change at FINAL VISIT	-53.0	6.3	0.001**
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS
Change at FINAL VISIT	-1.4	0.4	0.001**
Body Weight (lbs)			
Baseline	201.0	206.0	NS
Change at FINAL VISIT	-1.4	-2.4	NS

* - All patients on diet therapy at Baseline

**- Statistically significant

Monotherapy with GLUCOPHAGE may be effective in patients who have not responded to sulfonylureas or who have only a partial response to sulfonylureas or who have ceased to respond to sulfonylureas. In such patients, if adequate glycemic control is not attained with GLUCOPHAGE monotherapy, the combination of GLUCOPHAGE and a sulfonylurea may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

A 29-week, double-blind, placebo-controlled study of GLUCOPHAGE and glyburide, alone and in combination, was conducted in obese NIDDM patients who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see Table 2). Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG and HbA_{1c} of 14 mg/dL, 3 mg/dL and 0.2%, respectively. In contrast, those randomized to GLUCOPHAGE (up to 2.5 g/day) did not experience a deterioration in glycemic control, but rather a slight improvement, with mean reductions in FPG, PPG and HbA_{1c} of 1 mg/dL, 6 mg/dL and 0.4%, respectively. The combination of GLUCOPHAGE and glyburide was synergistic in reducing FPG, PPG and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Compared to results of glyburide treatment alone, the net differences with combination treatment were -77 mg/dL, -68 mg/dL and -1.8%, respectively (see Table 2).

Table 2. Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or Glucophage (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Plasma Glucose, HbA_{1c} and Body Weight, at Final Visit (29-week study)

				P-values		
	Comb (n = 213)	Glyb (n = 209)	GLU (n = 210)	Glyb vs Comb	GLU vs Comb	GLU vs Glyb
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS	NS	NS
Change at FINAL VISIT	-63.5	13.7	-0.9	0.001**	0.001**	0.025**
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS	NS	0.007**
Change at FINAL VISIT	-1.7	0.2	-0.4	0.001**	0.001**	0.001**
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS	NS	NS
Change at FINAL VISIT	0.9	-0.7	-8.4	0.011**	0.001**	0.001**

* - All patients on glyburide, 20 mg/day, at Baseline

** - Statistically significant

The magnitude of the decline in fasting blood glucose concentration following the institution of GLUCOPHAGE therapy is proportional to the level of fasting hyperglycemia. Non-insulin-dependent diabetics with higher fasting glucose concentrations will experience greater declines in plasma glucose and glycosylated hemoglobin.

GLUCOPHAGE has a modest favorable effect on serum lipids, which are often abnormal in NIDDM patients. In clinical studies, particularly when baseline levels were abnormally elevated, GLUCOPHAGE, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol and LDL cholesterol levels and had no adverse effects on other lipid levels (see Table 3).

Table 3.
Summary of Mean Percent Reduction of Major Serum Lipid Variables at Final Visit (29-week study)

	Glucophage vs. Placebo (% Change from Baseline)		Combined Glucophage/Glyburide vs. Monotherapy (% Change from Baseline)		
	Glucophage (n=141)	Placebo (n=145)	Glucophage (n=210)	Glucophage/ Glyburide (n=213)	Glyburide (n=209)
Total Cholesterol	-5%*	1%	-2%	-4%**	1%
Total Triglycerides	-18%	1%	-3%**	-8%**	4%
LDL-Cholesterol	-8%*	1%	-4%**	-6%**	3%
HDL-Cholesterol	2%	-1%	5%	3%	1%

* P <0.05 vs. Placebo
** P <0.05 vs. Glyburide

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tends to remain stable or may even decrease somewhat (see Tables 1 and 2).

In summary, metformin-treated patients showed significant improvement in all parameters of glycemic control (FPG, PPG and HbA_{1c}), stabilization or decrease in body weight, and a tendency to improvement in the lipid profile, particularly when baseline values are abnormally elevated.

Pharmacokinetics

Absorption and Bioavailability:

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 μg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Elimination:

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 4) is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations:

NIDDM Subjects:

In the presence of normal renal function, there are no differences between single or multiple dose pharmacokinetics of metformin between diabetics and nondiabetics (see Table 4), nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency:

In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see Table 4).

Hepatic Insufficiency:

No pharmacokinetic studies have been conducted in subjects with hepatic insufficiency.

Geriatrics:

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Table 4).

Pediatrics:

No pharmacokinetic studies have been conducted in pediatric subjects.

Gender:

Metformin pharmacokinetic parameters did not differ significantly in diabetic and nondiabetic subjects when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with NIDDM, the antihyperglycemic effect of GLUCOPHAGE was comparable in males and females.

Race:

No studies of metformin pharmacokinetic parameters according to race

Table 4. Select Mean (± S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE

Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	C_{max}[b] (µg/ml)	t_{max}[c] (hrs)	Renal Clearance (ml/min)
Healthy, nondiabetic adults:			
500 mg SD[d] (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg SD (74)[e]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg t.i.d. for 19 doses[f] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with NIDDM:			
850 mg SD (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg t.i.d. for 19 doses[f] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[g], healthy nondiabetic adults:			
850 mg SD (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±58)
Renal-impaired adults: 850 mg SD			
Mild (CL_{cr}[h] 61-90 ml/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 ml/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 ml/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] - All doses given fasting except the first 18 doses of the multiple dose studies;
[b] - Peak plasma concentration;
[c] - Time to peak plasma concentration;
[d] - SD = single dose;
[e] - Combined results (average means) of five studies: mean age 32 years (range 23-59 yrs).
[f] - Kinetic study done following dose 19, given fasting.
[g] - Elderly subjects, mean age 71 years (range 65-81 years).
[h] - CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2.

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INDICATIONS AND USE

GLUCOPHAGE (metformin hydrochloride tablets), as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia cannot be satisfactorily managed on diet alone.

GLUCOPHAGE may be used concomitantly with a sulfonylurea when diet and GLUCOPHAGE or a sulfonylurea alone do not result in adequate glycemic control.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. Loss of blood glucose control in diet-managed patients may be transient, thus requiring only short-term pharmacologic therapy. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of GLUCOPHAGE alone or GLUCOPHAGE plus a sulfonylurea should be considered.

If, after a suitable trial of such treatments, glucose control still has not been achieved, consideration should be given to the use of insulin. Judgments should be based on regular clinical and laboratory evaluations.

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CONTRAINDICATIONS:

GLUCOPHAGE is contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).

2. GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS).

3. Known hypersensitivity to metformin hydrochloride.

4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

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WARNINGS

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical

problems and multiple concomitant medications. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia or dehydration. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

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The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis and may

be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).

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SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY:

The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 1027 patients who were randomly assigned to one of five treatment groups (*Diabetes*, 19 (Suppl.2):747-830, 1970; *Diabetes*, 24 (Suppl.1):65-184, 1975).

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) or diet plus a fixed dose of phenformin (100 mg per day), had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone, resulting in discontinuation of both these treatments in the UGDP study. Total mortality was increased in both the tolbutamide- and phenformin-treated groups and this increase was statistically significant in the phenformin-treated group. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of GLUCOPHAGE and alternative modes of therapy.

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Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other related oral antidiabetic drugs, in view of the similarities in mode of action and chemical structure among the drugs in each category.

PRECAUTIONS

General:

Monitoring of renal function - GLUCOPHAGE is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION).

Before initiation of GLUCOPHAGE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition - Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (See Drug Interactions), should be used with caution.

Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and scans with contrast materials) - Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states - Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued.

Surgical procedures - GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake - Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE.

Impaired hepatic function - Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels - A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of previously controlled diabetic - A diabetic patient previously well controlled on GLUCOPHAGE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and

metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia - Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose: - When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This

phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

Information for Patients:

Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms,

which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE.

GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

Laboratory Tests:

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Drug Interactions:

Glyburide: In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage and Oral Sulfonylurea Therapy).

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12%

smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient

monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses

up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in-vivo* micronuclei formation test (mouse bone marrow).

Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis.

Pregnancy:

Teratogenic effects:

Pregnancy Category B. Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal

concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers:

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in children have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted.

Geriatric Use:

Controlled clinical studies of GLUCOPHAGE did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see also DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Lactic Acidosis: See WARNINGS, PRECAUTIONS and OVERDOSAGE Sections.

Gastrointestinal Reactions: Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more

frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE with meals (see DOSAGE AND ADMINISTRATION).

Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, GLUCOPHAGE should be temporarily discontinued.

For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: During initiation of GLUCOPHAGE therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolves spontaneously.

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Dermatologic Reactions: The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy.

Hematologic: (See also PRECAUTIONS). During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered.

DRUG ABUSE AND DEPENDENCE:

GLUCOPHAGE possesses no pharmacodynamic properties, either primary or secondary, which could be expected to result in abuse as a recreational drug or addiction.

OVERDOSAGE:

Hypoglycemia has not been seen even with ingestion of up to 85 grams of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see

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WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION:

There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE or any other pharmacologic agent. Dosage of GLUCOPHAGE must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. GLUCOPHAGE should be given in divided doses with meals and should be started at a low dose, with gradual dose escalation, as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see below, USUAL STARTING DOSE), fasting plasma glucose should be used to determine the therapeutic response to GLUCOPHAGE and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLUCOPHAGE, either when used as monotherapy or in combination with sulfonylurea.

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Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of GLUCOPHAGE may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Usual Starting Dose:

In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

GLUCOPHAGE 500 mg Tablets:

The usual starting dose of GLUCOPHAGE 500 mg tablets is one tablet b.i.d., given with the morning and evening meals. Dosage increases should be made in increments of one tablet every week, given in divided doses, up to a maximum of 2500 mg per day. GLUCOPHAGE can be administered twice a day up to 2000 mg per day (e.g., 1000 mg b.i.d. with morning and evening meals). If a 2500 mg daily dose is required, it may be better tolerated given t.i.d. with meals.

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GLUCOPHAGE 850 mg Tablets:

The usual starting dose of GLUCOPHAGE 850 mg tablets is one tablet daily, given with the morning meal. Dosage increases should be made in increments of one tablet every OTHER week, given in divided doses, up to a maximum of 2550 mg per day. The usual maintenance dose is 850 mg b.i.d. with the morning and evening meals. When necessary, patients may be given 850 mg t.i.d. with meals.

Transfer from Other Antidiabetic Therapy:

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to GLUCOPHAGE, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant GLUCOPHAGE and Oral Sulfonylurea Therapy:

If patients have not responded to four weeks of the maximum dose of GLUCOPHAGE monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing GLUCOPHAGE at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are

currently available only for metformin plus glyburide (glibenclamide). Published clinical information exists for the use of metformin with either chlorpropamide, tolbutamide or glipizide. No published clinical information exists regarding concomitant use of metformin with acetohexamide or tolazamide.

With concomitant GLUCOPHAGE and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant GLUCOPHAGE and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea).

- If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUCOPHAGE and the maximum dose of an oral sulfonylurea, institution of insulin therapy and discontinuation of these oral agents should be considered.

REVISED PACKAGE INSERT

GLUCOPHAGE® (metformin hydrochloride tablets) — 500 mg and 850 mg

Specific Patient Populations:

GLUCOPHAGE is not recommended for use in pregnancy or for use in children.

The initial and maintenance dosing of GLUCOPHAGE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE.

In debilitated or malnourished patients, the dosing should also be conservative and based on a careful assessment of renal function.

HOW SUPPLIED:

GLUCOPHAGE® (brand of metformin hydrochloride tablets) is supplied as white, unscored, film-coated, cylindrical, biconvex tablets, available in the following strengths:

500 mg	*Bottles of 100*	*NDC*
850 mg	*Bottles of 100*	*NDC*

Tablets are debossed with the letters "GL" and either "500" or "850" to indicate strength.

Caution: Federal law prohibits dispensing without prescription. Store at controlled room temperature 15° to 30° (59°-86°F).

12/28/94 Submission

Patient Information About Glucophage

(Glu-co-fage)
Generic Name: Metformin Hydrochloride
(Met-FOR-min Hi-dro-CLOOR-eyed)

To be revised at a later date.

What is the Most Important Information about Glucophage?

Glucophage is used to treat type II diabetes. It should only be used if you have seriously tried and failed to treat diabetes by diet and exercise without taking medicines. As with other medicines for diabetes, you must continue to diet and exercise while taking Glucophage.

Glucophage can increase the risk of a rare but sometimes fatal condition called lactic acidosis (LACK-tick ASS-sid-dose-is). Lactic acidosis may, however, also occur in people who are not taking Glucophage, particularly when the circulation fails. Because the risk of this problem is increased in people with inadequate kidney or liver function who take Glucophage, people with kidney or liver problems should not take this medicine. Your doctor will need to perform blood tests on you from time to time to be sure your kidneys and liver are functioning normally. Lactic acidosis can also occur when a serious illness develops quickly such as with a heart attack, severe infection, dehydration, stroke, or extremely high blood sugar levels. Glucophage should be temporarily discontinued if any such situation develops.

It is also important that if you have any illness, even minor, that can result in dehydration because of decreased food or fluid intake, diarrhea or vomiting, that you promptly contact your doctor.

Some of the symptoms of lactic acidosis include: feeling very tired or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or having slow or irregular heart beats. Stop taking Glucophage and call your doctor right away if you notice these symptoms or particularly if your medical condition has suddenly changed. Lactic acidosis is a medical emergency that must be treated in the hospital.

You should also avoid excessive alcohol consumption while taking Glucophage because it also increases the risk of lactic acidosis. Before starting Glucophage treatment, make sure that your doctor knows about all the other medicines that you are taking.

What is Glucophage?

Glucophage is used to treat type II diabetes, which is also known as non-insulin-dependent diabetes mellitus (NIDDM).

Diabetes is caused by the inability of the body to produce enough insulin and/or respond normally to the insulin present. Insulin helps the body use the food we eat to produce energy. When there is not enough insulin, sugar cannot get into the body's cells where it is needed, and it builds up in the blood where it can cause damage. The main goal of treating diabetes is to get the blood sugar down to normal levels. Blood sugar can be lowered by diet and exercise, anti-diabetic pills, and insulin.

Until the availability of Glucophage, all the approved anti-diabetic pills were from the same chemical group, which is called sulfonylureas. Drugs in this group lower blood sugar by causing more of the body's own insulin to be released. Glucophage lowers blood sugar by helping the body to respond better to its own insulin.

Because sulfonylureas and Glucophage lower the blood sugar by different means, they can be used together as well as separately. For people whose blood sugar cannot be lowered by either a sulfonylurea or Glucophage alone, the two medicines can be very effective when used together.

Exercising and maintaining a proper diet are essential to controlling diabetes. **As with any medicine for diabetes, Glucophage should only be used by people who have first endeavored to control their diabetes by exercise and dieting.** You must continue to exercise and follow a proper diet even if you take Glucophage. You may later be able to regain control of your diabetes with diet and exercise, and, therefore, be able to stop the Glucophage treatment or cut back on the dosage.

Who Should Not Take Glucophage?

Warning: People with liver or kidney problems should not take Glucophage.

A small number of people have developed a serious condition while taking Glucophage. It is called lactic acidosis and it has occurred in about 3 people in 100,000 who take this drug for a full year. When lactic acidosis does occur, it is fatal in up to half the cases. Because kidney function decreases as people get older, older people and people with kidney and liver problems are most at risk to develop lactic acidosis. As with most medications, your doctor will want to use the lowest dose of Glucophage possible. Your doctor also may need to perform laboratory tests at least once a year to check for any liver or kidney problems.

What Other Problems Might Be Caused by Glucophage?

You should also be aware that there is some evidence that the oral anti-diabetic drugs, including Glucophage, increase the risk of fatal heart problems. In one study in patients with diabetes, a drug related to Glucophage and a drug from the sulfonylurea group of anti-diabetic medicines appeared to increase the number of deaths due to heart problems. Experts are not sure what the real risk is for heart problems, if any, from taking Glucophage or any other anti-diabetic medicine. Fortunately, a large study will be completed within two years and is expected to answer these questions. For now, patients and their physicians should take into account this possible risk when they consider Glucophage or any other oral anti-diabetic medication.

Glucophage may also interfere with "contrast agents" that people are given by injection (into a blood vessel) either before or during certain special X-ray examinations. You may need to stop taking Glucophage for several days if you are having such an X-ray examination or if you are having surgery. When these procedures or surgery are scheduled, be sure to remind your doctors ahead of time that you are taking Glucophage.

How Should I Take Glucophage?

Drug Interaction Warning: As with most medicines, remind your doctor that you are taking Glucophage when any new medicine is prescribed or a change is made in already prescribed medicine. As with most medicines, Glucophage can interfere with some other drugs doing their job and some other drugs can interfere with the action of Glucophage.

Tell your doctor if you desire to become pregnant or have become pregnant. As with other oral anti-diabetic medicines, you should not take Glucophage during pregnancy. Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of Glucophage if you are nursing a child.

Glucophage can interfere with the body's use of vitamin B_{12}. In very rare cases, this can cause anemia or a reduction of the number of red blood cells. Your doctor should check roughly every year that this problem is not developing.

What Should I Avoid While Taking Glucophage?

Alcohol Warning: Consuming alcohol can increase the risk of lactic acidosis. Avoid excessive use of alcohol while taking this drug.

What Are the Possible Side Effects of Glucophage?

When treatment is started with Glucophage, about 30 percent of people experience some stomach problems. These problems include diarrhea, nausea, vomiting, bloating, passing gas, and anorexia. These often go away when people take Glucophage for a while and begin to control their diabetes. Some people may need to have their dose lowered or stop taking the medicine, either temporarily or permanently. While some abdominal discomfort is common during the first weeks of treatment, never assume that severe abdominal pain is due to Glucophage, particularly after you have been on the same dose for several weeks. Inform your doctor about unusual abdominal pain or other symptoms as you usually would.

About 3 percent of people taking Glucophage complain of an unpleasant or metallic taste in their mouth.

How Can I Get Additional Information?

This leaflet summarizes the most important information about Glucophage. If you would like more information, talk to your doctor or other health care provider. There is also a leaflet written for health professionals that your pharmacist can let you read.

Blister Pack Draft labeling 11/11/94 Submission

DRAFT

Lot Exp

GLUCOPHAGE
(METFORMIN HYDROCHLORIDE)

GLUCOPHAGE
(METFORMIN HYDROCHLORIDE) 500 mg TABLETS

500 MG

GLUCOPHAGE
(METFORMIN HYDROCHLORIDE) 500 mg TABLETS

List 6060-00

Patient Starter Units — Not For Sale

See bottom or side of carton
for expiration date and lot number

GLUCOPHAGE
(METFORMIN HYDROCHLORIDE) 500 mg TABLETS

Professional package — not child resistant.
Keep out of reach of children.
Each tablet contains 500 mg of metformin hydrochloride
See enclosed package insert for dosage information.
Caution: Federal law prohibits dispensing without prescription.
Store between 15°–25°C (59°–77°F)
Dispense in light-resistant container

GLUCOPHAGE is a registered trademark of Lipha (Lyonnaise Industrielle Pharmaceutique). Licensed to Bristol-Myers Squibb Company.

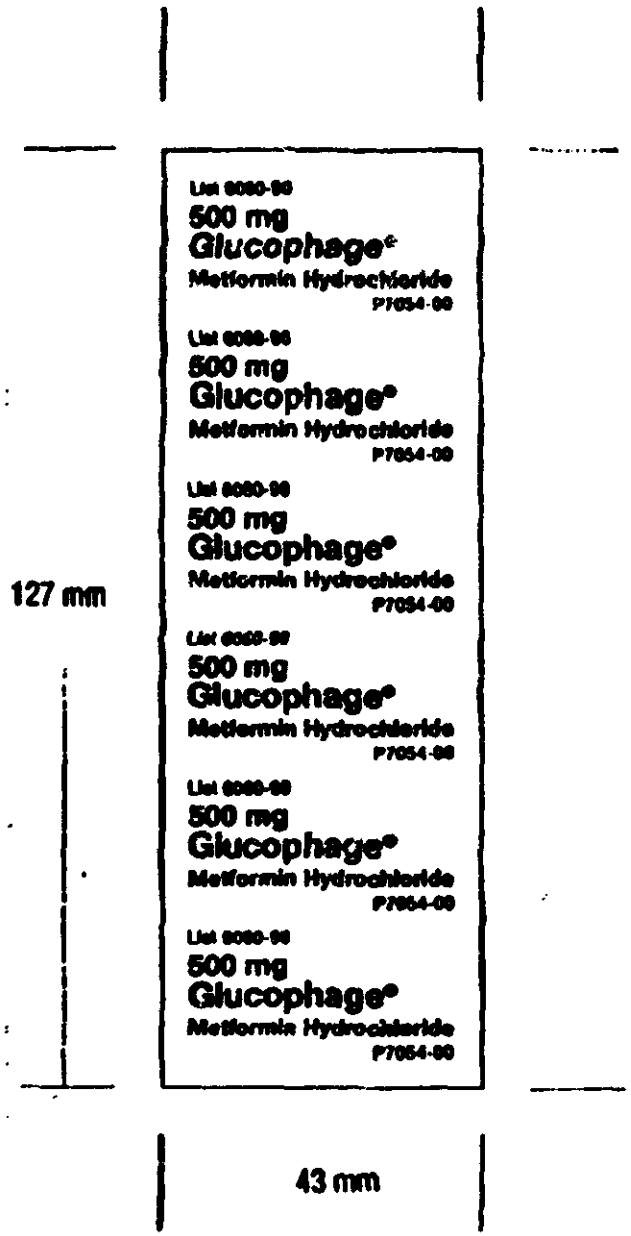
Manufactured by
Lipha Pharmaceuticals Ltd. Hitchin, UK

GLUCOPHAGE
(METFORMIN HYDROCHLORIDE) 500 mg TABLETS

BLACK ON FOIL

6060-90
P7054-00
9-29-94

DRAFT



Original Submission
9/29/93
Vol. 4

ITEM 4 — SAMPLES, METHODS VALIDATION AND LABELING

4.3 LABELING

4.3.1 Labels

GLUCOPHAGE® LABEL 500 mg X 100 TABLETS

LEFT	CENTER	RIGHT
See package insert for dosage information. Dispense in light resistant container. Store between 15-30°C (59 - 86°F).	NDC XXXX-XXXX-XX 100 Tablets GLUCOPHAGE® TABLETS Metformin Hydrochloride 500 mg Manufactured for: LIPHA PHARMACEUTICALS, INC. NEW YORK, NY 10019-2701	UPC CODE HERE XXXX-XXXX-XX CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. LOT #XXX EXP. XX/XX/XX

GLUCOPHAGE® LABEL 500 mg X 500 TABLETS

LEFT	CENTER	RIGHT
See package insert for dosage information. Dispense in light resistant container. Store between 15-30°C (59 - 86°F).	NDC XXXX-XXXX-XX 500 Tablets GLUCOPHAGE® TABLETS Metformin Hydrochloride 500 mg Manufactured for: LIPHA PHARMACEUTICALS, INC. NEW YORK, NY 10019-2701	UPC CODE HERE XXXX-XXXX-XX CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. LOT #XXX EXP. XX/XX/XX

4.3.1 Labels (Continued)

GLUCOPHAGE® LABEL 850 mg X 100 TABLETS

LEFT	CENTER	RIGHT
See package insert for dosage information. Dispense in light resistant container. Store between 15-30°C (59 - 86°F).	NDC XXXX-XXXX-XX 100 Tablets GLUCOPHAGE® TABLETS Metformin Hydrochloride 850 mg Manufactured for: LIPHA PHARMACEUTICALS, INC. NEW YORK, NY 10019-2701	UPC CODE HERE XXXX-XXXX-XX CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. LOT #XXX EXP. XX/XX/XX

GLUCOPHAGE® LABEL 850 mg X 300 TABLETS

LEFT	CENTER	RIGHT
See package insert for dosage information. Dispense in light resistant container. Store between 15-30°C (59 - 86°F).	NDC XXXX-XXXX-XX 300 Tablets GLUCOPHAGE® TABLETS Metformin Hydrochloride 850 mg Manufactured for: LIPHA PHARMACEUTICALS, INC. NEW YORK, NY 10019-2701	UPC CODE HERE XXXX-XXXX-XX CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. LOT #XXX EXP. XX/XX/XX

PATENT INFORMATION

METFORMIN HYDROCHLORIDE **LIPHA PHARMACEUTICALS, INC,**

ITEM 13 – PATENT INFORMATION

To the best of Lipha Pharmaceuticals, Inc.'s knowledge, there exists no currently effective patent which claims metformin, or which claims a method of using metformin, with respect to which a claim of patent infringement could reasonably be asserted against any person engaged in the manufacture, use, or sale of the drug.

Gerard E. Daniel, M.D.
Chairman, President &
Chief Executive Officer

Date 9/27/93

EXCLUSIVITY SUMMARY

EXCLUSIVITY SUMMARY FOR NDA # 20-357 SUPPL # ____

Trade Name Glucophage Generic Name metformin HCl

Applicant Name Lipha Pharmaceuticals HFD # 510

Approval Date If Known ____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) ____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

____

____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

____

____

Form OGD-011347 Revised 7-90

cc: Original NDA Division File HFD-85 Mary Ann Ward Holovac

HFD-600 HFD-510/JShort

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years (in cover letter)

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product. N/A

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

John C Short
Signature
Title: Consumer Safety Officer

11/17/94
Date

Signature of Office/
Division Director

12-1-94
Date

cc: Original NDA Division File HFD-85 Mary Ann Ward

MEDICAL REVIEW

Shortc

Group Leader's Note DEC 16 1994

NDA 20-357:

Metformin to Lower Blood Glucose in Type 2 Diabetes Mellitus

Date: 11/25/94

Sponsor: Lipha Pharmaceutical Co.

Summary

1. The use of sulfonylurea and biguanide therapy for type 2 diabetes mellitus remains controversial but justified in some patients.
2. Metformin appears to be at least as effective and probably no less safe than sulfonylurea agents.
3. Metformin is significantly different from phenformin in its potential to cause lactic acidosis
4. Metformin's effect on cardiovascular mortality is potentially a much more important concern than lactic acidosis.
5. The controlled studies have a possibly statistically significant excess of deaths associated with metformin therapy.
6. There is no other convincing evidence linking metformin therapy to cardiovascular disease.

RECOMMENDED REGULATORY ACTION: APPROVAL

Introduction

This NDA has been the subject of a very extensive, perhaps unprecedented, primary medical officer review. Because of the large amount of controlled study and post-marketing data as well as the experience with the related agent, phenformin, three reviewers were assigned to this NDA. All have worked more or less independently and have reached different opinions. Dr. Cueriguian has performed a review focusing on efficacy but has also included a safety review and overall risk-benefit assessment. Dr. Innerfield has performed primarily a safety review but has also looked at some efficacy issues. Dr. Stadel, a highly qualified epidemiologist, has specialized in certain aspects of safety such as the mortality outcome in the

controlled trials and assessment of post-marketing experience. He has also defined the parameters by which a post-marketing study would be designed to address remaining safety issues. The sponsor has complied with our preliminary request by submitting a fully acceptable study proposal. This NDA was also presented to the E&M Advisory Committee within 6 months of its submission. While the primary reviews were completed by that time, addenda to these reviews have followed. It would be fair to say that we have held an on-going debate about the interpretation of the data as well as our methodology used to analyze the data. In the end, this exceptional review approach has been ideally suited to identifying and judging all the problems associated with this therapy and the related public policy considerations. I would go so far as to say that our metformin review serves as a case study of the difficulties involved in reconciling individual scientific judgements and regulatory philosophies as well as the challenge the Agency continually faces in walking the fine line between assessment of therapies and directing the practice of medicine.

It will not be necessary for me to cover the drug's undisputed efficacy in improving glycemic control. I would like to examine the remaining issues as responses to the following questions:

1. What is the justification for sulfonylurea (SU) and biguanide therapies in type 2 diabetics?

This question has to be asked because Dr. Innerfield has questioned the whole premise of oral SU or biguanide therapy. A consideration of the SU agents also provides a frame of reference. If the risk/benefit relationship for SU therapy is deemed marginally acceptable, then metformins's risk/benefit relationship should be at least equal of better in order for approval to be recommended.

The UGDP study results do continue to haunt any serious consideration of oral anti-diabetic therapy. A roughly 2.5 times excess over the untreated control groups in cardiovascular mortality was found in patients treated with either a SU (tolbutamide) or biguanide (phenformin). The study was extensively criticized but, nonetheless, used as a basis for a warning contained to this day in the labeling of all SU drug products and in the labeling of phenformin until it was withdrawn. Despite the UGDP taint, it has been a reasonable regulatory policy to allow the SU agents to stay on the market with that strong warning. In my opinion, SU therapy has provided benefits that patients wanted and probably in most cases would be willing to pay for with the incremental mortality risk suggested by the UGDP study.

It must be admitted, however, that the label warning has probably not adequately inhibited the inappropriate use of these agents. The over-use of these drugs deserves a measured series of responses from the Agency. It would not at all be surprising if SU therapy does add to cardiovascular mortality of diabetics. SU agents work simply by causing insulin release. While untreated type 2 diabetics are insulinopenic relative to their degree of hyperglycemia, they have absolute hyperinsulinism. SU therapy further worsens this excessive insulin exposure. Hyperinsulinism is now viewed as an important independent risk factor for cardiovascular disease. The increment of drug-induced hyperinsulinism that occurred in the UGDP study, itself, could probably account for much of the excess mortality.

Probably too many diabetics are on SU therapy. We also now have evidence that patients are probably taking excessive dosages of these drugs as Dr. Gueriguian recently discovered in a review of an NDA for

a reformulated glyburide product. He found that the maximum recommended conventional dose is between two and three times the dose of this new formulation which causes maximum therapeutic response. This discovery was made possible because he had asked that a dose response study be performed. Previous SU approvals were based on NDAs that typically did not provide dose response information. We suspect that other SU products are also being used at doses in excess of those required to produce maximum response. We should therefore not be satisfied with the anti-diabetic oral therapy *status quo* but instead have a planned regulatory approach to be described below.

The SUs clearly have a mechanism of action which leads to a result strongly linked to atherosclerogenesis, but that does not absolve the biguanides from concerns about their contributing to cardiovascular mortality. Biguanides impair mitochondrial oxidative metabolism. It is this effect which when exaggerated leads to lactic acidosis. It is quite possible that even a small amount of mitochondrial dysfunction in already under perfused coronary tissue could tip the critical balance leading to pump dysfunction, ischemia, arrhythmias, and/or infarction. The lack of direct evidence for such effects is not reassuring since no studies have been adequately designed to look at this problem.

For the time being, we should assume that SUs and biguandies are in the same boat in terms of the overall concern about their effects of the total or cardiovascular mortality.
The above question then applies equally to both classes. In order for metformin to be approved, it would be necessary but not sufficient in itself to justify the use of SUs. The strongest case that can be made for SU therapy in general is that improved glycemic control has short and probably long-term benefits in diabetics, and many type 2 patients are unable or unwilling to use diet alone or insulin therapy to control their condition. There is probably a defined subgroup of type 2 diabetics that most experts would agree are appropriately treated with oral therapy. There is probably a larger group of diabetics who could adequately control their hyperglycemia with diet but are unwilling or have not received enough encouragement from their physicians to do so. Those patients who have "failed" diet and SU therapy and gone onto insulin therapy are at very high risk of developing complications. The fact that the second category far exceeds the size of the first category does not mean that the SUs should not be available for those who need it. It does highlight the need to alter the practice of physicians and the behavior of patients with respect to the second category.

Fortunately we will have some data that may allow the *status quo* to be changed. A well-designed and adequately powered study to compare mortality of metformin, SU, and diet therapy is underway in the UK. What if results confirm the same 2.5X excess mortality seen in the UGDP study for one or both of these agents? I would be convinced that the first patient category is even smaller than we thought and that the patients in the second category are paying too high a cost to allow these agents to stay on the market. It is now hard to specify the excess mortality threshold that, if exceeded, would lead to withdrawal recommendation. We will hope that it will not be necessary to cross that bridge. In the meantime, with no more information than available now, I do not believe we can make a stand against metformin alone as a kind of chastened re-visiting of the UGDP data.

2. Is metformin different from phenformin?

Without reviewing all the details, there are abundant biochemical, cellular, animal, and clinical data bearing on this question. I believe that taken together, they very convincingly show that metformin is much less likely to cause lactic acidosis than phenformin with doses resulting in comparable clinical effect. I do not think we should emphasize this fact except when asked to justify approval should that be our decision. Generally, we should take advantage of the healthy concern derived from the association of metformin with a de-marketed drug in order to promote caution by patients and physicians who use metformin.

3. What are the safety issues in this NDA?

Metformin presents but two significant concerns, lactic acidosis and cardiovascular mortality. Abdominal symptoms suggest a lesser, more theoretical concern.

Abdominal effects

Metformin does cause some degree of abdominal pain or discomfort in most patients during the titration phase of therapy. In fact, the proposed titration scheme is designed as much to minimize this adverse reaction as to individualize dosage on the basis of glycemic response. We might assume that this problem is more of a trivial and passing inconvenience. However, the mechanism for this effect is unclear. It is conceivable that drug-induced alterations in mitochondrial function could ultimately lead to increased oxygen demand across the splanchnic bed. Pain might therefore be due to ischemia or tissue level oxygen lack. Even though the symptoms of this effect resolve over a few weeks, it is possible as Dr. Innerfield suggests that patients, particularly with pre-existing mesenteric arterial insufficiency, would continue to be at higher risk of bowel infarction while on therapy.

While we should continue to be alert for serious abdominal events associated with therapy, I think it is highly unlikely that this pain results from an oxygen pryvic state. First, mucosal cell metabolism is highly anaerobic to begin with. Interestingly, the primary substrate in this tissue is glutamine, though after deamination it is metabolized through the glycolytic pathway simply as glucose. Subsequent metabolism of pyruvate/lactate through the TCA cycle and oxidative phosphorylation in the mitochondria are very limited. Certainly, metformin could increase in humans, and has increased in animals, lactate in the mesenteric/portal drainage. Pain could result from accumulation of lactate in the mesenteric tissue just as it causes muscle cramps during anaerobic exercise. Lactate accumulation, however, results in increased microcirculation blood flow. This would oppose ischemia unless there was "steal" from an under-perfused region to one that is better perfused.

A second reason for reassurance on this point is that there is no evidence for increased major bowel events in controlled and post-marketing experience. Admittedly, we could have missed fairly significant increments in these problems above already increased background rates compared with the normal population. There is a separate but additional consequence of metformin's association with abdominal pain,

Occasionally a patient's symptoms due to a serious, but non-drug related, process will be falsely attributed to the drug and thereby delay treatment. This hazard is sufficiently addressed in the product labeling.

Lactic Acidosis

Lactic acidosis presents more of a problem for public relations than for a favorable risk/benefit finding. While this rare complication of metformin therapy deserves attention and requires cautious use of the drug, it should be viewed within the therapeutic context for patients with a life-threatening disease.
Assuming a worse case scenario of about 10^6 patients on the drug in the US with a reporting rate of .06 per 1,000 patient-years, there would be 60 cases of lactic acidosis and as many as 30 fatalities due to lactic acidosis per year in the US. The rate is about .03 per 1,000 p-y in France where metformin has been widely used for many years with minimal emphasis on the acidosis issue. In Canada, no metformin-associated lactic acidosis deaths have yet been reported. It is therefore hoped that with a concerted educational campaign there will be far fewer occurrences of lactic acidosis projected in the above worst case scenario.

A safety profile comparison of metformin and the SU agents puts the lactic acidosis issue into proper perspective. While SUs do not cause lactic acidosis, they have caused fatalities from hepatitis, exfoliative dermatitis, aplastic anemia, pancreatitis, and SIADH. By far, their most common adverse reaction and cause of death is hypoglycemia. The biguanides themselves do not cause hypoglycemia. In country-wide epidemiologic surveys from Europe and Canada, deaths attributed to SUs have consistently and substantially exceeded on a normalized basis total or lactic acidosis associated deaths caused by metformin treatment. Unlike the SUs, metformin has not been linked with any other fatal complication besides lactic acidosis. This is an advantage for metformin in the sense that it does not cause fatal reactions which are spread out among multiple organ systems. On the other hand, metformin causes a single, distinctive problem that is easily identified and likely to be reported. Overall, the safety profile of metformin, at least with respect to non-cardiovascular fatal reactions, appears to be better than that of the SUs.

There is no doubt that metformin has and will continue to cause lactic acidosis. The occasional metformin-induced lactic acidosis death will repetitively stimulate second guessing about this NDA approval should that be our decision. While the decision to withdraw phenformin because of the lactic acidosis problem was fully justified, it does not necessarily follow that a related drug which causes lactic acidosis, albeit at a much smaller rate, should not be approved. Diabetes mellitus is a disease that causes much misery and premature death. Metformin therapy provides benefits to these patients which justify the slight risk of developing lactic acidosis.

Effects on total mortality

For me as a practicing physician, lactic acidosis presents far less safety concern than does the question about metformin's effect on total or cardiovascular mortality. We again must look back at the UGDP results. If the magnitude of excess deaths is confirmed for metformin therapy itself, it would far outweigh a concern

about lactic acidosis. It would overwhelm the benefits attributable to improved glycemic control. It would present a safety profile acceptable only for a very small minority of the general type 2 population. Dr. Innerfield has correctly pointed out an excess of deaths from the pivotal NDA studies in patients receiving metformin therapy compared with those who received placebo or glyburide. Clearly this substantiates concern about the ultimate risk of metformin therapy. However, I believe that Dr. Innerfield has presented, indeed advocated, this crucial finding in a way that overstates the case. Dr. Stadel put this issue into an appropriate perspective in his 5/19/94 review. For my own understanding, I have summarized the deaths which occurred in these studies below. Dr. Edward Nevius has provided, at my request, probability values as calculated by Fisher's Exact Test for one-sided comparisons. Without commenting on Dr. Innerfield's statistical methodology which is unspecified, I understand from Dr. Nevius that the above method is appropriate. Furthermore, I will not question whether it is reasonable to attribute deaths which occurred in the extension periods to drug exposure during the controlled periods. This extremely conservative approach is simply accepted at face value.

US Study No. 87-1D-6023

A 29 week, placebo controlled trial of metformin in patients with relatively mild diabetes, i.e., those who had failed dietary therapy alone.

	metformin	placebo
randomized	143	146
completed	112	105
deaths		
control	0	0
extension	0	0
continued to 1C	85 (76%)	75 (71%)

US Study 87-2D-6023

A 29 week double-blinded comparison of metformin, glyburide, and metformin+glyburide in more severely affected type 2 patients, i.e., those who had failed to improve on maximum dose glyburide therapy.

	metformin	glyburide	met+gly
randomized	210	209	213
completed	157	174	192
deaths			
blinded	1	0	0
extention	2	0	4
contributed to 1C	132 (63%)	142 (67%)	168 (79%)

metformin vs. glyburide	*p=.23*
met+gly vs. glyburide	*p=.085*
met+[met+gly] vs. glyburide	*p=.096*

Thus, no deaths were seen in the 1D study of patients with milder diabetes, and all the deaths observed in these controlled studies came from the 2D study of more severely affected patients. Of the 7 deaths, 6 can be presumed to be cardiovascular related. One death which occurred during the open label extension (study 1C) was due to suicide. Dr. Stadel pointed out that a statistically significant greater 79% of patients who had been on the met+gly combined therapy continued in the extension study compared with that of glyburide's 67% and metformin's 63%. This, in part, could account for the imbalance of deaths observed across the three treatment groups during the extension period.

There certainly are more deaths among those who received therapy that included metformin compared with those who did not receive metformin. However, there are no statistically significant differences in outcomes among treatment groups within the 2D study and its 1C extension. If deaths from both blinded studies and their extensions are pooled according to the following comparison:

$[Metformin_{1D}+Metformin_{2D}+Met\text{-}Gly_{2D}]$ vs. $[Placebo_{1D}+Glyburide_{2D}]$

then the comparison does reach statistical significance ($p= .033$) as Dr. Innerfield correctly points out but, I believe, overstates. The above pooling is an appropriate comparison, but it is not the whole story. Few deaths are expected from the mildly affected diabetics of the the 1D study, but deaths occurring in the 2D study are not surprising. Statistical significance is achieved only by adding patients from the study in which deaths are not expected to the denominator of patients not exposed to metformin. Lumping in the mildly affected 1D patients does not add to the numerator of either the metformin or non-metformin treated proportions. Increasing the denominator of those not exposed to metformin has the mathematical effect of producing a statistically significant difference even though the denominator of the metformin exposed group is also increased.

I agree with Dr. Stadel that this is a weak signal, but I am sure all involved would agree that it cannot be ignored as we systematically pursue a definitive answer to this critical question. What is our proposed plan to resolve this question? In the UK, a well-designed study is underway which in some ways is a re-running of the UGDP study. This study will be very informative on long-term outcomes including total/cardiovacular mortality associated with metformin and sulfonylurea therapies. In addition the sponsor has agreed to perform according to our specifications a controlled, unblinded study of metformin therapy compared with standard therapy over a 6 month period. Though this study is primarily designed to define the incidence of lactic acidosis, it is more than adequately powered to detect differences in other major outcomes such as death and hospitalizations. The six month observation period is too short to allow consequences of slowly progressive processes such as coronary atherosclerosis to be detected. However, metformin's possible effect on cardiac events is most likely to result from metabolic changes which confer risk immediately and non-cumulatively. The six month duration is certainly sufficient to follow up on the issue of excess treatment associated deaths in the pivotal studies.

The only problem I have continued to struggle with is whether the approved drug product labeling should include information about the excess deaths in the controlled studies. This is an issue which can not be adequately explained in a few words. On the other hand, a simple understanding that more deaths were seen in metformin treated patients could only improve the caution with which the drug is used. I could argue either position.

4. What other evidence supports the hypothesis of metformin's untoward effect on the cardivascular system?

Dr. Innerfield has pursued the observation of excess, presumably cardiovascular deaths in the controlled studies with a careful look at other relevant cardiac-related outcomes. I feel that it is necessary to go into extensive detail in evaluating his findings and conclusions since they have not previously been addressed. I have asked the sponsor to prepare data summaries which I have reproduced below.

A. ELECTROCARDIOGRAM CHANGES

Dr. Innerfield discovered that there is a statistically significant difference between metformin and non-metformin treatment groups in the number of patients who showed EKG changes at the end of the controlled studies compared with baseline EKG.
Further analysis of this observation was complicated by the fact that the interpretation of "*normal*" or "*abnormal*" (and significance of the latter), with regard to 12-lead electrocardiograms on participants in the two U.S. pivotal double-blind studies, was entirely left to each individual investigational site; and there was no provision made for central electrocardiographic reading.

The NDA originally contained a summary of frequency, by treatment group, of patients with ECG's showing "significant" change from baseline for the 1D and 2D studies. "Significant change" included not only ECGs which were considered to be "*normal*" at baseline and "*abnormal*" at final visit but also those which were interpreted as being "*abnormal*" at baseline and "*normal*" at final visit. This table therefore provided the most conservative summary of "significant change" on EKG from baseline to final visit. Clearly, further interpretation is necessary to determine the clinical significance of this preliminary result.

The following tables, even with this conservative interpretation of "significant change" from baseline, show that, in contrast to Dr. Innerfield's statements, in neither study is there a statistically significant difference between treatment groups, based on Fisher's Exact test:

U.S. Study No. 87-1D-6023

	Significant ECG Change at Final Visit		
	Yes	**No**	**Total**
Metformin	19 (15%)	110 (85%)	129
Control	9 (7%)	117 (93%)	126

Fisher's exact test p-value = 0.071

U.S. Study No. 87-2D-6023

	Significant ECG Change at Final Visit		
	Yes	**No**	**Total**
Metformin	38 (10%)	349 (90%)	387

Control	13 (7%)	175 (93%)	188

Fisher's exact test p-value = 0.277

The sponsor provided in the original NDA submission an individual patient listing based on ECG interpretation at each investigational site of all patients with an "abnormal" ECG at final visit. This listing therefore does not include those patients whose "significant change" had been from "*abnormal*" at baseline to "*normal*" at final visit. NDA table 20.0 for each of these studies does include patients whose ECGs changed from "*abnormal*" at baseline to "*normal*" at final visit. In the 1D study, 4 metformin-exposed patients had ECGs which were "*abnormal*" at baseline but "*normal*" at final visit. In the 2S study, 7 metformin-exposed patients and 1 glyburide-exposed patient had ECGs changing from "*abnormal*" at baseline to "*normal*" at final visit. It appears that Dr. Innerfield did not understand or take into account this presentation of the EKG data.

The following tables summarize those patients with significantly changed ECGs over the course of the study which were abnormal at final visit. None of these treatment group differences is statistically significant:

U.S. Study No. 87-1D-6023

	Significantly Abnormal ECG at Final Visit		
	Yes	**No**	**Total**
Metformin	15 (12%)	114 (88%)	129
Control	9 (7%)	117 (93%)	126

Fisher's exact test p-value = 0.284

U.S. Study No. 87-2D-6023

	Significantly Abnormal ECG at Final Visit		
	Yes	**No**	**Total**
Metformin	31 (8%)	356 (92%)	387
Control	12 (6%)	176 (94%)	188

Fisher's exact test p-value = 0.612

In his review of 5/20/94, Dr. Innerfield has pooled all metformin-exposed patients with "significant change" from baseline in their ECGs. This yields 57 metformin-exposed patients and 22 unexposed patients. He calculated the percentages of patients with such changes based on the "n" of all randomized patients, rather than the "n" of patients with both baseline and final visit ECGs. Based on the total "n" and this most conservative interpretation of change, he determined that 10.1% of patients exposed to metformin had significantly changed ECGs (57 of 566), compared to 6.2% of unexposed patients (22 of 355). He then concluded that the metformin-exposed group had an "excess risk" for EKG changes of 3.9%.

If the appropriate "n" consists of only patients with both baseline and final visit ECGs, these percentages for this conservative assessment become 11.0% for patients exposed to metformin (57 of 516) and 7% for unexposed patients (22 of 314). In the following tables, the results of such pooling, based on the described "n"s, are summarized:

U.S. Pooled Studies (All Patients Randomized)

	Significant ECG Change at Final Visit		
	Yes	**No**	**Total**
Metformin	57 (10%)	509 (90%)	566
Control	22 (6%)	333 (94%)	355

Fisher's exact test p-value = 0.052

U.S. Pooled Studies (Patients with Final Visit ECG)

	Significant ECG Change at Final Visit		
	Yes	**No**	**Total**
Metformin	57 (11%)	459 (89%)	516
Control	22 (7%)	292 (93%)	314

Fisher's exact test p-value = 0.067

Thus, based on the pooling of data on all "significantly changed" ECGs, which includes changes from "*abnormal*" to "*normal*", and using an "n" comprised of all randomized patients, there is borderline statistical significance for metformin-exposed patients. When the "n" used consists of all patients with both a baseline and a final visit ECG, the p value is not significant at the <0.05 level.

If the tables are reconstructed, pooling only patients with significantly changed and abnormal ECGs at final visit, there are no statistical differences between metformin-exposed and control groups, as shown:

U.S. Pooled Studies (All Patients Randomized)

	Significantly Abnormal ECG at Final Visit		
	Yes	**No**	**Total**
Metformin	46 (8%)	520 (92%)	566
Control	21 (6%)	333 (94%)	355

Fisher's exact test p-value = 0.241

U.S. Pooled Studies (Patients with Final Visit ECG)

	Significantly Abnormal ECG at Final Visit		
	Yes	**No**	**Total**
Metformin	46 (9%)	470 (91%)	516
Control	21 (7%)	293 (93%)	314

Fisher's exact test p-value = 0.294

The sponsor, in an attempt to satisfy Dr. Innerfield's interest in a blinded re-interpretation of the ECGs, did have all the ECG's re-evaluated by a well-qualified cardiologist and electrocardiographer under conditions of blinding as to treatment group. Dr. Innerfield was not satisfied that the re-evaluation was limited to only the ECGs which were reported as changed (in one direction or the other) during the course of the trial. He felt that this amounted to a "flirtation with dishonesty" since the sponsor favored itself by not including all ECGs in the re-analysis. I would agree to some extent with Dr. Innerfield that the ideal, most conservative approach would have been to throw all the dice again. However, I do not think that the company's approach is unreasonable all things considered. Furthermore, I do believe that to nearly call this dishonesty reveals an unwarranted antagonism to a company which has attempted mightily to be responsive to our requests.

According to the cardiologist's review, the electrocardiograms, as originally reported by the investigational sites, had been significantly "over-read". Many tracings considered "*abnormal*" by the sites were, in fact,

"*normal*", according to the blinded reviewer. Given the high degree of "over-reading", it seems unlikely, as suggested by Dr. Innerfield, that the sponsor willfully selected ECGs and held back others since the ECGs submitted for reinterpretation were considered to be the "*abnormal*" ones. Dr. Innerfield also suggested that the sponsor had sought this re-evaluation because of "dissatisfaction with primary results". I believe that the sponsor was appropriately responding to concerns which had been raised by Dr. Innerfield himself at the advisory committee hearing. .

Dr. Innerfield goes back to his own re-analysis of the original Appendix 7. Not satisfied with the resubmitted Appendix 7 based on the independent expert's report, he creates new categories of ECG abnormalities. He then finds an excess risk for metformin-exposed patients of 6.6 ± 4%. These new categories are: "normal to abnormal", "abnormal to normal", and "abnormal to abnormal but with a significant change".

If the data from the original Appendix 7 are consistently approached in this fashion, the following comparisons result:

U.S. Study No. 87-1D-6023

	ECGs Changes at Final Visit (Normal to Abn., Abn. to Normal, Abn. to Abn. but with Signif. Change)		
	Yes	**No**	**Total**
Metformin	26 (18%)	117 (82%)	143
Control	14 (10%)	132 (90%)	146

Fisher's exact test p-value = 0.041*

U.S. Study No. 87-2D-6023

	ECGs Changes at Final Visit (Normal to Abn., Abn to Normal, Abn. to Abn. but with Signif. Change)		
	Yes	**No**	**Total**
Metformin	52 (12%)	371 (88%)	423
Control	25 (12%)	184 (88%)	209

Fisher's exact test p-value = 1.000

Dr. Innerfield notes that "pooling glyburide patients in with this analysis seems to help to obscure these differences". By this I believe he means that, because the 2D study shows no difference in ECG changes between treatment groups, pooling this with the 1D study where there happens to be borderline statisitical significance should be avoided because it undermines his hypothesis. How can he expect to have it both ways depending on how it supports his contention? He has no problem pooling deaths across studies in order to achieve statistical significance. He also fails to acknowledge in his analyses the inclusion of abnormal ECGs gone normal as a significant ECG change at final visit. This category is obviously of dubious clinical significance.

Using this scheme, the pooled analysis, with p-values, is as follows:

U.S. Pooled Studies (All Patients Randomized)

	ECG Changes at Final Visit (Normal to Abn., Abn. to Normal, Abn. to Abn. but with Signif. Change)		
	Yes	No	Total
Metformin	78 (14%)	488 (86%)	566
Control	39 (11%)	316 (88%)	355

Fisher's exact test p-value = 0.224

U.S. Pooled Studies (Patients with Final Visit ECG)

	ECG Changes at Final Visit (Normal to Abn., Abn. to Normal, Abn. to Abn. but with Signif. Change)		
	Yes	**No**	**Total**
Metformin	78 (15%)	438 (85%)	516
Control	39 (12%)	275 (87%)	314

Fisher's exact test p-value = 0.305

The consulting cardiologist categorized the reviewed ECGs according to the table found on the following page. This was provided by the sponsor as a revision of the original Appendix 7 data:

		87-1D-6023			87-2D-6023		
Expert Reading of Baseline & Final Visit ECG	**TTreatment-Emergent Yes/No?**	**Met**	**Plac**		**Met**	**Gly**	**M + G**
Normal to Normal	N	7	3		14	12	13
?Abnormal to ?Abnormal	N	1	0		2	0	5
Abnormal to Normal	N	5	1		0	0	0
Abnormal to Less Abnormal	N	1	0		0	0	0
?Abnormal to Normal	N	2	3		0	0	0
Abnormal to Abnormal	N	5	2		0	6	8
Normal to Abnormal	Y	3	1		3	1	1
Normal to ?Abnormal	Y	1	0		0	1	2
?Abnormal to Abnormal	Y	1	0		0	1	2
?Abnormal to blank	Y	0	2		0	0	0
Abnormal to Abnormal Change	Y	0	1		0	0	0
Abnormal to blank	Y	0	1		1	2	0
?Abnormal to ?Significant	Y	0	0		1	0	0
Normal to blank	Y	0	0		1	0	0
Abnormal to ?Abnormal	Y	0	0		0	1	0
Abnormal to Essentially Unchanged	Y	0	0		0	1	0
Abnormal to Increased Abnormality	Y	0	0		0	0	1

The sponsor states that if the types of change are limited to "normal to abnormal", "?abnormal to abnormal", "abnormal to increased abnormality" and "abnormal to ?abnormal", the following comparisons result, based on the pooled studies:

U.S. Pooled Studies (All Patients Randomized)

	Significant ECG Changes at Final Visit Based on Expert Review		
	Yes	**No**	**Total**
Metformin	11 (2%)	555 (98%)	566
Control	5 (1%)	350 (99%)	355

Fisher's exact test p-value = 0.614

If the 1D and 2D studies are pooled, based on the blinded re-analysis contained in revised Appendix 7, and confined to treatment-emergent changes, as noted above, the following comparisons result:

U.S. Pooled Studies (All Patients Randomized)

	Treatment-Emergent ECG Changes at Final Visit Based on Expert Review		
	Yes	**No**	**Total**
Metformin	17 (3%)	549 (97%)	566
Control	12 (3%)	343 (97%)	355

Fisher's exact test p-value = 0.847

Summary of the ECG Issue

The only statistically significant difference between treatment groups is found in the 1D study. Significance results only by including ECGs which were "*abnormal*" at baseline and reverted to "*normal*" at the final visit. On the other hand, the 2D study, even using this approach, demonstrated absolutely no difference. By any other reasonable analysis, the quest for treatment-associated ECG changes comes up empty.

B. CORONARY ARTERY DISEASE

In attempting to build a case for metformin's negative cardiovasular effects, Dr. Innerfield then turns to looking at events attributable to coronary artery disease. Curiously, he begins with a criticism of the sponsor's assessment of terms referable to "coronary artery disease". Dr. Innerfield implies that looking at "treatment emergent" events is inappropriate. It seems to me that in the assessment of adverse events, a treatment emergent approach is most appropriate. His criticism is unwarranted. In fact, it can be seen that a number of the cardiovascular adverse events were not treatment emergent, particularly from the non-U.S. controlled studies.

In the 1D study, there were more patients in the metformin group with "coronary artery disease" events than in the placebo group (5 events per 143 patients vs. 1 event per 146 patients). In the 2D study on the other hand, there were 3 events per 423 patients exposed to metformin and 6 events per 209 patients exposed to glyburide. Using the pooled analysis across all controlled studies, there are no statistically significant differences between occurrence of coronary artery disease in metformin-exposed patients versus controls, as shown in the following table:

All Studies Pooled

	Patients with Adverse Event Terms Referable to "Coronary Artery Disease"		
	Yes	No	Total
Metformin	14 (2%)	798 (98%)	812
Control	11 (2%)	513 (98%)	524

Fisher's exact test p-value = 0.681

Contrary to Dr. Innerfield's contention, there is no evidence from these data of an excess of coronary artery disease-related events in metformin-exposed patients compared with controls.

C. ARRHYTHMIAS

In looking at the issue of metformin-associated arrhythmias, Dr. Innerfield again seems to question the appropriateness of using a treatment-emergent approach. It turns out that for this particular listing many, if not most, of the patients in both the non-U.S. as well as the U.S. controlled studies had antecedent comparable problems or Baseline ECG evidence of PVCs. In the 1D study, 4 of the 5 metformin-exposed

patients fell into this category, and the remaining patient had a single episode of mild palpitations. In the 2D study, of the 2 metformin-exposed patients with "arrhythmia", one was attributed to excess thyroid hormone replacement while the other occurred in a patient with a prior history of "arrhythmia". Of 2 metformin-exposed patients with "tachycardia", one had a history of rheumatic heart disease and atrial arrhythmias while the other had a spontaneously resolved intermittent rapid heart rate. All other terms reported were essentially "palpitations"; and, for a number of patients, these palpitations had been present prior to study entry. In the non-U.S. controlled studies, the only case of tachycardia occurred in a patient who had a history of atrial disease and pacemaker implantation. All other terms were "palpitations"; and, in the study with the most reports of this kind, this was frequently part of a symptom complex considered to be due to hypoglycemia.

Thus, in a more careful look at the nature of terms consistent with arrhythmias, the majority were neither treatment emergent nor well defined rhythm disturbances. In the pooled study analysis, there is no statistically significant difference between treatment groups in occurrence of adverse events possibly attributable to cardiac arrhythmias.

All Studies Pooled

	Patients with Adverse Event Terms Referable to "Arrhythmias"		
	Yes	**No**	**Total**
Metformin	25 (3%)	787 (97%)	812
Control	8 (2%)	516 (98%)	524

Fisher's exact test p-value = 0.103

C. CARDIOVASCULAR DISEASE

This category encompasses the majority of patients involved in both the previously noted terms related to "coronary artery disease" and "arrhythmias". Most of these patients therefore reappear under the listings of adverse event terms associated with cardiovascular disease. Here, too, many of these events are not truly treatment-emergent or were symptoms, like palpitations, which were not necessarily due to arrhythmias. Among the remaining patients in these listings, the majority of events are hypertension, which for most patients in all treatment groups was not treatment-emergent.

Other than these patients and patients with venous events (e.g., phlebitis), in U.S. Study No. 87-1D-6023, there were 2 patients with transient ischemic attacks (TIA) in the metformin group (one of whom was on 0 mg/day of metformin at the time) and 1 patient with a TIA in the placebo group. In the 2D study, other

than patients mentioned above, there were 2 metformin-exposed patients with TIAs (both of whom had long-standing hypertension), 1 patient who had an asymptomatic carotid bruit at final visit, 1 patient with long-standing hypertension who developed congestive heart failure and "cardiomyopathy", and 1 patient with cold feet (coded as "peripheral vascular disease").

From reviewing the listings, it is unclear how Dr. Innerfield arrived at the number of 52 events for metformin patients and 21 for control patients in the pooled listing. However, if his figures are used to calculate p-values for between group comparisons, it is seen in the following table that the p-value is not significant at a p value 0.05, in contrast to Dr. Innerfield's contention. While significance is approached, this is such a mishmash of pre-existent and treatment-emergent problems of a very wide variety that it is very difficult to come to any suspicion of a treatment effect.

All Studies Pooled

	Patients with Adverse Event Terms Referable to Cardiovascular Disease		
	Yes	**No**	**Total**
Metformin	52 (6%)	760 (94%)	812
Control	21 (4%)	503 (96%)	524

Fisher's exact test p-value = 0.065

E. CONCLUSIONS ABOUT SAFETY ISSUES RAISED BY DR. INNERFIELD

The occurence of an apparent excess of deaths in the metformin exposed compared with the non-exposed patients approaches statistical significance. The implication of this observation should be resolved as quickly as possible on the basis of robust clinical studies. On the other hand, there is no case to be made for an association of metformin therapy with treatment emergent ECG changes, cardiac events, arrhythmias, or cardiovascular disease.

Sic et Non[1]

I believe that Dr. Innerfield has made a very important contribution though it is clear that I do not agree with some of his observations and conclusions. He has conscientiously reviewed this NDA and left no stone unturned. His approach is precisely what was needed in this review of a NDA which has presented complex issues and potential for controversy. In this exceptional case, we have not achieved concensus though I believe reasonable attempts were made among reviewers to hear each others points. Generally, this has served to increase the quality of our reviews. It is also very exceptional that I have felt the need to resort to some detail in the criticism of a collegue's analysis. I feel very badly about this because I know that Dr. Innerfield is motivated by the best of intentions. I believe his experience as the physician of a patient who almost died of phenformin-induced lactic acidosis is responsible for an almost obsessional view that metformin as a close cousin should not be approved. Despite his concerted and frequently brilliant efforts, his approach has, at times, been more rhetorical than scientific.

Recommended Regulatory Action:

Approval

12/16/94

Alexander Fleming, M.D.

---

1 (Yes or No), the title of Peter Abelard's treatise written in 1091 in which he juxtaposed many of the teachings of the Church in a point-counter point fashion so as to point out their contradiction. One of his points was that there are always rhetorical augments that can be found to support a chosen position. He believed, however, that the application of logic and precise language allow truth to be achieved.

MAY 20 1994

Medical Officer Review of an NDA Amendment

NDA 20-357
Metformin

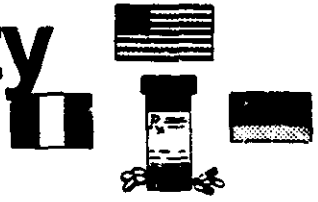
Amendment #22

Submitted: 12 May 1994
Received: 13 May 1994
Assigned: 13 May 1994
Reviewed: 18 May 1994

Metformin Comparative Safety

NDA 20-357

Randomization Group



	Controls	Metformin	p value
Cardiovascular Events	80	128	0.05
Hospitalizations	22	44	0.1
Deaths	0	6.16	0.01
Lactic Acidosis	0	1.76	ns

(expressed per 1000 PYE)

On 22 March 1994 the following [internal] memo was faxed to Lipha Pharmaceuticals, Inc.:

3/22/94 : Memo to Alexander Fleming (Group Leader)

As per request of the DMEDP advisory committee (18 Mar 1994), I would like to call Lipha to ask for the following information:-

1) All "significantly changed" EKG's from Cat i (57 met + 22 control + ?open enrollment) patients a subset of which is listed on page 08A-01592 (Vol 1.74)

2) Available follow-up on all of those patients

3) All EKG's available for patients who died in controlled trials sorted by study and by exposure (±) to metformin

4) Pooled listing sorted by study and by exposure to metformin (±) of patients who died in all controlled trials

5) Pooled listing sorted by study and by exposure to metformin (±) of all patients with any terms associated with coronary artery disease in all controlled clinical trials

6. Pooled listing sorted by study and by exposure to metformin (±) of all patients with any terms associated with arrythmias in all controlled clinical trials

7. Pooled listing sorted by study and by exposure to metformin (±) of all patients with any terms associated with cardiovascular disease in all controlled clinical trials

8. Pooled listing sorted by duration of all patients with any terms associated with cardiovascular disease, coronary disease, arrhythmias, or death in all open clinical trials or phases

The amendment received is in direct response to that telefacsimile.

"Item 1" was addressed initially by Lipha as follows:

(Points 1 & 2): All "significantly changed" ECGs from Category I trials (U.S. *controlled* clinical trials), with available follow-up information.

N.B. Significantly changed EKG's from the *open-enrollment* study were requested, and the request appears to have been ignored. In its place, the sponsor sent out all of the EKG's identified as changed, and only those, to some cardiologist for reanalysis. This analysis had conclusions which deviated from the original analysis.

The sponsor noted clinically "significant EKG changes from baseline" occurred as follows:

		Significant Change From Baseline	
Study No.	**Treatment**	**Yes**	**No**
87-1D	**Metformin**	**19 (15%)**	**110 (85%)**
	Placebo	**9 (7%)**	**117 (93%)**
87-2D	**Metformin**	**14 (8%)**	**169 (92%)**
	Glyburide	**13 (7%)**	**175 (93%)**
	Combination	**24 (12%)**	**180 (88%)**
Pooled (Sic!)	**Metformin (Monotherapy)**	**33 (11%)**	**279 (89%)**

Only "pooling" metformin monotherapy patients did not appear to make much sense, especially when true pooling based on exposure revealed 57 (10.1%) significantly changed EKG's in patients exposed to metformin as opposed to 22 (6.2%) in unexposed patients. **This amounts to an excess risk of +3.9% which has a [significant] 95% CI around it of +0.324% to +7.3%).**

These EKG's originally listed by the sponsor as "significantly changed from baseline" in Table 242 **(Vol 1.74, p. 08A-01592)** emanated from Appendices 7 of the study reports **(Volume 1.119, p. 08B-05345 and Volume 1.156, p, 08B-18582).** Of these EKG's, 78 were seen in metformin patients and 39 in controlled patients.

According to my review of the cardiologist's reanalysis, 17 of 564 (3%) metformin patients showed significant changes from baseline versus 6 of 354 (1.7%) controls. This 1.3% excess trend is not significant at the $p<0.1$ level. Nevertheless, this reanalysis is flawed by sampling only those cardiograms originally read as showing change. In short, the sponsor had "little to lose and everything to gain." Indeed, any reanalysis prompted by dissatisfaction with primary results is open to question. To then only reanalyze [the incriminating] positive results is flirtation with dishonesty.

1° EKG Change from Baseline - Pooled Data from Appendices #7

	Voltage	ST-T	Rhythm	Not clear	*87-1D*	87-2D	Totals
Metformin	6	42	27	3	*26*	52	78
Controls	2	18	17	2	*14*	25	39
diff	ns	ns	ns	ns	*p<0.05*	ns	ns

Note that in the 87-1D placebo controlled study there were 26 of 143 (18.2%) metformin patients with EKG changes versus 14 of 146 (9.6%) placebo patients for an **excess risk of 6.6 ± 4% with a 95% CI of 0.67 to 16.5%.** Note also that pooling glyburide patients in with this analysis seems to help to obscure these differences.

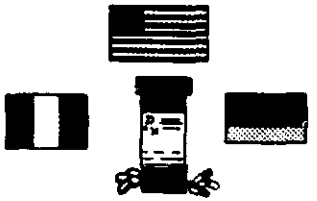
In its look at patients with any terms referable to "coronary artery disease" the sponsor chose to regard only "treatment-emergent" events. Interestingly enough, if one ignores "chest discomfort" as a non-specific symptom, then in the 87-1D study there were 5/143 (3.5%) metformin patients versus 1/146 (0.7%) placebo patients with "coronary artery disease" events for an **excess metformin risk over placebo of 2.81 ± 1.68% with a 90% CI of 0.0380 to 5.59%.** However, in the 87-2D study there were 3/423 (0.7%) metformin patients (with 1 death) versus 6/209 (2.87%) glyburide monotherapy patients with "coronary artery disease" events for an **excess glyburide monotherapy "coronary artery disease" event risk over pooled-metformin therapy of 2.16 ± 1.23% with a 90% CI of 0.14 to 4.18%**. Pooling across all studies shows 14/812 (1.7%) metformin patients versus 11/524 (2.1%) placebo patients with "coronary artery disease" events for an excess control risk over metformin of 0.38 ± 0.78% (ns).

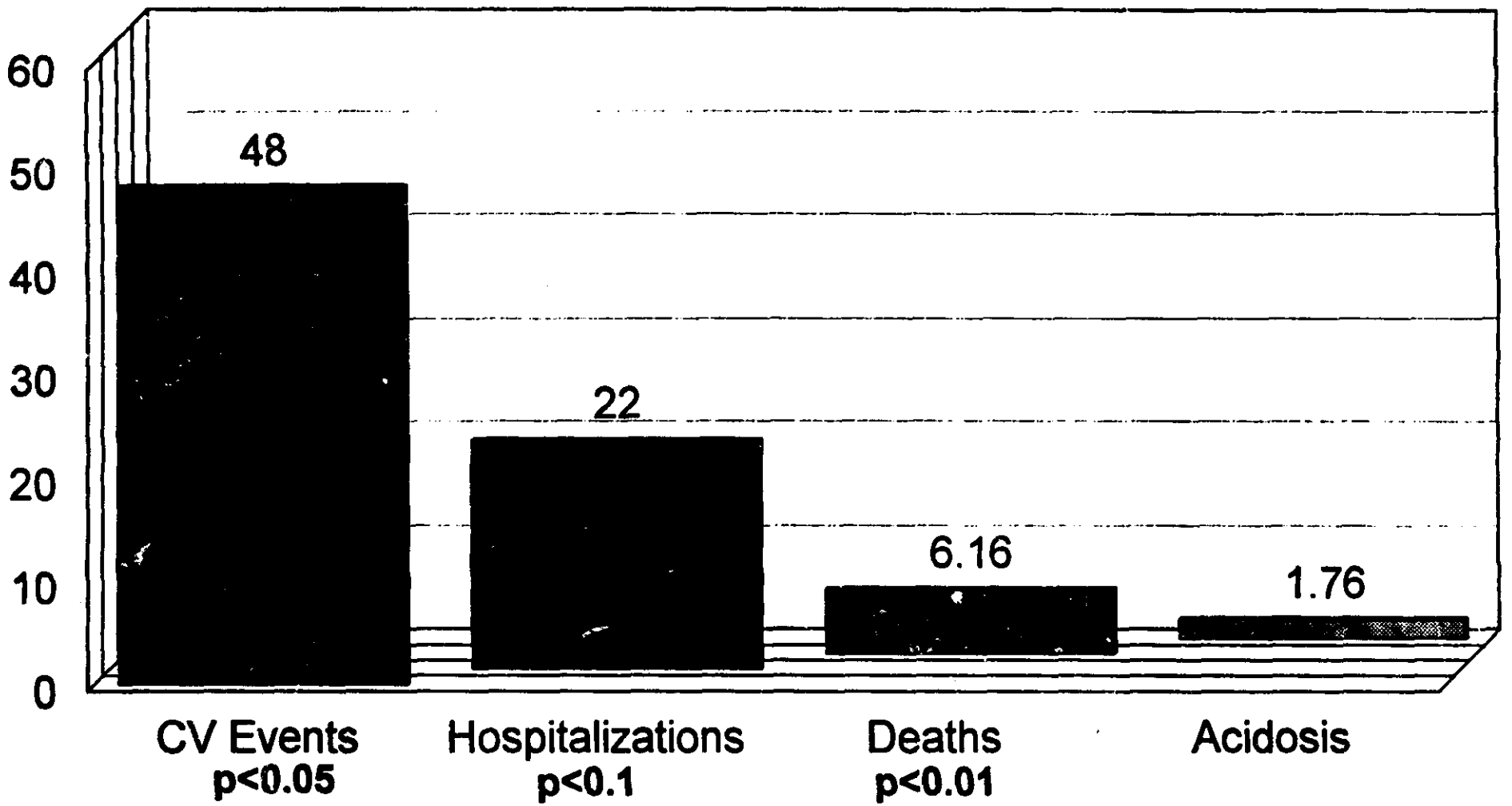
In its look at patients with any terms referable to "arrhythmias" the sponsor also chose to regard only "treatment-emergent" events. There were 25/812 (3.1%) metformin patients versus 8/524 (1.5%) control patients with "arrhythmia" events for an **excess metformin risk over control of 1.55 ± 0.81% with a 90% CI of 0.217 to 2.89%.**

In its look at patients with any terms referable to "cardiovascular disease" as well the sponsor chose to regard only "treatment-emergent" events. Interestingly enough, if one ignores "hypertension" or venous-side abnormalities, there were 52/812 (6.4%) metformin patients versus 21/524 (4.0%) control patients with "cardiovascular-arterial" events for an **excess metformin risk over control of 2.4 ± 1.21% with a 95% CI of 0.0181 to 4.77%.**

Metformin Excess /1000 PYE

Over Controls





Conclusions:

.) The sponsor's reanalysis *not only in and of itself*, but of only positive EKG's represents a significant bias and is flawed.

2) In the US trials, **EKG abnormalities** *per se* appear to be significantly **(+3.9%)** *over*-represented in metformin patients ($p<0.05$), and **(+6.6%)** *over*-represented when compared to placebo patients in particular ($p<0.1$).

3) Again in the US trials, **"ischemic-" or "coronary artery disease-" related events appear to be (+2.81%)** *over*-represented in metformin patients when compared to placebo patients ($p<0.1$) *but* **(-2.16%)** *under*-represented when compared to glyburide monotherapy ($p<0.1$).

4) Across *all* trials, **"arrhythmias"** appear to be **(+1.55%)** *over*-represented in metformin patients when compared to controls ($p<0.1$). This would appear to argue in favor of the original EKG analysis.

5) **Finally, most significantly, and across all trials, "cardiovascular (arterial)" events - a** majority of which are represented by combining #3 ("coronary artery disease") and #4 ("arrhythmias") **- are significantly (+2.4%)** ***over*-represented in metformin patients when compared to controls** ($p<0.05$).

6) Thus although metformin may exacerbate coronary artery disease, and although glyburide may exacerbate coronary artery disease even worse than metformin, what may be *an over-riding arrhythmogenic effect of metformin may serve to induce significantly more [cardiovascular] morbidity* **(48 excess cardiovascular events/ 1000 PYE across all controlled trials** [$p<0.05$]; **22 excess hospitalizations/1000 PYE in the UKPDS** [$p<0.1$]) *and highly significant [cardiovascular] mortality* **(6.16 excess metformin deaths per 1000 PYE in the US trials** [$p<0.01$]) *than controls* despite the latter group having included the more potently ischemogenic sulfonylureas.

Recommendations:

The suggestion for non-approval is but a tad further strengthened by this submission.

Ronald Jay Innerfield, M.D.,
Medical Officer
19 May 1994

Noted.
Will take issue with some of these points in my review.

5/20/94

NDA 20-357
HFD-500/Bilstad
HFD-510/Chiu/Ysern/Jordan/Hertig/Fleming/Gueriguian/Stadel/Innerfield/Short/Sobel
HFD-713/Nevius/Marticello
FD-426/Hunt

MAY 17 1994

Medical Officer Safety Review of an Original NDA Submission

NDA 20-357
Metformin

rev 2.1

Volumes Reviewed: 1.1, 1.67, 1.69, 1.70, 1.74-1.85, 1.88-1.96, 1.98-1.103, 1.108, 1.149, 1.150, 1.153, 1.169, 1.189, 1.202-204

Amendments: #2, #s4-12, #s15-17, #19

Safety Issues: Categories i and ii

$$\Rightarrow$$

TABLE of CONTENTS

Drug: *Metformin*
Sponsor: Lipha Pharmaceuticals
Document: NDA
Submission Date: Sep 29, 1993
Document Date: Sep 29, 1993
Referral Date: Oct 7, 1993
Review Dates: Oct 7, 1993 - Apr 18, 1994

1. INTRODUCTION:

NIDDM (non-insulin dependent diabetes mellitus) accounts for 90-95% of the total number of patients with diabetes mellitus[1]. It is certainly less homogeneous than IDDM (insulin-dependent diabetes mellitus) although the majority (70%) of patients who comprise NIDDM manifest obesity as some basis of their pathophysiology. The evidence for this is: (1) not only are they obese at diagnosis[2], but (2) their disease dissipates with weight loss significant to the order of 5.00 to 10.00 kg/m^2 of Body Mass Index (BMI)[3]; [4,5,6,7] and (3) it is more difficult for obese NIDDM patients to lose weight than their obese non-diabetic counterparts[8]. Nutritional status is therefore a key pathogenic component of a majority of patients with NIDDM. Nevertheless, insufficient insulin secretion to overcome hepatic [and peripheral] insulin resistance seems to be the common pathophysiologic thread weaving its way throughout disorders currently classified as NIDDM[9].

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1 Harris MI, in National Diabetes Data Group, eds. Diabetes in America: diabetes data compiled in 1984. Bethesda, .:National Institutes of Health, Chapter VI, 1985: publication no. 85-1468

2 Neverhart J, Knowler WC, and Bennett PH, in National Diabetes Data Group, eds. Diabetes in America. Chapter IV, loc.cit.

3 Bistrian BR, Blackburn GL, Flatt JP, Sizer J, Scrimshaw NS, and Sherman M, *Diabetes* 25:494, 1976

4 Genuth SL, *Am. J. Clin. Nutr* 32:2579, 1979

of hypoglycemia than either the metformin or glyburide monotherapy groups, but this was attributed to: the protocol design (maximum dose of glyburide, held constant, with variations in metformin dose); the lack of a hypoglycemic effect with metformin monotherapy; and the lack of change in dose of glyburide, post-randomization, or variation in glyburide dose during the study, for patients on glyburide monotherapy. No episodes of severe hypoglycemia occurred and all episodes responded to conservative management.

7.2.2.6 Reviewer's Conclusions

This reviewer has made the following observations: (1) In this particular group, patients treated with metformin alone showed a very minimal improvement of their glycemic parameters, e.g., -0.4% unit of HbA1c; (2) The same patients treated with glycuride alone show no improvement, in fact a slight worsening of their glycemic parameters, e.g., +0.2% units of HbA1c; (3) By contradistinction, the group treated with the combination of metformin+ glyburide shows a rather dramatic improvement, e.g., -1.7% units of HbA1c.

Thus, two important conclusions can be derived: (1) That metformin and glyburide are synergistic in their effects, i.e., the sum of their individual activities (e.g., -0.2 % of HbA1c in this case), is much less than their combined activities (e.g., -1.7% of HbA1c) -- a 750% increase between additive and synergistic effects! and (2) When patients have been shown to be essentially unresponsive to glyburide (sulfonylurea failure), the addition of metformin to glyburide seems somehow to restore glyburide activity. The practical consequence of this observation is: Patients who have shown primary or secondary failure might be considered to be treated with the sulfonylurea+metformin combination, instead of withdrawing sulfonylurea therapy and replacing it with metformin treatment.

Of course, such recommendations can be made only if the three treated groups were comparable. In addition, the Company has not performed the studies thast unequivocally prove that synergisms does indeed exist, or defined the groups in which synergism may exist, or even determined the lowest dose effective in combination therapy as opposed to monotherapy using metformin. A last remark: Combination therapy is different depending on whether one is using it in patients in whom glyburide aloine is still effective, or in patients who have experienced a primary or secondary failure of sulfonylurea therapy.

It's more important to again emphasize the following: In this study too, the Company has failed to determine the lowest dose effective in most patients. This is again due to the protocolar choice of titrating upward based on FPG values alone after relatively short equilibrating intervals. As a result, a hodge-podge of doses were used and not a single one was tested for true efficacy. Under the circumstances, it is very difficult to recommend approval of the drug, though its efficacy seems to be real and significant, and the possibility of a synergism between sulfonylureas and metformin is strongly suggested.

8. NON-PIVOTAL CLINICAL STUDIES

8.1 First Non-Pivotal Study: Study No. MET/AM/84/DORF1

8.1.1 Description of Study

8.1.1.1 Title, Objective and Rationale

Non-U.S. Study No. MET/AM/84/DORF1 "A Study of Metformin in Type II Non-Insulin-Dependent Diabetics (NIDDM) Who Are ≥ '20 Percent More Than Ideal Body Weight (IBW)" was conducted to evaluate the safety and efficacy of metformin in the patient population described in the title whose prior treatment for diabetic obesity failed due to inadequate diet therapy, ineffective or

poorly tolerated weight reduction treatment or other anti-diabetic therapy not resulting in weight reduction. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

8.1.1.2 Experimental Design

Non-U.S. Study No. MET/AM/84/DORF1, conducted in Paris, France from May, 1984 to December, 1987, was a randomized, parallel group (two), double-blind, single-center study comparing the safety and efficacy of 60 days of treatment with either metformin (up to 2,550 mg/day) or placebo in 51 obese (≥20% more than IBW), NIDDM outpatients whose prior treatment for diabetic obesity had been unsuccessful. I

Eligible patients, following randomization, were started on metformin (or placebo), 850 mg t.i.d, with meals (2,550 mg/day, total dose). In the event of digestive intolerance, this dose was reduced to two tablets per day (1700 mg). All patients, whether randomized to receive study drug or placebo, were placed on a calorie-restricted diet, low in sugar, adapted to their degree of obesity.

8.1.1.3 Demographics

A total of 51 patients were randomized to treatment with 25 receiving metformin and 26 receiving placebo. The patients ranged in age from 29-73, with a mean age of 54. There were 43% males and 57% females.

8.1.1.4 Safety Considerations

Adverse experiences/intercurrent medical events (AE/IMEs) were recorded at each monthly visit.

8.1.1.5 Efficacy Endpoints

The Sponsor considered the following as the primary efficacy measures were FPG, PPG, HbA1c, fasting plasma insulin, body weight, total cholesterol, and triglycerides. We have made our comments on this subject in our review of pivotal studies, mainly that only HbA1c can be considered as a primary efficacy endpoint.

8.1.1.6 Statistical Approaches

Observed values and change from baseline values were compared for all efficacy measures. The primary analyses were the within- and between-treatment comparisons of change from baseline values. The incidence of AE/IMEs was compared between treatment groups using Fisher's Exact Test, when there was an incidence of four or greater in a treatment group.

8.1.2 Results and Conclusions

8.1.2.1 Patient Comparability

Demographic characteristics of the two treatment groups are stated to comparable at baseline. Of note, eight patients assigned to metformin had been on metformin (and were on metformin, alone or with sulfonylurea) *up until study entry*, as were five patients assigned to placebo -- an obvious confounding factor.

8.1.2.2 Patient Disposition

Of the 51 randomized patients, 35 completed the study. Of the 16 patients who withdrew from the study, nine were discontinued due to AE/IMEs: four patients from the metformin group (16%) vs.

five patients from the placebo group (19%). Two (8%) of the four metformin group patients discontinued for gastrointestinal side-effects, as did four (15%) of the five placebo group patients.

8.1.2.3 Efficacy Data

Within treatment group comparison of final visit to baseline values showed that metformin treatment resulted in significant decreases in FPG, PPG and HbA_{1c} compared to nonsignificant decreases for placebo (although between-treatment comparisons were not statistically significant). For FPG, the metformin group had a 53 mg/dL decrease from baseline whereas the placebo group decreased 19 mg/dL. Metformin treatment also resulted in a significant decrease in total cholesterol and a nonsignificant decrease in triglycerides. Placebo treatment resulted in nonsignificant decreases in both of these lipid parameters. Both groups had experienced significant reductions in body weight at final visit, without significant difference between treatments.

8.1.2.4 Safety Data

In general, metformin was well tolerated throughout the duration of the study. A total of 30 AE/IMEs were reported in 20 of the 51 patients enrolled in the study (10 patients in each treatment group). The most common AE/IMEs were gastric pain, diarrhea, and nausea. There were no deaths.

8.1.2.5 Sponsor's Conclusions

The sponsor concluded that this study, conducted in NIDDM patients poorly controlled by earlier diet therapy, weight reduction therapy or anti-diabetic treatment, suggests that metformin is a safe, well-tolerated, and effective treatment in such patients. Due to the limited number of subjects per group and the high proportion of dropouts, overall, no clear-cut between-treatment differences were detected. Furthermore, the observation that approximately 50% of patients in both groups had been on metformin (either alone or with sulfonylurea) before or at study entry, without any washout period, makes interpretation of results more difficult.

8.1.2.6 Reviewer's Conclusions

This is a totally flawed study, for the following reasons: (1) Few patients; (2) large number of dropouts, which ring a safety alarm; (3) heterogeneous population admitted to the study; and (4) additional difficult to evaluate effect of the dietary rules. For these reasons, the study is useless for efficacy analysis, and does raise some concerns from a safety viewpoint.

8.2 Second Non-Pivotal Study: Study No. MET/GB/85/DORNA

8.2.1 Description of Study

8.2.1.1 Title, Objective and Rationale

Non-U.S. Study No. MET/GB/85/DORNA: "A Double-Blind Randomized Study Comparing Diet and Metformin to Diet and Placebo in the Treatment of Moderately Controlled Obese Non-Insulin-Dependent Diabetic Patients" was conducted to evaluate the safety and efficacy of metformin and diet in the patient population described in the title. The rationale for the study was scientific evidence of the antihyyperglycemic effect associated with the drug.

8.2.1.2 Experimental Design

Non-U.S. Study No. MET/GB/85/DORNA, conducted in Nottingham, Great Britain from Feb., 1985 to Feb., 1988., was a randomized, parallel group (two), double-blind, single center study comparing the safety and efficacy of eight months of treatment with either metformin (up to 3000

mg/day) or placebo in 62 obese NIDDM patients. In this study, the 500 mg dosage strength of metformin was used.

Patients were started on 500 mg metformin per day, with dose escalation to 2,000 mg every day, by weekly increments of 500 mg (although the option existed to increase the metformin dose to 3,000 mg/day, if glycemic control was not achieved by Visit 2). Patients were instructed to reduce the dose by one tablet per day if gastrointestinal side effects developed.

8.2.1.3 Demographics

A total of 62 patients were randomized (30 patients to metformin and 32 patients to placebo). The patients ranged in age from 38 to 67, with a mean age of 54. There were 42% males and 58% females.

8.2.1.4 Safety Considerations

Adverse experiences/intercurrent medical events (AE/IMEs) were recorded at each visit. There were no other assessments related to safety.

8.2.1.5 Efficacy Endpoints

Efficacy parameters included FPG, HbA_1, fasting plasma insulin, body weight, blood pressure, total cholesterol, triglycerides, and C-Peptide.

8.2.1.6 Statistical Approaches

Observed values and change from baseline values were compared for all efficacy measures. The primary analyses were the within- and between-treatment comparisons of change from baseline values. Patient were stratified according to baseline HbA_1 levels (< or >12.5%), with a subgroup analysis of results accordingly performed. The incidence of AE/IMEs was compared using Fisher's Exact Test.

8.2.2 Results and Conclusions

8.2.2.1 Patient Comparability

Sponsor states that the demographic characteristics of the two treatment groups were comparable at baseline. Our Statistician may concur or disagree.

8.2.2.2 Patient Disposition

Of the 62 patients randomized patients, 60 completed the study. Two patients from the placebo group were discontinued from the study due to AE/IME (due to a myocardial infarction and abdominal pain, respectively).

8.2.2.3 Efficacy Data

Mean changes from baseline at Final Visit for key efficacy parameters clearly show that metformin was superior to placebo in improving parameters of glycemic control, with highly statistically significant decreases from baseline in FPG and HbA_1 (-57 mg/dl and -1.5 % units, respectively), compared to increases in these parameters in placebo-treated patients (+50 mg/dl and +1.7% units, respectively). In metformin-treated patients, fasting plasma insulin levels simultaneously were decreased. Body weight remained stable in both patient groups.

8.2.2.4 Safety Data

Metformin was well tolerated throughout the course of the study. Fifty percent of patient's in the metformin group complained of diarrhea, compared to 22% in the placebo group (net difference of 28%). Constipation was experienced by 19% of placebo patients compared to 10% of metformin patients.

8.2.2.5 Sponsor's Conclusions

The sponsor concludes that this study suggests that metformin is a safe, well-tolerated, and effective treatment for obese patients with NIDDM, who are moderately controlled with diet management. The results of the analysis indicated that metformin and diet were superior to placebo and diet in meaningfully lowering FPG and HbA_1, as well as in lowering total cholesterol and triglycerides, both in patients with HbA_1 < and >12.5% (although the magnitude of change in glycemic parameters was greatest for patients with higher levels of glycosylated hemoglobin at baseline).

8.2.2.6 Reviewer's Conclusions

This small study is of better quality than the previous one, though it is unhelpful --like all the submitted studies -- in trying to determine the lowest effective dose. The difference in HbA1c between the treated and untreated patients, at the end of the study period, is a rather remarkable 3.2% units; which is almost too good to be true, given that the drug is usually able to improve patients by about 1-2% units.

8.3 Third Non-Pivotal Study: Study No. MET/AM/86/DORF2

8.3.1 Description of Study

8.3.1.1 Title, Objective and Rationale

Non-U.S. Study No. MET/AM/86/DORF2 : "Study of Metformin in Carbohydrate Intolerant Subjects (WSHO CRITERIA, 1980) Who are ≥ 20% More Than Ideal Body Weight (IBW)" was conducted to evaluate the safety and efficacy of metformin in the patient population described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

8.3.1.2 Experimental Design

Non-U.S. Study No. MET/AM/86/DORF2, conducted in Paris, France from January, 1986 to October, 1990, was a randomized, parallel group (two), double-blind, single-center study comparing the safety and efficacy of 60 days of treatment with either metformin (up to 2,550 mg/day) or placebo in 50 obese (≥20% more than IBW) outpatients with impaired glucose tolerance but fasting normoglycemia, whose prior treatment for obesity had been unsuccessful. The 850 mg dosage strength of metformin was used in this study.

Eligible patients, following randomization, were started on metformin (or placebo), 850 mg t.i.d, with meals (2,550 mg/day, total dose). In the event of digestive intolerance, this dose was reduced to two tablets per day (1700 mg). All patients, whether randomized to receive study drug or placebo, were placed on a calorie-restricted diet, low in sugar, adapted to their degree of obesity.

8.3.1.3 Demographics

A total of 50 patients were randomized (25 to metformin; 25 patients to placebo). The patients ranged in age from 16 to 76, with a mean age of 41. There were 22% males and 78% females.

8.3.1.4 Safety Considerations

Adverse experiences/intercurrent medical events (AE/IMEs) were recorded at each monthly visit.

8.3.1.5 Efficacy Endpoints

The Sponsor again states that the primary efficacy measures were FPG, PPG, HbA1c, fasting plasma insulin, body weight, total cholesterol, and triglycerides. Please refer to my numerous comments on the subject, above.

8.3.1.6 Statistical Approaches

Observed values and change from baseline values were compared for all efficacy measures. The primary analyses were the within- and between-treatment comparisons of change from baseline values. The incidence of AE/IMEs was compared between treatment groups using Fisher's Exact Test when there was an incidence of four or greater in a treatment group.

8.3.2 Results and Conclusions

8.3.2.1 Patient Comparability

Demographic characteristics of the two treatment groups were comparable at baseline, at least on the basis of the Sponsor's conclusions..

8.3.2.2 Patient Disposition

Nine patients withdrew from the study. Five patients (20%), in the METFORMIN group, withdrew due to adverse experiences/-intercurrent medical events (AE/IMEs), and two patients (8%), in each treatment group, withdrew due to personal problems.

8.3.2.3 Efficacy Data

At final visit, changes from baseline for fasting plasma insulin, FPG and HbA_{1c} were small and generally nonsignificant in both groups. (These results may have been expected since this was a patient population with impaired glucose tolerance but with fasting normoglycemia at baseline). There was a mean decrease in fasting plasma insulin of 3 μIU/mL at Day 60 in the metformin group, compared to a mean increase of 0.1 μIU/mL in the placebo group. Both the metformin and placebo groups had significant reductions in postprandial plasma insulin (both groups had decreases of 34 μIU/mL at Day 60 [p=0.001]), postprandial glucose, body weight (5.8 kg for the metformin group and 5.5 kg for the placebo group) and total cholesterol. Metformin also caused a significant decrease in triglycerides. There were no significant differences between the treatment groups.

8.3.2.4 Safety Data

More patients in the metformin group reported AE/IMEs than in the placebo group (17 vs. 3, p <0.001). The AE/IMEs reported in the metformin group were generally consistent with its known gastrointestinal side-effect profile. Diarrhea was experienced by 52% of patients receiving metformin compared to 12% of patients receiving placebo.

Forty-one patients completed all visits (18 on metformin and 23 on placebo, p = 0.160). Five patients (20%) in the metformin group discontinued due to an AE/IME vs. none in the placebo group (p <0.001). Three (12%) of the five were terminated prematurely because of gastrointestinal system side-effects. A patient on lithium for manic depression was noted to have an increase in serum

lithium level which, although without clinical consequences, suggested the possibility of pharmacokinetic drug interaction. This patient also discontinued the study prematurely. No deaths occurred during the study.

8.3.2.5 Sponsor's Conclusions

The sponsor concluded that in this study, both metformin and placebo achieved a major reduction in body weight, which was the intent of the low-calorie tailored diet consisting of at least 30% fewer calories per day than their usual intake. The effect of the low-calorie diet also probably contributed to the significant and relevant drop to normal mean values in PPG levels. No differences between metformin and placebo were observed in this study which was performed on patients with impaired glucose tolerance and with normal FPG values at baseline, although the clear drop in total cholesterol values observed at 30 days in the metformin patients, which was significantly different from the smaller decrease in the placebo group ($p=0.014$), suggests an additional beneficial effect of metformin. Discontinuations and the lack of hard data on patients for periods of more than 60 days reduce the interpretation of additional findings. Finally, the findings of increased serum lithium levels with concomitant metformin administration suggests a possible pharmacokinetic interaction of these compounds, probably at the renal level.

8.3.2.6 Reviewer's Conclusions

The only useful conclusion that one can reasonably derive from this study is the following: That the drug should not be used in patients with a pre-diabetic condition, i.e., in patients with only impaired glucose tolerance. On the other hand, since there is some evidence of metformin-induced increase in insulin-sensitivity, it might not be unreasonable to test the drug in a well-designed "prevention trial."

8.4 Fourth Non-Pivotal Study: Study No. MET/GB/86/CAMP1

8.4.1. Description of Study

8.4.1.1 Title, Objective, and Rationale

Non-U.S. Study No. MET/GB/86/CAMP1 : "Comparative Trial of Metformin and Glipizide in Diet-Failed Type II Diabetics" was conducted to evaluate the safety and efficacy of Metformin versus glipizide in the patient population described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

8.4.1.2 Experimental Design

Non-U.S. Study No. MET/GB/86/CAMP1, conducted in Lundin Links, Fife, the United Kingdom, from March, 1985 to January, 1987, was a randomized, parallel-group (two), open-label, single center study, comparing the safety and efficacy of one year of treatment with either metformin or glipizide in 50 NIDDM outpatients who were not adequately controlled with diet alone. In this study, the 500 mg dosage strength of metformin and the 5 mg dosage strength of glipizide were used (both of commercial source).

Patients in the metformin group received an initial dosage of 500 mg, bid, adjusted, thereafter, whenever random venous plasma glucose levels were greater than 180 mg/dL. The maximum dosage of metformin was 3000 mg/day. Patients in the glipizide group received an initial dosage of 5 mg/day, adjusted, thereafter, whenever random venous plasma glucose levels were greater than 180 mg/dL. The maximum dosage of glipizide was 30 mg/day. If random venous plasma glucose levels fell below 72 mg/dL, the dose of either drug was reduced or discontinued.

8.4.1.3 Demographics

A total of 50 patients entered this study – 25 in the metformin group and 25 in the glipizide group. The patients ranged in age from 40 to 70, with a mean age of 58. There were 32% males and 68% females.

8.4.1.4 Safety Considerations

Adverse experiences/intercurrent medical events (AE/IMEs) were sought and recorded at each visit.

8.4.1.5 Efficacy Endpoints

The Sponsor states again that the primary efficacy parameters consisted of FPG, HbA_1, body weight, HDL cholesterol, HDL subfractions (HDL-2 and HDL-3), total cholesterol, triglycerides, and urinary albumin excretion rate. We consider HbA1c to be the primary efficacy parameter, and other endpoints as being supportive (e.g., FPG), or secondary (e.g., triglycerides).

8.4.1.6 Statistical Approaches

Observed values and change from baseline values were compared for all efficacy parameters and laboratory parameters. The primary analyses were the within- and between-treatment comparisons of change from baseline values at each visit. The incidence of AE/IMEs was compared between the two treatment groups.

8.4.2 Results and Conclusions

8.4.2.1 Patient Comparability

Demographic characteristics of the two groups were comparable at baseline, according to the Sponsor.

8.4.2.2 Patient Disposition

Of the 50 randomized patients, 43 completed the study. Two patients (one in the metformin group and one in the glipizide group) withdrew from the study due to AE/IMEs (both patients had malignancies).

8.4.2.3 Efficacy Data

Metformin and glipizide were equally effective in lowering fasting plasma glucose, at Final Visit (changes at week 52 of -73 mg/dl and -58 mg/dl, respectively). Although metformin had a greater effect on HbA, than did glipizide (decrease of 3% units with metformin vs. decrease of 2% units with glipizide), the between-treatment comparison was not statistically significant. Mean body weight decreased with metformin (-2.5 kg), whereas it increased with glipizide (+2.6 kg) ($p = 0.001$). In this one year study, both groups had increases in total cholesterol and triglyceride levels, of greater magnitude with glipizide, but between-treatment differences were not significant.

8.4.2.4 Safety Data

Both treatments were well tolerated and there was no difference in AE/IME incidence between treatments, p=0.208).

8.4.2.5 Sponsor's Conclusions

The sponsor concluded that this study demonstrated that metformin was a safe, effective and well-tolerated long-term treatment when used to treat patients with Type II, NIDDM who had failed to respond to treatment with diet alone. Metformin and glipizide were equally effective in lowering FPG and HbA_1. Metformin was superior to glipizide, however, in reducing body weight. The results of the lipid profile and urinary albumin excretion rate revealed no statistically significant change from baseline in either treatment group.

8.4.2.6 Reviewer's Conclusions

The only useful conclusion I can derive from this study is the following: There are certain patients who, under certain circumstances, elicit -- under treatment with metformin -- increased plasma total cholesterol and triglyceride values. I am somewhat at a loss to explain these facts; on the other hand, one cannot simply ignore them.

8.5 Fifth Non-Pivotal Study: Study No. MET/AM/88/DUCHI

8.5.1 Description of Study

8.5.1.1 Title, Objective and Rationale

Non-U.S. Study No. MET/AM/88/DUCHI [Vol.:1.167; Pg.:08B-21839]: "Study on Mean Term Efficacy of Metformin vs. Gliclazide on Insulin Resistance in Diabetics" was conducted to evaluate the safety and efficacy of metformin versus gliclazide in the patient population described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

8.5.1.2 Experimental Design

Non-U.S. Study No. MET/AM/88/DUCHI, conducted in Paris, France from December, 1988 to December, 1989, was a randomized, open-label, parallel group (two), multicenter (14 private-practice based physicians) study, comparing the efficacy and safety of 3 months of treatment with metformin or gliclazide in 61 NIDDM outpatients, who were either not controlled by diet alone or by diet plus oral anti-diabetic agents (sulfonylureas). The 850 mg dosage strength of metformin was used in this study and the 80 mg dosage strength of gliclazide.

Metformin was administered as one tablet per day (850 mg qd) for one week, then two tablets per day (850 mg bid) for the remainder of the study. Gliclazide was administered by progressive dose titration, based upon glycemic control, up to a maximum of three tablets per day (80 mg tid).

8.5.1.3 Demographics

A total of 61 patients were randomized: 33 patients to metformin and 28 patients to gliclazide. The patients ranged in age from 31-65, with a mean age of 55. There were 49% males and 51% females.

8.5.1.4 Safety Data

Adverse experiences and intercurrent medical events (AE/IMEs) were recorded at each visit.

8.5.1.5 Efficacy Endpoints

Primary efficacy parameters consisted of fasting plasma insulin, fasting and postprandial plasma glucose (PPG) levels, HbA_{1c}, total cholesterol, triglycerides, and body weight.

8.5.1.6 Statistical Approaches

Observed values and change from baseline values were compared for all efficacy parameters. The primary analyses were the within- and between-treatment comparisons of change from baseline values. In addition, a final visit analysis was performed on the efficacy parameters. The final visit was defined as Day 90 or the last post-baseline visit at which a patient had data recorded. The incidence of AE/IMEs were compared between treatment groups using Fisher's Exact Test.

8.5.2 Results and Conclusions

8.5.2.1 Patient Comparability

Demographic characteristics of the two groups were comparable at baseline.

8.5.2.2 Patient Disposition

Of the 61 randomized patients, 57 completed the study. One patient on metformin was discontinued prematurely from study participation because of carcinomatosis (prior malignancy), manifest one day after starting study medication.

8.5.2.3 Efficacy Data

Both treatments effectively and significantly decreased FPG, PPG and HbA_{1c} but metformin significantly lowered fasting plasma insulin levels whereas they increased with gliclazide ($p = 0.006$). Body weight decreased by a mean of 2.4 kg with metformin at Final Visit, compared to a 0.1 kg decrease with gliclazide. However, this difference was not statistically significant ($p = 0.112$).

8.5.2.4 Safety Data

Metformin was, in general, well tolerated throughout the course of the study. A total of 24 AE/IMEs in 14 patients were reported during the study (21 AE/IMEs in eleven patients who received metformin vs three AE/IMEs in three patients who received gliclazide, $p=0.065$).

8.5.2.5 Sponsor's Conclusions

The sponsor concluded from this study that metformin, at a daily dose of 1700 mg, was equivalent to gliclazide, at a daily dose of 240 mg, in degree of glycemic control in Type II, NIDDM patients who were either not adequately controlled by previous diet therapy or oral anti-diabetic monotherapy. The investigators reported that treatment of NIDDM over a three month period brought about identical improvement in blood glucose control, when evaluated by blood glucose and HbA_{1c} measurements. In contrast, fasting serum insulin levels were significantly reduced with metformin as compared to gliclazide. This was associated with a slight body weight reduction in the group treated with metformin. Metformin was safe and reasonably well tolerated.

8.5.2.6 Reviewer's Conclusions

The reviewer does not disagree with the Sponsor's conclusions, limited as those may be in their scope and significance.

8.6 Sixth Non-Pivotal Study: Study No. MET/S/86/HERMA

8.6.1 Description of Study

8.6.1.1 Title, Objective and Rationale

Non-U.S. Study No. MET/S/86/HERMA [Vol.:1.160; Pg.:08B-19555]: "Study of Metformin, Glibenclamide, and Their Combination, in Patients With Type II Diabetes" was conducted to evaluate the safety and efficacy of metformin, glibenclamide and the combination in Type II NIDDM patients. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

8.6.1.2 Experimental Design

Non-U.S. Study No. MET/S/86/HERMA [Vol.:1.160; Pg.:08B-19555], conducted in the Dalby health district of Sweden from January, 1986 to November, 1989, was a randomized, parallel group (three), double-blind, double-placebo controlled, multicenter (five centers) study of the relative efficacy and safety of metformin, glibenclamide or metformin + glibenclamide in optimizing glycemic control in 144 NIDDM outpatients, in patients not well-controlled with diet alone or monotherapy alone. Although patients were initially randomized to either monotherapy (metformin or glibenclamide) or low-dose combination therapy, all patients could eventually receive combination therapy at high dose, should it be required. The 500 mg dosage strength of metformin and the 1.75 and 3.5 mg dosage strengths of micronized glibenclamide were used in this study. Matching placebos for each active drug were also used.

After being screened and following a two-week diet/placebo run-in phase, 144 patients were randomized into one of three treatment groups: metformin (MM)(38 patients); glibenclamide (GG)(34 patients); or low dose metformin + glibenclamide (MGL)(72 patients), according to an unequal randomization schema of 1:1:2. Following randomization, the patients entered a two-segment treatment phase consisting of a dose-titration phase of variable duration and a maintenance phase (6 months in duration). During the dose-titration phase, patients not achieving glycemic control with monotherapy or low-dose combination therapy, could have the alternate drug added and/or be advanced to higher doses of combination therapy. At the end of the 6 month maintenance period, patients entered a two-week placebo close-out phase after which they were discontinued from the protocol.

8.6.1.3 Demographics

A total of 144 patients were randomized: 38 to metformin, 34 to glibenclamide and 72 to the combination. The patients ranged in age from 34 to 74, with a mean age of 60. There were 64% males and 36% females.

8.6.1.4 Safety Considerations

Evaluation of safety consisted of laboratory assessments and the collection of adverse experiences/intercurrent medical events.

8.6.1.5 Efficacy Endpoints

Primary efficacy parameters for the study consisted of fasting blood glucose (FBG), HbA_{1c}, meal stimulation tests (consisting of administration of a test meal, with measurement of blood glucose, insulin, and C-Peptide levels prior to and for 3 hours following the test meal), body weight, triglycerides and cholesterol.

8.6.1. 6 Statistical Approaches

Observed values and change from baseline values were compared for all efficacy and safety measures to assess the relative efficacy and safety of metformin and glibenclamide and metformin in combination with glibenclamide. The primary analyses were the within- and between-treatment comparisons of change from baseline values. These analyses were done for all randomized patients (Groups M [metformin], G [glibenclamide], and M+G [metformin + glibenclamide]) and for two subgroups of patients. One subgroup consisted of those patients who were maintained on monotherapy or low dose combination therapy (Groups MM, GG, and MGL) and the other subgroup consisted of those patients who were maintained on standard (high) combination therapy (Groups M/G, G/M, and MGH).

8.6.2 Results and Conclusions

8.6.2.1 Patient Comparability

Demography characteristics of the treatment groups were comparable at baseline.

8.6.2.2 Patient Disposition

Twenty patients were discontinued from the study for various reasons. Sixteen patients were discontinued from the study due to AE/IMEs: nine patients initially randomized to the metformin treatment group (8 MM, 1 M/G) primarily for Digestive System symptoms; three patients initially randomized to the glibenclamide treatment group (3 GG), all for hypoglycemia; and four patients initially randomized to the combination treatment group (1 MGL, 3 MGH), for various reasons (hypoglycemia, hyperglycemia, diarrhea, leukemia).

8.6.2.3 Efficacy Data

For those patients whose hyperglycemia could be controlled on monotherapy or low dose combination therapy (66% of MM patients, 62% of GG patients and 75% of MGL patients), all three treatment groups experienced similar substantial improvement in glycemic control. The metformin monotherapy group had an average decrease from baseline in FBG of 35 mg/dL, the glibenclamide group had a decrease of 38 mg/dL and the combination group's mean decrease was 38 mg/dL.

After 5-9 months on treatment, there was no significant difference among these groups with respect

to FBG or other efficacy parameters including: HbA_{1c}, glucose (AUC glucose from a meal stimulation test), and lipid profile (total cholesterol, HDL, LDL, and triglycerides). However, patients in the metformin monotherapy group (Group MM) had a decrease in plasma insulin over time in contrast to increases in plasma insulin in the other treatment groups (Groups GG and MGL). Moreover, C-Peptide and body weight remained stable in the MM group but increased in the GG and MGL group. Statistical analyses revealed these differences to be significant, also.

9. OVERVIEW OF EFFICACY

Most of the clinical trials in this NDA utilized an escalating dose regimen – more often every week but sometimes every two weeks – based on nothing else than the principle of forced upward titration barely corrected by the often subjective notion of patient expected tolerance of the proposed higher dose. The other studies suffer a similar weakness.

The efficacy variables used to assess the effects of metformin in target patient populations were numerous and, I must say, used in a manner which shows a rather profound lack of clear objectives and a lack of understanding of the real purposes of the used tests, a list of which now follows:

- Fasting plasma glucose (FPG)
- Postprandial plasma glucose (PPG) or Oral glucose tolerance test (2-hour) plasma glucose (OGTT [2-hour] PG)
- Glycosylated hemoglobin (HbA_{1c} or HbA_1)

- Body weight (in lbs. for U.S. studies; in kg for non-U,S, studies)
- Total serum cholesterol (CHOL)
- Plasma triglycerides (TRIG)

Table 3 presents a composite of results for all controlled studies in the pooled data base, showing mean changes from baseline at final visit for the key efficacy parameters.

9.1 Fasting Plasma Glucose

Among the two U.S. pivotal Category I studies and the seven non-U.S. supportive Category II studies, fasting plasma glucose (FPG) was measured as a primary efficacy parameter in all but non-U.S. Study No. MET/D/86/BERGI, a diet-controlled study. In addition, FPG was not a relevant endpoint in non-U.S. Study No. MET/AM/86/DORF2, since these subjects with impaired glucose tolerance did not have fasting hyperglycemia.

Of the seven remaining studies, metformin, as a monotherapeutic agent, lowered FPG at final visit, relative to baseline, in a highly statistically significant fashion in six of the seven studies, comprised of populations of obese NIDDM patients considered to be diet failures (two studies: U.S. Study No. 87-1D-6023 and MET/GB/85/DORNA) and heterogeneous, primarily obese, NIDDM populations with possible prior exposure to oral hypoglycemic agents (four studies). In U.S. Study No. 87-2D-6023, conducted in NIDDM patients considered to be sulfonylurea failures, the within-treatment group decrease in FPG in patients randomized to metformin monotherapy was not statistically significant. However, since patients randomized to glyburide in this study had an increase in FPG at final visit, the difference between these monotherapy arms was statistically significant, in favor of metformin monotherapy.

Metformin was statistically superior to placebo in its effect on FPG in two of three placebo-controlled studies ($p < 0.001$), including pivotal U.S. Study No. 87-1D-6023 and MET/GB/85/DORNA. In the remaining placebo-controlled study (MET/AM/84/DORF1), the between-treatment difference bordered on statistical significance ($p = 0.108$) although in this study, almost one-third of patients randomized to metformin had been on metformin (alone or with sulfonylurea) at baseline, compared to one-fifth of placebo patients, thereby perhaps accounting for the less marked difference.

Metformin was comparable to the oral sulfonylureas, gliclazide (Non-U.S. Study No. MET/AM/88/DUCHI), glipizide (Non-U.S. Study No. MET/GB/86/CAMP1) and glibenclamide (Non-U.S. Study No. MET/S/86/HERMA) in its FPG-lowering effect in three of four active-controlled studies and was superior to glyburide ($p < 0.05$) in U.S. Study No. 87-2D-6023 (see above), conducted in patients considered to be sulfonylurea failures, which included at least one month of maximum dose glyburide.

Metformin, when added to continued sulfonylurea therapy in patients considered to be sulfonylurea failures (or suboptimally responding to sulfonylureas), had a highly significant and relevant lowering effect on FPG (U.S. Study No. 87-2D-6023), both within the treatment group and in comparison to monotherapy with either continued glyburide or metformin. This effect was also seen in non-U.S. Study No. MET/S/86/HERMA in patient subgroups beginning on glibenclamide monotherapy and requiring the addition of metformin for optimal glycemic control. In addition, combined metformin/glibenclamide therapy, at low dose, was as effective as metformin monotherapy or glibenclamide monotherapy in lowering FPG in patients with apparently less marked baseline hyperglycemia in this study.

9.2 Postprandial or Post-glucose Load Plasma Glucose (PPG)

Among the two U.S. pivotal Category I studies and the seven non-U.S. supportive Category II studies, the level of postprandial or post-glucose load plasma glucose (PPG) was a primary efficacy variable in both U.S. studies (placebo- and active-controlled), as well as in two placebo-controlled non-U.S. studies (one of which was conducted in patients with abnormal glucose tolerance but fasting

normoglycemia) and two active-controlled studies.

Metformin, as monotherapy, significantly lowered PPG at final visit, relative to baseline values, in one of the two placebo-controlled studies conducted in NIDDM subjects (pivotal U.S. Study No. 87-1D-6023). In the other study (non-U.S. Study No. MET/AM/84/DORF1), there was a decrease in the metformin group which approached statistical significance (p = 0.062). Between treatment comparisons (metformin vs. placebo) were statistically significant only in U.S. Study No. 87-1D-6023, wherein the metformin group had a mean decrease in PPG of 75 mg/dL compared to a mean increase of 12 mg/dL in the placebo group (p-value = 0.001). In non-U.S. Study No. MET/AM/84/DORF1, the metformin group experienced a mean decrease in PPG of 49 mg/dL compared to a mean increase of 1 mg/dL in the placebo group, but this difference did not achieve statistical significance (p = 0.169). In the remaining placebo-controlled study measuring this parameter (non-U.S. Study No. MET/AM/86/DORF2), both the metformin group and the placebo group had comparable decreases in PPG (40 and 34 mg/dL, respectively), which might have been attributable to strict dietary measures and resultant weight loss in this study in obese patients with fasting normoglycemia and impaired glucose tolerance. (Since mean *baseline* values for PPG were normal in both the metformin and placebo groups [140 and 130 mg/dL, respectively], minimal change would have been predicted in the metformin group, since metformin does not affect plasma glucose levels in normoglycemic subjects).

Among the three active-treatment comparison studies, metformin as monotherapy significantly lowered PPG at final visit, relative to baseline, in one study (non-U.S. Study No. MET/S/86/HERMA), with a mean decrease of 51 mg/dL. In U.S. Study No. 87-2D-6023, carried out in a population considered to be sulfonylurea failures (including maximum dose glyburide, administered until randomization), metformin monotherapy had no significant effect on PPG (mean decrease of 1 mg/dL), however, neither did maximum dose glyburide (mean increase of 2 mg/dL) (p = 0.731, between treatment comparison). In non-U.S. Study No. MET/AM/88/ DUCHI, comparing metformin to gliclazide, the metformin group had a mean decrease in PPG of 27 mg/dL compared to a mean decrease in PPG of 53 mg/dL with gliclazide (p = 0.226, between treatment comparison). (The metformin group decrease from baseline approached statistical significance [p = 0.067] whereas the gliclazide group decrease was statistically significant [p = 0.001]). However, it should be noted that in this study, the maximum dose of metformin was set at 1,700 mg/day, in contrast to a maximum dose of up to 2,550 mg/day in U.S. studies, and up to 3,000 mg/day in British studies.

Metformin, when added to continued sulfonylurea therapy in patients considered to be sulfonylurea failures (or suboptimally responding to sulfonylureas) (pivotal U.S. Study No. 87-2D-6023 [Vol.:1.120), had a highly significant and relevant lowering effect on PPG (a decrease of 59 mg/dL, p = 0.001), both within the treatment group and in comparison to monotherapy with either metformin or glyburide (MG vs. M, p = 0.001, MG vs. G, p = 0.001). As was the case for FPG, this effect was also seen in non-U.S. Study No. MET/S/86/HERMA, in patient subgroups beginning on glibenclamide monotherapy and requiring the addition of metformin for optimal glycemic control. This group, with apparently more severe NIDDM, experienced a mean decrease in PPG of 79 mg/dL, relative to baseline. In fact, the three patient subgroups in this study which ultimately required high dose combination therapy of metformin plus glibenclamide (those starting on glibenclamide and then having metformin added; those starting on metformin and then having glibenclamide added; and those starting on low dose

combination therapy and requiring high dose combination therapy for glycemic control) experienced substantial decreases in PPG, (average decrease of 91 mg/dL, range: 77-116 mg/dL). In addition, in this same study, combined metformin/glibenclamide therapy, at low dose, significantly decreased PPG (a decrease of 36.7 mg/dL, p = 0.006, compared to baseline) in patients with less marked baseline hyperglycemia.

9.3 Glycosylated Hemoglobin

Glycosylated hemoglobin was a primary efficacy variable in all nine studies: both U.S. pivotal studies as well as all seven non-U.S Category II studies. Because of methodological weaknesses and inconsistencies, the greatest reliability concerning the impact of metformin on this parameter should be placed on U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023, large multicenter studies wherein all HbA_{1c} determinations were performed by a central laboratory (SciCor, Inc.) with a defined normal (non-diabetic) range for HbA_{1c} of 3.3-6.8%.

Metformin as monotherapy decreased HbA_{1c} in all three placebo-controlled studies performed in patients with NIDDM. In U.S. Study No. 87-1D-6023, there was a mean decrease in HbA_{1c} of 1.4% (p = 0.001) compared to a mean increase with placebo of 0.4% (M vs. P, p = 0.001). In non-U.S. Study No. MET/GB/85/DORNA, there was a mean decrease of HbA_1 of 1.5% in the metformin group (p = 0.002) compared to a mean increase of 1.7% in the placebo group (p = 0.001)(M vs. P, p = 0.001). In non-U.S. Study No. MET/AM/84/DORF1, there was a mean decrease of 1.1% in HbA_{1c} in the metformin group (p = 0.032) while the placebo group also had a mean decrease of 1.3% (p = 0.052) (M vs. P, p = 0.759). However, in this latter study, a relatively high proportion of patients in the metformin group were already on metformin (alone or with sulfonylurea) at baseline, thereby casting a note of unreliability on the baseline HbA_{1c} values and making comparison of changes difficult. In the single diet-controlled study (non-U.S. Study No. MET/D/86/BERGI), there was a small decrease in HbA_1 with metformin of 0.2% compared to no change with placebo (M vs. P, p = 0.482). The reason for this small effect is not clear although there was a very high drop out rate in both arms in this study and compliance information is lacking.

Among the four studies with an active treatment comparison, metformin, as monotherapy, caused a small but significant decrease in HbA_{1c} (0.4%) at final visit in U.S. Study No. 87-2D-6023 (p = 0.004), conducted in patients considered to be *sulfonylurea failures*. All patients had been on glyburide up until the time of randomization. (The glyburide monotherapy group in this study had a mean increase in HbA_{1c} of 0.2% at final visit. M vs. G, p = 0.001). In non-U.S. Study No. MET/GB/86/CAMP1, conducted in NIDDM patients considered to be *diet failures*, there was a highly significant decrease in HbA_1 in the metformin group of 2.8% (p = 0.001), relative to a decrease of 1.8% in the glipizide group (p = 0.003), without any statistically significant difference between treatment groups (M vs. G, p = 0.166). In non-U.S. Study No. MET/AM/88/DUCHI, which included NIDDM patients with *prior exposure to oral hypoglycemic agents*, the metformin group had a mean decrease from baseline in HbA_{1c} of 0.8% (p = 0.032), compared to a mean decrease of 0.7% in the gliclazide group (p = 0.237), although between treatment group differences were not significant. In this study, the maximal dose of metformin was 1700 mg/day, in contrast to most of the other studies, using between 2.5 and 3.0 g/day, as maximum, but I don't think that this was the primary reason for the extent of the observed efficacy on this parameter. In patients maintained on metformin monotherapy in non-U.S. Study No. MET/S/86/HERMA (patients *poorly controlled on diet or prior sulfonylurea therapy*), there was a mean decrease in HbA_{1c} of 0.9%, compared to a 1.3% decrease in patients maintained on glibenclamide monotherapy and a 1.2% decrease in those continued on low dose combination therapy.

Metformin, when added to continued sulfonylurea therapy in patients considered to be sulfonylurea failures (or suboptimally responding to sulfonylureas) (pivotal U.S. Study No. 87-2D-6023), had a highly significant and relevant lowering effect on HbA_{1c} of 1.7% ($p = 0.001$), compared to the previously mentioned decrease of 0.4% with metformin monotherapy (M vs. MG, $p = 0.001$) and the increase in HbA_{1c} of 0.2% in the glyburide group (G vs. MG, $p = 0.001$). Apparently the Sponsor failed to see (and certainly fails to mention) that a very interesting thing may be happening here: A very unusual kind of synergistic behavior between sulfonylureas and metformin, in that the latter seems to restore the efficacy of the former. As was the case for other parameters of glycemic control, this effect was also seen in non-U.S. Study No. MET/S/86/HERMA with combined metformin/glibenclamide therapy. All three patient subgroups in this study, ultimately requiring high dose combination therapy of metformin plus glibenclamide, experienced substantial decreases in HbA_{1c}, averaging 2.2%. In addition, in this same study, combined metformin/glibenclamide therapy, at low dose, also significantly decreased HbA_{1c} by 1.2%, compared to baseline ($p = 0.001$), in patients with less marked baseline glucose abnormalities.

9.4 Body Weight

Effects on body weight were sought in all nine studies, including the two U.S. pivotal studies and the seven non-U.S. Category II studies. Both the U.S. studies and the non-U.S. studies were conducted in predominantly obese NIDDM populations and, in accord with general principles of management of diabetes mellitus, included emphasis on dietary control.

In the three placebo-controlled studies performed in patients with NIDDM, metformin monotherapy resulted in a statistically significant decrease in body weight at final visit, compared to baseline, in two of the three studies, including U.S. Study No. 87-1D-6023. The magnitude of this weight loss was 0.6 kg in U.S. Study No. 87-1D-6023 and 3.5 kg in non-U.S. Study No. MET/AM/84/DORF1 . In the third study, patients in the metformin group had no change from baseline body weight. on the other hand, these three studies, patients in the placebo group lost comparable amounts of weight (1.1 kg in U.S. Study No. 87-1D-6023 of 6 months' duration, 4.0 kg in non-U.S. Study No. MET/AM/84/DORF1 of 2 months' duration, 1.1 kg in non-U.S. Study No. MET/GB/85/DORNA of 8 months' duration) and there was no statistically significant differences between response to metformin or placebo. Thus, the differences in the glycemic control achieved with metformin cannot be attributed to body weight loss in these studies, since changes of the same magnitude in this parameter occurred with metformin and placebo. In the diet-controlled study (non-U.S. Study No. MET/D/86/BERGI of 2 years' duration), both groups also lost statistically significant and comparable amounts of weight (2.8 kg with metformin compared to 3.5 kg with diet alone). In non-U.S. Study No. MET/AM/86/DORF2 of 2 months' duration, conducted in obese subjects with impaired glucose tolerance, and with a strong emphasis on diet, both metformin and placebo groups lost comparable amounts of weight, which were statistically significant (5.8 kg for the metformin group and 5.5 kg for the placebo group). Overall, one can then conclude that metformin does not seem to affect body weight directly, one way or another. Had it shown. on average, an increase of body weight, compared to placebo, we would have then considered this to be a safety issue. But this does not appear to be the case.

Four studies compared metformin monotherapy to various sulfonylurea treatments. In U.S. Study No. 87-2D-6023 of 6 months' duration, metiormin resulted in a significant decrease in body weight at final visit, relative to baseline (3.8 kg decrease), compared to a 0.3 kg decrease in patients continuing on glyburide (M vs. G, $p = 0.001$). In non-U.S. Study No. MET/GB/86/CAMP1 of 12 months' duration, conducted in NIDDM not previously exposed to oral hypoglycemic agents, metformin resulted in a weight loss of 1.9 kg ($p = 0.008$) compared to a weight gain of 2.4 kg in the glipizide treatment group ($p = 0.013$) (M vs. G, $p = 0.001$). In non-U.S. Study No. MET/AM/88/DUCH of 3 months' duration, patients in the metformin group lost a mean of 2.4 kg at final visit, compared to no change in the gliclazide group (M vs. G, $p = 0.112$). In non-U.S. Study No. MET/S/86/HERMA, in patients continuing on metformin monotherapy (group MM), there was a mean weight loss of 0.4 kg, compared to a mean weight gain of 2.8 kg in the group continuing on glibenclamide monotherapy (group GG) (MM vs. GG,

p = 0.001). Thus, these studies serve to illustrate a key difference between responses in body weight with metformin vs. sulfonylureas in NIDDM subjects, in that metformin patients tended to lose weight or maintain stable weight, whereas patients on sulfonylureas tended to gain weight, often significant in degree. However, it cannot be argued that thius latter poinbt has been proved conclusively. Thus, we would not recommend, at this time, that such representations be made in either the labeling or the promotional materials or observations made to physicians, particularly by Company representatives.

Addition of metformin to ongoing sulfonylurea (glyburide) therapy in U.S. Study No. 87-2D-6023 of 6 months' duration, resulted in a slight increase in body weight (0.5 kg, p = 0.048). In non-U.S. Study No. MET/S/86/HERMA, patient groups requiring high doses of both metformin and glibenclamide (patient groups M/G, G/M and MGH) all tended to have gained weight by the end of the 6 month treatment phase (0.8 kg for group M/G, 1.9 kg for group G/M and 0.2 kg for group MGH). There was no statistically significant differences in body weight response between these treatment subgroups. –

9.5 Total Serum Cholesterol

The level of total serum cholesterol was a secondary efficacy parameter in all nine studies, both the two U.S. pivotal studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) and the seven non-U.S. Category II studies.

Metformin, as monotherapy, resulted in modest decreases in total cholesterol in all four placebo-controlled studies (including non-U.S. Study No. MET/AM/86/DORF2, conducted in patients with impaired glucose tolerance) ranging from decreases of 9 to 18 mg/dL (an average decrease of 6.5% from baseline values), and all within-treatment changes being statistically significant or borderline significant, p = 0.075). Between treatment comparisons of metformin to placebo were significant in U.S. Study No. 87-1D-6023 and non-U.S. Study No. MET/GB/85/DORNA (p = 0.024 and 0.046, respectively). In the single diet-controlled study (non-U.S. Study No. MET/D/86/BERGI, metformin and diet both caused modest but statistically significant increases in total cholesterol, compared to baseline values, but the study suffered from a high dropout rate as well as inability to assess compliance.

Metformin, as monotherapy, resulted in decreases in mean total cholesterol levels at final visit in three of the four active treatment comparison studies, although the magnitude of the decreases was modest, ranging from decreases of 4 to 10 mg/dL. In non-U.S. Study No. MET/GB/86/CAMP1, both the metformin and the glipizide treatment groups experienced mean increases in total cholesterol (21 and 20 mg/dL, respectively), significantly different from baseline. The reason for this result is unclear.

The addition of metformin to ongoing sulfonylurea therapy resulted in a decrease in total serum cholesterol of 9 mg/dL (p = 0.001) in U.S. Study No. 87-2D-6023. In this same study, patients continuing on glyburide alone, had a mean increase in total cholesterol at final visit of 3 mg/dL. In non-U.S. Study No. MET/S/86/HERMA, the addition of metformin to ongoing sulfonylurea therapy (group G/M) resulted in an increase in total serum cholesterol of 11 mg/dL, although, in the same study, low dose and high dose combination therapy with metformin and glibenclamide (groups MGL and MGH) had decreases in total cholesterol at final visit of 4 and 27 mg/dL, respectively.

From subgroup analyses performed on data generated in U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023, it appears that metformin has its greatest effect on total serum cholesterol levels when the levels are higher than normal at initiation of metformin therapy. Such conclusions are not proved, however; and since the data are contradictory, no claim or representation can be made in either the labeling or the promotional materials and presentations, except that physicians ought to be instructed to follow their patients cholesterolemic picture, as they would in all diabetics.

9.6 Total Serum Triglyceride

The level of total serum triglyceride was a primary efficacy variable in all nine studies, including the

two U.S. pivotal studies and the seven non-U.S. Category II studies. Metformin, as monotherapy, resulted in modest decreases in total triglyceride in all four placebo-controlled studies (including non-U.S. Study No. MET/AM/86/DORF2, conducted in patients with impaired glucose tolerance but normal fasting glycemia), ranging from decreases of 14 to 39 mg/dL (average of 30 mg/dL, representing an average decrease of 14.3% from baseline values). Within-treatment changes were statistically significant in U.S. Study No. 87-1D-6023 and in Non-U.S. Study No. MET/AM/86/DORF2. Between treatment (metformin vs. placebo) comparisons approached statistical significance in U.S. Study No. 87-1D-6023 ($p = 0.085$) and in non-U.S. Study No. MET/GB/85/DORNA ($p = 0.051$), wherein the placebo group experienced a mean increase in triglyceride levels of 33 mg/dL. In the single diet-controlled study (non-U.S. Study No. MET/D/86/BERGI), metformin and diet both caused increases in total triglycerides (30 mg/dL with metformin [$p = 0.057$] and 63 mg/dL with diet alone [$p = 0.001$]) and the between treatment comparison approached statistical significance, in favor of metformin ($p = 0.130$).

Metformin, as monotherapy, resulted in decreases in mean total triglyceride levels at final visit in three of the four active treatment comparison studies. In U.S. Study No. 87-2D-6023, the metformin group had a mean decrease from baseline of 23 mg/dL ($p = 0.011$) compared to a mean decrease of 26 mg/dL in the group continuing on glyburide ($p = 0.444$). Comparison of median values at final visit revealed a decrease of 7 mg/dL for the metformin group compared to a median increase of 7 mg/dL for the glyburide group. In non-U.S. Study No. MET/S/86/HERMA, the treatment group maintained on metformin monotherapy (group MM) had a mean decrease in serum triglyceride levels at final visit of 8 mg/dL compared to an increase of 8 mg/dL in the group maintained on glibenclamide monotherapy. This difference between groups was not statistically significant, however ($p = 0.512$). In non-U.S. Study No. MET/AM/88/DUCHI, the metformin treatment group had a mean decrease of 5 mg/dL in total serum triglyceride level at final visit compared to a mean increase of 30 mg/dL in the gliclazide group. This difference between groups was, again, not statistically significant, however ($p = 0.421$). In non-U.S. Study No. MET/GB/86/CAMP1, in contrast, the metformin group as well as the glipizide group both had increases in total serum triglyceride levels at the end of the study, 5 mg/dL for the metformin group and 17 mg/dL for the glipizide group. (In this study, both groups also had mean increases in total serum cholesterol level at study end).

The addition of metformin to ongoing sulfonylurea (glyburide) therapy (metformin/glyburide treatment group) in U.S. Study No. 87-2D-6023, resulted in a mean increase of 1 mg/dL in total serum triglyceride level at final visit. However, in contrast, the median value showed a decrease of 14 mg/dL from baseline. Median change from baseline values for the metformin monotherapy and glyburide monotherapy groups were, respectively, -7 mg/dL and +7 mg/dL.

In non-U.S. Study No. MET/S/86/HERMA, patients maintained on low dose combination therapy (metformin + glibenclamide) had a mean decrease in total serum triglyceride level of 6 mg/dL at final visit. The three high dose combination groups (M/G, G/M, and MGH) varied in response for this variable, as follows: Group M/G had a mean decrease of 77 mg/dL, the G/M group had a mean increase of 11 mg/dL and the MGH group had a mean decrease of 44 mg/dL.

Overall, and generously assuming that there is an effect, I am not convinced that any such highly hypothetical effect of metformin on circulating triglycerides can conceivably possess any clinically significant effect. Thus, no mention ought to be permitted in either labeling or promotional material, of these facts, except to say that the drug does not appear to have any significant effect, one way or another, on plasma triglycerides.

9.7 Fasting Plasma Insulin and Fasting Plasma C-peptide

Fasting plasma C-peptide, or FPT, as another studied secondary efficacy variable. In all studies measuring FPI, there were no statistically significant increases in FPI in metformin-treated patient groups, with respect to baseline. In conjunction with this lack of increase in FPI was the considerable improvement in glycemic control in patient populations, lending support to the contention that

metformin does not achieve its antihyperglycemic effect by stimulating insulin release. Levels of fasting plasma C-peptide were also consistent with metformin's non-insulin stimulating mechanism of action.

10. OVERVIEW OF SAFETY

10.1 Significant Events or Leads

10.1.1 Deaths During Drug Use

Deaths included those deaths that occurred during metformin treatment (either alone or in combination with sulfonylureas) or within 30 days of discontinuation of metformin treatment. However, for the non-U.S. Phase IV studies, all deaths are noted here regardless of temporal relationship to study medications since precise dates for discontinuation of metformin could not be determined.

A total of 14 patients died during the conduct of the eleven studies comprising the NDA data base and involving 9,526 NIDDM patients (two U.S. Phase III, controlled, randomized Category I studies; seven non-U.S., controlled, randomized Category II Studies; and two non-U.S. uncontrolled Phase IV studies).

There was one death in the U.S. Phase III studies (U.S. Study No. 87-2D-6023), from cardiovascular disease, occurring in a patient who had been randomized to metformin. One patient died of cancer in non-U.S. Study No. MET/GB/86/CAMP1 while on glipizide, and one patient died of an apparent myocardial infarction in non-U.S. Study No. MET/S/86/HERMA while on glibenclamide/metformin. Eleven patients died in non-U.S. Study No. Phase IV study MET/AM/87/PHASE, involving 4374 patients for a study duration of six months.

10.1.2 Serious and Potentially Serious AE/IMEs

A "serious AE/IME", using the criterion in CRF 21:312:32(a), is defined as "... any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer or overdose..." A "potentially serious AE/IME" was defined as a medical event that was potentially fatal or life-threatening.

U.S. Phase III Studies (Pooled): Serious/potentially serious AE/IMEs, by body system, for the pooled U.S. Phase III studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) are presented in Table 4. Inspection of the data for the number of patients reporting serious/potentially serious AE/IMEs revealed few differences among treatment groups for any body system.

Non-U.S. Phase IV Studies: Serious/potentially serious AE/IMEs, by body system, for non-U.S. Phase IV (Non-U.S. Study No. MET/D/86/-HAUPT) are summarized in Table 6. Of the 3,724 patients who contributed evaluable data, 156 (4%) had serious or potentially serious AE/IMEs and 105 (3%) had events that occurred in the Digestive System. All other body systems had an occurrence rate of <1% for serious or potentially serious AE/IMEs. The only particular events with an occurrence rate of ≥1% for serious or potentially serious AE/IMEs were diarrhea (53 patients, 1%) and nausea/vomiting (39 patients, 1%). All other events had an occurrence rate of <1%.

The CRF for non-U.S. Study No. MET/AM/87/PHASE was not designed to collect comprehensive AE/IME data. In an effort to be consistent across all studies regarding categorization of AE/IMEs, all serious/potentially serious AE/IMEs were identified by the Primary Medical Officer (PMO) at Lipha.

From a total of 4,252 patients, 84 AE/IMEs were considered to be either serious or potentially serious according to the PMO. Fifty-six (56) of these patients were also represented as patients who discontinued due to adverse experiences/-intercurrent medical events.

10.1.3 Potential Toxicities

As known for biguanides in general, metformin use can be associated with the occurrence of lactic acidosis. Certain experts argue that the incidence of such occurrence may be vastly different among the biguanides. It has been reported, in epidemiological studies, that metformin has the lowest incidence of lactic acidosis of any biguanide which is or has been commercially available. On the other hand, it is entirely possible that the "lesson" of phenformin was learned and applied in the case of metformin use: Not to prescribe biguanides in certain high-risk categories of patients and, generally speaking, being simply well aware of the danger. Under the circumstances, the Sponsor's attribution to metformin to its special structural differences, significant pharmacokinetic and metabolic differences and significant differences in their actions and reactivity on a molecular level between the two drugs may be only partially responsible for the results of the epidemiological observations. Let us remind ourselves that phenformin was the first biguanide to be tested and introduced in the marketplace on the basis of a rational process: Mole for mole, it is much more active than metformin.

It has been reported that metformin use in France since 1984 accounts for approximately 2.5 million patient-years of exposure to metformin. Cases of metformin-associated lactic acidosis (MALA) occurring in France, from 1984 to the present, where the use of metformin is the greatest and where detailed pharmacovigilance information -- based, more or less, on spontaneous reporting -- is available, are relatively constant over time. Per 1,000 patient-years, there has been an average of 0.03 cases of MALA each year (approximately 1 case per 33,000 patient-years), with 0.015 fatal cases per 1,000 patient-years. In Sweden, where, likewise, careful adverse event reporting and usage information is available, a similar incidence rate exists (0.024 cases per 1,000 patient-years), with 0.012 fatalities directly attributable to the acidosis per 1,000 patient-years. There is no indication that this incidence is increasing, despite steady increases in metformin usage and, in fact, in Sweden, and in the Sponsor's own words, "the incidence appears to have decreased more than threefold compared to an earlier five-year period of evaluation." This is , in my eyes, which seems further suggestive evidence that good prescribing practices may improve the safety profile of the drug. The Sponsor argues that a number of cases considered to be MALA do not have supportive evidence (i.e., blood metformin levels) to unequivocally establish this diagnosis and, thus, the incidence of MALA may be even less than these figures indicate, but is self-serving sophistry. The general and constant reality of epidemiological estimation of side-effects rates is one of underestimation, rather than of overestimation. In fact, Dr. Stadel, our epidemiologist, has given us printed evidence to the effect that in a similar case (where death is the end-point to be reported) a 1-10 underestimation of actual incidences is a rule in the case of spontaneous reporting. Thus, we can estimate the actual death incidence due to lactic acidosis during metformin use as 1.5-2 fatalities per 10,000 patient-years -- not an inconsequential number. I am not saying that this actually what is happening in Europe, or what will happen in the United States when the drug is introduced in the marketplace. What I am saying, however, is that this figure of 1.5-2 deaths per 10,000 patient-years is one that I feel compelled and justified to retain in my risk-versus-benefit analysis of metformin. Finally the Sponsor offers the following rationalizations: that

"comparative risk estimates for fatal adverse reactions for products which continue to be widely used include a death rate from anaphylaxis with penicillin use of 0.02 patients per 1,000 patients treated and a death rate from thromboembolism amongst oral contraceptive users of 0.01 to 0.03 per 1,000 patient-years. Estimates of fatal hypoglycemic reactions due to use of oral sulfonylureas average 0.020 per 1,000 patient-years. " Also, that "at the time of phenformin's withdrawal from most world markets, estimates of phenformin-associated lactic acidosis in the U.S. varied from 0.25 to 4.0 cases per 1,000 patient-years, with a mortality rate of from 0.125 to 2.0 per 1,000 patient years." These figures, interesting as they may be, only strenghten the following general regulatory approach: That drug development and usage should include all adequate precautions to minimize such fatal events, even though we readily agree that there is always a price to be paid for the benefit that one derives from useful drugs. One of the essential precautions, for example, is to define, as rigorously as necessary, the least dose that is effective in most patients, thus enabling us to write a useful labeling section on posology applicable to the majorityt of patients, and also allowing the physician to know how to custom tailor treatment to an individual patient's needs. This is particularly applicable when dealing with long-term treatments of a chronic conditions such as diabetes – a condition that affects so many millions of Americans.

All cases of MALA have occurred in the setting of at least one or more acute or chronic illnesses, known to be either a direct risk factor for the development of lactic acidosis in patients taking metformin (e.g., acute or chronic renal impairment) or an independent risk factor for lactic acidosis (acute or chronic cardiovascular disease, pulmonary disease with hypoxia, sepsis or acute or chronic hepatic disease with or without associated alcoholism). Patients >70 years of age appear to be at greatest risk for development of MALA, probably due to the presence of borderline or frank renal impairment, greater likelihood of associated illnesses, more diagnostic or surgical interventions and multiple concomitant medications, often inappropriately combined.

Excepting lactic acidosis, the side-effect profile of metformin apppears, at this stage, relatively unremarkable though not unimportant or trivial. In controlled clinical trials of metformin vs. placebo, the only body system with an increased incidence of treatment-emergent events was the digestive system. Mild to moderate gastrointestinal symptoms, consisting primarily of intermittent diarrhea, nausea and abdominal discomfort (alone or in combination) tend to occur when metformin therapy is first started and sometimes disappear spontaneously as therapy is continued. The incidence of such symptoms is comparable in patients treated with metformin as monotherapy and in patients treated with metformin plus a sulfonylurea, and appear to be responsible for diarrhea (for example) in about one-third of the treated population. Such an occurrence may seem trivial to the clinical monitor of a company who, fortunately, does not suffer from such symptoms. However, such symptoms can be debilitating in an already diabetic patients, particularly if they affect a semi-chronic status. In controlled clinical trials reported herein, between 1% and 8% of patients terminated study participation prematurely because of gastrointestinal side-effects, and this indicates that, in daily usage, a relatively sizeable compliance problem may become apparent. In large open-label non-U.S. Phase IV studies of metformin monotherapy or metformin plus continued sulfonylurea therapy, involving more than 7,000 patients (approximately half of whom were treated for three months and the remainder for six months), approximately 3% of patients discontinued study participation prematurely because of gastrointestinal side-effects.

A subclinical side-effect is depression of serum vitamin B_{12} levels in patients receiving metformin, either alone or in combination with sulfonylureas. In the U.S. controlled clinical trials presented in this NDA, 7% of 566 patients exposed to metformin for 29 weeks developed subnormal serum vitamin B_{12} levels. Combining published information of long-term (>2 years) metformin use, it appears that approximately 13% of patients receiving metformin for such a duration will have subnormal serum vitamin B_{12} levels. Despite this, reported cases (published and unpublished) of megaloblastic anemias have been rare so far (five cases, including three published cases; none in U.S. studies) and there is no known report of neurologic disorders on the basis of vitamin B_{12} deficiency and metformin use.

As suggested by the sponsor, it is recommended that patients receiving metformin, either alone or in combination with sulfonylureas, have serum vitamin B_{12} levels monitored annually, with implementation of parenteral vitamin B_{12} treatment, should a subnormal serum vitamin level be identified.

Metformin appears to have a lesser propensity to induce hypoglycemia, when administered as monotherapy (unless, theoretically, other extenuating circumstances are present, such as acute alcohol excess). However, since metformin can be used in combination with sulfonylureas, hypoglycemia can and does occur under such circumstances. From the data analyzed in this NDA, the incidence of hypoglycemia in patients newly exposed to either sulfonylurea or metformin plus sulfonylurea appears to be comparable. All cases of hypoglycemia that have occurred during the course of the studies reported in this NDA in patients receiving both metformin and a sulfonylurea would be categorized as mild, since they either spontaneously disappeared or were relieved by food intake. For the most part they were also single occurrences. In no instance was there a hypoglycemic episode which could be considered severe (i.e., requiring assistance of another person and/or resulting in coma or seizures).

10.2 Other Drug-Related Safety Issues

10.2.1 Adverse Experiences Incidence Tables

For the pooled U.S. studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) and for the randomized non-U.S. studies (Studies MET/AM/84/DORF1 , MET/AM/86/DORF2, MET/GB/86/CAMP1, MET/GB/85/DORNA [Vol.:1.159; Pg.:19194], MET/AM/88/DUCHI and MET/S/86/-HERMA), Tables 7 and 8, respectively, list individual AE/IMEs reported by at least 9% of the patients in one or more treatment groups. In addition, these listings include AE/IMEs that had differences in incidence between any two treatment groups of at least 5%.

As can be seen, digestive system symptoms, consisting of diarrhea, nausea/vomiting and abdominal discomfort were the most frequent AE/IMEs reported in both groups of pooled randomized studies in the metformin-containing treatment arms. In non-U.S. Phase IV Study No. MET/D/86/HAUPT, involving 3724 patients treated with metformin/sulfonylurea, the incidence of individual AE/IMEs as shown in Table 9, reflects the higher incidence of Digestive System AE/IMEs, such as diarrhea (7%),nausea/vomiting (5%) and abdominal discomfort (4%).

Hypoglycemia was comparably infrequent in the metformin, placebo and glyburide arms (2%, <1% and 3%, respectively) of the U.S. pooled Phase III studies, although it should be recalled that the glyburide-treated patients (from U.S. Study No. 87-2D-6023) had been on the same dose of glyburide for at least one month, prior to study entry, without dosage changes during the course of the study. In contrast, the incidence of hypoglycemia was increased in the metformin/glyburide treatment group (18%), although this was never severe. In the pooled randomized non-U.S. studies, the incidence of reported hypoglycemia by treatment group was 5% for metformin, 0 for placebo, 14% for sulfonylurea and 33% for metformin/sulfonylurea (the latter from a single study, MET/S/86/HERMA, and including patients on both low dose and high dose combination therapy). In these studies, the sulfonylurea monotherapy group, for the most part, was comprised of patients in whom sulfonylurea therapy was being newly initiated and thus, more accurately than in the U.S. study, reflects the incidence of hypoglycemia in sulfonylurea-treated patients. In non-U.S. Phase IV Study No. MET/D/86/HAUPT, the incidence of hypoglycemia in metformin/sulfonylurea-treated patients was <1%.

Available data on incidence of AE/IMEs for non-U.S. Study No. MET/AM/87/PHASE are summarized in Table 10, below. Although the CRF for this study was not designed to collect comprehensive AE/IME data, limited AE/IME information was collected on the CRF relative to gastrointestinal complications/events under the heading "Digestive Intolerance". Although specific AE/IMEs were not recorded, an assessment of the severity of the digestive intolerance for each patient was made (no intolerance, mild, moderate, severe, very severe).

10.2.2 Clinical Findings

10.2.2.1 Routine Laboratory Results

General Considerations: Analyses of routine clinical chemistry and hematology data, related to safety, were undertaken in order to identify general changes in patient populations and to identify individual patients with clinically significant abnormalities for laboratory parameters. Tests are discussed by organ systems, as follows:

- Liver function tests;
- Kidney function tests (including urinalysis);
- Electrolytes;
- Hematology: RBC parameters;
- Hematology: WBC/platelet parameters.

For each laboratory parameter, general changes in values for patient populations were sought through analysis of means and change from baseline data and through analyses of shift tables. Mean values at baseline and final visit and change from baseline values for patient populations must be interpreted with caution since many changes in means, while statistically significant, are not clinically significant and represent small shifts within the normal range. Conversely, small changes in means may mask clinically significant changes for a few individual patients. To help identify trends in patient populations that may not have been apparent from an analysis of mean values, shift tables were used

to analyze the distribution of patients at baseline and final visit with respect to the normal range for each laboratory safety parameter.

Overall, few clear differences among the treatment groups (metformin, placebo, sulfonylurea, and metformin/sulfonylurea combinations) were noted for liver function tests, kidney function tests, electrolytes, and hematology parameters, and, where noted, differences were usually small. Therefore, neither extensive analyses nor tabular summaries of these laboratory data are provided in this item. Rather, the number of patients who experienced laboratory abnormalities within the clinically significant range and any clinically significant difference between the treatment groups will be noted using the U.S. Category I Phase III studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023), wherein all laboratory analyses were performed by the same central laboratory (SciCor, Inc).

10.2.2.1.1 Liver Function Tests

Individual patients with clinically significant abnormalities in liver function tests were defined as those patients meeting one or more of the following criteria: SGOT >3x ULN (i.e. upper limit of normal, using the SciCor normal ranges); SGPT >3x ULN; total bilirubin >2x ULN; and alkaline phosphatase >2x ULN.

In the U.S. placebo-controlled study (U.S. Study No. 87-1D-6023) only two patients, one in each treatment group (metformin and placebo), had clinically important abnormalities for liver function tests, both involving alkaline phosphatase. The metformin patient (*Patient 2/23*) (who also had renal function test abnormalities), was thought to have had either hemorrhagic pancreatitis or viral hepatitis and the abnormalities in liver and kidney function parameters, were tentatively attributed to this intercurrent illness. The placebo patient (*Patient 12/08*) had an elevated alkaline phosphatase level at baseline and, intermittently, throughout the course of the study.

In the U.S. active treatment comparison study (U.S. Study No. 87-2D-6023), there were eight patients in the metformin group, six patients in the glyburide group, and three patients in the metformin/glyburide group, that had clinically important abnormalities for liver function tests, as follows:

In the metformin group, three patients (*Patients 6/25, 11/29, and 22/02*) had increased levels of liver enzymes that were attributed by the Sponsor to poor glycemic control. All three patients were terminated from the study. In addition, three patients had clinically abnormal liver function tests that were attributed to concurrent disease (*Patient 7/14*--increased bilirubin attributed Gilbert's disease; *Patient 8/18*--increased SGOT/SGPT levels attributed to viral hepatitis; *Patient 21/21*--increased alkaline phosphatase levels attributed to fatty infiltration of the liver), and one patient (*Patient 17/33*) had increased liver enzyme levels attributed to concomitant medication. Finally, one patient (*Patient 11/21*) had a transient, unexplained rise in total bilirubin that quickly returned to normal.

In the glyburide group, three patients (*Patients 7/19, 10/30, and 11/03*) had increases in liver enzymes (SGOT/SGPT and/or alkaline phosphatase) that were attributed to fatty infiltration of the liver and one patient (*Patient 3/11*) had increases in liver enzymes that were attributed to study medication (glyburide). In addition, two patients had transient increases in either liver enzymes (*Patient 5/21*; attributed to lab error) or total bilirubin (*Patient 11/19*; unexplained) that quickly returned to normal. In the metformin/glyburide group, all three patients with clinically significant liver enzymes (*Patient 5/21*; attributed to lab error) or total bilirubin (*Patient 11/19*; unexplained) that quickly returned to normal.

In the metformin/glyburide group, all three patients with clinically significant liver function tests had abnormalities attributed to concurrent diseases: one patient (*Patient 5/06*) had increased liver enzyme levels attributed to fatty liver, one patient (*Patient 5/23*) had increased liver enzyme and bilirubin levels attributed to hepatitis (this patient was terminated from the study due to proteinuria), and one patient (*Patient 7/06*) had fluctuating levels of liver enzymes throughout the study that decreased after starting insulin therapy after the end of the study.

10.2.2.1.2 Renal Function Tests

Individual patients with clinically significant abnormalities in kidney function tests were defined as those patients meeting one or more of the following criteria: blood urea nitrogen >40 mg/dL; serum creatinine >2.0 mg/dL; serum uric acid >10 mg/dL; and urine protein ≥2+ at final determination but negative at baseline. In the U.S. placebo-controlled study (U.S. Study No. 97-1D-002), two patients in the metformin group had clinically important abnormalities for kidney function. *Patient 2/23*, as previously discussed, with moderate elevation of uric acid level and lesser elevations of urea nitrogen and creatinine, was thought to have either hemorrhagic pancreatitis or viral hepatitis. *Patient 4/15* had clinically important elevations in creatinine levels at Visit 6.1 and lesser elevations in creatinine levels at prior visits and urea nitrogen levels at this visit and prior visits. Data from follow-up visits showed a return to normal creatinine levels after discontinuation of study medication.

In the U.S. active treatment comparison study (U.S. Study No. 97-2D-0002), there were no patients in the metformin group, no patients in the glyburide group, and four patients in the metformin/glyburide group with clinically important abnormalities for kidney function. In the metformin/glyburide group, all four patients had increased uric acid levels that were clinically significant and attributed to concomitant medication (*Patient 1/11*, hydrochlorothiazide; *Patient 2/14*,

10.2.2.1.3 Hematology: RBC Parameters

Individual patients with clinically significant abnormalities in RBC parameters were defined as those patients meeting one or more of the following criteria: hemoglobin <10 g/dL; hematocrit <30%; RBC count <3.0 x $10^6/\mu L$; and mean corpuscular volume (MCV) ≤70 or >105 fL.

In the U.S. placebo-controlled study (U.S. Study No. 87-1D-6023), two patients in the metformin group and three patients in the placebo group met one or more of these criteria. In the metformin group, *Patients 12/19* and *17/02* had significantly higher values for MCV on one or more occasions accompanied by values for RBC count that were generally at the lower limit of the normal range. There were no abnormalities of serum vitamin B_{12} or folic acid levels in these two patients, however.

In the placebo group, *Patients 4/01, 12/20, and 13/08* had significantly lower values for MCV on one or more occasions with values for RBC count that were generally at the upper limit of the normal range.

In the U.S. active treatment comparison study (U.S. Study No. 87-2D-602), one patient in the metformin group, three patients in the glyburide group, and four patients in the metformin/glyburide group met one or more of the above criteria.

In the metformin group, *Patient 16/16* had an increased value for MCV at Visit 0 (Baseline) and a significantly increased value at an initial interim visit (Visit 0.1), values of 99 and 107 fL, respectively, but generally normal values for other hematology parameters. The MCV returned to normal at subsequent visits.

In the glyburide group, two patients had significantly low values for hemoglobin and/or hematocrit on one or more occasions with corresponding values for RBC count that were below the lower limit of the normal range; these anemias were attributed to bleeding from uterine fibroids and menorrhagia (*Patient 4/26*) and post-operative hemorrhage (*Patient 8/20*), respectively. In addition, one patient (*Patient 14/02*) had abnormally low values for hematology parameters at visit 0.0 that were attributed to a laboratory error.

In the metformin/glyburide group, two patients had microcytosis that was present at Baseline and throughout the study that was attributed to unknown etiology (*Patient 5/25*) or thalassemia minor (*Patient 7/29* [also had an increased uric acid level]). In addition, one patient (*Patient 15/14*) had macrocytosis of uncertain etiology that was present at Baseline and throughout the study. Another patient (*Patient 4/07*) had an abnormally low MCV value at Visit 11 that was accompanied by subnormal values for hemoglobin, hematocrit, and serum vitamin B_{12} (this patient was subsequently found to have iron deficiency in addition to subnormal vitamin B_{12} and was begun on iron and vitamin B_{12} supplementation).

10.2.2.1.4 Hematology:WBC/Platelet Parameters

Individual patients with clinically significant abnormalities in WBC/platelet parameters were defined as those patients meeting one or more of the following criteria: WBC count $<2.5 \times 10^3$/uL; neutrophils <1000/uL; lymphocytes >75% in differential WBC; and platelets $<100 \times 10^3$/uL.

In the U.S. placebo-controlled study (U.S. Study No. 97-1D-6023), two patients (*Patients 6/14 and 9/06*), both in the placebo group, met one or more of these criteria. Both patients had modest leukopenia due to neutropenia. The changes were persistent in both patients without apparent clinical consequences; etiology was not investigated further.

In the U.S. active treatment comparison study (U.S. Study No. 97-2D-6023), there were two patients in the metformin group and three patients in the metformin/glyburide group who met one or more of these criteria.

In the metformin group, one patient (*Patient 6/04*) had repeatedly low platelet counts (present, however, at baseline) that resulted in termination at Visit 7 and one patient (*Patient 19/05*) had a single, isolated clinically abnormal value for platelet count that was attributed to lab error.

In the metformin/glyburide group, one patient (*Patient 7/16*) had repeatedly low platelet counts that were attributed to cirrhosis of the liver and splenomegaly. One patient (*Patient 7/21*) had abnormal values for several WBC parameters at final visit (Visit 11) that were normal on repeat testing and were considered to have been a laboratory error. One patient (*Patient 16/20*) had leukopenia of unknown etiology throughout the study.

10.2.2.1.5 Serum Electrolytes

Individual patients with clinically significant abnormalities in serum electrolytes were defined as those patients meeting one or more of the following criteria: sodium <122 mEq/L; potassium <3.0 or >5.7 mEq/L; bicarbonate <16 or >40 mEq/L; chloride <80 mEq/L; anion gap >22 mEq/L; and calcium <7.5 or >12 mg/dL with albumin ≥4 g/dL.

In the U.S. placebo-controlled study (U.S. Study No. 97-1D-6023), only one patient met one or more on these criteria. *Patient 4/22*, in the placebo group, had an elevated value for serum potassium at Visit 8. At the same time, this patient had a value for serum bicarbonate that was slightly below normal. The patient was asymptomatic, was not on potassium supplementation, and the value was not considered clinically significant.

In the U.S. active treatment comparison study (U.S. Study No. 97-2D-6023), there were six patients in the metformin group, one patient in the glyburide group, and two patients in the metformin/glyburide group that met one or more of these criteria.

In the metformin group, two patients (*Patients 8/15 and 8/35*) had isolated, abnormally low values for serum bicarbonate but with accompanying anion gap values that were in the acceptable range. Two patients had isolated, abnormally low values for calcium that were either unexplained

(*Patient 6/01*) or attributed to laboratory error (*Patient 7/02*). One patient (*Patient 9/04*) had a transient, abnormally high value for potassium that was unexplained, and one patient (*Patient 17/25*) had an increased calculated anion gap of unknown etiology.

In the glyburide group, one patient (*Patient 6/20*) had a transient abnormally low value for serum bicarbonate that was unexplained (the accompanying anion gap was in the acceptable range, however).

In the metformin/glyburide group, one patient (*Patient 9/28*) had an abnormally low value for serum potassium despite potassium chloride supplementation that may have been related to gout or concomitant medication (hydrochlorothiazide). This patient also had clinically significant laboratory abnormalities for uric acid levels. *Patient 16/06* had electrolyte values at a single visit which were considered to be spurious: the patient was clinically well and repeat evaluations were normal.

10.2.2.2 Vital Signs

In analyzing the pooled U.S. Phase III studies, generally, very few patients had clinically important abnormalities of vital signs at either baseline or final visit. Treatment group differences were minimal. Individual patients with clinically significant abnormalities for vital signs were defined as those patients meeting one or more of the following criteria: systolic blood pressure ≤100 mm Hg, pulse rate ≤55 or >100 bpm, and body temperature >100° F. In the U.S. placebo-controlled study (U.S. Study No. 87-1D-6023 [Vol.:1.104; Pg.:08B-00001]) there were 28 patients in the metformin treatment group and 29 patients in the placebo group with clinically important abnormal values for vital signs. Generally, these abnormalities were transient. However, there were several patients with consistently (four or more measurements) low systolic blood pressure. Of these, three patients (*Patients 4/17, 10/2, 10/28*) were in the metformin group and eight patients (*Patients 2/20, 4/23, 5/13, 7/4, 8/3, 10/7, 10/12, and 12/16*) were in the placebo group. In addition, there was one patient (*Patient 5/13*) in the placebo group with multiple (three or more) pulse rate measurements of ≤55 bpm. In the U.S. active treatment comparison study (U.S. Study No. 87-2D-6023), there were 40 patients in the metformin treatment group, 23 patients in the glyburide group, and 40 patients in the metformin/glyburide group with clinically important abnormal values for vital signs. As observed in the U.S. placebo-controlled study (U.S. Study No. 87-1D-6023), these abnormalities were generally transient.

However, consonant with the placebo-controlled study, there were several patients with consistently (four or more measurements) low systolic blood pressure. Of these, one patient (*Patient 4/8*) was in the metformin treatment group, 0 patients were in the glyburide group, and three patients (*Patients 3/17, 10/5, and 14/23*) were in the metformin/glyburide group. There were also several patients with multiple (three or more) abnormal pulse rate measurements. Of the patients with three or more pulse rate measurement of >100 bpm, two patients (*Patients 6/25 and 9/27*) were in the metformin treatment group and one patient (*Patient 16/30*) was in the glyburide group. Of the patients with three or more pulse rate measurement ≤55 bpm, two patients (*Patients 3/19 and 11/22*)

were in the glyburide group and one (*Patient 3/2*) was in the metformin/glyburide group.

10.2.2.3 Specialized Tests - Vitamin B_{12} and Folic Acid

10.2.2.3.1 Vitamin B_{12} and Folic Acid

Because of historical information on the known safety profile of metformin and the class of biguanides, special attention was devoted to analysis of:

- Vitamin B_{12} and folic acid;
- Fasting plasma lactate.

Results for serum vitamin B_{12} and folic acid levels for U.S. Phase III studies are summarized in Table 11 (means and changes from baseline) and 12 (shift tables).

In U.S. Study No. 87-1D-6023, there was a substantial difference between treatment groups for treatment effects on serum vitamin B_{12}. In the metformin group, the mean serum vitamin B_{12} level decreased from 490 pg/mL at baseline to 384 pg/mL at final visit (Normal Range: 200-900 pg/mL), with a mean change from baseline of -105 pg/mL. In contrast, in the placebo group, the mean vitamin B_{12} level increased slightly from 514 pg/mL at baseline to 528 pg/mL at final visit, with a mean change from baseline of +12 pg/ml

As shown in In Table 12, shift analysis supported the interpretation of decreased serum vitamin B_{12} levels in the metformin group: 13 patients (11%) in the metformin group had normal values for vitamin B_{12} at baseline and subnormal values at final visit compared to 0 patients with similar shifts in the placebo group.

For serum folic acid levels, there was only a small difference between treatment groups and only one patient on metformin went from a normal value at baseline to a subnormal value at final visit.

U.S. Study No. 87-2D-6023 also showed substantial differences between treatment groups for serum vitamin B_{12} levels. Folic acid levels did not reveal such differences (see Table 11).

In the metformin group, the mean serum vitamin B_{12} level decreased from 554 pg/mL at baseline to 411 pg/dL at final visit, with a mean change from baseline of -144 pg/mL. These data are consistent with data for the metformin treatment group in the U.S. placebo-controlled study described above.

In the metformin/glyburide group, there was a similar decrease; the mean serum vitamin B_{12} level went from 535 pg/mL at baseline to 401 pg/mL at final visit, with a mean change from baseline of -138 pg/mL.

In the glyburide group, in contrast, the mean serum vitamin B_{12} level increased slightly from 522 pg/mL at baseline to 541 pg/mL at final visit, with a mean change from baseline of +13 pg/mL.

Thus, there were substantial differences among the treatment groups at final visit for serum vitamin B_{12} even though mean values remained with the normal range. Shift tables (see Table 12) showed that 15 patients (9%) in the metformin group and 11 patients (6%) in the metformin/glyburide group had normal values for serum vitamin B_{12} at baseline and low (i.e. below the normal range) at final visit, compared to only one patient (<1%) with similar shifts in the glyburide group. These data support the trend toward lower serum vitamin B_{12} levels in patients treated with metformin, either alone or in combination. In this study, there was no effect of any treatment on serum folic acid levels.

Thus, there appears to be an association between metformin and decreases in serum vitamin B_{12} levels, though the Sponsor asserts that "the data from these studies provide no evidence of a relationship of these decreases to plasma metformin levels. The apparent lack of any relationship was confirmed by regression analysis of data for both studies (U.S. Study No. 87-1D-6023, r^2 <0.10; U.S. Study No. 87-2D-6023, r^2 <0.0117)."

Patients with Clinically Significant Abnormalities: Individual patients with clinically significant values for serum vitamin B_{12} and folic acid levels were defined as those patients with vitamin B_{12} levels <200 pg/mL and/or folic acid levels <2.0 ng/mL.

In the U.S. placebo-controlled study **(U.S. Study No. 87-1D-6023)**, 16 patients in the metformin group and two patients in the placebo group had clinically significant abnormalities for serum vitamin B_{12} or folic acid.

In the metformin group, 14 patients had serum vitamin B_{12} levels <200 pg/mL at one or more study visits (*Patients 1/14, 2/18, 2/22, 3/12, 5/02, 9/01, 9/08, 9/21, 10/27, 11/14, 12/15, 12/17, 12/21, 13/09*). Of these 14 patients, one patient had an abnormally low baseline value and three others had values which could be considered "borderline" at baseline. No patients were anemic and only one patient (*Patient 9/21*) had a slightly increased MCV (101 fL).

In the placebo group, one patient (*Patient 5/11*) had an abnormally low serum vitamin B_{12} value at interim Visit 0.1 and Visit 9 (no baseline values available). *Patient 7/07* had an abnormally low serum vitamin B_{12} value at baseline, which was confirmed on repeat testing and the patient was started on parenteral vitamin B_{12} following a Schilling test.

In the metformin group, two patients (*Patients 6/01 and 10/28*) had abnormally low serum folic acid levels. Patient 10/28 also had an abnormally low value at baseline. There were no patients in the placebo group with abnormally low serum folic acid levels. In the U.S. active treatment comparison study **(U.S. Study No. 87-2D-6023)**, 16 patients in the metformin group, three patients in the glyburide group, and 17 patients in the metformin/glyburide group had clinically significant

abnormalities for serum vitamin B_{12} or folic acid levels.

In the metformin group, 16 patients (*Patients 1/32, 7/22, 10/10, 11/21, 11/26, 12/09, 12/34, 14/26, 15/13, 15/20, 15/29, 17/14, 17/21, 18/06, 18/28, and 21/07*) had serum vitamin B_{12} levels <200 pg/mL at final visit. Of these 16 patients, six patients had baseline levels of vitamin B_{12} that were "borderline" low and two patients (*Patients 10/10 and 15/13*) were diagnosed as having *pernicious anemia. In the glyburide group, two patients (Patients 16/08 and 17/24)* had serum vitamin B_{12} levels <200 pg/mL at final visit. One patient (*Patient 16/08*) had a significantly low vitamin B_{12} level at baseline (114 pg/mL) and the other with a "borderline" low level at baseline.

In the metformin/glyburide group, 16 patients (*Patients 1/17, 2/11, 4/07, 4/21, 8/11, 9/08, 9/13, 9/21, 11/19, 11/24, 13/20, 15/14, 15/25, 16/10, 20/11, and 21/24*) had serum vitamin B_{12} levels <200 pg/mL at final visit. Of these 16 patients, five patients had a significantly low vitamin B_{12} level at baseline and seven patients had baseline levels of vitamin B_{12} that could be considered "borderline" low. In addition, Patient 4/07 was noted to have a concomitant microcytic anemia. Patient 15/14 had increased MCV values (macrocytosis) throughout the study, including baseline.

There were 0 patients in the metformin group, one patient (*Patient 14/21*) in the glyburide group, and one patient (*Patient 18/11*) in the metformin/glyburide group with serum levels of folic acid below 2.0 ng/mL. In neither case was the low serum folic acid level associated with low levels of serum vitamin B_{12} or any other clinically abnormal hematological finding.

The clinical significance of all of this is difficult to fathom at present, since I have not seen any study that would allow me to make a practical recomendation as to how to address this issue, if an issue indeed does exist. For example, there is no reason or basis, for the time being, to recommend that all patients on metformin receive regular B12 injections or just have their B12 levels monitored. We will have to wait and allow the practising community to perform the necessary research and observations in this area.

10.2.2.3.2 Fasting Plasma Lactate

- *U.S. Studies:* Results for fasting plasma lactate levels for U.S. Phase III studies are summarized in Tables 13 (means and changes from baseline) and 14 (shift tables). In U.S. Study No. 87-1D-6023, a comparison of mean values and change from baseline values for fasting plasma lactate of the metformin and placebo groups revealed no clinically significant differences between the treatment groups at final visit. In fact, mean fasting plasma lactate levels for the two groups remained essentially unchanged throughout the study: mean levels at baseline were 1.41 mmol/L and 1.40 mmol/L for the metformin and placebo groups (Normal Range: 0.3-2.0 mmol/L), respectively, with mean change from baseline values at final visit of +0.04 mmol/L (*metformin*) and 0.00 mmol/L (placebo).

Shift tables supported the similarity of outcome for this parameter in the two treatment groups: 12 patients (9%) in the metformin group and 13 patients (9%) in the placebo group shifted from

normal plasma levels of lactate at baseline to high values at final visit; and 12 patients (9%) in the metformin group and 12 patients (8%) in the placebo group shifted from high levels at baseline to normal levels at final visit. In this study, there were no patients with fasting plasma lactate levels ≥4 mmol/L. Furthermore, a plot of the maximum metformin plasma level vs. the corresponding lactate level showed no evidence of a relationship.

In U.S. Study No. 87-2D-6023, mean values and change from baseline values for fasting plasma lactate also revealed no clinically significant differences among the treatment groups at final visit. However, the metformin and metformin/glyburide treatment groups did show slight mean increases at final visit, in contrast to the slight mean decrease shown by the glyburide group.

For the metformin group, mean fasting plasma lactate level increased slightly from 1.47 mmol/L at baseline to 1.54 mmol/L at final visit, with a mean change from baseline of +0.08 mmol/L. For the metformin/glyburide group, the mean fasting plasma lactate level increased similarly from 1.45 mmol/L at baseline to 1.51 mmol/L at final visit, with a mean change from baseline of +0.06 mmol/L. For the glyburide group, on the other hand, the mean fasting plasma lactate level decreased slightly from 1.45 mmol/L to 1.42 mmol/L at final visit, with a mean change from baseline of -0.01 mmol/L. Shift tables showed that 21 patients (10%) in the metformin group and 22 patients (10%) in the metformin/glyburide group had normal (or low) values at baseline and high values at final visit, compared to 11 patients (5%) with similar shifts in the glyburide group.

Patients with Clinically Significant Abnormalities: Fasting plasma lactate levels ≥4.0 mmol/L were defined as clinically significant. In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), there were three patients meeting this criterion at one or more visits: one patient in the metformin group and two patients in the placebo group. In the **metformin group**, *Patient 12/09* had moderately elevated plasma lactate levels at a number of study visits and a level of 4.0 mmol/L at Visit 5. Levels of other electrolytes were within normal limits throughout the study. In the **placebo group**, *Patient 1/19* had a plasma lactate level of 5.3 mmol/L at Visit 5 (possibly due to a difficult venipuncture) and *Patient 5/12* had a plasma lactate level of 4.6 at Visit 7. For both patients, levels of other electrolytes were generally within normal limits throughout the study.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023 [Vol.:1.120; Pg.:08B-05357]**), there were four patients in the metformin group, four patients in the glyburide group, and four patients in the metformin/glyburide group meeting the criterion for clinically significant abnormalities in fasting plasma lactate at one or more visits.

In the **metformin group**, four patients (*Patients 6/35, 12/34, 18/03, and 19/17*) had higher than normal plasma lactate levels at a number of study visits and transient, abnormally high lactate levels (≥4 mmol/L) at one or two visits. In the **glyburide group**, three patients (*Patients 7/05, 10/26, and 15/19*) had transient levels of fasting plasma lactate that exceeded 4 mmol/L. In addition to these three patients, one patient (*Patient 4/33*) had repeatedly high lactate levels without any known etiology. In the **metformin/glyburide group**, three patients (*Patient 2/02, 8/09, and 12/14*) had higher than normal plasma lactate levels at a number of study visits and transient,

abnormally high lactate levels (≥4 mmol/L) at one or more visits; all three patients were well, however.

There were no instances of lactic acidosis in either study. Certain general observations may be useful at this point. For example, a slight rise in lactatemia has no individual clinical significance but does suggest that the drug influences lactate metabolism at therapeutic doses, well under those that caused any change in animal models. This supports the idea that metformin has some relationship to phenformin, at least as far as induction of lactatemia is concerned.

10.2.3.2 Demography-Based Differential Drug Effects

In general, the overall incidence of AE/IMEs was comparable in males and females in all pooled studies. No clear patterns emerged except that in the U.S. and non-U.S. randomized studies, more females tended to report Digestive System symptoms than did males. This was accounted for by a higher incidence of diarrhea and nausea/vomiting in females.

In the pooled U.S. studies, the percentage of AE/IMEs occurring in those patients <65 and those ≥65 were comparable. The older age group, however, tended to report more asthenia, more Digestive System symptoms and to experience more hypoglycemia in these studies. In the pooled non-U.S. randomized study, the percentage of AE/IMEs occurring in patients ≥65 was greater than in those <65. Older patients in these studies also reported more asthenia. In the large Phase IV study (MET/D/86/HAUPT), somewhat greater percentages of AE/IMEs were reported by older patients, but no patterns of AE/IME occurrence could be detected. No clear racial differences in occurrence of AE/IMEs were noted excepted for a greater incidence of Digestive System symptoms in whites compared to blacks.

10.2.3.3 Drug-Induced Effects on Diseases

This discussion addresses the safety considerations in the administration of metformin to patients with established disease and includes analyses of AE/IMEs for patients receiving metformin alone or in combination with sulfonylureas by:

- baseline severity of NIDDM (as reflected by baseline FPG);
- renal impairment;

10.2.3.3.1 Baseline Diabetes Severity

Incidence of AE/IMEs by body system and by baseline value for fasting plasma glucose (<200 mg/dL vs. ≥200 mg/dL) for patients receiving metformin (either as monotherapy or in combination with sulfonylureas) were extracted from for the pooled Phase III U.S. studies. The AE/IME profile, by body system, for patients with FPG <200 mg/dL at baseline was essentially the same as that for patients with FPG ≥200 mg/dL at baseline. The only difference between the two groups of any note (>5%) was observed for the Respiratory System: 40% of the patients with baseline FPG <200 mg/dL reported AE/IMEs for this body system vs. 4% of the patients with baseline FPG ≥200

mg/dL.

10.2.3.3.2 Renal Impairment

Overview: Since metformin's primary elimination pathway is via the kidneys, decreases in renal function have considerable potential for having a negative impact on safety, through resultant metformin accumulation, producing an increased lactate load and risk of lactic acidosis.

Categorization of patients was attempted on the basis of basis serum creatinine (<1.4 mg/dL vs. ≥1.4 mg/dL) for the data generated from the U.S. Phase III controlled studies and the non-U.S. Category II studies. However, there were not enough patients with serum creatinine levels ≥1.4 mg/dL in these data bases to allow meaningful comparisons of these categories.

A published study by Sirtori et al showed that there was a significant prolongation of the half-life of metformin disappearance from plasma ($t_{½\,b}$) in renal-impaired patients (due to significantly reduced total plasma metformin clearance and renal plasma clearance) and a significant correlation between the $t_{½\,b}$ and the creatinine clearance ($r=0.88$, $p<0.001$). Tucker et al . studied the disposition of single doses of metformin in diabetic and non-diabetic subjects, having a spectrum of creatinine clearances ranging from 47-179 ml/min. On combining selected plasma and urine pharmacokinetic data from these subjects, a highly significant linear correlation was observed between metformin plasma renal clearance and creatinine clearance ($r=0.85$, $p<0.001$). There was also a significant linear correlation between metformin plasma total oral clearance and creatinine clearance ($r=0.66$, $p<0.01$), as well as between metformin plasma renal clearance and age ($r=0.76$).

In U.S. Study No. 90-13-6023 , decreases in the clearance of metformin with aging resulted in a 76% larger maximum plasma concentration (C_{max}) and an 85% larger maximum whole blood concentration ($C_{max,b}$) in elderly individuals, and a 60% larger extrapolated AUC (AUCX) in plasma and 70% larger AUCX in whole blood in the elderly group. These changes were primarily attributed to declining renal function in older patients, although there may be an independent function of age and suggest that the use of metformin in elderly patients carries a greater risk of potential metformin accumulation and its consequences.

Stocks et al. measured trough serum metformin levels, as well as serum lactate levels, in 15 NIDDM patients with normal renal function and in 18 diabetics on long-term metformin who were incidentally found to have renal insufficiency. Metformin serum concentrations were significantly higher in the patients with renal function impairment compared to those with normal renal function, on all dosing levels. Regression analysis indicated a linear relationship between lactate and serum metformin levels ($r=0.51$, $p<0.0001$). Lactate levels, however, were only slightly increased in the renal-impaired group compared to the group with normal renal function. Post-marketing surveillance reports (since 1984) of serious AE/IMEs in patients on metformin with abnormal renal function reveal that two-thirds of the cases of lactic acidosis (Total=99) had renal dysfunction (primary or contributory factor).

10.2.3.4 Disease-Induced Effects on Drug

10.2.3.4.1 Cardiovascular and Pulmonary Disease

Acute or chronic cardiovascular disease and acute or chronic pulmonary disease can both be considered independent risk factors for lactic acidosis, since they are conditions with a potential for tissue hypoxia and increased anaerobic metabolism with excess lactate production, on the basis of either poor tissue perfusion or poor tissue oxygen delivery. In addition, patients with such illnesses, particularly chronic cardiac disease, are very likely to be on one or more concomitant medications (e.g., diuretics, ACE-inhibitors) which can cause acute changes in fluid balance and may result in changes in renal perfusion and, consequently, renal function (particularly if the latter is borderline to begin with). This, in turn, could have deleterious consequences as far as the ability of the kidneys to eliminate metformin and resultant metformin accumulation, in turn, can further increase the lactate burden.

Among the 99 cases of lactic acidosis identified through post-marketing surveillance (73 cases from France and 26 cases from other countries), there were 15 patients (15%) with coexistent chronic cardiac disease. Diffuse vascular disease or hypertension, often in association with acute vascular occlusive events, was the background in 19 cases (19%). Six cases (6%) of the 99 cases had acute or chronic respiratory distress as the background for the development of lactic acidosis.

10.2.3.4.2 Chronic Hepatic Disease and Alcoholism

Since the liver is normally the major site of extraction of lactate from the blood, impairment of hepatic function by intrinsic disease or by the excessive acute or chronic ingestion of alcohol may interfere with this process and contribute to or induce hyperlactatemia and lactic acidosis. When increased lactate production and decreased utilization are simultaneously present, such as may occur with metformin plus excess alcohol intake, the extraction capacity of the liver may be even further taxed and lactate accumulation may occur. Cases of lactic acidosis occurring in alcoholics taking metformin have been previously described.

Among the 99 cases of lactic acidosis, identified through post-marketing surveillance, chronic 'hepatic' disease, secondary to chronic ethanol abuse, was associated with 17 of the cases (17%). Nine of these patients had an acute hepatorenal syndrome at the time that lactic acidosis developed.

Ethanol abuse was present in three other cases. In one case, an acute week-long alcoholic binge (with the background of chronic ethanol abuse) resulted in fatal lactic acidosis.

10.2.3.5 Drug-Drug Interaction

This section reviews the interactions of metformin with other drugs likely to be prescribed for the same patient population.

10.2.3.5.1 Metformin/Sulfonylurea in Combination vs. Metformin Monotherapy

Based on the analysis of U.S. Phase III Study No. 83-2D-6023, metformin/sulfonylurea combination therapy reflected the combined AE/IME profiles of the individual drugs for individual AE/IMEs as well as for body systems. The sole important exception to this overall trend was for the symptom of hypoglycemia, where the incidence of AE/IMEs for the treatment group receiving metformin/sulfonylurea was substantially higher than that of either of the monotherapy treatment groups. An increased incidence of hypoglycemia in this group, however, probably relates to two factors involved in the protocol design.

Firstly, as previously noted, all patients, prior to randomization, were on maximum dose glyburide (20 mg/day), for at least one month, and, despite such therapy, were considered to be "sulfonylurea failures". In fact, the mean fasting plasma glucose of the randomized population, as a whole, while on maximum dose glyburide (i.e., baseline determination) exceeded 250 mg/dL. As seen in the efficacy analysis, the group randomized to glyburide (in reality, *continuation* on glyburide) had deterioration of glycemic control during the course of the study and, thus, would not have been expected to experience much hypoglycemia.

Secondly, in order to facilitate interpretation of outcome, the protocol was designed to hold the glyburide dose constant at 20 mg/day in both the glyburide alone arm and the metformin/glyburide arm. In the event of hypoglycemia, the metformin dose was modified. This would be contrary to the course taken in clinical practice, where, in the event of hypoglycemia, the dose of sulfonylurea (which stimulates release of insulin) would be the more logical one to modify.

10.2.3.5.2 Review of the Findings of the Clinical Pharmacology Drug Interaction Studies, Relative to Safety

Single dose drug interaction studies were performed in healthy non-diabetic volunteers with metformin and the following drugs, considered to be representative of their class:

- Cimetidine (H_2-receptor antagonist) [Vol.:1.54; Pg.:06-003352]
- Nifedipine (calcium channel blocking agent) [Vol.:1.55; Pg.:06-003625]
- Propranolol (b-blocking agent) [Vol.:1.60; Pg.:06-004998]
- Furosemide (loop diuretic) [Vol.:1.56; Pg.:06-003903]
- Ibuprofen (non-steroidal anti-inflammatory agent) [Vol.:1.58; Pg.:06-004514]

A single dose drug interaction study was also performed in healthy diabetic volunteers with metformin and glyburide. Although there were no clinically relevant AE/IMEs occurring during the conduct of these single dose drug interaction studies, conducted for the most part in healthy volunteers, based on pharmacokinetic analysis, the following general statements can be made:

- Co-administration of cimetidine with metformin significantly increased plasma and whole blood metformin levels. Total and renal clearance of metformin was also decreased with cimetidine co-administration although this was not statistically significant. There was no effect of metformin on cimetidine pharmacokinetics. Theoretically, these observations suggest a potential impact with chronic use of both products, including possible

accumulation of metformin. It must be emphasized that I was not able to find direct study testing the possibility of interaction between metformin and at least the more commonly used sulfonylureas, seeing that both drugs may sometimes be prescribed for combination therapy. This is a weakness in the submission. It should be at least addressed in the labeling.

- Metformin plasma and whole blood concentration-related parameters increased during metformin and nifedipine co-administration, but metformin urinary excretion increased even more and metformin plasma elimination half-life was not affected. It appeared that nifedipine in some way increased the bioavailability of metformin, but without resultant accumulation of metformin. There was no effect of metformin on nifedipine kinetics.

- There were no significant changes in pharmacokinetics of either metformin or propranolol during co-administration of these drugs.

- Pharmacokinetic interactions which might have an impact on chronic use of metformin and furosemide include the observation that furosemide significantly increased metformin concentration-related parameters, while not affecting the plasma or whole blood half-life or clearance. It was considered that furosemide increased the bioavailability of metformin. Conversely, metformin co-administration resulted in a decrease in bioavailability of furosemide. The importance of this interaction (15-22% increase in metformin concentration and 13-31% decrease in furosemide concentration with single dose administration) will depend on the magnitude of the interaction when the two drugs are administered chronically. Currently, such information is not available.

- During the metformin/ibuprofen drug interaction study, no significant pharmacokinetic interaction was noted.

- During the single dose drug interaction study of metformin/glyburide, conducted in subjects with mild-to-moderate NIDDM, no effect of glyburide on metformin pharmacokinetics was noted during co-administration. Metformin decreased glyburide absorption by approximately 25% which was judged to be clinically insignificant.

10.2.3.6 Withdrawal Phenomena

There is no evidence of significant withdrawal effects apart from the loss of glycemic control.

10.2.3.7 Drug Abuse Potential

Glucophage® (brand of metformin hydrochloride) possesses no pharmacodynamic properties, either primary or secondary, which could be construed as conferring on it the potential for abuse as a recreational drug. Metformin has displayed no addictive liability or habit-forming activity in over thirty years of worldwide marketing experience. Consequently, no prospective studies were undertaken to further explore this property and the drug is not being proposed for scheduling as a controlled

substance.

11. LABELING REVIEW

11.1 Introductory statement

I shall now reproduce the labeling provided by the Sponsor, with my remarks in BOLD CAPITALS and in PARENTHESES, whenever I feel they are justified.

11.2 Drug Description

Metformin hydrochloride is a white or off-white crystalline compound with a molecular weight of 165.63. The empirical formula is $C_4H_{12}ClN_5$. Metformin hydrochloride is freely soluble in water and thus readily dialyzable. It is practically insoluble in acetone, ether and chloroform. The pK_a of metformin hydrochloride is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68 [Vol.:1.2; Pg.:03-000006]. Inactive ingredients are povidone, magnesium stearate and hydroxypropyl methylcellulose (hypromellose) coating.

11.3 Clinical Pharmacology

GLUCOPHAGE improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose [REDUCTION IN GLYCATED HEMOGLOBIN VALUES SHOULD BE PROVIDED AS THE FIRST AND MOST IMPORTANT EFFICACY END-POINTS]. Unlike sulfonylureas it does not reduce plasma glucose to hypoglycemic levels at therapeutic doses. Concomitant use of GLUCOPHAGE and an oral sulfonylurea may be effective in patients poorly controlled with either agent alone [THE SECOND HYPOGLYCEMIC AGENT SHOULD BE INTRODUCED AFTER THE EFFECTS OF THE FIRST ONE HAVE REACHED A STEADY-STATE AND HAVE BEEN QUANTITATED ADEQUATELY]. Monotherapy with GLUCOPHAGE may be effective in patients who have not responded to or who have ceased to respond to sulfonylureas. Body weight of individuals on GLUCOPHAGE tends to remain stable or may even decrease. [THE LAST SENTENCE SHOULD BE REPLACED BY: BODY WEIGHT OF INDIVIDUALS ON GLUCOPHAGE SHOULD BE MONITORED AND APPROPRIATE MEASURED TAKEN IF IT INCREASES ABNORMALLY. IT USUALLY IS NOT AFFECTED MUCH BY TREATMENT.] [Note: This sentence shouyld probably best under PRECAUTIONS].

GLUCOPHAGE has a [OMIT LAST TWO WORDS; REPLACE WITH: MAY HAVE A MODEST] favorable effect on serum lipid profiles, lowering mean fasting serum triglyceride, total cholesterol and LDL-cholesterol levels toward normal . [OMIT THE LAST TWO WORDS.]

Bioavailability after oral administration of a 500-mg GLUCOPHAGE tablet is greater than after administration of an 850-mg tablet. This lack of proportionality reflects dose-dependent absorption, rather than an alteration in elimination . Food decreases the extent, and slightly delays the absorption of GLUCOPHAGE .

No metabolites of metformin have been identified in man. The absorbed fraction is eliminated via

the renal route. Elimination half-life in plasma is approximately 5.6 hours . Pharmacokinetics of metformin are unaffected by multiple dosing in diabetics and non-diabetics with normal renal function .

Total oral plasma clearance of metformin is lower in healthy, [OMIT LAST WORD elderly subjects as compared to healthy, [OMIT LAST WORDyoung individuals . [ADD: VERY CAUTIOUS ADMINISTRATION TO THE ELDERLY IS MANDATED.]

11.4 Indications and usage

GLUCOPHAGE tablets are indicated:

1. as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia cannot be managed on diet alone;

2. in patients with NIDDM whose hyperglycemia cannot be managed by diet and a maximum dosage of a sulfonylurea;

GLUCOPHAGE tablets are effective alone or in combination with a sulfonylurea for the above indications. GLUCOPHAGE tablets may be used concomitantly with a sulfonylurea when diet and maximum recommended doses of either GLUCOPHAGE or sulfonylurea alone do not result in adequate glycemic control .

[ADD: THE LONG-TERM OBJECTIVE OF THERAPY SHOULD BE TO REDUCE GLYCATED HEMOGLOBIN VALUES TO THE UPPER NORMAL RANGE OR TO THE LOWER ABNORMAL RANGE.]

11.5 Contraindications

GLUCOPHAGE is contraindicated in patients with:

1. abnormalities of renal function (serum creatinine levels ≥1.5 mg/dl in males and ≥1.4 mg/dl in females);
2. conditions associated with acute or chronic hypoxemia ;
3. acute or chronic alcoholism ;
4. impaired hepatic function;
5. known hypersensitivity to metformin ;
6. diabetic ketoacidosis, with or without coma.

GLUCOPHAGE is also temporarily contraindicated in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials.

11.6 Warnings [THE UNDERLINED PARTS OF THE FOLLOWING WARNING SHOULD APPEAR IN A BOX AT THE TOP OF FIRST PAGE OF LABELING]

Lactic acidosis is a serious and often fatal metabolic complication which can **[OMIT LAST WORD, REPLACE BY: has]** occur**[RED]** **[ADD: IN A VERY SMALL NUMBER OF PATIENTS TREATED WITH METFORMIN. ALSO ADD A SENTENCE HERE TO BE PROVIDED BY OUR EPIDEMIOLOGIST, APPRECIATING AS BEST AS POSSIBLE THE RISK OF LACTIC ACIDOSIS PER PATIENT-YEAR OF TREATMENT.]** **[IT IS]** due to metformin accumulation during treatment with GLUCOPHAGE. MOST CASES HAVE OCCURRED IN ASSOCIATION WITH SERIOUS ACUTE MEDICAL ILLNESSES, PARTICULARLY THOSE WHICH INCLUDE DEHYDRATION, DETERIORIATION OF RENAL FUNCTION / AND/OR HYPOTENSION. HOWEVER, METFORMIN ASSOCIATED LACTIC ACIDOSIS CAN ALSO RESULT FROM CHRONIC CONDITIONS SUCH AS ALCOHOL ABUSE AND SLOWLY DEVELOPING RENAL INSUFFICIENCY. Lactic acidosis often has an insidious onset and nonspecific symptomatology which may include gastrointestinal symptoms, myalgias, malaise, respiratory distress and increasing somnolence. The patient and the patient's physician must be aware of the possible importance of such symptoms. GLUCOPHAGE should be **[IMMEDIATELY]** withdrawn until the situation is clarified by determination of serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels and even blood metformin levels.

The average incidence of lactic acidosis associated with metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in patients with significant organic or functional renal insufficiency WHICH MAY OCCUR SUDDENLY IN ACUTELY ILL PATIENTS. **[OUR EPIDEMIOLOGIST SHOULD REVIEW THIS SECTION ANC CORRECT IT, IF NEEDED].**

Lactic acidosis is a medical emergency which must be treated in a hospital setting. GLUCOPHAGE should be discontinued immediately. Prompt hemodialysis is recommended to remove the accumulated metformin. When metformin hydrochloride has played a significant etiologic role in the lactic acidosis, such management often results in prompt reversal of symptomatology and recovery.

11.7 Precautions

11.7.1 General

Renal function should be assessed before initiation of GLUCOPHAGE and monitored at least annually; GLUCOPHAGE should be discontinued with evidence of even mild renal impairment.

Concomitant medication(s) which may affect renal function and/or renal blood flow or results in significant hemodynamic change should be used with caution.

GLUCOPHAGE should be discontinued for at least 48 hours prior to the use of iodinated contrast materials as lactic acidosis has been seen in diabetic patients continuing to take GLUCOPHAGE and undergoing parenteral contrast studies. **[THIS PARAGRAPH SHOULD APPEAR IN BOLD IN THE LABELING.]**

Use of GLUCOPHAGE in patients prone to develop hypoxic states must be carefully considered as conditions characterized by hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. GLUCOPHAGE therapy should be discontinued when such events occur .

Although gastrointestinal disturbances are the most common adverse reactions to GLUCOPHAGE, patients should be instructed to notify the physician immediately at the onset of any of these symptoms (particularly if accompanied by hyperventilation), because these symptoms may herald the onset of lactic acidosis .

GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure and should not be restarted until the patient's renal function has been evaluated as normal . **[THIS PARAGRAPH SHOULD APPEAR IN BOLD IN THE LABELING.]**

Patients should be warned against excessive alcoholic intake, as alcohol is known to potentiate the effect of metformin on the dynamics of lactate metabolism .

Measurement of serum vitamin B_{12} levels on an annual basis is advised and any apparent deficiency should be investigated and treated . **[ANNUAL VITAMIN B12 INJECTIONS GIVEN EMPIRICALLY MAY BE A COST EFFECTIVE ALTERNATIVE. HOWEVER, SUCH THERAPY CAN MASK THE APPEARANCE OF MEGALOBLASTIC ANEMIA DUE TO FOLATE DEFICIENCY , WHICH CAN OCCUR AS THE RESULT OF NUTRITIONAL DISORDERS INCLUDING MALABSORPTION SYNDROMES AND ETHANOL ABUSE.**

A diabetic patient who develops laboratory abnormalities or clinical illness should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Acidosis of either form necessitates withdrawing GLUCOPHAGE immediately. **[THIS PARAGRAPH SHOULD APPEAR IN BOLD IN THE LABELING.]**

Hypoglycemia may occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or when GLUCOPHAGE is used concomitantly with other glucose-lowering agents .

Loss of control of blood glucose may occur when the patient is exposed to stress such as fever, trauma, infection, or surgery. At such times it may be necessary to discontinue GLUCOPHAGE and administer insulin.

11.7.2 Information for Patients

Patients should be informed of the following:

1. the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy;

2. the risks of lactic acidosis, its symptoms, and conditions that predispose to its development;

3. to discontinue GLUCOPHAGE immediately and promptly notify their health practitioner if nausea, vomiting, abdominal pain, hyperventilation, myalgias, malaise, or other nonspecific symptoms occur;

4. to avoid excessive alcohol intake while receiving GLUCOPHAGE;

5. the risk of hypoglycemia, its symptoms and treatment and conditions that predispose to its development;

6. the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of renal function and urine and/or blood glucose.

11.7.3 Laboratory Tests

[THE FOLLOWING TESTS SHOULD BE PERFORMED ON PATIENTS RECEIVING METFORMIN THERAPY:]

1. regular monitoring of blood glucose and glycosylated hemoglobin;

2. initial and periodic monitoring of renal function; [OMIT THE SENTENCE AND REPLACE WITH: URINALYSIS, SERUM CREATININE AND BLOOD UREA NITROGEN TO MONITOR RENAL FUNCTION, AT THE START OF THERAPY AND EVERY 3-6 MONTHS WHILE THERAPY CONTINUES.

3. annual monitoring of serum vitamin B_{12} levels or holo-TC II and hemoglobin/hematocrit. [REPLACE LAST SENTENCE WITH: SERUM VITAMIN B12, TRANSCOBALAMIN AND HEMOGLOBIN/HEMATOCRIT ANNUALLY].

11.7.4 Drug Interactions

1. A single dose metformin-glyburide drug interaction study in subjects with NIDDM has shown an approximately 20% decrease in glyburide AUC (AREA UNDER THE CURVE FOR A PLOT OF DRUG CONCENTRATION VS. TIME]and C_{max} [MAXIMUM DRUG COINCENTRATION REACHED] but no change in either metformin pharmacokinetics or pharmacodynamic parameters [IN BOLD: NO STUDIES OF METFORMIN'S INTERACTION WITH OTHER SULFONYLUREAS HAVE BEEN PERFORMED.].

2. Drugs which are eliminated by renal tubular secretion have the potential for increasing metformin plasma levels by decreasing metformin renal clearance. Such interaction between metformin and oral cimetidine has been observed .

3. A single dose metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Both the plasma C_{max} and blood C_{max} of metformin were increased by 22% and the blood AUC was

increased by 15%. It appears that furosemide increases the bioavailability of metformin. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller,respectively, than when administered alone. The terminal half-life was decreased by 32%. It is likely that furosemide's bioavailability decreased with metformin .

4. A single dose metformin nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, accompanied by an increase in urinary excretion. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine kinetics.

5. The results of a single dose interaction study with metformin and propranolol showed that propranolol caused an insignificant decrease in plasma metformin concentrations (approximately 6%) in healthy volunteers. Metformin had no significant effects on propranolol kinetic parameters.

6. A single dose drug interaction study was conducted in healthy volunteers with metformin and ibuprofen. The only change noted was a modest shortening of the T_{max} [TIME AT WHICH THE MAXIMUM DRUG CONCENTRATION IS REACHED] of both compounds, with co-administration.

7. Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed for loss of glycemic control. When such drugs are withdrawn from a patient receiving GLUCOPHAGE, the patient should be observed closely to avoid hypoglycemia.

11.7.5 Carcinogenesis, Mutagenesis, Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively, (approximately 3.2 and 2.6 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis). No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential of metformin was found in a battery of *in vitro* and *in vivo* mutagenicity studies .

Fertility of male or female rats (evaluated at dose levels as high as 600 mg/kg/day, or approximately 2.1 times the maximum recommended human daily dose on a mg/m^2 basis) was unaffected by metformin administration.

11.7.6 Pregnancy

Reproduction studies performed in rats and rabbits at doses up to about 2.1 times the maximum recommended human daily dose on a mg/m^2 basis have revealed no evidence of harm to the fetus or teratogenic potential due to metformin administration. Determination of fetal concentrations demonstrated a partial placental barrier to metformin .

11.7.7 Labor and Delivery

No information on this topic is presented in the proposed labeling

11.7.8 Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to plasma . Similar studies have not been conducted in nursing mothers. **[ADD: CAUTION SHOULD BE USED WHEN ADMINISTERING THE DRUG TO NURSING MOTHERS.]**

11.7.9 Pediatric Use

Safety and effectiveness in children have not been established. Studies in maturity-onset diabetes of the young have not been conducted.

11.7.10 Geriatric Use

Total oral plasma clearance of metformin was approximately 37% lower in healthy, elderly subjects as compared to healthy, young individuals. Volume of distribution and bioavailability were unaffected, resulting in a longer half-life in elderly subjects. The decrease in clearance resulted in a 76% higher maximum plasma concentration. The change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function .

11.8 Adverse reactions

Lactic acidosis **[UNDERLINE PRECEDING TWO WORDS, AND ADD A ":"]** (see Warnings and Precautions) .

Hyperlactatemia. mild elevation of fasting venous plasma lactate levels may occur during GLUCOPHAGE therapy. There is no consistent trend for GLUCOPHAGE to increase fasting lactate levels in subjects with lactate levels above the accepted upper limit of normal prior to treatment. Levels of venous plasma lactate above the upper limit of normal (but less than 5 mmol/L) in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis . **[THIS LAST SENTENCE SHOULD BE EITHER OMITTED OR MODIFIED. AS IS IT SUGGESTS THAT METFORMIN SHOULD BE USED EVEN IN THE EVENT OF HYPERLACTACIDEMIA, I SUGGEST THE FOLLOWING WORDING: Levels of venous plasma lactate above the upper limit of normal (but less than 5 mmol/L) in patients taking Glucophage MANDATE CESSATION OF THERAPY EVEN THOUGH SUCH LEVELS do not necessarily indicate impending lactic acidosis]**

Gastrointestinal: diarrhea, nausea, vomiting, abdominal bloating or increased flatulence, and anorexia are the most common and are dose-related. These symptoms are generally transient .

Special senses: approximately 3% of patients may complain of an unpleasant metallic taste in the mouth during initiation of therapy .

Hematologic: approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels .

11.9 Drug abuse and dependence

[No information on this topic is presented in the proposed labeling.]

11.10 Overdosage

Very limited information is available on the results of massive overdosage with GLUCOPHAGE. In suicide attempts, hypoglycemia has not been seen even with ingestion of up to 40 grams, but lactic acidosis has occurred under such circumstances. Hemodialysis is recommended for suspected metformin overdosage in order to facilitate removal of accumulated product .

11.11 Dosage and administration

[AFTER MEASURING THEIR GLYCATED HEMOGLOBIN VALUES, PATIENTS SHOULD INITIALLY BE ADMINISTERED 500 MG/D OR 850 MG/D, FOLLOWED BY AN UPWARD TITRATION TO 850MG B.I.D. THIS DOSE SHOULD BE MAINTAINED FOR THREE MONTHS AFTER WHICH GLYCATED HEMOGLOBIN SHOULD BE MEASURED AGAIN. IF THE RESULTS ARE NOT SATISFACTORY, THE PATIENTS SHOULD BE GIVEN 850 MG T.I.D. FOR ANOTHER THREE MONTHS AFTER WHICH GLYCATED HEMOGLOBIN SHOULD BE MEASURED AGAIN. IF THE THIRD GLYCATED HEMOGLOBIN VALUE SHOWS AN IMPROVEMENT OVER THE SECOND, THE DOSAGE SHOULD BE MAINTAINED. IF NOT, THE PATIENT SHOULD BE AGAIN GIVEN 850 MG B.I.D.]

[THE REST OF THE PARAGRAPH SHOULD BE MODIFIED TO BE CONSISTENT WITH THE PREVIOUS PARAGRAPH, I.E. THE FIRST PARAGRAPH OF SECTION 11.11 .]

There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOPHAGE and dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg.

During initial titration, GLUCOPHAGE should be given in divided doses with meals, starting at a low dose to reduce gastrointestinal side effects. Dosage increases, when required, should be made in increments of no more than one 500-mg tablet every week or one 850-mg tablet every other week. Dosage decreases should be made based on tolerance and effectiveness.

When transferring patients from oral hypoglycemic agents other than chlorpropamide no transition

period is necessary.

If patients have not responded to 4 weeks of the maximum dose of GLUCOPHAGE monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing GLUCOPHAGE at the maximum dose.

GLUCOPHAGE should not be used in patients >70 years of age.

In older patients and in debilitated or malnourished patients, the initial and maintenance dosing should be conservative and should be based on careful assessment of renal function.

11.12 How Supplied

GLUCOPHAGE Tablets are white, unscored, film-coated, cylindrical, biconvex tablets, available in the following strengths:

500 mg Bottles of 100	NDC
850 mg Bottles of 100	NDC

12. MEDICAL REVIEWER'S CONCLUSIONS AND RECOMMENDATIONS

12.1 Evolution of diabetes treatment modalities

12.1.1 Current advances

There are a number of significant advances occurring currently in the field, such that one might expect a dramatic improvement in the treatment of this disease during the next decade. These advances are in large part due to the following developments:

(1) During the last decade, the FDA has organized a number of informal encounters and formal meetings between experts from Academia, Industry and Government, to determine the known natural history and the probable physiopathological mechanisms of the diabetic complications. Later, the FDA helped define, again with expert outside help, a list of validated and feasible drug efficacy endpoints for each diabetic complication. Recently, the DCCT study conducted by the NIH proved that improvements of HbA1c of a certain magnitude do have clinically significant impact on the other diabetic complications (*neuropathy, retinopathy, and nephropathy*), thus confirming the causal relationships between hyperglycemia and the advent of the diabetic complications. The currently acceptable efficacy end-points fall into three categories: (a) direct efficacy end-points, clinical (e.g., reduction of the number of renal transplants in patients treated with the drug); (b) direct efficacy end-point, non-clinical (e.g., quantitative nerve histomorphometry); and, (c) surrogate efficacy end-points (e.g., *nerve* conduction velocity in *neuropathy*, or *microalbuminuria* in *nephropathy*).

(2) Academia and Industry discovered a number of new agents that could now be tested properly, given that proper efficacy end-points were now available.

The combination of these two series of events has increased the possibility that new anti-diabetic drugs may well be approved in the foreseeable future. Such drugs will be able to either correct hyperglycemia (albeit through various and different mechanisms of action than sulfonylureas), or attempt to directly mitigate or even correct the signs and symptoms of the various diabetic complications but without affecting glycemic levels.

12.1.2 Modalities of treatment

The FDA's worldwide experts have advised us that glycated hemoglobin values reflect the best current estimator of glycemic control of the diabetic. Also, that the aim of the treatment with hypoglycemic agents would be to attempt to bring glycemic values either to the upper range of normal values or to the lower range of abnormal values.

12.1.3 Different drugs that may be available in the future

We foresee the approval, within five to ten years, of any of the following two drug categories:

(1) New antihypoglycemic agents possessing one or more of following spectrum of effects/mechanisms of actrion: (a) increased secretion of endogenous insulin; (b) improved glucose transport into the insulin-target cells; (c) increased responsiveness of the insulin-receptors; and, (d) reduced synthesis and secretion of glucose.

(2) Non-hypoglycemic antidiabetic agents that will correct either the microvasculopathic (e.g., aldose reductase inhibitors), or the macrovasculopathic complications of diabetes.

12.2 Regulatory rules for the review of hypoglycemic antidiabetic agents

12.2.1 Efficacy end-points for hypoglycemic agents

HbA1c is considered to be a primary end-point, with FPG and other determinations of glycemia as supportive end-points. Glycated hemoglobin measurements have several advantages: they are slowly equilibrating, rather inert measurements, and they better sum up the complete effect of drug treatment over a 3-6 month period preceding the actual measurement. In other words, they measure better the overall effect of the drug. In addition, the quantitative correlation between improvement of HbA1c values and the clinical significance of treatment effects are now better appreciated. FPG, and other measures of glycemia, have also certain advantages: They affords a rapid and (in the latter case) a semi-quantitative appreciation of the immediate results of therapy. Being rapidly-equilibrating glycemic parameters, they can be used in a quantitative fashion provided that the effect of the drug on glycemia has attained its acme. Practically, as daily treatment is pursued with a given fixed dose regimen, FPG mesurements have to be performed serially till their values achieve a steady-state. Then, and only then, can one assert that a given dose has had its full and final impact on glycemia.

12.2.2 Safety issues and risk-versus-benefit analysis

The amount of improvement of HbA1c values is critical. Most experts agree, and the DCCT studies confirmed this in type I diabetic patients (and it is reasonable to extend most of their conclusions to type II diabetics), that an improvement of 1.0 to 1.5% units may be considered to have a favorable and clinically significant effect on the diabetic complications. In case lower corrective values are achieved, the safety of the drug has to be analyzed with a fine-tooth comb and even a potential for serious or severe toxicity should militate in favor of the rejection of the drug. For, after all, diabetes is a chronic condition which requires long-term (even lifetime) treatment. Under the circumstances, a drug has to be proved to be extremely safe if its efficacy is marginal. The fact that no actual toxicity has been seen in an NDA is neither here nor there: We all know that all drugs are toxic, and that their true safety profile can only be fully ascertained long after its approval -- if ever. Therefore, it appears to be wise to reject low or marginal efficacy hypoglycemic agent if serious doubts persist about their near absolute safety. For drugs resulting in a 1.0 to 1.5% units improvement of HbA1c values, a more traditional approach for the estimation of drug safety is perfectly adequate, since such drugs are fully expected to have a positive impact on the diabetic complications. Drugs with more than 1.5% units improvement of HbA1c values can be considered to be very effective.

12.3 Risk-versus-benefit analysis for Metformin

12.3.1 Favorable characteristics of metformin

Metformin should eventually be included in the antidiabetic armamentarium, and for the following main reasons:

(1) It is a relatively effective hypoglycemic agent, with an average effect of about 1.5% units reduction in HbA1c values in adequately treated patients;

(2) Its mechanism of action is different than that of sulfonylureas, currently the only hypoglycemic available in the U.S. markets. Sulfonylurea use is thwarted by the advent of so-called primary or secondary failure, i.e., the existence of an insufficient corrective effect on hyperglycemia in certain patients under sulfonylurea treatment. Thus, in such patients, the replacement by or the addition with an other hypoglycemic agent is an important addition to our therapeutic modalities;

(3) There are some indications that the addition of metformin to patients in whom sulfonylurea therapy is not effective anymore seems to restore sensitivity to continued sulfonylurea treatment. The probable mechanism of action is as follows: As proven with the addition of insulin to patients in whom sulfonylurea therapy has been ineffective, the reduction (with another agent) of glycemia has been shown to restore sulfonylurea effectiveness in such patients. In all probability, the same mechanism is in effect with metformin. In any event, this shows that the combination treatment with sulfonylurea and metformin has more than additive, i.e., a synergistic effect. This is, of course, a very desirable action, though it needs to be further delineated and established during future clinical research activities.

12.3.2 Worrisome features of the NDA as it presently stands

There is a fact of life that we have to state emphatically: If and when metformin is approved, a very

small yet finite number of treated patients will lapse into lactic acidosis and roughly one-third to a half of those will die. This is, essentially, predictable, though we do not know the exact frequency of such events. Under the circumstances, therefore, one is obligated to do whatever feasible at this stage to minimize this (and the other) toxicities of metformin, lest one be accused of being at least partly responsible for serious or lethal effects of the drug.

12.3.3 Proposed approach to our problem

Simply stated, the Company has to do something that it has not done as yet: To determine, in a representative sample of the indicated population, the LEAST DOSE THAT IS EFFECTIVE IN MOST PEOPLE.

The Sponsor affirms that they achieved this in their pivotal trials, where treatment was started at a low dose then force-titrated upward every week or every twqo weeks, and FPG values were also determined. The Sponsor states, in a communication dated 2/6/94: " It is clear that with each *incremental* increase in metformin dose, an additional effect on decreasing FPG is seen." This is factually true, but the Sponsor's conclusion from such data – that the higher metformin doses were more effective – is at best unproved, at worse incorrect. First, the facst: In two relatively recent publications (Kuzaya T et al. (1991). Diabetes Res Clin Pract 11: 147-53; and Kawazu S et al. (1987) Diabetes 36: 221-4, testing oral hypoglycemics in, respectively, 146 and about a hundred diabetics) the FPG values *continued* to *decrease* after 2 weeks, and even after 4 weeks of continued treatment at a fixed dose. In consequence, experts advise: "Patients on [oral hypoglycemics] should have blood glucose values measured once a month and glycosylated hemoglobin levels... once every three months to alert the clinician to the possible need to adjust therapy." (Peters AL & Davidson MB (1990), Clin Geriatr Med 6: 903-21). And why should it be otherwise when it comes to testing the full efficacy of a given dose of a new drug? The fact that FPG *measurements* quickly reflect changes in glycemia doesn't exclude the possibility that, over a relatively long period of time, the effect of a particular oral hypoglycemic agent, used at a given dose, may continue to correct the metabolic abnormality. Thus, it follows that if this happens, then FPG values will also decrease and take a while to stabilize. It is when FPGs values have stabilized (i.e., one has obtained at least two consecutive constant values of FPG) that the full effect of the tested dose can be assessed.

Therefore, we still need to obtain a proper dose response curve, using (for example) 700, 1400 and 2800 mg/d posology. We can suggest two acceptable ways of doing that, both approaches entailing the same basic protocolar methodology, i.e., the concurrent administration of different doses of the drug to randomely selected comparable and representative (stochastic) diabetic patients.

(1) Patients are treated for 3-6 months and, at the end of that period, HbA1c values are measured and compared to their eapective baseline values.

(2) Patients are treated as above and, for each dose level, FPG values are determined till they achieve steady state, thus indicating that the hypoglycemic agent has achieved its full pharmacologic effect at a given tested dose. Then, as in the previous case, the end-of-treatment FPG values are compared to their respective baseline values.

We thus believe that the choice of efficacy end-point during the determination of a dose-response curve is not crucial -- one could choose either FPG or HbA1c. What is crucial, however, is to continue to give the drug till the changes in the chosen endpoint cease altogether, indicating that the full effect of the drug is expressed in that particular endpoint value. The HbA1c value, when measured at baseline and after 3 to 6 months of treatment, is a better and more stable indicator of the full effect of a given dose. This is due to the fact that it responds more slowly to variations in glycemia. Over a longer period of treatment with a single given dose, this relative inertia of HbA1c values, will allow a better determination of maximal drug effect, provided that the treatment is maintained for at least 3 months. The observation, in "several hundred [diabetic] patients [that i]n about 50% [of them] [HbA1c] and FPG levels change... inm different directions from one visit to the next... [and that t]he two tests cannot be used interchangeably in the evaluation of diabetic control," (Aleyassine H et al. (1980), Diabetes Care 3: 508-14) is further proof that once a test is chosen, it should be used appropriately in order to make the results of a given study meaningful and interpretable. And if FPG is chosen as an end-point, drug treatment at a given dose ought to be continued for as many weeks as required to stabilize the decreasing levels of FPG in the treated patients.

Sadly, the Sponsor failed to do this. A weekly or semimonthly upward titration of dose is not adequate testing of a given dose, even though the FPG values continue to decrease with continued upwardly-dosed treatment. And to argue that this continuous fall of FPG (during a weekly upward adjustment of dose) is proof of the better effectiveness of the larger dose is a patent sophistry.

Finally, the labeling has to be corrected to inform the practising physician and the patient as well about about the exact modalities of treatment with metformin.

12.3.4 Primary Medical Officer's Final Recommendation

Metformin should be approved but only after the minimally effective dose has been determined by any of the above protocols, or any other that would legitimately achieve the same objective, i.e., to determine the minimally effective dose in the average patient.

For the time being, therefore, we are recommending deferral of approval until sufficient data are submitted to establish this dose.

12.3.5. Addendum After the Advisory Committee Meeting

The Advisory Committee Members, in their March 18, 1994 meeting, recommended approval of the drug with two provisos:

[1] That dosing be done in the following manner in individual patients: AFTER MEASURING THEIR GLYCATED HEMOGLOBIN VALUES, PATIENTS SHOULD INITIALLY BE ADMINISTERED 500 MG/D OR 850 MG/D, FOLLOWED WITHIN A WEEK OR TWO WITH AN UPWARD TITRATION TO 850MG B.I.D. THIS DOSE SHOULD BE MAINTAINED FOR THREE MONTHS AFTER WHICH GLYCATED HEMOGLOBIN SHOULD BE MEASURED AGAIN. IF THE RESULTS ARE NOT SATISFACTORY, THE

PATIENTS SHOULD BE GIVEN 850 MG T.I.D. FOR ANOTHER THREE MONTHS AFTER WHICH GLYCATED HEMOGLOBIN SHOULD BE MEASURED AGAIN. IF THE THIRD GLYCATED HEMOGLOBIN VALUE SHOWS AN IMPROVEMENT OVER THE SECOND, THE DOSAGE SHOULD BE MAINTAINED. IF NOT, THE PATIENT SHOULD BE BE RETURNED TO THE 850 MG B.I.D. DOSE].

[2] That a post-marketing surveillance be instituted to assess the rate of mortality of patients treated with metformin, according to a protocol submitted by our Dr. Bruce Stadel, Division Epidemiologist. The Committee approved unanimously Dr. Stadel's proposal. In fact, three members advocated a much more stringent protocol.

It seems reasonable in the Company's best interest to perform a dose-response study prior to engaging in the post-marketing surveillance.

Under these circumstances, and if the above conditions are met, I have no objections in recommending approval of the drug.

John L. Guerigulan, M.D.
Primary Reviewing Medical Officer
March 22, 1994

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Table 1.
Number of Patients Reported in the ISS Dataset by Treatment: All Studies

Study No.	Metformin	Placebo	Sulfonylurea	Met + Sulf	Total
U.S. Studies	351 (38%)	145 (16%)	209 (23%)	213 (23%)	918
Non-U.S. Randomized Studies	221 (43%)	134 (26%)	87 (17%)	72 (14%)	514
Non-U.S. Phase IV Studies					
MET/D/86/HAUPT	-	-	-	3724 (100%)	3724
MET/AM/87/PHASE[1]	4374 (100%)	-	-	-	4374
Total	4946	279	296	4009	9530

[1] Treatment: Predominantly metformin alone or in combination with sulfonylureas.

Table 2. Dosage Summary – All Studies in Integrated Data Base

Protocol	Duration of Treatment Period (Weeks)	Number of Patients from METFORMIN Groups	Statistic	Daily Dose of Metformin at Final Visit of Treatment Period			
				500-1000 mg/day	>1000-2000 mg/day	>2000-3000 mg/day	>3000 mg/day
87-1D-6023	29	143	n (%)	10 (7%)	20 (14%)	110 (79%)	0
87-2D-6023							
Monotherapy	29	210	n (%)	7 (3%)	15 (7%)	182 (89%)	0
METFORMIN + Glyb	29	213	n (%)	23 (11%)	46 (22%)	142 (67%)	0
MET/AM/84/DORF1	8	25	n (%)	0	0	24 (100%)	0
MET/AM/84/DORF2	8	25	n (%)	0	3 (14%)	18 (86%)	0
MET/GB/85/DORNA	32	30	n (%)	5 (17%)	17 (57%)	8 (27%)	0
MET/GB/86/BERGI	104	48	n (%)	0	44 (100%)	0	0
MET/GB/86/CAMP1	52	25	n (%)	10 (40%)	8 (32%)	7 (28%)	0
MET/AM/88/DUCHI	12	33	n (%)	0	32 (100%)	0	0
MET/S/86/HERMA							
Monotherapy	36	39	n (%)	9 (22%)	12 (32%)	17 (46%)	0
METFORMIN + Glyb	36	72	n (%)	32 (44%)	18 (25%)	22 (31%)	0
MET/D/86/HAUPT[1]	12	3724	n (%)	1931 (54%)	1450 (40%)	211 (6%)	1 (<1%)
MET/AM/87/PHASE[2]	26	4374	n (%)	355 (11%)	2956 (89%)	0	0

[1]Predominantly METFORMIN in combination with Glibenclamide.
[2]Predominantly METFORMIN alone or in combination with sulfonylurea.

TABLE 3.
Tabular Summary of Controlled Clinical Trials Included in the Integrated Summary of Efficacy

Protocol No., Country, (No. of invest.)	Study Design (Max. Daily Dose of M and Study Duration in Wks.)	Treatment Groups	No. Patients per Treatment Group (withdrawals)	Major Outcomes of Primary Efficacy Variables — Mean Change from Baseline at Final Visit					
				FPG (mg/dL)	PPG[1] (mg/dL)	HbA_{1c}[2] (%)	BW[3] (kg)	Chol (mg/dL)	Trig (mg/dL)
87-1D-6023, U.S. (13)	DB, PC, PG (2550 mg for 29 wks)	M	143 (31)	-83.04	-74.77	-1.37	-1.44	- 9.45	-38.74
		P	149 (41)	6.27	11.89	0.42	-2.38	1.81	1.93
87-2D-6023, U.S. (20)	DB, AC, PG (2500 mg for 29 wks)	M	210 (83)	- 0.86	- 1.27	-0.36	-3.43	- 4.00	-22.96
		G	209 (36)	13.73	2.20	0.24	-0.86	2.81	-26.15
		M+G	213 (21)	-63.47	-58.72	-1.69	0.91	- 9.25	1.42
MET/AM/84/DORF1, France (2)	DB, PC, PG (2550 mg for 8 wks)	M	23 (5)	-58.87	-48.64	-1.09	-3.50	-17.31	-37.77
		P	26 (11)	-19.09	0.85	-1.33	-4.01	-13.09	-21.97
MET/AM/86/DORF2, France (2)	DB, PC, PG (2550 mg for 8 wks)	M	28 (7)	2.34	-39.62	-0.29	-6.76	-17.49	-14.18
		P	25 (2)	- 2.09	33.82	0.34	-6.50	-12.97	-17.21
MET/GB/85/DORNA, England (1)	DB, PC, PG (3000 mg for 32 wks)	M	30 (6)	-57.01	-	-1.50	0.62	-17.86	-29.86
		P	32 (2)	50.14		1.73	-1.06	5.93	32.57
MET/D/86/BERGI, W.Germany (2)	OL, PG (1700 mg for 104 wks)	M	46 (21)	-	-	-0.24	-2.77	17.13	36.13
		Diet alone	51 (22)			0.03	-3.80	43.97	83.16
MET/GB/86/CAMP1, Scotland (1)	OL, AC, PG (3000 mg for 52 wks)	M	25 (5)	-74.67	-	-2.77	-1.93	20.66	5.06
		Glip	25 (2)	-60.93		-1.77	2.43	19.86	16.83
MET/AM/88/DUCHI, France (13)	OL, AC, PG (1700 mg for 12 wks)	M	33 (3)	-20.81	-26.69	-0.82	-2.36	-16.17	- 4.61
		Gliclazide	28 (1)	-30.04	-52.89	-0.74	-0.09	- 9.21	30.01
MET/S/86/HERMA, Sweden (10)	DB, AC, PG (3000 mg for 36 wks)	M short	36 (10)	-62.60	-	-	-	-	-
		Glib short	34 (6)	-62.45	-	-	-	-	-
		M+Glib short	72 (4)	-69.82	-	-	-	-	-
		M mono	24 (8)	-35.36	-50.97	-0.83	-0.77	- 6.96	- 4.15
		Glib mono	21 (4)	-38.11	-36.22	-1.26	2.84	4.86	7.50
		M+Glib low	47 (2)	-38.17	-36.66	-1.16	0.59	- 3.80	- 6.78
		M with Glib	13 (1)	-109.26	-77.26	-2.32	0.81	8.20	-76.96
		Glib with M	13 (2)	- 87.10	-79.24	-2.02	1.89	11.06	16.04
		M+Glib high	18 (3)	-109.33	-116.46	-2.11	0.24	-26.78	-44.17

[1] For 87-1D-6023 and 87-2D-6023: Oral Glucose Tolerance Test following a 75 gram glucose load was given.
[2] For MET/GB/85/DORNA, MET/D/86/BERGI, and MET/GB/86/CAMP1: HbA1 levels were measured in these studies.
[3] For 87-1D-6023 and 87-2D-6023: Weight was measured in pounds (lbs).

Table 4.
Serious/Potentially Serious AE/IMEs by Body System:
U.S. Phase III Studies (Pooled)[1]

Treatment Group	Metformin	Placebo	Glyburide	Met + Glyb
Total Number of Patients	n=351	n=146	n=209	n=213
Patients with any AE/IME	303 (86%)	114 (78%)	171 (82%)	186 (88%)
Patients with Serious/Potentially Serious AE/IMEs	26 (7%)	9 (6%)	12 (6%)	8 (4%)
Body as a Whole	6 (2%)	2 (1%)	4 (2%)	1 (<1%)
Cardiovascular	9 (3%)	2 (1%)	5 (2%)	1 (<1%)
Digestive	7 (2%)	1 (<1%)	2 (1%)	2 (<1%)
Metabolic & Nutritional Disorders	3 (<1%)	1 (<1%)	2 (1%)	1 (<1%)
Musculoskeletal	0	1 (<1%)	0	1 (<1%)
Respiratory	4 (1%)	0	1 (<1%)	0
Skin and Appendages	0	0	0	1 (<1%)
Urogenital	3 (<1%)	2 (1%)	0	0
Intercurrent Illness	0	1 (<1%)	0	2 (<1%)

[1] Studies 57-1D-6023 and 57-2D-6023.

Table 5.
Serious/Potentially Serious AE/IMEs by Body System:
Non-U.S. Randomized Studies (Pooled)[1]

Treatment Group	Metformin	Placebo	Sulfonylurea	Met + Sulf
Total Number of Patients	**n=176**	**n=83**	**n=87**	**n=72**
Patients with any AE/IME	**110 (63%)**	**32 (39%)**	**50 (57%)**	**61 (85%)**
Patients with Serious/Potentially Serious AE/IME	**20 (11%)**	**4 (5%)**	**7 (8%)**	**14 (19%)**
Body as a Whole	6 (3%)	3 (4%)	0	0
Cardiovascular	3 (2%)	1 (1%)	1 (1%)	3 (4%)
Digestive	7 (4%)	1 (1%)	2 (2%)	0
Metabolic & Nutritional Disorders	1 (<1%)	0	2 (2%)	7 (10%)
Musculoskeletal	1 (<1%)	0	0	0
Nervous	3 (2%)	0	1 (1%)	2 (3%)
Respiratory	3 (2%)	0	0	0
Skin & Appendages	1 (<1%)	0	1 (1%)	0
Special Senses	1 (<1%)	0	0	0
Urogenital	1 (<1%)	0	0	2 (3%)

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/86/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA

Table 6.
Serious/Potentially Serious AE/IMEs by Body System:
!MET/D/86/HAUPT

Body System	Metformin + Sulf
Total Number of Patients	n=3724
Patients with any AE/IME	664 (18%)
Patients With Any Serious/Potentially Serious AE/IME	156 (4%)
Body as a Whole	17 (<1%)
Cardiovascular	7 (<1%)
Digestive	105 (3%)
Metabolic & Nutritional Disorders	5 (<1%)
Musculoskeletal	5 (<1%)
Nervous	20 (<1%)
Skin & Appendages	6 (<1%)
Special Senses	6 (<1%)

Table 7.
Frequently Reported AE/IMEs by Symptom:
U.S. Controlled Phase III Studies (Pooled)

AE/IME	Metformin	Placebo	Glyburide	Met+Glyb
Total Number of Patients	**n=351**	**n=145**	**n=209**	**n=213**
Any AE/IME	**303 (86%)**	**114 (79%)**	**171 (82%)**	**188 (88%)**
Diarrhea	**177 (50%)**	**21 (14%)**	**25 (12%)**	**95 (45%)**
Nausea/Vomiting	**98 (28%)**	**14 (10%)**	**17 (8%)**	**54 (25%)**
URI	75 (21%)	32 (22%)	46 (22%)	67 (31%)
Asthenia	44 (13%)	16 (11%)	20 (10%)	24 (11%)
Headache	43 (12%)	18 (12%)	17 (8%)	29 (14%)
Abdominal Discomfort	40 (11%)	8 (6%)	22 (11%)	27 (13%)
Accidental Injury	32 (9%)	8 (6%)	16 (8%)	18 (8%)
Flatulence	32 (9%)	8 (6%)	15 (7%)	22 (10%)
Flu Syndrome	30 (9%)	8 (6%)	16 (8%)	18 (8%)
Back Pain	29 (8%)	10 (7%)	20 (10%)	13 (6%)
Arthralgia	26 (7%)	15 (10%)	15 (7%)	22 (10%)
Indigestion	25 (7%)	8 (6%)	8 (4%)	25 (12%)
Urinary Tract Infection	23 (7%)	13 (9%)	12 (6%)	18 (8%)
Myalgia	23 (7%)	12 (8%)	20 (10%)	13 (6%)
Pharyngitis	20 (6%)	7 (5%)	10 (5%)	19 (9%)
Vaginitis	12 (3%)	11 (8%)	16 (8%)	5 (2%)
Paresthesia	9 (3%)	12 (8%)	8 (4%)	10 (5%)
Thirst	7 (2%)	8 (6%)	8 (4%)	3 (1%)
Hypoglycemia	7 (2%)	1 (<1%)	7 (3%)	38 (18%)

[1] Studies: U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023.

Table 8.
Frequently Reported AE/IMEs by Symptom:
Non-U.S. Randomized Studies (Pooled)[1]

AE/IME	Metformin	Placebo	Sulfonylurea	Met+Sulf[2]
Total Number of Patients	**n=176**	**n=83**	**n=87**	**n=72**
Any AE/IME	**110 (63%)**	**32 (39%)**	**50 (57%)**	**61 (85%)**
Diarrhea	**57 (32%)**	**12 (14%)**	**1 (1%)**	**12 (17%)**
Nausea/Vomiting	**30 (17%)**	**4 (5%)**	**4 (5%)**	**3 (4%)**
Abdominal Discomfort	**23 (13%)**	**5 (6%)**	**3 (3%)**	**9 (13%)**
Indigestion	12 (7%)	3 (4%)	2 (2%)	3 (4%)
Asthenia	12 (7%)	1 (1%)	7 (8%)	22 (31%)
URI	8 (5%)	2 (2%)	7 (8%)	9 (13%)
Hypoglycemia	**8 (5%)**	**0**	**12 (14%)**	**24 (33%)**
Taste Disorder	8 (5%)	0	2 (2%)	2 (3%)
Constipation	7 (4%)	7 (8%)	3 (3%)	5 (7%)
Headache	7 (4%)	3 (4%)	2 (2%)	11 (15%)
Sweating Increased	7 (4%)	0	5 (6%)	5 (7%)
Dizziness	**6 (3%)**	**3 (4%)**	**8 (9%)**	**17 (24%)**
Lower Respiratory Tract Infection	**4 (2%)**	**0**	**3 (3%)**	**4 (6%)**
Urinary Tract Infection	**4 (2%)**	**0**	**2 (2%)**	**4 (6%)**
Thirst	**3 (2%)**	**1 (1%)**	**1 (1%)**	**8 (11%)**

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/85/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA.
[2] Consists of data from one study only: Non-U.S. Study No. MET/S/86/HERMA. The sulfonylurea used in this study was micronized glibenclamide.

Table 8. (cont'd)
Frequently Reported AE/IMEs by Symptom:
Non-U.S. Randomized Studies (Pooled)[1]

AE/IME	Metformin	Placebo	Sulfonylurea	Met+Sulf[2]
Abnormal Vision	3 (2%)	0	3 (3%)	5 (7%)
Pruritus	2 (1%)	1 (1%)	0	4 (6%)
Tremulousness	2 (1%)	0	14 (16%)	23 (32%)
Polyuria	2 (1%)	0	4 (5%)	5 (7%)
Appetite Increased	1 (<1%)	0	11 (13%)	6 (8%)
Anxiety/Tension	1 (<1%)	0	1 (1%)	4 (6%)
Angina Pectoris	1 (<1%)	0	0	3 (4%)

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/85/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA.
[2] Consists of data from one study only: Non-U.S. Study No. MET/S/86/HERMA. The sulfonylurea used in this study was micronized glibenclamide.

Table 9.
Frequently Reported AE/IMEs by Symptom:
Non-U.S. Study No. MET/D/86/HAUPT (Phase IV)

AE/IME	Metformin+Sulf
Total Number of Patients	n=3724
Any AE/IME	664 (18%)
Diarrhea	250 (7%)
Nausea/Vomiting	197 (5%)
Abdominal Discomfort	164 (4%)

Table 10.
Number of Patients Reporting Digestive Intolerance:
Non-U.S. Study No. MET/AM/87/PHASE (Phase IV)

	Digestive Intolerance		
Level of Intolerance	**Month 1**	**Month 3**	**Month 6**
Total Number of Patients	n=4252	n=4201	n=4158
No Intolerance	3282 (78%)	3376 (85%)	3412 (89%)
Mild	455 (11%)	419 (11%)	301 (8%)
Moderate	277 (7%)	134 (3%)	94 (2%)
Severe	188 (3%)	36 (1%)	11 (<1%)
Very Severe	51 (1%)	15 (<1%)	7 (<1%)

Table 11. U.S. Phase III Studies: Serum Vitamin B_{12} and Folic Acid Levels: Summary of Means and Changes from Baseline

Study No.	Folic Acid (NR: 2.5-17.0 ng/mL)	Vitamin B_{12} (NR: 200-900 pg/mL)
87-1D-6023		
Metformin		
Baseline Mean	8.9	490
FINAL VISIT	-0.9	-105
Placebo		
Baseline Mean	10.6	514
FINAL VISIT	+0.2	+12
87-2D-6023		
Metformin		
Baseline Mean	10.6	554
FINAL VISIT	+0.3	-144
Glyburide		
Baseline Mean	9.7	522
FINAL VISIT	+0.6	+13
Met+Glyb		
Baseline Mean	9.8	535
FINAL VISIT	-0.2	-138

Table 12. U.S. Phase III Studies: Serum Vitamin B_{12} and Folic Acid Levels: Summary of Shift Tables

Study No.	Folic Acid Normal and/or High to Low	Vitamin B_{12} Normal and/or High to Low
87-1D-6023		
Metformin	1 (<1%)	13 (11%)
Placebo	0	0
87-2D-6023		
Metformin	0	15 (9%)
Glyburide	2 (1%)	1 (<1%)
Met+Glyb	1 (<1%)	11 (6%)

Table 13.
Fasting Plasma Lactate: Summary of Means and Changes From Baseline (All Studies with Available Data)

Study No.	Lactate (NR: 0-2 mmol/L)
87-1D-6023	
Metformin	
Baseline Mean	1.41
FINAL VISIT	+0.04
Placebo	
Baseline Mean	1.40
FINAL VISIT	0.00
87-2D-6023	
Metformin	
Baseline Mean	1.47
FINAL VISIT	+0.08
Glyburide	
Baseline Mean	1.45
FINAL VISIT	-0.01
Met+Glyb	
Baseline Mean	1.45
FINAL VISIT	+0.06

Table 14.
Fasting Plasma Lactate:
Summary of Shift Tables
(All Studies with Available Data)

Study No.	Fasting Plasma Lactate Shifts	
	Normal and/or Low to High	High to Normal
87-1D-6023		
Metformin	12 (9%)	12 (9%)
Placebo	13 (9%)	12 (8%)
87-2D-6023		
Metformin	21 (10%)	8 (4%)
Glyburide	11 (5%)	12 (6%)
Met+Glyb	22 (10%)	15 (7%)

short

I N T E R O F F I C E M E M O R A N D U M

DATE: 27 January 1993

FROM: Bruce Stadel, MD, MPH
Medical Officer/Epidemiology, HFD 510 Bruce V Stadel

SUBJECT: NDA 20-357
Metformin (Lipha Pharmaceuticals)

TO: Ronald Innerfield, MD
Medical Officer/Endocrine Group 2, HFD 510

This replies to your request that I review NDA 20-357 with regard to strategies for evaluating the risk of lactic acidosis fatalities if metformin is approved for U.S. marketing. I have divided my comments into two sections: (1) recommendations for a postapproval study; (2) supporting information from the NDA and other sources.

RECOMMENDATIONS FOR POSTAPPROVAL STUDY

I recommend that, if metformin is found to be approvable for marketing based upon currently established procedures for NDA review, the approval itself should be contingent upon a binding agreement, between the FDA and the Sponsor, that the Sponsor will establish and maintain a registry of persons exposed to metformin in the U.S., and will periodically link this exposure data to national death registry data. Optimally, this should be done in the context of a large randomized trial which would register exposure to both metformin and one or more control treatments, and then compare overall and cause-specific death rates for the metformin and control group(s). If a sufficiently large randomized trial proves to be infeasible, an observational (nonrandomized) cohort study should be considered, using methods similar to those described above, except that: (1) exposure to the metformin and the control treatment(s) would be registered without randomization, and (2) analytic methods for observational cohort studies would be used for the detection and control of confounding.

If a decision is made to approve metformin contingent upon the type of study described above, I recommend that the following steps be taken in negotiation of a study protocol:

1) The Division should prepare a briefing document for the Sponsor which explains the study objectives and defines the requirements for developing a protocol. If you wish, I could prepare a working draft of the briefing document, and revise this in collaboration with you.

2) The Division should meet with the Sponsor to review the briefing document and negotiate any changes that are warranted in the protocol development requirements.

3) The Sponsor (or its contractor) should develop and submit a complete written protocol to the Division.

4) The Division should obtain written peer review of the protocol by at least two independent reviewers, and communicate the findings to the Sponsor.

5) The Sponsor should submit a revised protocol, which responds to the issues raised by the reviewers, for final negotiation with the Division.

SUPPORTING INFORMATION

A need for national registration and mortality follow-up of persons exposed to metformin, if the drug is approved for U.S. marketing, is supported by the following considerations:

1. The number of reported deaths from lactic acidosis and the litigious atmosphere which led to the 1979 withdrawal of approval of all NDAs for phenformin emphasize the general importance -- to diabetics, physicians, the Sponsor, and the Agency -- of establishing a visible and credible "safety net" if metformin is approved for U.S. marketing.

2. The NDA emphasizes that, in countries where metformin has been marketed, only about three cases of drug-associated lactic acidosis per 100 000 person-years (PY) of use have been reported, on average, to the regulatory authorities; approximately one-half of these have been fatal. (Table 1) However, it is known that adverse drug experience (ADE) reporting to regulatory authorities is incomplete, and thus underestimates true incidence -- even for serious events that are clinically distinct, such as lactic acidosis associated with metformin or other biguanide hypoglycemics.

   Table 2 provides data relevant to the underestimation of biguanide-associated lactic acidosis by regulatory reporting, from a two-part study in Switzerland -- where phenformin, buformin, and metformin were all available to physicians during the years 1972-77.

   - Part I of Table 2 shows results from a retrospective mail questionnaire which requested information about cases of biguanide-associated lactic acidosis from physicians in all parts of Switzerland except the city of Basel. This

methodology is similar to regulatory reporting in that physicians are motivated to report the clinical event only after it has occurred. The findings are also similar to those from regulatory reporting: for metformin, eight per 100 000 person-years (PY) of use were found, compared to the average of three cases per 100 000 PY shown in Table 1. For phenformin, 64 cases per 100 000 PY of use were found, which is identical to the finding from Swedish regulatory reporting for the years 1975-77. (NDA, page 08A-08119)

- In contrast, Part 2 of Table II shows the results from prospective identification of biguanide-associated lactic acidosis cases in the city of Basel. In this part of the Swiss study, physicians were recruited to identify cases before they occurred. For phenformin, 480 cases per 100 000 PY of use were found, compared to 64 per 100 000 PY from the retrospective questionnaire. Likewise, for buformin, 292 cases per 100 000 PY were found, compared to 40 cases per 100 000 PY from the retrospective questionnaire. No cases were found for metformin in the prospective part of the study, but the 95% confidence interval is very compatible with the 7-fold difference seen for phenformin and buformin.

From the Swiss study, it appears that reporting to regulatory authorities represents only about 1/7th, or 15%, of the true incidence of biguanide-associated lactic acidosis. In my experience, this is consistent with other findings on the completeness of regulatory reporting for serious events that are clinically distinctive.

3. The clinical trials supporting the NDA were restricted to persons without renal disease or other conditions that are are considered by the Sponsor to be contraindications. While this is appropriate for the trials themselves, it also means that the trials provide no information on the risk of lactic acidosis that may arise in the U.S. if the drug is not used as labeled. The following quotations from the 6 April 1979 Federal Register publication on the withdrawal of approval of NDAs for phenformin are pertinent in this regard:

   - "The 1970-1976 labeling did not result in limiting the use of phenformin to those patients for whom it was not contraindicated . . ."

   - "The current labeling . . . is designed to restrict its use to only those patients with none of the lactic acidosis predisposing risk factors."

- "The current labeling cannot reasonably be expected to result in the detection of those persons for whom phenformin is contraindicated."

4. Finally, I am concerned about the possibility that alcohol usage may synergize with metformin to increase the risk of lactic acidosis even when the metformin blood level is normal (<5 ug/ml), or nearly so. Table 3 compares metformin blood levels for lactic acidosis cases reported in the NDA who did and who did not have "ethanolism" listed as a COSTART term. The cases with metformin levels of 5-9 ug/ml were 2.0 times more likely than the cases with levels of 10 ug/ml or higher to have "ethanolism," and the cases with level of <5 ug/ml were 2.7 times more likely to have this term.

Table 1

Reporting of Metformin-Associated Lactic Acidosis
to Regulatory Authorities
in Countries Where Metformin is Marketed

PY = Person-years
CI = Confidence Interval

Country	Years	PY of Treatment	Cases (N)	Per 100 000 PY	(95% CI)
U.K.	1976-86	400 000	11	2.8	(1.1-4.4)
Switzer-land	1972-77	29 800	2	6.7	(0-16.0)
Sweden	1972-81	83 500	7	8.4	(2.2-14.6)
	1987-91	100	3	.0	(0-6.4)
Canada	1972-82	56 000	0		(-)
France	1984-92	2 476 061	73	2.9	(2.3-3.6)
TOTAL		3 145 461	96 46% fatal	3.1	(2.4-3.7)

Source: Adapted from NDA, page 02 000512.

TABLE 3

Metformin-Associated Lactic Acidosis Cases
In Countries Where Metformin is Marketed
By
Drug Level and History of Alcoholism

Drug Level (ug/ml)	History of Alcoholism Yes	No	OR	(95% CI)
10+	5 (25%)	30 (29%)	1.0	(reference)
5-9	2 (10%)	6 (6%)	2.0	(0.3-12.8)
<5	9 (45%)	20 (19%)	2.7	(0.8-9.3)
unk	4 (20%)	49 (47%)		
	24	105		

Source: Computed from Adverse Drug Experience reports submitted in the NDA.

cc: NDA 20-357
Division file
HFD 510 Sobel/Troendle/Fleming/Gueriguian/Innerfield

Table 2

Retrospective Physician Questionnaire Versus Prospective Study
Identification of Biguanide-Associated Lactic Acidosis
Switzerland, 1972-77

Phen = Phenformin
Bu = Buformin
Met = Metformin
PY = Person-years
CI = Confidence Interval

Retrospective Physician Questionnaire
(All of Switzerland Except City of Basel)

Drug	PY of Treatment	Cases (N)	per 100 000 PY	(95% CI)
Phen	6 241	4	64	(1-127)
Bu	52 649	21	40	(23-57)
Met	24 226	2	8	(0-20)

Prospective Study
(City of Basel)

Drug	PY of Treatment	Cases (N)	/ 100 000 PY	(95% CI)
Phen	417	2	480	(55-1730)
Bu	4 458	13	292	(133-450)
Met	1 070	0		(0-344)

Source: Adapted from NDA, PAGE 08A 08118.

NOV 29 1994

NDA 20357
Lipha Pharmaceuticals
Drug: Glucophage

Received: 11/24/94
Reviewed: 11/29/94
Doct: N20357B/G105

FINAL SAFETY UPDATE
Amendment # 24 (5/19/94)
Amendment # 34 (11/21/94)

Introductory Comments

We have received, from Lipha Pharmaceuticals, four volumes -- the first one in February 27, 1994; the second one in May 24, 1994 and the last two in November 25, 1994 -- as safety updates of NDA 20357, Glucophage tablets, an hypoglycemic agent belonging to the biguanide chemical family. The first volume was reviewed, I am told, by Dr. Ron Innerfeld. I have been asked to review the other three as a final safety update for this NDA.

For information, glucophage (or, generically, metformin) has been recommended for approval by our Advisory Committee members, the Group Leader, as well as this reviewer.

First and foremost it should be indicated that the approval was contingent upon the following two conditions:

(1) Labeling modifications suggested by ourselves and the Advisory Committee members. It should be stated that the Company has accepted all these modifications. In addition, during a meeting held November 28, 1994, and chaired by our Division Director, a few modifications were suggested by some of the participants, and in particular by our Pharmackoniticist. The Company will receive and, no doubt,

respond positively to these additional corrections. By common accord, the participants of that meeting seem to feel that this latest draft of the labeling is final and is most satisfactory, inasmuch as it would be extremely helpful to both prescribed physicians and treated patients.

(2) Specific phase IV studies, to be performed by the Company, to address the last uncertainties with respect to potential safety issues, and particularly lactic acidosis but also possible cardiovascular mortality increase. Indeed,metformin belongs, as stated above to the chemical class of biguanides. Another biguanide -- phenformin -- was implicated, almost two decades ago, in a number of deaths after lactic acidosis and was therefore removed from the marketplace by the then Secretary of Health and Human Services Califano. Given the balance of all available evidence, metformin has been shown to be much less harmful than phenformin in this regard. Nothing in the initial NDA seems to suggest any unmanageable situation, particularly if one compares expected benefits from known or potantial toxicities. Nevertheless, our Advisory Committee members recommended a phase IV follow-up study and our Dr. Bruce Stadel, divisional epidemiologist, suggested a very reasonable and feasible protocol for such a study. This issue is discussed elshewhere and does not belong in this review specifically geared for a final safety update of the drug. Suffice it to say that the Company and the Agency seem to have agreed on a protocol for this follow-up phase IV study. The only difference to iron out is the length of the study: The company would like it to be for six months, the Agency ought to insist to obtain a full year.

Safety Update 17, dated February 23, 1994

As stated in my introductory paragraph, I have was told earlier: that particular amendment was reviewed by Dr. Ron Innerfeld. The reader is therefore referred directly to it.

Safety Update 24, dated May 19, 1994

This particular update incorporated all the adverse events occurring in France, during the calendar year 1993 -- at least those which were reported to Lipha S.A. and which,

in turn, where transmitted by the Company to the French National Commission on Pharmacovigilance. In addition, the following items were also included in this particular amendment: A general discussion of the above reported cases, particularly referring to the cases of lactic acidosis; and a number of safety reports received from Australia, Belgium, Canada, Germany, Sweden, and Switzerland.

The most important information is that, during the 1993 calendar year, 15 cases of lactic acidosis were reported in France, 7 of which occurred in individuals with impaired renal function, and five of which were due to overdosing during a suicide attempt. This justifies our requirement to have the Company perform a phase IV study to estimate with greater precision than heretofore the incidence of lactic acidosis in a treated U.S. population, particularly since the mortality rate in the 10 non-suicidal lactic acidosis cases was 70%. On the other hand, not all reported cases of lactic acidosis occurred during the course of a normal treatment. Indeed, as stated above, one third of the lactic acidosis cases were linked to voluntary overdosing by people attempting suicide. The record also shows that at least some of these patients had documented psychiatric problems, presumably antedating their treatment with metformin.

The mortality incidence of deaths by lactic acidosis is estimated at 19 per 1,000,000 human years, based on the known sales figures in France during 1993. The incidence of lactic acidosis is estimated at 30 per 1,000,000 human years. Ths latter is to be compared with the following previously obtained estimates:1984-85 (40 cases per 1,000,000 human years), 1985-86 (30), 1986-87 (25), 1987-88 (38); 1988-89 (32), 1989 (32), 1990 (30), 1992 17). Thus, a certain consistency is apparent in the 1984-1993 period, at least in the number of reported cases. In addition, since the lactic acidosis potential of biguanides has been heavily reported, it is lilely that undereporting should be of a lesser magnitude than on average.

During 1993, France show only 1 case of reported hypoglycemia, suggesting that this particular side-effect may well have been underreported. Still, metformin -- atleast on theoretical grounds --should be less conducive to hypoglycemia than oral sulfonylureas.

Other serious or severe reaction reports from France include the following: Jaundice (1 case), acute renal insufficiency (1), pulmonary fibnrosis (1), and suicide attempts (5). The causality between metformin and the above-mentionned adverse events is not established. The jaundice was apparently due to cholelithiasis.

The reports from the other countries are less complete and sophisticated than the French one, and do not reveal any novel finding. The following items may be of interest: (1) a report of a drug interaction between metformin and phemprocoumon (an anticoagulant), (2) a case of chronic vaginal candidiasis which improved after metformin withdrawal and recurred upon reintroduction of the biguanide therapy, and, (3) a case of alopecia with no evidence of conclusive metformin involvement in its genesis.

Safety Update 34, dated November 21, 1994

This particular update lists and discusses in some length all the adverse events reported in the following countries: Australia, Belgium, France, Germany, New Zealand, the Netherlands, the United States (from clinical trials conducted in the country), and Sweden, through October, 1994. As expected, the greatest details are available only from the French reports. In addition, fifteen published worldwide reports are appended to the submission, concerning the safety of metformin.

A careful scrutiny of the supplied data does not raise any novel concerns with respect to the safety of the drug. Dr. Innerfield's original safety review of the NDA had raised a concern about the potential for untoward cardiovascular effects for metformin. Outside experts (e.g., members of our Advisory Committee, representatives of the American Diabetes Association, and other invited experts, including Dr. Turner from England, the monitor of the ongoing UKPDS trial) didn't seem to think that this concern was based on substantive data. This submission itself does not seem to support such concerns, nor does it allow it to be put conclusively to rest. We can, however, offer the following comments: (1) Sulfonylureas have been found to cause excess deaths during the UGDP trial and the language that has been introduced in their labelling, as a result of

that observation, is also present in the proposed metformin labeling; and, (2) the phase IV study that the Company has accepted to perform, on the suggestion of our Dr. Stadel, may well address this issue, though its main focus is on lactic acidosis.

The final recommendation is to approve provided that the Company sends us a protocol for the study suggested by Dr. Stadel and mandated by our Advisory Committee, and that the Company accepts a 1-year period for the length of that study.

John L. Gueriguian
Medical Officer
11/29/94

for Dr. Fleming
11/29/94

cc.
The File
Dr. Sobel
Dr. Troendle
Dr. Fleming
Dr. Stadel
Dr. Gueriguian

Safety Update Review

February 23, 1994
#17-94

VIA FEDERAL EXPRESS, #1297777725
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #17
Update on Safety Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

Enclosed is an update on safety information, subsequent to our NDA submission on September 29, 1993. These data are derived from our long-term, open-label safety study, identified as U.S. Study No. 89-1C-6023 (*"The Safety and Effectiveness of Long-Term, Open-Labeled Metformin Treatment in Obese, Non-Insulin Dependent, Diabetes Mellitus (NIDDM) Patients--An Extension Study of Protocols #87-1D-6023 and #87-2D-6023"*).

This study, which continues to be under analysis, was described, in general, in Item 8, Section 8.5.3.1.1 (*Volume 1.81, Pages 08A-00604 through 08A-00610*) of the NDA. Also included were narrative summaries on all patients prematurely terminated for either an adverse experience/intercurrent medical event or significantly abnormal laboratory result and for all patients who had died (*Item 8, Section 8.16.1, Volume 1.189, beginning on Page 08B-29753*).

The current submission consists of the following:

PART 1.A

Table I.a. **A listing of all adverse experiences/side-effects reported during the study** (including those present at "Baseline"), by both COSTART Body System and specific events, according to **severity** of event.

The numbers of patients reporting events in any COSTART Body System and the numbers of events within that Body System are provided, as well as the numbers of individual events.

As noted on the page preceding this table, multiple episodes of the same event have been counted only once, listed according to the **worst** reported severity. (It should be noted that severity was judged *by the individual investigator* and no standard severity scale guidelines were provided for any event).

Table I.b. This table lists those events, according to severity, which were thought, *by the individual investigator*, to have **any** relationship (possible, probable or definite) to study drug administration.

The numbers of such patients reporting events, according to COSTART Body System, and the numbers of events within that Body System are provided, as well as the numbers of individual events and their severity (listed according to **worst** severity, if occurring more than once).

Table I.c. This table lists those events which, according to the investigator, were thought to have any relationship to study drug administration by event and **by suspected relationship**. As with "severity", the highest degree of causality was used, when an event occurred more than once with different investigator-assessed causality relationships.

PART 1.B
Appendix 5.9, Part 3 of 13, Electrolytes/Lactate
(for Final Report of Study No. 89-1C-6023)

This listing provides individual patient electrolye and lactate values, as well as the calculated anion gap (one page per patient), for all enrolled patients in Study No. 89-1C-6023, alphabetically by investigator and according to prior treatment group (i.e., treatment group during the prior double-blind studies).

It should be noted that values given for Visit 1.00 may represent the Final Visit value from the prior double-blind study (Study No. 87-1D-6023 or Study No. 87-2D-6023) or may be a true "Baseline" value (i.e., blood sampling while on no anti-diabetic medication or while on other anti-diabetic treatment [e.g., open-label sulfonylurea], prior to enrollment in Study No. 89-1C-6023, if a hiatus occurred between the two studies of more than two weeks). Thus, patients may have been on any of the following regimens at the time of that visit: metformin alone, metformin + glyburide, glyburide alone, placebo, diet only, other commercially available sulfonylurea, or even insulin. At the present stage of our analysis of the data, the precise information, relative to this visit, is not available on the listing.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided. Please provide one CLINICAL copy to Dr. Ronald Innerfield.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies

INTEROFFICE MEMORANDUM

DATE: 30 September 1994

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology Bruce V Stadel

SUBJECT: Proposal for Phase IV Safety Study
NDA 20-357/Glucophage (metformin)/Lipha Pharmaceuticals

TO: Solomon Sobel, MD
Director, Division of Metabolism & Endocrine Drug Products

The Division has received a draft proposal from Lipha for a Phase IV Safety Study of metformin (attachment 1), in response to the Division's letter to Lipha, of 29 July 1994, requesting such a proposal (attachment 2).

Lipha's draft proposal is dated 31 August 1994. However, I did not learn of the document's existence until 20 September, when Mr. John Short asked me if I had reviewed it. I replied that I was unaware of the draft proposal, and Mr. Short offered to provide a copy. I received a copy from Mr. Short later on 20 September, with a note that he could not find the archival copy, and had obtained another by fax from Lipha. (attachment 3)

In my opinion, the draft proposal from Lipha is self-explanatory and provides a well-considered approach, on a preliminary basis, to each of the five issues that are specified on page 2 of the Division's 29 July letter as being important for a "satisfactory" Phase IV Study protocol, i.e.: representativeness, confounding, power, validation, and timeliness. I therefore recommend that:

1) An internal meeting be scheduled involving appropriate staff from DMEDP and the Division of Biometrics, for review of the Lipha draft proposal, to identify issues for discussion with Lipha prior to Lipha's submission of an actual detailed protocol.

2) A subsequent meeting be scheduled with Lipha, to discuss the issues identified in the meeting described under (1) above. (Lipha has requested such a meeting, on page 2 of the cover letter for the 31 August draft proposal submission.)

3) Formal written review be solicited from an ad hoc panel of experts, of the actual detailed protocol submitted by Lipha after the meeting described under (2) above, in accordance with the procedures described on page 1 of the Division's 29 July letter.

cc:
NDA 20-357
HFD 510/FlemingA/GuerriganJ/ShortJ/StadelB
HFD 730/MarticelloD

E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: DEC 29 1994

FROM: Gregory A. Burkhart, MD (HFD-733)
Epidemiology Branch

William R. Fairweather, PhD (HFD-715)
Chief, Statistical Application & Research Branch

SUBJECT: NDA 20-357 Metformin

TO: The File

This memo deals with statistical and epidemiological issues that have arisen regarding the analysis and interpretation of deaths observed in clinical studies of this product. We reviewed the following documents:

- Dr. Stadel's memo "Death Review - NDA 20-357 . . ." dated May 18, 1994
- Dr. Innerfield's Medical Officer review dated May 19, 1994 (safety section only)
- Dr. Innerfield's Memo to File dated July 18, 1994
- Dr. Stadel's memo dated August 18, 1994 and reissued September 9, 1994 responding to Dr. Innerfield's July 18 memo

The purpose of our review is to evaluate the appropriateness of the statistical and epidemiological methods used by Drs. Innerfield and Stadel in their analyses of the number of deaths during metformin's use in clinical trials. It is not an independent reanalysis of the original data.

Background

Study 1D was a 29-week comparison of metformin to placebo, and 143 and 146 patients were randomized to these treatments, respectively.

Study 2D was a 29-week comparison of metformin (210 patients randomized), glibenclamide (209) and metformin/glibenclamide (213).

Study 1C was an open enrollment continuation of both 1D and 2D. In this study, all patients received metformin and some also received glibenclamide. Study 1C lasted 4x29=116 weeks.

NDA 20-357 Metformin

Overall, 20 deaths occurred in the studies contained in NDA 20-357, with

1 occurring in Study 2D,
6 occurring in Study 1C,
2 occurring in other controlled trials - one on glibenclamide and one on metformin/glibenclamide, and
11 occurring among 4,374 patients in France in a study comparing metformin to metformin/sulfonylurea. The focus of the documents cited above was primarily on the 7 deaths that occurred in the 2D and 1C studies.

These 7 deaths all occurred while the patients were receiving either metformin or metformin/glibenclamide. Five of the deaths were due to cardiovascular events. There were no deaths among patients who received only glibenclamide or glibenclamide followed by any metformin. Also, all deaths occurred to patients originally enrolled in 2D; no patients in either treatment group of the 1D study died. The patients in 1D had less advanced or less serious disease than did those in 2D.

Approximately 210 patients were entered into each of the three treatment arms of Study 2D (Table 1). A relatively larger proportion on the metformin/glibenclamide combination completed study 2D. Of those who completed 2D, approximately the same proportion entered 1C (Table 2). By design, all patients in 1C received metformin.

There are a number of issues here:

- Is an Intent-to-Treat analysis meaningful?
- Should the 1D and 2D patients be pooled for analysis?
- Are external controls necessary for the interpretation of these observed mortality rates?
- Are analyses of simple proportions meaningful?
- Were statistical analyses correctly performed?
- Were the studies large enough to permit a meaningful assessment of deaths?

Intent-to-Treat

Dr. Innerfield evaluates the survival of the patients in the 1D and 2D studies in accordance with their original randomization either to any metformin or to control - an Intent-to-Treat (ITT) analysis - despite the fact that after the initial 29-week period, all patients who continued into Study 1C for possibly another 116 weeks received metformin. He states that the difference in proportion of deaths between those randomized to any metformin and those randomized to glibenclamide at the beginning of 1D and 2D is significant at the $P<.05$ level.

Dr. Innerfield's choice to analyze the patients in 1C based upon their initial assignment in 1D and 2D ignores their exposure to metformin in 1C. In fact, patients nominally assigned to the "control" group actually received about 4 times as much exposure to metformin as to their control medication, not counting any concomitant glibenclamide they received in 1C.

Because of the study design, there are few statistically valid comparisons available from the 1D/2D/1C study. The ITT analysis is possible but doesn't reflect the actual experiment very well. Dr. Stadel recognized these limitations to the ITT analysis and proposed or conducted alternative analyses.

Pooling of 1D and 2D

Dr. Innerfield pooled all of the data (564 patients randomized to any metformin in 1D or 2D vs 354 patients on any control), although there appears to be a different level of risk between patients in 1D and those in 2D because of the different entry criteria.

Dr. Stadel did not combine patients from 1D with those in 2D, focusing only on patients in 2D followed into 1C. In our opinion, Dr. Stadel's approach is more appropriate in this case.

External controls

The only valid comparisons available from these studies are limited to Studies 1D and 2D. In fact, this comparison does not yield a significant difference in mortality because only one death occurred during this period.

There is no internal control group for the 1C study because experience on 1D and 2D helped determine who was available for entry into 1C. This could have biased the entry criteria for 1C in ways that are unpredictable. However, the data of these studies provide one or more cohorts of experience on metformin, for durations of four or five 29-week periods depending on whether the patient was initially randomized to any metformin.

Because 1C provided no comparative data, historical mortality rates may be more informative as a means of comparing the observed mortality during metformin exposure. Investigation of the impact of such issues as sequence of exposure, an increasing hazard rate with time, and cause-specific mortality would require more data than available in 1D, 2D and 1C.

Dr. Stadel attributes the increased incidence of death on metformin to selection bias because the proportions entering 1C of those randomized in 2D are different. However, as shown in Tables 1 and 2 this difference is mainly due to the difference in

proportions completing 2D. Dr. Stadel does not go far enough in supporting his conjecture in that he did not evaluate the available demographic data at the time points of interest.

As a way of assessing the impact of metformin exposure, we believe that Dr. Stadel should have extended his discussion about the UGDP mortality findings. Given a mean age of 50-55 and slightly more females than males, one would expect 4-5 deaths during metformin exposure in 2D and 1C based upon the mortality in the general population. The UDGP data might have provided more information regarding expected mortality.

Simple proportions

There were a substantial number of dropouts from each of the treatment groups, so that the number of patients exposed is not constant. A life table analysis is more appropriate than comparisons of simple proportions under these circumstances. Concentrating on the simple comparison between the 7 deaths among "metformin" patients versus 0 deaths among "control" patients, as Dr. Innerfield did, does not provide a correct estimate of variation and therefore does not provide a correct assessment of statistical significance. This point is less important perhaps than the fact that 6 of the deaths occurred when there was no longer an appropriate control group in the study.

Correctness of analyses

We were unable to reproduce Dr. Innerfield's life-table analysis. He may have used the person-time remaining as the person-time at risk. The appropriate denominator is the person-time observed.

Dr. Innerfield uses various confidence coefficients (99%, 95%, 90%) in his comparisons, apparently trying to show with what confidence each comparison is statistically significant. One generally fixes the level of confidence desired and then calculates the confidence intervals for the specified level of confidence.

Both Dr. Innerfield and Dr. Stadel make some comparisons among the three 2D/1C treatment groups by comparing proportions two at a time and by using statistics which do not account for the multiplicity of comparisons and the lack of prespecification of the comparisons to be made. A more appropriate approach for comparing proportions in three groups would be to use a chi-square test, as in Tables 1 and 2.

Size of studies

Dr. Innerfield notes that failure to observe any deaths in Study 1D may be due to lack of power (ie, small sample size for an event of such low probability of occurrence). Indeed, the total number of patients in each treatment group was very small, especially considering that the product in question is related to phenformin, that it will be available after marketing to a large number of patients, and that there is interest in a rare event (death) as an outcome variable.

Conclusions

1. Studies 1D and 2D were not designed to detect an increased risk of mortality associated with metformin use relative to a control group. Each study was underpowered from a sample size perspective to contrast metformin mortality with that of the control groups.

2. For the observational continuation of these studies (1C), there was no appropriate control group available against which to contrast the mortality experience in patients on long term metformin therapy. Thus, the deaths on Study 1C may or may not be unusual in number. The validity of the comparison of the number of deaths among those initially randomized to any metformin to that among those initially randomized to the control is suspect.

3. Because of the differential duration of patient exposure in each study, appropriate statistical methods to estimate incidence rates, compute confidence intervals and to compare incidence rates require adjustments for exposure duration, especially if pooled data from several sources are used. Dr. Stadel's analyses are thus more appropriate for this purpose.

The conclusions reached by Dr. Innerfeld with regard to estimates and comparisons of mortality risk are suspect because of inattention to the three points stated above.

The conclusions reached by Dr. Stadel with regard to comparisons and estimates of risk are more appropriate because his review recognizes the impact of the study design on the limitations for causal inference and his methods of analysis more appropriately account for the study design and exposure patterns.

The major limitations to drawing any inferences regarding increased mortality risk are the small number of patients, the short duration of exposure and lack of an appropriate control

group. These studies are simply inadequate to fully address the question, and further external sources must be sought for this information.

Gregory A. Burkhart, MD

William R. Fairweather, PhD

Concur:

Robert T. O'Neill, PhD
Acting Director, Office of
Epidemiology and Biostatistics

cc:HFD-520/NDA 20-357
HFD-715/Dr. Fairweather
HFD-733/Dr. Burkhart
HFD-710/chron
HFD-500/Dr. Bilstad
HFD-510/Sobel, Fleming, Gueyffier, Steidl, Short

2.8 Summary of the Clinical Data

2.8.1 Overview

2.8.1.1 Introduction

Guanidines have been recognized for their ability to reduce blood glucose levels in animals since 1918. Metformin hydrochloride, (Glucophage®), a metabolically stable disubstituted biguanide derivative of guanidine, was developed in 1957 by Aron Laboratories in Suresnes, France. Initial preclinical and early clinical studies of metformin were performed primarily in France, while in the United States, the monosubstituted biguanide, phenformin, was developed. A third biguanide, the monosubstituted buformin, was described shortly thereafter, but has had minor clinical usage.

The introduction and clinical use of biguanides followed closely upon that of sulfonylureas, the other major class of drugs for the treatment of Type II non-insulin dependent diabetes mellitus (NIDDM). In the U.S., only the biguanide phenformin was developed, being approved for clinical use in 1959. In contrast, in Europe and elsewhere, all three biguanides were eventually developed. Glucophage® brand of metformin became commercially available in France and in the United Kingdom in 1959, in Canada in 1972 and is currently marketed in more than 80 countries, including countries throughout western Europe, the

Scandinavian countries, Australia, New Zealand, most of the Mediterranean and Middle Eastern countries, Africa, South and Central America and elsewhere.

The reputation of biguanides became "tarnished" during the 1970's when an association between the administration of phenformin and the occurrence of lactic acidosis was identified. This led to the withdrawal of commercially available phenformin in a number of countries, including the United States in 1977. In contrast, Glucophage (metformin hydrochloride) has never been withdrawn from the market of any country for either reasons of efficacy or safety. As pointed out by Sterne and Jurien, it is a "mistake to mingle all the biguanides." (*see reference 9, Item 8*).

Extensive worldwide experience with metformin has been gained over more than a quarter of a century. Considerable domestic and foreign clinical data are available which attest to both the safety of metformin when used appropriately and its important role in therapy, particularly in the treatment of the obese, non-insulin dependent diabetic.

2.8.1.2 Clinical Development of Metformin in the U.S.

In the mid-1980s Lipha Pharmaceuticals, Inc. initiated preliminary planning for its U.S. clinical development of metformin and on February 24, 1986 an IND application, together with Phase I study protocols, was submitted for oral

metformin hydrochloride and subsequently approved by the FDA's Division of Metabolism and Endocrine Drug Products (IND #27,966).

On May 29, 1986, a meeting was held with the Division and Lipha, at the Division's request, to discuss the overall plan and direction of metformin development. It was agreed at that meeting that, subsequent to completion of the Phase I clinical pharmacology/mechanism studies, Phase III-type studies could commence (FDA Meeting Memorandum, May 29, 1986).

On December 3, 1986 a second meeting was held with the Division and Lipha, at Lipha's request, to discuss Phase III protocol designs and efficacy endpoints. Suggestions from the Division were received and this resulted in Lipha's convening a group of clinical experts in diabetes in March, 1987, to act as a Steering Committee and provide advice to the company regarding the optimal protocol design, target diabetic populations, appropriate clinical endpoints and recommendations regarding potential clinical investigators. Consensus was reached by the Steering Committee members on the design of two major studies involving obese non-insulin dependent diabetic subjects (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023). An additional recommendation was to employ a central laboratory for all blood and urine analyte measurements, so as to avoid difficulties in interpretation of results due to differing methodologies, normal ranges, etc. This was thought to be particularly important for such key analytes as glycosylated hemoglobin and lipids.

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In March, 1988, the first patient was enrolled into Phase III Study No. 87-1D-6023 After additional written communications with the Division regarding study design, Phase III Study No. 87-2D-6023 was initiated in Sept., 1988. These two Phase III multicenter, randomized, double-blind, controlled parallel arm studies were completed, respectively, in May and July, 1991.

An additional meeting was held between Lipha and the Division on March 22, 1990 to discuss various perspectives as to the appropriate maximal doses to be used in long-term rodent carcinogenicity studies. Lipha complied with recommendations of the Division with regard to these studies.

Finally, a pre-NDA meeting was held between Lipha and the Division on July 8, 1992, to discuss with the Division the proposed elements of the current metformin NDA. Preliminary results of key efficacy and safety parameters from the two pivotal Phase III metformin studies were also provided by Lipha at that time. The present submission is in accord with advice received from the Division at that meeting with reference to such areas as the phraseology of the Indications and Claims section of the metformin Package Insert, inclusion of a comparison of metformin and phenformin and the related issue of lactic acidosis, analysis of all relevant safety issues, efforts at appropriate subgroup analyses and the inclusion of final reports of both rodent carcinogenicity studies.

2.8.1.3 Organization and Design Features of Metformin Clinical Studies

Since the first clinical report on metformin in 1957, cumulative, predominantly foreign, published experience has amassed which provides information on large numbers of diabetic (and non-diabetic) patients of all types. This has helped to empirically establish precedents for the clinical use of metformin, including administration, dosage and therapeutic indications. This same clinical experience over more than thirty years has simultaneously helped to more clearly define metformin's safety profile, particularly with reference to the stability of incidence of lactic acidosis.

The metformin development program pursued by Lipha Pharmaceuticals, Inc. has been designed to verify perceptions regarding metformin's usefulness, through carefully conducted controlled studies, as well as to identify and fill any gaps in the existent clinical (and pre-clinical) information base.

Clinical Pharmacology:

The objective of the U.S. clinical pharmacology/pharmacokinetic program carried out under Lipha's IND #27,966 was to supplement and provide information in some of the important areas that had not been previously addressed during the more than thirty years of clinical experience with metformin.

Phase I U.S. studies sought to further define the mechanism of metformin's blood glucose-lowering effect, through open-labelled, before/after type studies, with emphasis on clinical research techniques for assessment of metformin's effects on parameters of carbohydrate and lipid metabolism.

Among the other areas addressed were dose-response assessment, with comparison of pharmacokinetics and pharmacodynamic effects of various clinically relevant single doses of metformin, in a single-blind, placebo-controlled, four-way crossover study of the 850 mg dosage strength (U.S. Study No. 89-12-6023) and a double-blind, placebo-controlled, four-way crossover study of the 500 mg dosage strength (non-U.S. Study No. MET/GB/89/HOCKA). These formal pharmacology studies were supplemented by information from the two U.S. Phase III pivotal studies, gathered during the dose titration phases of these two studies.

Additional areas addressed included:

- a comparison of metformin pharmacokinetics in diabetics vs. non-diabetics (U.S. Study No. 89-12-6023);
- a comparison of metformin pharmacokinetics following single doses of metformin vs. the final dose of a multiple dose phase (U.S. Study No. 89-12-6023);
- the relative bioavailability of various formulations and dosage strengths of metformin (U.S. Study No. 89-11-6023 and non-U.S. Study Nos. Simbec 1 and 2);

- the effects of food vs. fasting on metformin pharmacokinetics (U.S. Study No. 89-11-6023);
- the effects of aging on metformin pharmacokinetics (U.S. Study No. 90-13-6023);
- various drug interaction studies, selected on the basis of drugs most likely to be co-prescribed in diabetic subjects and including a sulfonylurea (glyburide), an H_2-receptor antagonist (cimetidine), a calcium-channel blocking agent (nifedipine), a β-adrenergic blocking agent (propranolol), a non-steroidal anti-inflammatory agent (ibuprofen) and a loop diuretic (furosemide).

Controlled and Uncontrolled Clinical Studies:

Two pivotal controlled clinical trials conducted in the U.S. (Study Nos. 87-1D-6023 and 87-2D-6023), each of 29 weeks treatment duration, bear the primary supportive burden for the efficacy and safety conclusions of metformin therapy. These studies fulfill the statutory requirements for adequate and well-controlled trials and are defined as Category I studies.

Both studies were prospective, randomized, double-blind, multi-center, parallel arm studies, comparing the effects of metformin vs. placebo in a population of NIDDM patients unresponsive to dietary management alone (Study No. 87-1D-6023) or of metformin monotherapy vs. glyburide monotherapy vs. metformin plus glyburide in a population of NIDDM patients unresponsive or no longer responsive

to maximum dose sulfonylurea (Study No. 87-2D-6023). In Study No. 87-1D-6023, the 850 mg dosage strength of metformin was used, while in Study No. 87-2D-6023, the 500 mg dosage strength was used. Both studies had a dose titration period, followed by a maintenance phase, with a total treatment duration of 29 weeks. Together they involved 521 randomized NIDDM subjects. The primary analysis of these two Phase III studies involved the intent-to-treat population. An open-label, uncontrolled safety extension (Study No. 89-1C-6023) of these two studies, has recently been completed.

In addition, all studies known to have been conducted by the parent company Lipha S.A. and/or its subsidiaries from the time of its acquisition of Aron Laboratories, were reviewed from the perspective of study design, objectives, availability of case report forms, completion status and ability to audit the data base. Based on these considerations, ten of 110 non-U.S. studies were labeled as Category II. Although these studies were not designed with stringent regulatory requirements in mind, they, nevertheless, satisfied quality assessments and criteria consonant with objectives sought for metformin and are integrated into the data base generated from the above-described Category I U.S. studies.

Seven of the ten non-U.S. Category II studies were prospective, randomized, parallel arm controlled studies, comparing the effects of metformin to either placebo (three studies), active treatment (three studies: vs. the sulfonylureas glipizide, gliclazide or glibenclamide and glibenclamide plus metformin), or diet

alone (one study). Six of the seven studies involved patients with NIDDM whereas the seventh study involved patients with impaired glucose tolerance but with fasting normoglycemia. The studies varied in duration from 60 days to one year. Two open-label, uncontrolled Phase IV post-marketing studies (of 4 months and 6 months treatment duration, respectively) were also included because they involved approximately 8,000 diabetic subjects taking either metformin alone or metformin plus a sulfonylurea. The final study was a controlled pharmacokinetic and pharmacodynamic study involving NIDDM subjects, mentioned above (MET/GB/89/HOCKA). Data from these studies were reanalyzed by Lipha's designated statistical group, applying the same statistical approach to these non-U.S. studies as to the U.S. Category I studies.

The remaining 100 non-U.S. Lipha-sponsored studies have been classified as Category III. Approximately half of them are clinical pharmacology studies. Although these studies are deficient on the basis of one or more of the major assessment criteria mentioned above, and therefore are not integrated into the database, they are, nevertheless, included in Item 8 as supportive data. In addition, all Category III studies have been carefully reviewed for safety-related information and for serious adverse drug experiences and narrative summaries of the latter have been included in the Integrated Summary of Safety.

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Integrated Summary of Safety:

The integrated summary of safety (ISS) was compiled from three data bases: the U.S. Phase III Category I studies, the seven non-U.S. randomized, controlled Category II studies, and the two non-U.S. Phase IV studies. In addition, results/findings from published and unpublished reports, including post-marketing pharmacovigilance, are discussed in the ISS.

For the U.S. and non-U.S. randomized studies, all patients who were randomized to receive study medication were included in the demographic, patient disposition, and dosage summaries. For these studies, the safety analysis was carried out for the intent-to-treat (ITT) population, i.e., all patients who received study medication and were assessed for safety. In the case of a patient randomized to a treatment group but with no (or insufficient) medication records, it was assumed that the patient actually received study medication. For the non-U.S. Phase IV studies, all patients who were enrolled were included in the ISS. The numbers of patients reported in the ISS (safety analysis) are listed below in intext Table 15, page 186.

Drug exposure data for the ISS were integrated into a single data base and analyzed with respect to this large, combined patient population. Drug exposure was analyzed with respect to number of patients and length of exposure time. Each study population was broken down in terms of number of subjects treated within a defined dose range. For the U.S. Category I studies, mean total daily dosages of metformin are also available. Precise drug compliance data was not

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/08A-2 032.73	Y					13.800	F	1700	730.00	81	acidosis, lactic; death;		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 032.70						45.300			1825.00	83	acidosis, lactic; death; hemodialysis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/620		62.0000	6.940	19.4984458	4.0738028	14.530				87	acidosis, lactic; coma vigil; death; denydration; dyspnea; hypothermia	clonidine; dipyridamole; furosemide; trinitrine	Hx PVD	FR
/08A-2 032.41			7.150	22.0000000	7.4541821	6.050		2500		56	acidosis, lactic; anorexia; asthenia; coma, decerebrate; death; ethanolism, chronic; liver disease; renal failure; vomiting	glucidoral;	Leroy Guerin V, Thesis Med 1-81, 1979. The author states that the timing of the sample relative to dose and initiation of the event is vague, and that absence of metformin from blood does not <=> absence of metformin in hepatic tissue.	Fr
/08A-2 032.46		1.5540			4.0000000	17.400				66	abdominal pain; acidosis, lactic; angiography; coma; death; obtundation; polypnea; urinary tract infection	hydralazine; pindolol	Jamet P et al, Sem Hop Paris 56:473-474, 1980	Fr

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/352	Y	11.1000	7.030	3.8000000	5.4000000	30.000	F	2550		42	acidosis, lactic; death;	glibenclamide; a-methyldopa	hospitalized one month earlier for status asthmaticus without mention of renal failure or change in metformin Rx	FR
/325		4.1700	6.880	21.9836598	4.0000000	11.800				60	acidosis, lactic; anemia; circulatory failure; death; ethanolism; hemorrhage, GI; hepatic insufficiency; hip replacement surgery; hypertension; pulmonary edema; septicemia	amiloride; clonidine; dihydralazine; glafenine; hydrochlorthiazide; meprobamate	PT = 18%	FR
/253			7.070	20.0000000	14.1000000	10.600				63	acidosis, lactic; consciousness, altered; death; diarrhea; infection, pulmonary; malaise;	acebutolol; amiloride; chlorothiazide; glibenclamide		FR
/252		16.3000	6.660	17.4000000	4.0000000					68	abdominal pain; acidosis, lactic; agitation; anisocoria; death; hypotonia; ?ketoacidosis; nuchal rigidity; ventricular	acebutolol; glibenclamide; a-methyldopa		FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/624		1.0323			5.0000000	25.400			3650.00		fibrillation abdominal pain; acidosis, lactic; death; dehydration; diarrhea; dyspnea; shock; vomiting;	benfluorex; captopril; clorazepate; diltiazem; furosemide; gliclazide; thyroid extract; trinitrine	Rx gallstones	FR
/1249		1.7871	7.230	36.7500000	14.6656054	11.100				69	acidosis, lactic; diarrhea; dyspnea; heart block	ciprofibrate; glipizide; furosemide; naftidrofuryl; nicardipine; potassium chloride; terbutaline; terfenadine; theophylline	no hx of alcoholism noted	FR
/229		2.7750				17.600	M			73	acidosis, lactic; coma; death		->ER comatose no previous Hx available	FR
/584		3.2000	7.330	22.0000000	12.0000000					74	acidosis, lactic; congestive heart failure; death; leukopenia; rhabdomyolysis; renal failure; sciatica;	glibenclamide; nicardipine	rhabdomyolysis vs hypothyroidism	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											septicemia - staphylococcal; shock; tremulousness			
/88A-2 052.56 B										75	acidosis, lactic; coma; death; pulmonary edema; shock;		Lefort C et al, Est-Med 3:266-271, 1983	Fr
/88A-2 052.25 b			6.740	21.5000000	2.7682162						acidosis, lactic; bradycardia; death; obtundation; polypnea; shock	?glibenclamide;	Viot M. Thesis Med (Fac. Med Paris Ouest) 1978, 1-55 (BCA-490)	FR
/652		8.2251	7.070	21.0000000	6.0255958	11.560		850		78	acidosis, lactic; acute renal insufficiency; death	furosemide; methylprednisolone; oxybutynine; prazosin; ranitidine; trinitrine; verapamil	Presentation in anuric renal failure	FR
/88A-2 052.27 a			7.080			11.400		1000	3285.00	58	acidosis, lactic; albuminuria; glomerulonephritis (hx); paralytic; renal failure, moderate; urinary tract infection	penicillin; phenformin (100mg/day)	Bourdais A.;Legall F.;Soc Med Chirug Hop Formulations Sanitaires des Armees 3:287, 1969	FR
/88A-2			7.150			6.600		1600	+++	60	acidosis, lactic;		Larcan,A; Lambert H.	Fr

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
032.8											death; dialysis,peritoneal; renal failure, moderate		Journ.Ann.Diabetol.Hotel-Dieu,Flammarion. Paris p 99-133;/Larcan,A; Lambert N. et al Diabete Metab 5.2:103-112, 1979	
/346			7.120	18.0000000	9.0000000			1700		50	acidosis, lactic; ethanolism; cirrhosis; coma; death; dyspnea; hypothermia; renal failure	glibenclamide; spironolactone	ascites; renal shutdown	FR
/259			6.900	27.0000000	5.1400000					55	acidosis, lactic; anuria; consciousness, altered; death; distress, respiratory; myocardial infarction; fibrillation, ventricular	amobarbital trinitrine; chlorpropamide; codethylline; digoxin; disopyramide; dopamine; lorazepam	alcoholism and hepatocellular insufficiency	FR
/08A-2 032.64			7.000	14.3581999	3.5000000	29.600					abdominal pain; acidosis, lactic; cirrhosis; death; hemodialysis; hypothermia; intravascular coagulation, diffuse; pancreatitis,		Daumal M et al, Forum des clubs et associations francaise d'anesthesie et reanimation chirurgicale, Paris, 13-16 Sep 1984	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n In Days	Age	CoStart	Conc Rx	Review	Loc
											chronic; peripheral vascular insufficiency; polypnea;			
/08A-2 052.40			7.380	26.0000000	14.9623564	6.400			+++		acidosis, lactic; coma; death; liver disease; renal failure		Larcan,A; Lambert M. Journ.Ann.Diabetol.Hotel-Dieu,Flammarion. Paris p 99-133;/Larcan,A; Lambert M. et al Diabete Metab 5.2:103-112, 1979	Fr
/08A-2 052.66						5.400			1460.00	56	acidosis, lactic; anuria; congestive heart failure; death; hemodialysis;		Lambert M et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 052.52			7.240	16.0000000	8.3965329	6.000			1095.00	57	acidosis, lactic; death; embolism, pulmonary;		Larcan A; Lambert M et al, Ann Med Nancy Est 20:989-996, 1981//Perrot D et al, Med Urg 2(2):85-91, 1986	Fr
/08A-2 052.81						5.400			1460.00	58	acidosis, lactic; death		Lambert M et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 052.37			7.100	45.0000000	13.5893910	5.700			+++	59	acidosis, lactic; coma; death; renal failure, moderate		Larcan,A; Lambert M. Journ.Ann.Diabetol.Hotel-Dieu,Flammarion. Paris p 99-133;/Larcan,A; Lambert M. et al Diabete Metab	Fr

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
													5.2:103-112, 1979	
/600		1.0000	6.400	26.0000000	2.0000000	30.000				60	acidosis, lactic; ethanolism, chronic; hypoglycemia; death; rhabdomyolysis; shock	buflomedil; glibenclamide	Profound metabolic acidosis. Metformin levels significantly elevated despite hemodialysis x 4. ***NORMAL RENAL FUNCTION*** ***Alcoholism***	FR
/08A-2 032.58		7.0041	6.850	29.4442160	5.0000000	40.500				68	acidosis, lactic; death; hemodialysis		Perrot D et al, In Reunion del la Societe de Reanimation de la Langue Francaise. Paris 24 Nov 83, Paris, Expansion Scientifique Francaise 1983	Fr
/08A-2 032.59		2.0202				14.200				72	acidosis, lactic; death; hemodialysis; hepatic failure		Perrot D et al, In Reunion del la Societe de Reanimation de la Langue Francaise. Paris 24 Nov 83, Paris, Expansion Scientifique Francaise 1983	Fr
/08A-2 032.50			7.410	24.0000000	14.7978968	15.400			1460.00	73	acidosis, lactic; death;		Larcan A; Lambert R et al, Ann Med Nancy Est 20:989-996, 1981//Perrot D et al, Med Urg	Fr

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
													2(2):85-91, 1986	
/397		2.3500	6.950		8.9000000	12.000			180.00	74	acidosis, lactic; death; hemodialysis;	acenocoumarol	No response to hemodialysis.	FR
/757		1.3764	6.970	80.4081357	18.0000000	12.100					acidosis, lactic; death; ethanolism; hepatocellular insufficiency; hepatorenal syndrome; ASPVD; shock	acenocoumarol; glibenclamide	Hx cirrhosis, ASPVD	FR
/088A-2 052.77						7.600			1460.00	75	acidosis, lactic; death; hemodialysis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/762		1.9203	6.890	36.0000000	6.7034750	28.000				79	acidosis, lactic; asthenia; death; dehydration; ethanolism, chronic; hematemesis; shock	alginic acid; domperidone; ranitidine	Hx cirrhosis, esophageal varices	FR
/480		3.6000	7.280	15.9750000	7.1795958	7.500					acidosis, lactic; cardiovascular collapse; chills; death; endocarditis; lumbar pain; myocarditis; pericarditis; streptococci, group B; vertigo		chronic interstitial nephritis; mesenteric arterial occlusion; pericarditis; myocarditis; endocarditis; pneumonia	FR
/466		2.1201	7.140	27.1769949	9.0000000	15.000				82	abdominal pain;	allopurinol;	Abdominal pains -> dx ?	FR

BRR #/ NPR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review
											acidosis, lactic; death; epigastric pain;	amiloride; amiodarone; colchicine; gliclazide; hydrochothiazide; moxisylite; ranitidine	NI -> d/c oral antihypoglycemic/ start insulin -> restart oral antihyperglycemics -> "sudden aggravation of renal insufficiency" -> lactic acidosis and death
/624		6.1050	7.200	26.0000000	9.8855309	22.000				86	acidosis, lactic; coma, hyperosmolar; death; dehydration; humerus, fracture;	cyanocobalamin	Rx pernicious anemia. Hospitalized for non-surgical treatment of hip fracture.
/000-2 082.42		0.9880	7.370	18.4077198	10.5000000	21.100		2500	180.00	58	acidosis, lactic; anorexia; asthenia; coma, hepatic; death; ethanolism, chronic; cirrhosis; hemosiderosis; somnolence; vomiting	glucidoral;	Leroy Guerin V, Thesis Med 1-81, 1979. The author states that the timing of the sample relative to dose and initiation of the event is vague, and that absence of metformin from blood does not <=> absence of metformin in hepatic tissue.
/000-2 082.44		4.9950	7.270	15.0000000	6.7003867	6.320			5.00	75	acidosis, lactic; coma vigil; death; ethanolism; hemodialysis; hypertension; polypnea; renal		Guerin JM et al, Agressologie 21:253-256, 1980

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/547	Y	1.6000				11.000	M	2550	1000.00	59	acidosis, lactic; coma; death; dyspepsia; hemodialysis;		Several surgical interventions for "sigmoiditis."	FR
/667		2.4087	7.370	20.2488328	11.6000000					64	acidosis, lactic; death; dyspnea;	allopurinol; digoxin; enalapril; furosemide; glibenclamide; prazosin; triamterene	Abdominal pains -> dx ? MI -> d/c oral antihypoglycemix/ start insulin -> restart oral antihyperglycemics -> "sudden aggravation of renal insufficiency" -> lactic acidosis and death	FR
/59R		8.3000	6.890	26.8534441	5.0000000					75	acidosis, lactic; angiography; death; diffuse intravascular coagulation; hemodialysis; renal failure; shock	gliclazide	metabolic acidosis p angiography. Metformin levels significantly elevated despite hemodialysis x 6. Endotoxic shock c DIC and death.	FR
/08A-2 032.35 c		2.0000	7.160	17.0000000	5.8938625				730.00	80	acidosis, lactic; bradycardia; death; obtundation; polypnea; shock		Vict M. Thesis Med (Fac. Med Paris Ouest) 1978, 1-55 (BCA-490)	FR
/432		1.9600	7.230	17.0000000	6.9300000	17.200		3400		66	abdominal pain; acidosis, lactic; coma, hepatic; death; ethanolism;	atenolol; carbutamide; pentoxyphylline ;	PT 27%; bilirubin 35; hx pancreatitis; hypertension; bladder lithiasis. Death	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											hemodialysis	spironolactone	irreversible despite hemodialysis	
/OBA-2 052.11			6.710	35.0000000	4.3062575	39.000		24500	42.00	38	acidosis, lactic; anuria; coma; death; depression; ethanolism, chronic; ingestion, suicidal; peritoneal dialysis; shock	opipramol; phenobarbital	Blamuth et al, Nouv. Presse Medic. 5:261, 1976	Fr
/NE 126.00 1 (OBA-3 467;08 A-0182 3)		1.1766	7.170			10.400	F	850	2.00	70	pain; acidosis, lactic; angiography; coma; DIC; hepatorenal syndrome; shock; transaminase elevations; renal failure;	antithrombin III; beriplex; glibenclamide; iopamidol	Taken off insulin and put on oral agents <- c-peptide of 5.3ng/ml. Angiography for ASPVD for neurotrophic ulcers.	FRG
/OBA-2 052.95		1.8648	7.060	26.6133775	7.1000000	11.500		1500	<<<	64	acidosis, lactic; death; diarrhea; dyspepsia; dyspnea; fever; hypotension; pyuria; somnolence; vomiting		Lebech M; Olesen LL; Ugeskrift Laeger 152: 2511-12, 1990	FRG
/OBA-35 11								2550	240.00	52	?acidosis, lactic; death; diarrhea; dyspepsia; nausea; vomiting	digitoxin; furosemide; glibenclamide;	refused hospitalization	FRG

DES #/ NPR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/BA-01 826.1	Y	1.9700	6.850			6.100	F	2550		84	abdominal pain; acidosis, lactic; bradyarrhythmia; CHF; coma; death	clopamide; dihydroergocristine methane sulfonate; methyldigoxin; reserpine	Autopsy refused	FRG
/DBA-2 032.3			7.080			8.000		3000	23.00	71	acidosis, lactic; cardiovascular disease; death; pancreatitis;		Ditzel	FRG
/DBA-2 032.92		1.2210	7.080	28.7144164	8.4000000	7.080			9.00		acidosis, lactic; asthenia; coma; cyanosis; death; dehydration; dyspnea; nausea; pain, intracranial; pancreatitis; urinary tract infection; vomiting		Lebech M; Olesen LL; Ugeskrift Laeger 152: 2511-12, 1990	FRG
/BA-01 819.1			6.800			24.000		38250		48	acidosis, lactic; death; suicidal ingestion;	glibenclamide	Hospital unable to dialyse.	FRG
/DBA-2 032.91		1.0101	7.250	33.9703479	14.7000000	7.200	M	1500	3.00	76	acidosis, lactic; coma; cyanosis; death; dehydration; dyspnea; pancreatitis, chronic, calcific;		Lebech M; Olesen LL; Ugeskrift Laeger 152: 2511-12, 1990	FRG

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/BA-35 60	Y	1.1000	6.700	17.0000000	.18.4000000		M	2550		49	acidosis, lactic; coma; cyanosis; death; dehydration; hypothermia; pulmonary edema; renal failure, acute; shock	glibenclamide	a "spread infection". Renal failure developed AFTER admission with documented acidosis and DURING hospitalization. Lactate after death was 2.86 mM/L and metformin levels were 4.5 µg/ml.	FRG
/08A-2 052.95		12.3210	6.930	34.2846716	7.0000000	26.000		3000	1460.00	70	acidosis, lactic; death; diarrhea; dyspepsia; dyspnea; edema, pulmonary ;		Lebech M; Olesen LL; Ugeskrift Laeger 152: 2511-12, 1990	FRG
/08A-2 052.2			7.250			9.000			3.00	76	acidosis, lactic; death; pancreatitis; sepsis		Ditzel	FRG
/08A-2 052.18		1.3000	7.050	18.5780443	5.0000000	16.300		1095	240.00	84	acidosis, lactic; cardiovascular disease; coronary artery disease; death; digitalis toxicity; fibrillation, atrial; heart failure; myocardial infarction; nausea; vomiting; weakness	digitoxin; furosemide	Hermann LS et al, Acta Med Scand 209:519-520, 1981	SW
780085			7.300			9.100	F	500	180.00	70	acidosis, lactic;		Wilhelm BE; Nyrhed H; Eur	SWE

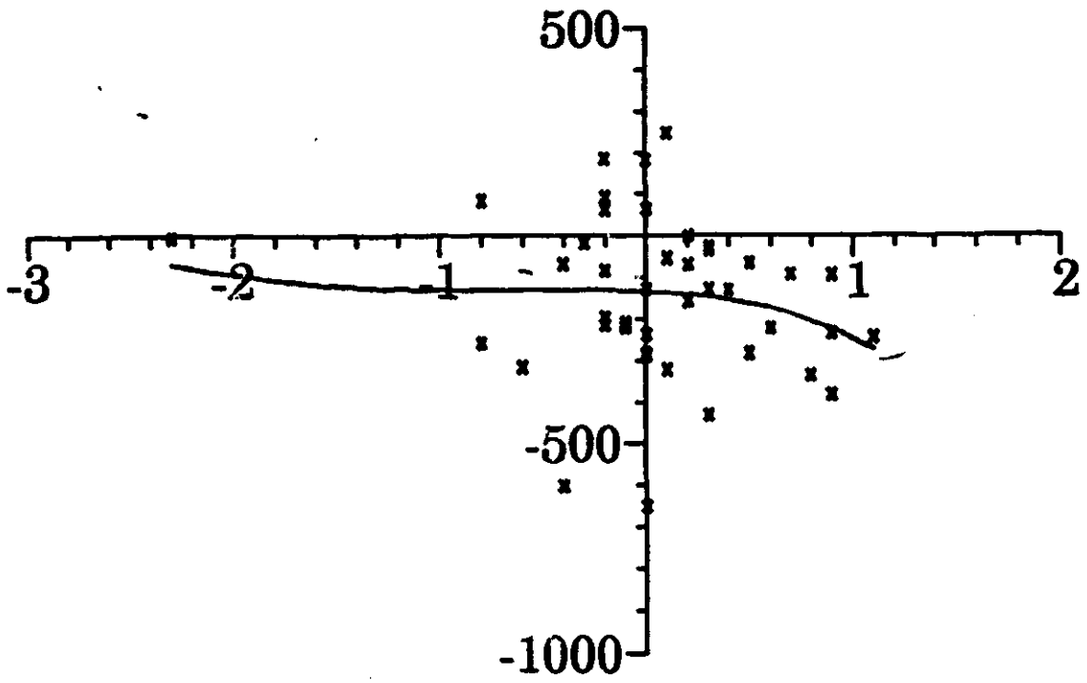
DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/8.12. 2.249. 5											death; myocardial infarction		J Clin Pharmacom 44:589-591, 1993	
760108 /8.12. 2.249. 15			7.300			12.400		1000	+++	65	acidosis, lactic; cerebrovascular accident; death;		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
932118 /LB06										70	acidosis, lactic; angiography; death; renal insufficiency	euglucon; furosemide	SADRAC Letter 11/15/93	SWE
810498 /8.12. 2.249. 12			7.000			14.800			+++	73	acidosis, lactic; death; renal failure		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
860139 /8.12. 2.249. 8			6.800			14.000					acidosis, lactic; colon carcinoma; death; hypertension		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
910524 /8.12. 2.249. 18			7.110			18.800			+++	76	acidosis, lactic; myocardial infarction;		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
841469 /LB02									25.00	78	acidosis, lactic; death;		SADRAC Letter 11/15/93	SWE
932118									4241.00	80	acidosis, lactic;		SADRAC Letter 11/15/93	SWE

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/LB05											death;			
770802 /LB01										85	acidosis; death;		SADRAC Letter 11/15/93	SWE
790693 /8.12. 2.249. 4			7.500			3.300		1500	970.00	67	acidosis, lactic; death; digoxin toxicity; renal failure	digoxin	Wilholm BE; Myrhed M; Eur J Clin Pharmacom 44:589-591, 1993	SWE
860945 /8.12. 2.249. 14			7.100			21.300			22.00	79	acidosis, lactic; congestive heart failure; death; rheumatoid arthritis	?digoxin	Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
782001 /8.12. 2.249. 3			7.100			19.000			970.00	82	acidosis, lactic; death; digoxin toxicity	digoxin	Wilholm BE; Myrhed M; Eur J Clin Pharmacom 44:589-591, 1993	SWE
920584 /LB03								2500	1275.00	70	acidosis, lactic; death;	acinil; digoxin; doloxene; mindiab; nitrazyn; teldenex;	SADRAC Letter 11/15/93	SWE
932044 /LB04								3000	5635.00	61	acidosis, lactic; death;		SADRAC Letter 11/15/93	SWE
891655			6.700						***	72	acidosis, lactic;		Wilholm BE; Myrhed M; Eur	SWE

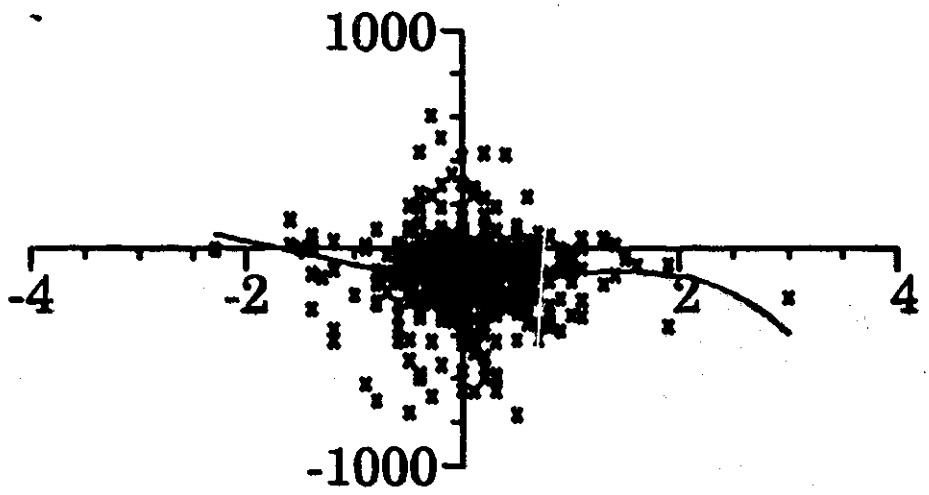
DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/8.12.2.249.17											atrial fibrillation; death		J Clin Pharm 44:589-591, 1993	
840387 /8.12.2.249.11			6.700						+++	75	acidosis, lactic; death; hypertension		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
820801 /8.12.2.249.9			7.100			14.000	M	1000	14.00	64	acidosis, lactic; congestive heart failure; death; ethanolism	?digoxin	Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
810064 /8.12.2.249.7			7.400			6.300				68	acidosis, lactic; congestive heart failure; death; hypertension; nephropathy	?digoxin	Wilholm BE; Myrhed M; Eur J Clin Pharmacom 44:589-591, 1993	SWE
822233 /8.12.2.249.10			7.000			22.400			14.00	78	acidosis, lactic; death; myocardial infarction;		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
/BA-01 814.6							F		270.00	56	acidosis, lactic	chlorpropamide;	MOIA	UK
/BA-01 818.3								1000		73	acidosis, lactic; shock	bumetanide; co-praxamol; digoxin;	MOIA	UK

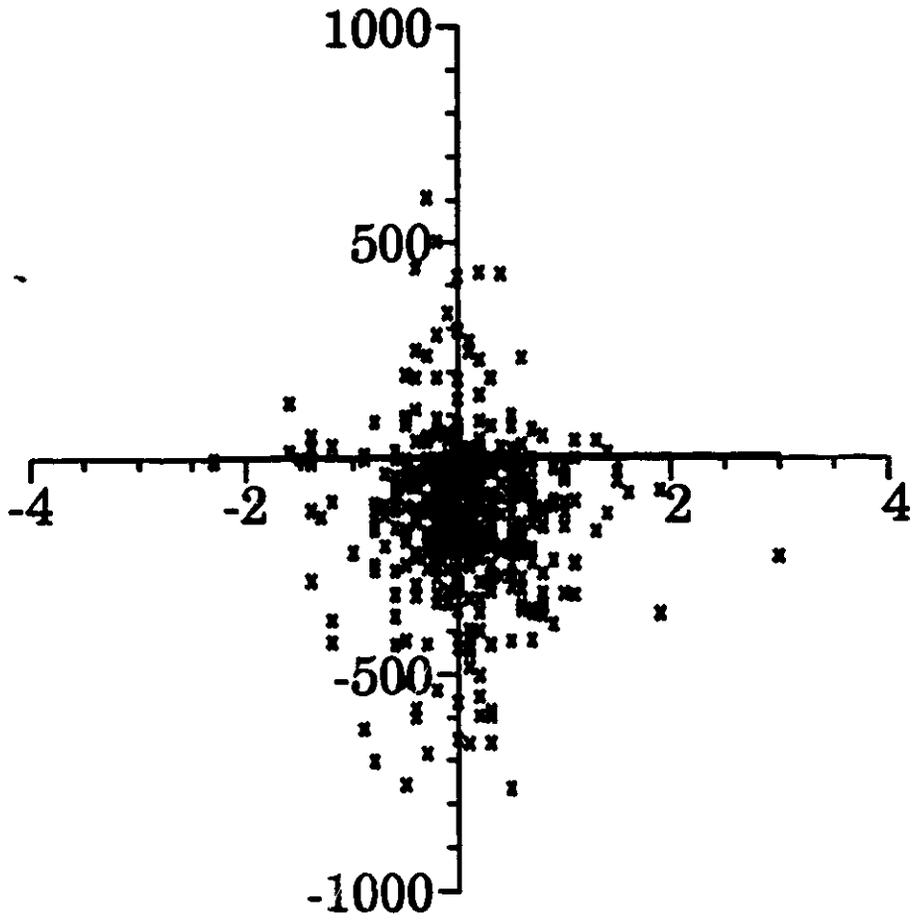
Lactic Acidosis +
Death in
Study 89-IC-6023
(Hospitalization)

B12 vs LACTATE IN PATIENTS WITH DIARRHEA

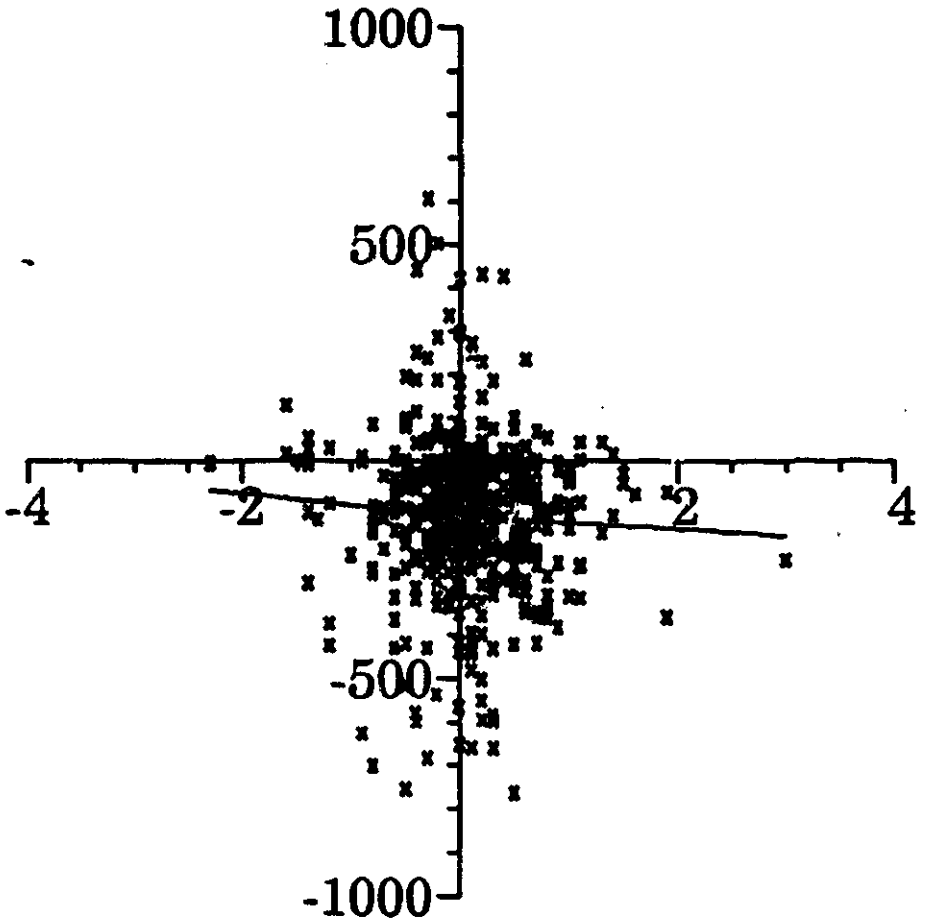


B12 vs. LACTATE IN ALL PATIENTS




1000
500
-500
-1000
-4
-2
2
4

```
BTITLE B12 vs. LACTATE IN ALL PATIENTS
VARIABLES B12, LACT
PARAMETERS COEF1, COEF2,COEF3
F   TION B12=COEF1*SIN(LACT)+COEF2*COS(LACT)+COEF3*EXP(LACT)
    STER
    PRINT
DATA

Beginning computation...
  Iteration   0.  Sum of squared deviations = 2.43224E+007
  Iteration   1.  Sum of squared deviations = 1.69881E+007
  Iteration   2.  Sum of squared deviations = 1.58867E+007
  Iteration   3.  Sum of squared deviations = 1.58867E+007
Stopped due to: Relative function convergence.


   ----  Final Results  ----

B12 vs. LACTATE IN ALL PATIENTS
Function: B12=COEF1*SIN(LACT)+COEF2*COS(LACT)+COEF3*EXP(LACT)
Number of observations = 509
Maximum allowed number of iterations = 50
Convergence tolerance factor = 1.000000E-010
Stopped due to: Relative function convergence.
Number of iterations performed = 3
Final sum of squared deviations = 1.58867E+007
Standard error of estimate = 177.191
Average deviation = 126.064
Maximum deviation for any observation = 728.878
   portion of variance explained (R^2) = 0.0000  (0.00%)
   sted coefficient of multiple determination (Ra^2) = -0.0094  (-0.94%)
Durbin-Watson test for autocorrelation = 1.928


            ----  Descriptive Statistics for Variables  ----

 Variable     Minimum value    Maximum value     Mean value      Standard dev.
----------   --------------   --------------   -------------   --------------
       B12              -764              604       -127.0923           176.36
      LACT              -2.3                3      0.06797642        0.5548782


                ----  Calculated Parameter Values  ----

 Parameter   Initial guess    Final estimate    Standard error       t        Prob(t)
----------   -------------   ----------------   --------------   ---------   -------
     COEF1               1        11.4836779         21.05657        0.55   0.58574
     COEF2               1       -107.796484         11.71074       -9.20   0.00001
     COEF3               1       -24.9760166         7.049351       -3.54   0.00043


                ----  Analysis of Variance  ----

  Source      DF    Sum of Squares     Mean Square     F value    Prob(F)
   ------   ----   --------------   --------------   ---------   -------
   ression      2        -86445.67        -43222.83Invalid x value for betai functi
     -1.38  0.00001
Error         506     1.58867E+007         31396.63
Total         508    1.580025E+007
```


1000
500
-500
-1000
-4
-2
2
4

BNonlin version 2.1 Copyright (c) 1992-1993 Phillip H. Sherrod.

Beginning computation...
teration 0. Sum of squared deviations = 2.43224E+007
eration 1. Sum of squared deviations = 1.69881E+007
teration 2. Sum of squared deviations = 1.58867E+007
fteration 3. Sum of squared deviations = 1.58867E+007
Stopped due to: Relative function convergence.

---- Final Results ----

Function: B12_CFB = COEF1*SIN(LACT_CFB) + COEF2*COS(LACT_CFB) + COEF3*
EXP(LACT_CFB)
Number of observations = 509
Maximum allowed number of iterations = 50
Convergence tolerance factor = 1.000000E-010
Stopped due to: Relative function convergence.
Number of iterations performed = 3
Final sum of squared deviations = 1.58867E+007
Standard error of estimate = 177.191
Average deviation = 126.064
Maximum deviation for any observation = 728.878
Proportion of variance explained (R^2) = 0.0000 (0.00%)
Adjusted coefficient of multiple determination (Ra^2) = -0.0094 (-0.94%)
Durbin-Watson test for autocorrelation = 1.928

---- Descriptive Statistics for Variables ----

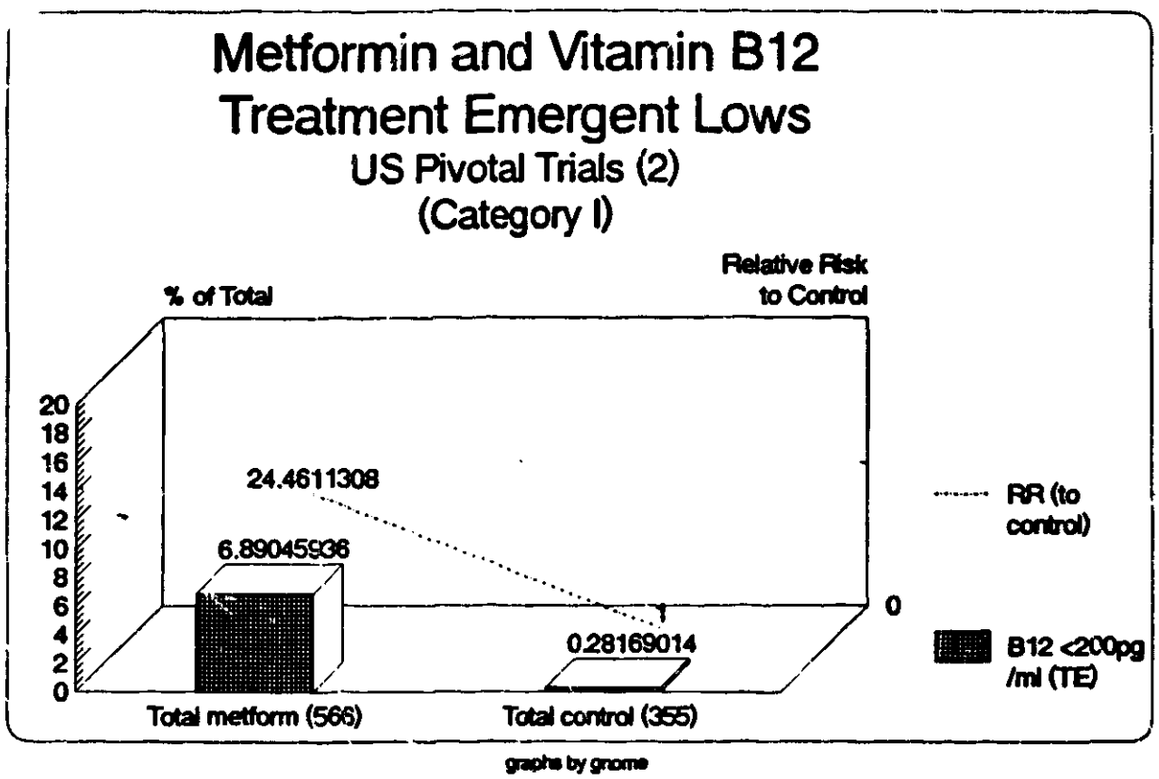
iable	Minimum value	Maximum value	Mean value	Standard dev.
B12_CFB	-764	604	-127.0923	176.36
LACT_CFB	-2.3	3	0.06797642	0.5548782

---- Calculated Parameter Values ----

Parameter	Initial guess	Final estimate	Standard error	t	Prob(t)
COEF1	1	11.4836779	21.05657	0.55	0.58574
COEF2	1	-107.796484	11.71074	-9.20	0.00001
COEF3	1	-24.9760166	7.049351	-3.54	0.00043

---- Analysis of Variance ----

Source	DF	Sum of Squares	Mean Square	F value	Prob(F)
Regression	2	-86445.67	-43222.83	Invalid x value for butai functi	
-1.38	0.00001				
Error	506	1.58867E+007	31396.63		
Total	508	1.580025E+007			


Metformin and Vitamin B12
Treatment Emergent Lows
US Pivotal Trials (2)
(Category I)
% of Total
Relative Risk
to Control
20
18
16
14
12
10
8
6
4
2
0
24.4611308
6.89045936
1
0
0.28169014
RR (to
control)
B12 <200pg
/ml (TE)
Total metform (566)
Total control (355)
graphs by gnome

Dose - Response

Drug-Dose Responses for Patient Visits

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	BMI	Rx#2_Dose	Cr
1	87-1D	A					
		Total:	129760.00	349350.00	4402.26	0.00	152.10
		Average:	831.79	2239.42	28.22	0.00	0.98
		Count:	156	156	156	156	156
		Maximum:	4495.00	2550.00	35.87	0.00	1.40
		Minimum:	10.00	0.00	23.04	0.00	0.00
		Variance:	649406.82	436154.15	9.58	0.00	0.04
		Standard Deviation:	805.86	660.42	3.10	0.00	0.19
	Total:		129760.00	349350.00	4402.26	0.00	152.10
	Average:		831.79	2239.42	28.22	0.00	0.98
	Count:		156	156	156	156	156
	Maximum:		4495.00	2550.00	35.87	0.00	1.40
	Minimum:		10.00	0.00	23.04	0.00	0.00
	Variance:		649406.82	436154.15	9.58	0.00	0.04
	Standard Deviation:		805.86	660.42	3.10	0.00	0.19
	87-2D	A					
		Total:	210980.00	386500.00	6933.12	0.00	247.00
		Average:	864.67	1584.02	28.41	0.00	1.01
		Count:	244	244	244	244	244
		Maximum:	5070.00	2500.00	45.12	0.00	1.50
		Minimum:	10.00	0.00	23.01	0.00	0.00
		Variance:	684637.69	1381260.92	16.20	0.00	0.03
		Standard Deviation:	827.43	1175.27	4.03	0.00	0.17
		D					
		Total:	258850.00	389000.00	8034.19	5480.00	300.60

Drug-Dose Responses for Patient Visits

Sex	Study_ID	Group	EFF23 (-2-) Cimetidine	Study_Rx_Dose	BMI	Rx#2_Dose glyburide	Cr
		Average:	914.66	1374.56	28.39	19.36	1.06
		Count:	283	283,	283	283	283
		Maximum:	5430.00	2500.00	37.67	20.00	1.60
		Minimum:	20.00	0.00	22.85	0.00	0.00
		Variance:	821006.22	1290801.48	10.48	12.32	0.04
		Standard Deviation:	906.09	1136.13	3.24	3.51	0.20
	Total:		469830.00	775500.00	14967.31	5480.00	547.60
	Average:		891.52	1471.54	28.40	10.40	1.04
	Count:		527	527	527	527	527
	Maximum:		5430.00	2500.00	45.12	20.00	1.60
	Minimum:		10.00	0.00	22.85	0.00	0.00
	Variance:		758489.23	1343592.13	13.13	99.84	0.04
	Standard Deviation:		870.91	1159.13	3.62	9.99	0.19
Total:			599590.00	1124850.00	19369.57	5480.00	699.70
Average:			877.88	1646.93	28.36	8.02	1.02
Count:			683	683	683	683	683
Maximum:			5430.00	2550.00	45.12	20.00	1.60
Minimum:			10.00	0.00	22.85	0.00	0.00
Variance:			734202.97	1240246.77	12.33	96.09	0.04
Standard Deviation:			856.86	1113.66	3.51	9.80	0.19
2	87-1D	A					
		Total:	153359.00	447525.00	5776.61	0.00	164.20
		Average:	778.47	2271.70	29.32	0.00	0.83
		Count:	197	197	197	197	197
		Maximum:	5020.00	2550.00	39.21	0.00	1.60
		Minimum:	10.00	0.00	21.30	0.00	0.00

Drug-Dose Responses for Patient Visits

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	BMI	Rx#2_Dose	Cr
		Variance:	574691.44	440585.56	12.37	0.00	0.03
		Standard Deviation:	758.08	663.77	3.52	0.00	0.18
	Total:		153359.00	447525.00	5776.61	0.00	164.20
	Average:		778.47	2271.70	29.32	0.00	0.83
	Count:		197	197	197	197	197
	Maximum:		5020.00	2550.00	39.21	0.00	1.60
	Minimum:		10.00	0.00	21.30	0.00	0.00
	Variance:		574691.44	440585.56	12.37	0.00	0.03
	Standard Deviation:		758.08	663.77	3.52	0.00	0.18
	87-2D	A					
		Total:	208506.00	446000.00	8760.72	0.00	236.50
		Average:	721.47	1543.25	30.31	0.00	0.82
		Count:	289	289	289	289	289
		Maximum:	5830.00	2500.00	39.24	0.00	1.30
		Minimum:	10.00	0.00	0.00	0.00	0.00
		Variance:	402253.95	1395188.04	26.24	0.00	0.03
		Standard Deviation:	634.23	1181.18	5.12	0.00	0.16
		D					
		Total:	231031.00	438750.00	9037.21	6000.00	261.20
		Average:	750.10	1424.51	29.34	19.48	0.85
		Count:	308	308	308	308	308
		Maximum:	3460.00	2500.00	37.26	20.00	1.80
		Minimum:	20.00	0.00	22.26	0.00	0.00
		Variance:	368864.92	1229894.24	18.44	9.47	0.03
		Standard Deviation:	607.34	1109.01	4.29	3.08	0.18

Drug-Dose Responses for Patient Visits

Sex	Study_ID	Group	EFF23 (Metformin)	Study_Rx_Dose	BMI	Rx#2_Dose (Glyburide)	Cr
	Total:		439537.00	884750.00	17797.93	6000.00	497.70
	Average:		736.24	1481.99	29.81	10.05	0.83
	Count:		597	597	597	597	597
	Maximum:		5830.00	2500.00	39.24	20.00	1.80
	Minimum:		10.00	0.00	0.00	0.00	0.00
	Variance:		385232.78	1313432.04	22.46	99.66	0.03
	Standard Deviation:		620.67	1146.05	4.74	9.98	0.17
Total:			592896.00	1332275.00	23574.54	6000.00	661.90
Average:			746.72	1677.93	29.69	7.56	0.83
Count:			794	794	794	794	794
Maximum:			5830.00	2550.00	39.24	20.00	1.80
Minimum:			10.00	0.00	0.00	0.00	0.00
Variance:			432572.21	1213210.10	20.00	93.78	0.03
Standard Deviation:			657.70	1101.46	4.47	9.68	0.17
Total:			1192486.00	2457125.00	42944.11	11480.00	1361.60
Average:			807.37	1663.59	29.08	7.77	0.92
Count:			1477	1477	1477	1477	1477
Maximum:			5830.00	2550.00	45.12	20.00	1.80
Minimum:			10.00	0.00	0.00	0.00	0.00
Variance:			576329.68	1225951.44	16.89	94.90	0.04
Standard Deviation:			759.16	1107.23	4.11	9.74	0.20

Drug-Dose Levels vs BMI vs SrCl for Patient Visits ± ADRs

(-1-)

Sex	Study_ID	EPI23	Study_Rx_Dose	BMI	Rx#2_Dose
1	87-1D				
	Total:	129760.00	349350.00	4402.26	0.00
	Average:	831.79	2239.42	28.22	0.00
	Count:	156	156	156	156
	Maximum:	4495.00	2550.00	35.87	0.00
	Minimum:	10.00	0.00	23.04	0.00
	Variance:	649406.82	436154.15	9.58	0.00
	Standard Deviation:	805.86	660.42	3.10	0.00
	87-2D				
	Total:	469830.00	775500.00	14967.31	5480.00
	Average:	891.52	1471.54	28.40	10.40
	Count:	527	527	527	527
	Maximum:	5430.00	2500.00	45.12	20.00
	Minimum:	10.00	0.00	22.85	0.00
	Variance:	758489.23	1343592.13	13.13	99.84
	Standard Deviation:	870.91	1159.13	3.62	9.99
Total:		599590.00	1124850.00	19369.57	5480.00
Average:		877.88	1646.93	28.36	8.02
Count:		683	683	683	683
Maximum:		5430.00	2550.00	45.12	20.00
Minimum:		10.00	0.00	22.85	0.00
Variance:		734202.97	1240246.77	12.33	96.09
Standard Deviation:		856.86	1113.66	3.51	9.80
2	87-1D				
	Total:	153359.00	447525.00	5776.61	0.00

Drug-Dose Levels vs BMI vs SFU for Patient Visits ± ADRs

(-2-)

Sex	Study_ID	[metformin] EFF23	Study_Rx_Dose	BMI	[glyburide] Rx#2_Dose
	Average:	778.47	2271.70	29.32	0.00
	Count:	197	197	197	197
	Maximum:	5020.00	2550.00	39.21	0.00
	Minimum:	10.00	0.00	21.30	0.00
	Variance:	574691.44	440585.56	12.37	0.00
	Standard Deviation:	758.08	663.77	3.52	0.00
	87-2D				
	Total:	439537.00	884750.00	17797.93	6000.00
	Average:	736.24	1481.99	29.81	10.05
	Count:	597	597	597	597
	Maximum:	5830.00	2500.00	39.24	20.00
	Minimum:	10.00	0.00	0.00	0.00
	Variance:	385232.78	1313432.04	22.46	99.66
	Standard Deviation:	620.67	1146.05	4.74	9.98
Total:		592896.00	1332275.00	23574.54	6000.00
Average:		746.72	1677.93	29.69	7.56
Count:		794	794	794	794
Maximum:		5830.00	2550.00	39.24	20.00
Minimum:		10.00	0.00	0.00	0.00
Variance:		432572.21	1213210.10	20.00	93.78
Standard Deviation:		657.70	1101.46	4.47	9.68
Total:		1192486.00	2457125.00	42944.11	11480.00
Average:		807.37	1663.59	29.08	7.77
Count:		1477	1477	1477	1477
Maximum:		5830.00	2550.00	45.12	20.00
Minimum:		10.00	0.00	0.00	0.00

Drug-Dose Levels vs BMI vs sFU for Patient Visits ± ADRs

(-3-)

Sex	Study_ID	EFF23 (Levetiracetam)	Study_Rx_Dose	BMI	Rx#2_Dose (Glyburide)
Variance:		576329.68	1225951.44	16.89	94.90
Standard Deviation:		759.16	1107.23	4.11	9.74

Drug/Dose Levels vs BMI v J in Patient Visits with ADRs

Sex	Study_ID	[Lisc Harmin] EFF23	Study_Rx_Dose	BMI	[Glyburide] Rx#2_Dose
1	87-1D				
	Total:	57469.00	130050.00	1646.30	0.00
	Average:	990.84	2242.24	28.38	0.00
	Count:	58	58	58	58
	Maximum:	4495.00	2550.00	35.49	0.00
	Minimum:	42.00	0.00	23.04	0.00
	Variance:	814434.65	416017.39	9.07	0.00
	Standard Deviation:	902.46	644.99	3.01	0.00
	87-2D				
	Total:	283572.00	445500.00	8741.51	3240.00
	Average:	920.69	1446.43	28.38	10.52
	Count:	308	308	308	308
	Maximum:	5070.00	2500.00	45.12	20.00
	Minimum:	10.00	0.00	22.85	0.00
	Variance:	789808.84	1369695.04	14.29	99.73
	Standard Deviation:	888.71	1170.34	3.78	9.99
Total:		341041.00	575550.00	10387.81	3240.00
Average:		931.81	1572.54	28.38	8.85
Count:		366	366	366	366
Maximum:		5070.00	2550.00	45.12	20.00
Minimum:		10.00	0.00	22.85	0.00
Variance:		794367.66	1303023.32	13.46	98.68
Standard Deviation:		891.27	1141.50	3.67	9.93
2	87-1D				
	Total:	54078.00	154700.00	2047.83	0.00

Drug/Dose Levels vs BMI vs [illegible] in Patient Visits with ADRs

(-2-)

Sex	Study_ID	[metformin] EFF23	Study_Rx_Dose	BMI	[glyburide] Rx#2_Dose
	Average:	772.54	2210.00	29.25	0.00
	Count:	70	70	70	70
	Maximum:	3404.00	2550.00	38.51	0.00
	Minimum:	10.00	0.00	21.30	0.00
	Variance:	594995.76	524328.57	12.91	0.00
	Standard Deviation:	771.36	724.11	3.59	0.00
	87-2D				
	Total:	221098.00	418750.00	9002.00	3090.00
	Average:	727.30	1377.47	29.61	10.16
	Count:	304	304	304	304
	Maximum:	5830.00	2500.00	39.24	20.00
	Minimum:	10.00	0.00	0.00	0.00
	Variance:	379202.21	1404599.18	24.03	99.64
	Standard Deviation:	615.79	1185.16	4.90	9.98
Total:		275176.00	573450.00	11049.83	3090.00
Average:		735.76	1533.29	29.55	8.26
Count:		374	374	374	374
Maximum:		5830.00	2550.00	39.24	20.00
Minimum:		10.00	0.00	0.00	0.00
Variance:		419902.84	1345288.92	21.97	96.71
Standard Deviation:		648.00	1159.87	4.69	9.83
Total:		616217.00	1149000.00	21437.64	6330.00
Average:		832.73	1552.70	28.97	8.55
Count:		740	740	740	740
Maximum:		5830.00	2550.00	45.12	20.00
Minimum:		10.00	0.00	0.00	0.00

Drug/Dose Levels vs BMI vs SFU in Patient Visits with ADRs

Sex	Study_ID	[metformin] EFF23	Study_Rx_Dose	BMI	[glybmide] Rx#2_Dose
Variance:		614718.04	1324769.72	18.10	97.77
Standard Deviation:		784.04	1150.99	4.25	9.89

Drug/Dose Levels vs BMI vs SFU in Patient Visits WITHOUT ADR

Sex	Study_ID	[metformin] EFF23	Study_Rx_Dose	BMI	[glyburide] Rx#2_Dose
1	87-1D				
	Total:	72291.00	219300.00	2755.96	0.00
	Average:	737.66	2237.76	28.12	0.00
	Count:	98	98	98	98
	Maximum:	4090.00	2550.00	35.87	0.00
	Minimum:	10.00	0.00	23.04	0.00
	Variance:	527904.90	448064.35	9.86	0.00
	Standard Deviation:	726.57	669.38	3.14	0.00
	87-2D				
	Total:	186258.00	330000.00	6225.80	2240.00
	Average:	850.49	1506.85	28.43	10.23
	Count:	219	219	219	219
	Maximum:	5430.00	2500.00	37.91	20.00
	Minimum:	20.00	0.00	22.85	0.00
	Variance:	711561.82	1304747.61	11.50	99.95
	Standard Deviation:	843.54	1142.26	3.39	10.00
Total:		258549.00	549300.00	8981.76	2240.00
Average:		815.61	1732.81	28.33	7.07
Count:		317	317	317	317
Maximum:		5430.00	2550.00	37.91	20.00
Minimum:		10.00	0.00	22.85	0.00
Variance:		657503.54	1154002.53	11.01	91.39
dard Deviation:		810.87	1074.25	3.32	9.56
2	87-1D				
	Total:	99281.00	292825.00	3728.78	0.00

Sex	Study_ID	[metformin] EFF23	Study_Rx_Dose	BMI	[glyburide] Rx#2_Dose
	Average:	781.74	2305.71	29.36	0.00
	Count:	127	127	127	127
	Maximum:	5020.00	2550.00	39.21	0.00
	Minimum:	10.00	0.00	21.30	0.00
	Variance:	563470.02	391173.12	12.07	0.00
	Standard Deviation:	750.65	625.44	3.47	0.00
	87-2D				
	Total:	218439.00	466000.00	8795.93	2910.00
	Average:	745.53	1590.44	30.02	9.93
	Count:	293	293	293	293
	Maximum:	4850.00	2500.00	38.76	20.00
	Minimum:	10.00	0.00	0.00	0.00
	Variance:	391320.54	1195744.85	20.74	99.65
	Standard Deviation:	625.56	1093.50	4.55	9.98
Total:		317720.00	758825.00	12524.71	2910.00
Average:		756.48	1806.73	29.82	6.93
Count:		420	420	420	420
Maximum:		5020.00	2550.00	39.21	20.00
Minimum:		10.00	0.00	0.00	0.00
Variance:		443651.92	1060378.87	18.21	90.33
Standard Deviation:		666.07	1029.75	4.27	9.50
i:		576269.00	1308125.00	21506.47	5150.00
Average:		781.91	1774.93	29.18	6.99
Count:		737	737	737	737
Maximum:		5430.00	2550.00	39.21	20.00
Minimum:		10.00	0.00	0.00	0.00

Drug/Dose Levels vs BMI vs SFU in Patient Visits WITHOUT ADR

Sex	Study_ID	[Levetiracetam] EFF23	Study_Rx_Dose	BMI	[Glyburide] Rx#2_Dose
Variance:		536491.42	1101987.78	15.66	90.79
Standard Deviation:		732.46	1049.76	3.96	9.53

Drug-Dose responses in the "Less-Obese" Metformin Visits

(-1-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB	BMI
1	87-1D	A				
		Total:	74025.00	210800.00	-109.10	2389.77
		Average:	813.46	2316.48	-1.20	26.26
		Count:	91	91	91	91
		Maximum:	4495.00	2550.00	3.90	28.85
		Minimum:	10.00	0.00	-4.50	23.04
		Variance:	736472.97	286871.15	1.92	2.22
		Standard Deviation:	858.18	535.60	1.39	1.49
	Total:		74025.00	210800.00	-109.10	2389.77
	Average:		813.46	2316.48	-1.20	26.26
	Count:		91	91	91	91
	Maximum:		4495.00	2550.00	3.90	28.85
	Minimum:		10.00	0.00	-4.50	23.04
	Variance:		736472.97	286871.15	1.92	2.22
	Standard Deviation:		858.18	535.60	1.39	1.49
	87-2D	A				
		Total:	122530.00	225000.00	-24.60	3902.91
		Average:	816.87	1500.00	-0.16	26.02
		Count:	150	150	150	150
		Maximum:	5070.00	2500.00	3.70	28.91
		Minimum:	10.00	0.00	-5.60	23.01
		Variance:	693550.16	1400000.00	2.33	2.50
		Standard Deviation:	832.80	1183.22	1.53	1.58
		D				
		Total:	173828.00	242000.00	-261.60	4491.57

Drug-Dose responses in the "Less-Obese" Metformin Visits

(-2-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB	BMI
		Average:	1016.54	1415.20	-1.53	26.27
		Count:	171	171	171	171
		Maximum:	4033.00	2500.00	4.00	28.97
		Minimum:	20.00	0.00	-5.70	22.85
		Variance:	793933.10	1295441.33	2.01	2.32
		Standard Deviation:	891.03	1138.17	1.42	1.52
	Total:		296358.00	467000.00	-286.20	8394.48
	Average:		923.23	1454.83	-0.89	26.15
	Count:		321	321	321	321
	Maximum:		5070.00	2500.00	4.00	28.97
	Minimum:		10.00	0.00	-5.70	22.85
	Variance:		756949.69	1346090.39	2.62	2.42
	Standard Deviation:		870.03	1160.21	1.62	1.56
Total:			370383.00	677800.00	-395.30	10784.25
Average:			898.99	1645.15	-0.96	26.18
Count:			412	412	412	412
Maximum:			5070.00	2550.00	4.00	28.97
Minimum:			10.00	0.00	-5.70	22.85
Variance:			754500.57	1239903.62	2.48	2.38
Standard Deviation:			868.62	1113.51	1.58	1.54
2	87-1D	A				
		Total:	55557.00	190400.00	-121.90	2153.05
		Average:	677.52	2321.95	-1.49	26.26
		Count:	82	82	82	82
		Maximum:	2412.00	2550.00	3.50	28.79
		Minimum:	12.00	0.00	-6.00	21.30

Drug-Dose responses in the "Less-Obese" Metformin Visits

(-3-)

Sex	Study_ID	Group	EFF23 [Metformin]	Study_Rx_Dose	EFF03_CFB [HbA1C]	BMI
		Variance:	292276.42	335676.68	3.14	2.94
		Standard Deviation:	540.63	579.38	1.77	1.71
	Total:		55557.00	190400.00	-121.90	2153.05
	Average:		677.52	2321.95	-1.49	26.26
	Count:		82	82	82	82
	Maximum:		2412.00	2550.00	3.50	28.79
	Minimum:		12.00	0.00	-6.00	21.30
	Variance:		292276.42	335676.68	3.14	2.94
	Standard Deviation:		540.63	579.38	1.77	1.71
	87-2D	A				
		Total:	72746.00	151000.00	-40.70	2508.82
		Average:	757.77	1572.92	-0.42	26.13
		Count:	96	96	96	96
		Maximum:	4210.00	2500.00	4.10	28.79
		Minimum:	20.00	0.00	-3.70	22.75
		Variance:	315823.72	1385308.16	2.34	2.79
		Standard Deviation:	561.98	1176.99	1.53	1.67
		D				
		Total:	122824.00	214500.00	-320.70	4023.16
		Average:	792.41	1383.87	-2.07	25.96
		Count:	155	155	155	155
		Maximum:	3460.00	2500.00	2.60	28.88
		Minimum:	20.00	0.00	-6.50	22.26
		Variance:	485732.04	1209094.69	2.30	3.57
		Standard Deviation:	696.94	1099.59	1.52	1.89

Drug-Dose responses in the "Less-Obese" Metformin Visits

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB	BMI
	Total:		195570.00	365500.00	-361.40	6531.98
	Average:		779.16	1456.18	-1.44	26.02
	Count:		251	251	251	251
	Maximum:		4210.00	2500.00	4.10	28.88
	Minimum:		20.00	0.00	-6.50	22.26
	Variance:		421030.62	1284931.99	2.95	3.28
	Standard Deviation:		648.87	1133.55	1.72	1.81
Total:			251127.00	555900.00	-483.30	8685.03
Average:			754.14	1669.37	-1.45	26.08
Count:			333	333	333	333
Maximum:			4210.00	2550.00	4.10	28.88
Minimum:			12.00	0.00	-6.50	21.30
Variance:			391242.81	1190308.01	3.00	3.21
Standard Deviation:			625.49	1091.01	1.73	1.79
Total:			621510.00	1233700.00	-878.60	19469.28
Average:			834.24	1655.97	-1.18	26.13
Count:			745	745	745	745
Maximum:			5070.00	2550.00	4.10	28.97
Minimum:			10.00	0.00	-6.50	21.30
Variance:			597318.26	1217880.43	2.77	2.75
Standard Deviation:			772.86	1103.58	1.67	1.66

Drug-Dose Responses in the "More-Obese" Metformin Visits

(-1-)

Sex	Study_ID	Group	EFF23 [Metformin]	Study_Rx_Dose	EFF03_CFB [InAc]	BMI
1	87-1D	A				
		Total:	48491.00	130050.00	-52.30	1766.84
		Average:	865.91	2322.32	-0.93	31.55
		Count:	56	56	56	56
		Maximum:	3533.00	2550.00	2.10	35.87
		Minimum:	11.00	0.00	-4.50	29.06
		Variance:	531670.44	244903.54	1.13	4.57
		Standard Deviation:	729.16	494.88	1.06	2.14
	Total:		48491.00	130050.00	-52.30	1766.84
	Average:		865.91	2322.32	-0.93	31.55
	Count:		56	56	56	56
	Maximum:		3533.00	2550.00	2.10	35.87
	Minimum:		11.00	0.00	-4.50	29.06
	Variance:		531670.44	244903.54	1.13	4.57
	Standard Deviation:		729.16	494.88	1.06	2.14
	87-2D	A				
		Total:	78002.00	136500.00	-7.00	2673.77
		Average:	962.99	1685.19	-0.09	33.01
		Count:	81	81	81	81
		Maximum:	4518.00	2500.00	3.10	45.12
		Minimum:	28.00	0.00	-5.10	29.03
		Variance:	728118.88	1348422.50	2.42	11.94
		Standard Deviation:	853.30	1161.22	1.56	3.46
		D				
		Total:	71339.00	139000.00	-132.30	3061.80

Drug-Dose Responses in the "More-Obese" Metformin Visits

(-2-)

Sex	Study_ID	Group	EFF23 [Metformin]	Study_Rx_Dose	EFF03_CFB [None]	BMI
		Average:	743.11	1447.92	-1.38	31.89
		Count:	96	96	96	96
		Maximum:	5430.00	2500.00	1.30	37.67
		Minimum:	40.00	0.00	-4.40	29.02
		Variance:	774510.71	1257703.99	1.38	4.23
		Standard Deviation:	880.06	1121.47	1.18	2.06
	Total:		149341.00	275500.00	-139.30	5735.57
	Average:		843.73	1556.50	-0.79	32.40
	Count:		177	177	177	177
	Maximum:		5430.00	2500.00	3.10	45.12
	Minimum:		28.00	0.00	-5.10	29.02
	Variance:		765279.79	1313192.25	2.27	8.07
	Standard Deviation:		874.80	1145.95	1.51	2.84
Total:			197832.00	405550.00	-191.60	7502.41
Average:			849.06	1740.56	-0.82	32.20
Count:			233	233	233	233
Maximum:			5430.00	2550.00	3.10	45.12
Minimum:			11.00	0.00	-5.10	29.02
Variance:			709223.12	1163516.00	2.00	7.36
Standard Deviation:			842.15	1078.66	1.42	2.71
2	87-1D	A				
		Total:	86924.00	236725.00	-161.20	3122.58
		Average:	886.98	2415.56	-1.64	31.86
		Count:	98	98	98	98
		Maximum:	5020.00	2550.00	3.60	39.21
		Minimum:	10.00	0.00	-5.40	29.28

Drug-Dose Responses in ... More-Obese" Metformin Visits

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB	BMI
		Variance:	742640.49	145963.21	2.94	6.04
		Standard Deviation:	861.77	382.05	1.71	2.46
	Total:		86924.00	236725.00	-161.20	3122.58
	Average:		886.98	2415.56	-1.64	31.86
	Count:		98	98	98	98
	Maximum:		5020.00	2550.00	3.60	39.21
	Minimum:		10.00	0.00	-5.40	29.28
	Variance:		742640.49	145963.21	2.94	6.04
	Standard Deviation:		861.77	382.05	1.71	2.46
	87-2D	A				
		Total:	123693.00	271000.00	-60.20	5596.10
		Average:	736.27	1613.10	-0.36	33.31
		Count:	168	168	168	168
		Maximum:	5830.00	2500.00	3.30	39.24
		Minimum:	10.00	0.00	-5.70	29.14
		Variance:	474088.47	1344352.32	2.75	6.56
		Standard Deviation:	688.54	1159.46	1.66	2.56
		D				
		Total:	90402.00	201250.00	-203.20	4512.61
		Average:	669.64	1490.74	-1.51	33.43
		Count:	135	135	135	135
		Maximum:	3110.00	2500.00	4.30	37.26
		Minimum:	20.00	0.00	-6.20	29.05
		Variance:	219602.47	1255932.78	2.95	5.87
		Standard Deviation:	468.62	1120.68	1.72	2.42

Drug-Dose Responses in ... More-Obese" Metformin Visits

(-4-)

[metformin]

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	HbA1c EFF03_CFB	BMI
	Total:		214095.00	472250.00	-263.40	10108.71
	Average:		706.58	1558.58	-0.87	33.36
	Count:		303	303	303	303
	Maximum:		5830.00	2500.00	4.30	39.24
	Minimum:		10.00	0.00	-6.70	29.05
	Variance:		361800.12	1308655.74	3.17	6.25
	Standard Deviation:		601.50	1143.96	1.78	2.50
Total:			301019.00	708975.00	-424.60	13231.29
Average:			750.67	1768.02	-1.06	33.00
Count:			401	401	401	401
Maximum:			5830.00	2550.00	4.30	39.24
Minimum:			10.00	0.00	-6.70	29.05
Variance:			460882.73	1160125.81	3.22	6.62
Standard Deviation:			678.88	1077.09	1.80	2.57
Total:			498851.00	1114525.00	-616.20	20733.70
Average:			786.83	1757.93	-0.97	32.70
Count:			634	634	634	634
Maximum:			5830.00	2550.00	4.30	45.12
Minimum:			10.00	0.00	-6.70	29.02
Variance:			554400.16	1161547.00	2.79	7.04
Standard Deviation:			744.58	1077.75	1.67	2.65

Drug_dose Responses in the Very Thin Metformin Diabetics

(-1-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB (HbA1c)	BMI
1	87-1D	A				
		Total:	24067.00	54400.00	-16.80	584.16
		Average:	1002.79	2266.67	-0.70	24.34
		Count:	24	24	24	24
		Maximum:	4495.00	2550.00	1.10	24.83
		Minimum:	98.00	0.00	-3.50	23.04
		Variance:	1642705.25	341180.56	1.16	0.28
		Standard Deviation:	1281.68	584.11	1.08	0.52
	Total:		24067.00	54400.00	-16.80	584.16
	Average:		1002.79	2266.67	-0.70	24.34
	Count:		24	24	24	24
	Maximum:		4495.00	2550.00	1.10	24.83
	Minimum:		98.00	0.00	-3.50	23.04
	Variance:		1642705.25	341180.56	1.16	0.28
	Standard Deviation:		1281.68	584.11	1.08	0.52
	87-2D	A				
		Total:	48211.00	73000.00	-13.70	1158.06
		Average:	1004.40	1520.83	-0.29	24.13
		Count:	48	48	48	48
		Maximum:	5070.00	2500.00	2.40	24.92
		Minimum:	60.00	0.00	-5.60	23.01
		Variance:	1060791.82	1343315.97	2.27	0.27
		Standard Deviation:	1029.95	1159.02	1.51	0.52
		D				
		Total:	38867.00	40000.00	-45.60	789.38

Drug_dose Responses in the Very Thin Metformin Diabetics
(-2-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB (HbA1c)	BMI
		Average:	1177.79	1212.12	-1.38	23.92
		Count:	33	33	33	33
		Maximum:	4033.00	2500.00	1.70	24.86
		Minimum:	20.00	0.00	-4.80	22.85
		Variance:	1338108.59	1364095.50	1.77	0.43
		Standard Deviation:	1156.77	1167.94	1.33	0.65
	Total:		87078.00	113000.00	-59.30	1947.44
	Average:		1075.04	1395.06	-0.73	24.04
	Count:		81	81	81	81
	Maximum:		5070.00	2500.00	2.40	24.92
	Minimum:		20.00	0.00	-5.60	22.85
	Variance:		1181031.17	1374790.43	2.35	0.35
	Standard Deviation:		1086.75	1172.51	1.53	0.59
Total:			111145.00	167400.00	-76.10	2531.60
Average:			1058.52	1594.29	-0.72	24.11
Count:			105	105	105	105
Maximum:			5070.00	2550.00	2.40	24.92
Minimum:			20.00	0.00	-5.60	22.85
Variance:			1287476.99	1272491.16	2.08	0.35
Standard Deviation:			1134.67	1128.05	1.44	0.59
2	87-1D	A				
		Total:	14391.00	42500.00	-3.00	431.32
		Average:	799.50	2361.11	-0.17	23.96
		Count:	18	18	18	18
		Maximum:	1561.00	2550.00	1.90	24.90
		Minimum:	221.00	1700.00	-3.70	21.30

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB	BMI
		Variance:	184721.58	124876.54	2.32	1.51
		Standard Deviation:	429.79	353.38	1.52	1.23
	Total:		14391.00	42500.00	-3.00	431.32
	Average:		799.50	2361.11	-0.17	23.96
	Count:		18	18	18	18
	Maximum:		1561.00	2550.00	1.90	24.90
	Minimum:		221.00	1700.00	-3.70	21.30
	Variance:		184721.58	124876.54	2.32	1.51
	Standard Deviation:		429.79	353.38	1.52	1.23
	87-2D	A				
		Total:	19649.00	29500.00	-0.40	549.05
		Average:	854.30	1282.61	-0.02	23.87
		Count:	23	23	23	23
		Maximum:	4210.00	2500.00	3.30	24.89
		Minimum:	20.00	0.00	-2.40	22.75
		Variance:	750347.08	1344045.37	2.32	0.54
		Standard Deviation:	866.23	1159.33	1.52	0.74
		D				
		Total:	42679.00	71500.00	-112.00	1286.85
		Average:	790.35	1324.07	-2.07	23.83
		Count:	54	54	54	54
		Maximum:	3460.00	2500.00	1.10	24.90
		Minimum:	38.00	0.00	-4.80	22.26
		Variance:	542064.12	1112568.59	2.09	0.47
		Standard Deviation:	736.25	1054.78	1.45	0.68

Drug_dose Responses in the Very Thin Metformin Diabetics
(-4-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	HbA1c EFF03_CFB	BMI
	Total:		62328.00	101000.00	-112.40	1835.90
	Average:		809.45	1311.69	-1.46	23.84
	Count:		77	77	77	77
	Maximum:		4210.00	2500.00	3.30	24.90
	Minimum:		20.00	0.00	-4.80	22.26
	Variance:		605135.26	1182071.18	3.05	0.49
	Standard Deviation:		777.90	1087.23	1.75	0.70
Total:			76719.00	143500.00	-115.40	2267.22
Average:			807.57	1510.53	-1.21	23.87
Count:			95	95	95	95
Maximum:			4210.00	2550.00	3.30	24.90
Minimum:			20.00	0.00	-4.80	21.30
Variance:			525493.15	1150889.20	3.17	0.69
Standard Deviation:			724.91	1072.80	1.78	0.83
Total:			187864.00	310900.00	-191.50	4798.82
Average:			939.32	1554.50	-0.96	23.99
Count:			200	200	200	200
Maximum:			5070.00	2550.00	3.30	24.92
Minimum:			20.00	0.00	-5.60	21.30
Variance:			941239.96	1216479.75	2.66	0.52
Standard Deviation:			970.18	1102.94	1.63	0.72

Drug-Dose Responses for Metformin Visits With Associated Diarrhea
(-1-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
1	87-1D	A			
		Total:	25158.00	89250.00	-34.70
		Average:	613.61	2176.83	-0.85
		Count:	41	41	41
		Maximum:	2210.00	2550.00	1.60
		Minimum:	10.00	0.00	-3.40
		Variance:	325621.75	424646.04	1.12
		Standard Deviation:	570.63	651.65	1.06
	Total:		25158.00	89250.00	-34.70
	Average:		613.61	2176.83	-0.85
	Count:		41	41	41
	Maximum:		2210.00	2550.00	1.60
	Minimum:		10.00	0.00	-3.40
	Variance:		325621.75	424646.04	1.12
	Standard Deviation:		570.63	651.65	1.06
	87-2D	A			
		Total:	17360.00	48000.00	2.40
		Average:	667.69	1846.15	0.09
		Count:	26	26	26
		Maximum:	3380.00	2500.00	2.60
		Minimum:	69.00	0.00	-1.90
		Variance:	390709.14	1072485.21	1.67
		Standard Deviation:	625.07	1035.61	1.29
		D			
		Total:	21622.00	41000.00	-43.10

Drug-Dose Responses for Metformin Visits With Associated Diarrhea
(-2-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
		Average:	800.81	1518.52	-1.60
		Count:	27	27	27
		Maximum:	2102.00	2500.00	0.70
		Minimum:	163.00	0.00	-3.90
		Variance:	236400.74	1082990.40	1.42
		Standard Deviation:	486.21	1040.67	1.19
	Total:		38982.00	89000.00	-40.70
	Average:		735.51	1679.25	-0.77
	Count:		53	53	53
	Maximum:		3380.00	2500.00	2.60
	Minimum:		69.00	0.00	-3.90
	Variance:		316528.02	1104663.58	2.26
	Standard Deviation:		562.61	1051.03	1.50
Total:			64140.00	178250.00	-75.40
Average:			682.34	1896.28	-0.80
Count:			94	94	94
Maximum:			3380.00	2550.00	2.60
Minimum:			10.00	0.00	-3.90
Variance:			324148.78	868948.90	1.76
Standard Deviation:			569.34	932.17	1.33
2	87-1D	A			
		Total:	29618.00	118575.00	-80.10
		Average:	604.45	2419.90	-1.63
		Count:	49	49	49
		Maximum:	2030.00	2550.00	3.60
		Minimum:	20.00	0.00	-4.00

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
		Variance:	218646.37	193188.25	1.93
		Standard Deviation:	467.60	439.53	1.39
	Total:		29618.00	118575.00	-80.10
	Average:		604.45	2419.90	-1.63
	Count:		49	49	49
	Maximum:		2030.00	2550.00	3.60
	Minimum:		20.00	0.00	-4.00
	Variance:		218646.37	193188.25	1.93
	Standard Deviation:		467.60	439.53	1.39
	87-2D	A			
		Total:	32932.00	98500.00	-38.20
		Average:	598.76	1790.91	-0.69
		Count:	55	55	55
		Maximum:	1370.00	2500.00	2.90
		Minimum:	86.00	0.00	-6.70
		Variance:	68242.58	1124462.81	2.40
		Standard Deviation:	261.23	1060.41	1.55
		D			
		Total:	28077.00	79000.00	-61.10
		Average:	684.80	1926.83	-1.49
		Count:	41	41	41
		Maximum:	3133.00	2500.00	1.70
		Minimum:	121.00	0.00	-4.50
		Variance:	279151.52	762938.73	1.93
		Standard Deviation:	528.35	873.46	1.39

Drug-Dose Responses for Metformin Visits With Associated Diarrhea
(-4-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
	Total:		61009.00	177500.00	-99.30
	Average:		635.51	1848.96	-1.03
	Count:		96	96	96
	Maximum:		3133.00	2500.00	2.90
	Minimum:		86.00	0.00	-6.70
	Variance:		160129.69	974582.25	2.36
	Standard Deviation:		400.16	987.21	1.54
Total:			90627.00	296075.00	-179.40
Average:			625.01	2041.90	-1.24
Count:			145	145	145
Maximum:			3133.00	2550.00	3.60
Minimum:			20.00	0.00	-6.70
Variance:			180120.15	783455.89	2.29
Standard Deviation:			424.41	885.13	1.51
Total:			154767.00	474325.00	-254.80
Average:			647.56	1984.62	-1.07
Count:			239	239	239
Maximum:			3380.00	2550.00	3.60
Minimum:			10.00	0.00	-6.70
Variance:			237551.57	822140.65	2.13
Standard Deviation:			487.39	906.72	1.46

Drug-Dose Responses for metformin Visits Without Diarrhea
(-1-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
1	87-1D	A			
		Total:	122516.00	340850.00	-161.40
		Average:	833.44	2318.71	-1.10
		Count:	147	147	147
		Maximum:	4495.00	2550.00	3.90
		Minimum:	10.00	0.00	-4.50
		Variance:	659101.70	270891.53	1.63
		Standard Deviation:	811.85	520.47	1.28
	Total:		122516.00	340850.00	-161.40
	Average:		833.44	2318.71	-1.10
	Count:		147	147	147
	Maximum:		4495.00	2550.00	3.90
	Minimum:		10.00	0.00	-4.50
	Variance:		659101.70	270891.53	1.63
	Standard Deviation:		811.85	520.47	1.28
	87-2D	A			
		Total:	200532.00	361500.00	-31.60
		Average:	868.10	1564.94	-0.14
		Count:	231	231	231
		Maximum:	5070.00	2500.00	3.70
		Minimum:	10.00	0.00	-5.60
		Variance:	710533.24	1389722.83	2.37
		Standard Deviation:	842.93	1178.87	1.54
		D			
		Total:	245167.00	381000.00	-393.90

Drug-Dose Responses for Metformin Visits Without Diarrhea
(-2-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
		Average:	918.23	1426.97	-1.48
		Count:	267	267	267
		Maximum:	5430.00	2500.00	4.00
		Minimum:	20.00	0.00	-5.70
		Variance:	804165.14	1282119.26	1.79
		Standard Deviation:	896.75	1132.31	1.34
	Total:		445699.00	742500.00	-425.50
	Average:		894.98	1490.96	-0.85
	Count:		498	498	498
	Maximum:		5430.00	2500.00	4.00
	Minimum:		10.00	0.00	-5.70
	Variance:		761358.31	1336765.74	2.50
	Standard Deviation:		872.56	1156.19	1.58
Total:			568215.00	1083350.00	-586.90
Average:			880.95	1679.61	-0.91
Count:			645	645	645
Maximum:			5430.00	2550.00	4.00
Minimum:			10.00	0.00	-5.70
Variance:			738719.63	1214409.93	2.31
Standard Deviation:			859.49	1102.00	1.52
2	87-1D	A			
		Total:	142481.00	427125.00	-283.10
		Average:	791.56	2372.92	-1.57
		Count:	180	180	180
		Maximum:	5020.00	2550.00	3.60
		Minimum:	10.00	0.00	-6.00

Drug-Dose Responses fo. .etformin Visits Without Diarrhea
(-3-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
		Variance:	548355.85	234561.63	3.04
		Standard Deviation:	740.51	484.32	1.74
	Total:		142481.00	427125.00	-283.10
	Average:		791.56	2372.92	-1.57
	Count:		180	180	180
	Maximum:		5020.00	2550.00	3.60
	Minimum:		10.00	0.00	-6.00
	Variance:		548355.85	234561.63	3.04
	Standard Deviation:		740.51	484.32	1.74
	87-2D	A			
		Total:	198434.00	427000.00	-103.10
		Average:	743.20	1599.25	-0.39
		Count:	267	267	267
		Maximum:	5830.00	2500.00	4.10
		Minimum:	10.00	0.00	-6.70
		Variance:	412053.73	1359999.44	2.58
		Standard Deviation:	641.91	1166.19	1.60
		D			
		Total:	213226.00	415750.00	-523.90
		Average:	735.26	1433.62	-1.81
		Count:	290	290	290
		Maximum:	3460.00	2500.00	4.30
		Minimum:	20.00	0.00	-6.50
		Variance:	365594.23	1233740.34	2.68
		Standard Deviation:	604.64	1110.74	1.64

Drug-Dose Responses for metformin Visits Without Diarrhea
(-4-)

Sex	Study_ID	Group	EFF23	Study_Rx_Dose	EFF03_CFB
	Total:		411660.00	842750.00	-627.00
	Average:		739.07	1513.02	-1.13
	Count:		557	557	557
	Maximum:		5830.00	2500.00	4.30
	Minimum:		10.00	0.00	-6.70
	Variance:		387880.49	1301109.75	3.13
	Standard Deviation:		622.80	1140.66	1.77
Total:			554141.00	1269875.00	-910.10
Average:			751.89	1723.03	-1.23
Count:			737	737	737
Maximum:			5830.00	2550.00	4.30
Minimum:			10.00	0.00	-6.70
Variance:			427582.58	1177109.43	3.15
Standard Deviation:			653.90	1084.95	1.77
Total:			1122356.00	2353225.00	-1497.00
Average:			812.12	1702.77	-1.08
Count:			1382	1382	1382
Maximum:			5830.00	2550.00	4.30
Minimum:			10.00	0.00	-6.70
Variance:			576940.94	1194987.37	2.78
Standard Deviation:			759.57	1093.15	1.67

Drug/Dose levels in patients with ADRs

Sex	Study_ID	EFF23	Study_Rx_Dose
	87-1D		
	Total:	72291.00	219300.00
	Average:	737.66	2237.76
	Count:	98	98
	Maximum:	4090.00	2550.00
	Minimum:	10.00	0.00
	Variance:	527904.90	448064.35
	Standard Deviation:	726.57	669.38
	87-2D		
	Total:	186258.00	330000.00
	Average:	850.49	1506.85
	Count:	219	219
	Maximum:	5430.00	2500.00
	Minimum:	20.00	0.00
	Variance:	711561.82	1304747.61
	Standard Deviation:	843.54	1142.26
Total:		258549.00	549300.00
Average:		815.61	1732.81
Count:		317	317
imum:		5430.00	2550.00
mum:		10.00	0.00
ance:		657503.54	1154002.53
Standard Deviation:		810.87	1074.25
2	87-1D		
	Total:	99281.00	292825.00
	Average:	781.74	2305.71
	Count:	127	127
	Maximum:	5020.00	2550.00
	Minimum:	10.00	0.00
	Variance:	563470.02	391173.12
	Standard Deviation:	750.65	625.44
	87-2D		
	Total:	218439.00	466000.00
	Average:	745.53	1590.44
	Count:	293	293
	Maximum:	4850.00	2500.00
	Minimum:	10.00	0.00
	Variance:	391320.54	1195744.85
	Standard Deviation:	625.56	1093.50
l:		317720.00	758825.00
rage:		756.48	1806.73
nt:		420	420
Maximum:		5020.00	2550.00
Minimum:		10.00	0.00
Variance:		443651.92	1060378.87
Standard Deviation:		666.07	1029.75

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Drug/Dose levels in patients with ADRs

Sex	Study_ID	EFF23	Study_Rx_Dose
Total:		576269.00	1308125.00
Average:		781.91	1774.93
Count:		737	737
Maximum:		5430.00	2550.00
Minimum:		10.00	0.00
Variance:		536491.42	1101987.78
Standard Deviation:		732.46	1049.76

GFR Changes vs

pH vs. electrolytes

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(1)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
87-1D	A	1.0			
		Total:	357.3426573		
		Average:	89.3356643		
		Count:	4		
		Standard Deviation:	6.9820719		
		1.1			
		Total:	298.6111111		
		Average:	99.5370370		
		Count:	3		
		Standard Deviation:	9.6447531		
		2.0			
		Total:	198.8888889		
		Average:	99.4444444		
		Count:	2		
		Standard Deviation:	10.5555556		
		2.1			
		Total:	100.0000000		
		Average:	100.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		3.0			
		Total:	280.0000000		
		Average:	93.3333333		
		Count:	3		
		Standard Deviation:	9.4280904		
		3.1			
		Total:	403.8888889		
		Average:	100.9722222		
		Count:	4		
		Standard Deviation:	17.6399825		
		3.2			
		Total:	100.0000000		
		Average:	100.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		4.0			
		Total:	13,576.5916028		
		Average:	102.8529667		
		Count:	132		
		Standard Deviation:	14.5998791		
		4.1			

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
		Total:	493.1313131		
		Average:	98.6262626		
		Count:	5		
		Standard Deviation:	12.0010203		
		4.2			
		Total:	166.6666667		
		Average:	83.3333333		
		Count:	2		
		Standard Deviation:	5.5555556		
		5.0			
		Total:	12,638.0193345		
		Average:	101.1041547		
		Count:	125		
		Standard Deviation:	16.7521991		
		5.1			
		Total:	626.8772894		
		Average:	104.4795482		
		Count:	6		
		Standard Deviation:	27.8903271		
		5.2			
		Total:	323.2773109		
		Average:	107.7591036		
		Count:	3		
		Standard Deviation:	30.4488106		
		5.3			
		Total:	112.5000000		
		Average:	112.5000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		5.4			
		Total:	112.5000000		
		Average:	112.5000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		6.0			
		Total:	12,565.3571429		
		Average:	104.7113095		
		Count:	120		
		Standard Deviation:	19.7838916		
		6.1			

		Average:	101.1558442		

Percent Change from Baseline by Study, by Rx Group, and by Visit

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
		Count:	7		
		Standard Deviation:	26.0062981		
		6.2			
		Total:	157.8947368		
		Average:	78.9473684		
		Count:	2		
		Standard Deviation:	21.0526316		
		6.3			
		Total:	91.6666667		
		Average:	91.6666667		
		Count:	1		
		Standard Deviation:	0.0000009		
		7.0			
		Total:	12,140.6349206		
		Average:	106.4967975		
		Count:	114		
		Standard Deviation:	20.6508353		
		7.1			
		Total:	400.0000000		
		Average:	100.0000000		
		Count:	4		
		Standard Deviation:	15.3093109		
		7.2			
		Total:	88.8888889		
		Average:	88.8888889		
		Count:	1		
		Standard Deviation:	0.0000006		
		8.0			
		Total:	11,658.4476634		
		Average:	104.0932827		
		Count:	112		
		Standard Deviation:	17.9496571		
		8.1			
		Total:	765.7808858		
		Average:	95.7226107		
		Count:	8		
		Standard Deviation:	18.8433976		
		8.2			

Average:		81.8181818
Count:		1
Standard Deviation:		0.0000000

(4) Percent Change from Baseline by Study, by Rx Group, and by Visit

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF B
87-1D	A	9.0			
		Total:	12,017.3151848		
		Average:	107.2974570		
		Count:	112		
		Standard Deviation:	20.0307708		
		9.1			
		Total:	277.1428571		
		Average:	92.3809524		
		Count:	3		
		Standard Deviation:	18.0827024		
		9.2			
		Total:	208.3333333		
		Average:	104.1666667		
		Count:	2		
		Standard Deviation:	4.1666667		
	Total:		80,949.6664350		
	Average:		103.7816236		
	Count:		780		
	Standard Deviation:		18.5918292		
	B	1.0			
		Total:	390.3571429		
		Average:	97.5892857		
		Count:	4		
		Standard Deviation:	8.4265093		
		2.0			
		Total:	495.4822955		
		Average:	99.0964591		
		Count:	5		
		Standard Deviation:	8.7478922		
		2.1			
		Total:	100.0000000		
		Average:	100.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		3.0			
		Total:	290.0000000		
		Average:	96.6666667		

Standard Deviation:		4.7140452
	3.1	
Total:		469.4444444

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(5)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
		Average:	117.3611111		
		Count:	4		
		Standard Deviation:	16.9393207		
		4.0			
		Total:	13,810.0813076		
		Average:	103.0603083		
		Count:	134		
		Standard Deviation:	16.1246418		
		4.1			
		Total:	377.0707071		
		Average:	94.2676768		
		Count:	4		
		Standard Deviation:	13.9476946		
		4.2			
		Total:	118.1818182		
		Average:	118.1818182		
		Count:	1		
		Standard Deviation:	0.0000006		
		5.0			
		Total:	12,395.3937729		
		Average:	102.4412709		
		Count:	121		
		Standard Deviation:	17.8193523		
		5.1			
		Total:	641.7099567		
		Average:	106.9516595		
		Count:	6		
		Standard Deviation:	7.8125678		
		6.0			
		Total:	12,065.4695305		
		Average:	105.8374520		
		Count:	114		
		Standard Deviation:	16.4306361		
		6.1			
		Total:	112.5000000		
		Average:	112.5000000		

Standard Deviation:		0.0000000
	7.0	
Total:		11,606.6492984
Average:		104.5644081
Count:		111

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(6)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF B
		Standard Deviation:	18.6929499		
		7.1			
		Total:	357.3015873		
		Average:	89.3253968		
		Count:	4		
		Standard Deviation:	8.1675690		
		7.2			
		Total:	283.3333333		
		Average:	94.4444444		
		Count:	3		
		Standard Deviation:	14.1639431		
		8.0			
		Total:	11,031.7465867		
		Average:	104.0730810		
		Count:	106		
		Standard Deviation:	18.1702629		
		8.1			
		Total:	445.0000000		
		Average:	111.2500000		
		Count:	4		
		Standard Deviation:	3.2004774		
		9.0			
		Total:	10,950.0019425		
		Average:	105.2884802		
		Count:	104		
		Standard Deviation:	20.5153497		
		9.1			
		Total:	498.3766234		
		Average:	99.6753247		
		Count:	5		
		Standard Deviation:	15.7593001		
Total:			76,438.1003474		
Average:			103.9974154		
Count:			735		

Total:			157,387.7667823
Average:			103.8863147
t:			1515
dard Deviation:			18.1799578
87-2D	A	1.0	

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(7)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
		Total:	415.1648352		
		Average:	103.7912088		
		Count:	4		
		Standard Deviation:	11.7547751		
		1.1			
		Total:	135.3535354		
		Average:	67.6767677		
		Count:	2		
		Standard Deviation:	23.2323232		
		2.0			
		Total:	290.9090909		
		Average:	96.9696970		
		Count:	3		
		Standard Deviation:	9.2212873		
		3.0			
		Total:	424.6153846		
		Average:	106.1538462		
		Count:	4		
		Standard Deviation:	19.8374393		
		3.1			
		Total:	225.8741259		
		Average:	112.9370629		
		Count:	2		
		Standard Deviation:	5.2447552		
		4.0			
		Total:	442.8571429		
		Average:	110.7142857		
		Count:	4		
		Standard Deviation:	11.8450885		
		4.1			
		Total:	100.0000000		
		Average:	100.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		

	5.0	
	Total:	330.1923077
	Average:	110.0641026
	Count:	3
	Standard Deviation:	1.9632555
	5.1	
	Total:	401.6666667
	Average:	100.4166667

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(8)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
		Count:	4		
		Standard Deviation:	6.4951905		
		5.2			
		Total:	200.0000000		
		Average:	100.0000000		
		Count:	2		
		Standard Deviation:	0.0000000		
		5.3			
		Total:	83.3333333		
		Average:	83.3333333		
		Count:	1		
		Standard Deviation:	0.0000000		
		6.0			
		Total:	20,587.4821012		
		Average:	105.0381740		
		Count:	196		
		Standard Deviation:	15.8004714		
		6.1			
		Total:	866.5018315		
		Average:	108.3127289		
		Count:	8		
		Standard Deviation:	20.4611636		
		6.2			
		Total:	222.2222222		
		Average:	111.1111111		
		Count:	2		
		Standard Deviation:	11.1111111		
		6.5			
		Total:	122.2222222		
		Average:	122.2222222		
		Count:	1		
		Standard Deviation:	0.0000006		

		7.0			
			Total:	20,009.0306915	
			Average:	105.3106879	
			Count:	190	
			Standard Deviation:	16.7176656	
		7.1			
			Total:	567.7020202	
			Average:	113.5404040	
			Count:	5	
			Standard Deviation:	5.8418954	

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(9)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CFB
87-2D	A	8.0			
			Total:	18,568.1540682	
			Average:	108.5856963	
			Count:	171	
			Standard Deviation:	17.5286603	
		8.1			
			Total:	540.0000000	
			Average:	108.0000000	
			Count:	5	
			Standard Deviation:	14.3527001	
		9.0			
			Total:	17,365.2841603	
			Average:	106.5354856	
			Count:	163	
			Standard Deviation:	18.1207906	
		9.1			
			Total:	680.5555556	
			Average:	97.2222222	
			Count:	7	
			Standard Deviation:	9.3859064	
		10.0			
			Total:	16,915.0804751	
			Average:	105.7192530	
			Count:	160	
			Standard Deviation:	16.1586716	
		10.1			
			Total:	197.2222222	
			Average:	98.6111111	
			Count:	2	
			Standard Deviation:	23.6111111	

		Total:	17,201.2601288
		Average:	108.8687350
		Count:	158
		Standard Deviation:	18.5046644
		11.1	
		Total:	308.5858586
		Average:	102.8619529
		Count:	3
		Standard Deviation:	48.3695552
	Total:		117,201.2699800

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(10)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
	Average:		106.4498365		
	Count:		1101		
	Standard Deviation:		17.3088809		
	C	1.0			
		Total:	290.4761905		
		Average:	96.8253968		
		Count:	3		
		Standard Deviation:	9.9760358		
		2.0			
		Total:	403.7062937		
		Average:	100.9265734		
		Count:	4		
		Standard Deviation:	10.1967748		
		2.1			
		Total:	120.0000000		
		Average:	120.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		3.0			
		Total:	120.0000000		
		Average:	120.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		4.0			
		Total:	484.6031746		
		Average:	96.9206349		
		Count:	5		
		Standard Deviation:	8.7192428		
		5.0			

Total:	310.0000000
Average:	103.3333333
Count:	3
Standard Deviation:	4.7140452

5.1

Total:	172.7272727
Average:	86.3636364
Count:	2
Standard Deviation:	13.6363636

5.2

Total:	114.2857143
Average:	114.2857143
Count:	1

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(11)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
		Standard Deviation:	0.0000004		

6.0

Total:	20,346.2351864
Average:	103.8073224
Count:	196
Standard Deviation:	32.6853117

6.1

Total:	920.1709402
Average:	102.2412156
Count:	9
Standard Deviation:	14.0458927

6.2

Total:	112.5000000
Average:	112.5000000
Count:	1
Standard Deviation:	0.0000000

7.0

Total:	19,417.1650572
Average:	101.1310680
Count:	192
Standard Deviation:	16.1679652

7.1

Total:	402.5000000
Average:	100.6250000
Count:	4
Standard Deviation:	7.9794658

7.2

Total:	100.0000000
Average:	100.0000000
Count:	1
Standard Deviation:	0.0000000

7.3

Total:	100.0000000
Average:	100.0000000
Count:	1
Standard Deviation:	0.0000000

7.4

Total:	112.5000000
Average:	112.5000000
Count:	1
Standard Deviation:	0.0000000

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(12)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
87-2D	C	8.0			
		Total:	18,822.7507215		
		Average:	101.1975845		
		Count:	186		
		Standard Deviation:	15.9086250		
		8.1			
		Total:	497.8632479		
		Average:	99.5726496		
		Count:	5		
		Standard Deviation:	11.7556327		
		8.2			
		Total:	100.0000000		
		Average:	100.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		9.0			
		Total:	18,200.4686980		
		Average:	101.1137150		
		Count:	180		
		Standard Deviation:	15.4123648		
		9.1			
		Total:	562.7380952		
		Average:	93.7896825		
		Count:	6		
		Standard Deviation:	10.4034307		
		9.2			

Total:	91.6666667
Average:	91.6666667
Count:	1
Standard Deviation:	0.0000009
9.3	
Total:	231.3131313
Average:	115.6565657
Count:	2
Standard Deviation:	6.5656566
9.4	
Total:	100.0000000
Average:	100.0000000
Count:	1
Standard Deviation:	0.0000000
10.0	

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(13)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
B					
		Total:	18,170.3171828		
		Average:	103.2404385		
		Count:	176		
		Standard Deviation:	15.9930418		
		10.1			
		Total:	505.4166667		
		Average:	101.0833333		
		Count:	5		
		Standard Deviation:	7.7799600		
		10.2			
		Total:	125.0000000		
		Average:	125.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		11.0			
		Total:	18,150.0788101		
		Average:	103.7147361		
		Count:	175		
		Standard Deviation:	15.9102588		
		11.1			
		Total:	193.2330827		
		Average:	96.6165414		
		Count:	2		
		Standard Deviation:	17.6691729		
		11.2			

	Total:	115.3846154
	Average:	115.3846154
	Count:	1
	Standard Deviation:	0.0000003

Total:		119,393.1007477
Average:		102.3077127
Count:		1167
Standard Deviation:		19.6325016
D	1.0	

	Total:	338.8888889
	Average:	112.9629630
	Count:	3
	Standard Deviation:	9.4426287
	2.0	

	Total:	305.3846154
	Average:	101.7948718
	Count:	3

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(14)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
		Standard Deviation:	10.4406529		
		3.0			

		Total:	200.6410256		
		Average:	100.3205128		
		Count:	2		
		Standard Deviation:	8.0128205		
		4.0			

		Total:	519.5238095		
		Average:	103.9047619		
		Count:	5		
		Standard Deviation:	26.9750872		
		5.0			

		Total:	228.5714286		
		Average:	114.2857143		
		Count:	2		
		Standard Deviation:	14.2857143		
		5.1			

		Total:	100.0000000		
		Average:	100.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		6.0			

		Average:	103.2414000		
		Count:	208		
		Standard Deviation:	14.6911128		
		6.1			
		Total:	822.4927850		
		Average:	102.8115981		
		Count:	8		
		Standard Deviation:	12.2011325		
		6.2			
		Total:	144.4444444		
		Average:	144.4444444		
		Count:	1		
		Standard Deviation:	0.0000000		
		7.0			
		Total:	20,496.1059774		
		Average:	101.4658712		
		Count:	202		
		Standard Deviation:	15.5888945		

GFR Percent Change from Baseline by Study, by Rx Group, and by Visit
(15)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF
87-2D	D	7.1			
		Total:	1,204.9475524		
		Average:	92.6882733		
		Count:	13		
		Standard Deviation:	13.4484862		
		7.3			
		Total:	185.7142857		
		Average:	92.8571429		
		Count:	2		
		Standard Deviation:	7.1428571		
		8.0			
		Total:	20,931.3800089		
		Average:	103.1102463		
		Count:	203		
		Standard Deviation:	19.4792221		
		8.1			
		Total:	607.4603175		
		Average:	101.2433862		
		Count:	6		
		Standard Deviation:	25.1014849		
		8.2			

Average:	87.0629371
Count:	2
Standard Deviation:	5.2447552
9.0	
Total:	20,465.5777556
Average:	103.3615038
Count:	198
Standard Deviation:	17.2520309
9.1	
Total:	1,129.1330891
Average:	112.9133089
Count:	10
Standard Deviation:	26.0105187
9.2	
Total:	256.3888889
Average:	85.4629630
Count:	3
Standard Deviation:	3.9042905
10.0	

Percent Change from Baseline by Study, by Rx Group, and by Visit

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CF B
		Total:	20,226.8620269		
		Average:	103.7274976		
		Count:	195		
		Standard Deviation:	16.0686323		
		10.1			
		Total:	366.9047619		
		Average:	91.7261905		
		Count:	4		
		Standard Deviation:	12.7945733		
		10.2			
		Total:	75.0000000		
		Average:	75.0000000		
		Count:	1		
		Standard Deviation:	0.0000000		
		11.0			
		Total:	20,420.4320679		
		Average:	105.2599591		
		Count:	194		
		Standard Deviation:	18.4679882		
		11.1			

Average:	101.1335578
Count:	9
Standard Deviation:	9.9696029

11.2

Total:	239.0909091
Average:	119.5454545
Count:	2
Standard Deviation:	10.4545455

11.3

Total:	219.0909091
Average:	109.5454545
Count:	2
Standard Deviation:	0.4545455

Total:	132,042.5746476
Average:	103.2389168
Count:	1279
Standard Deviation:	17.1708861

Total:	368,636.9453753
Average:	103.9292206
Count:	3547
Standard Deviation:	18.1420019

R Percent Change from Baseline by Study, by Rx Group, and by Visit
(17)

Study_ID	Group	Visit_No	(((Cr-Cr_CFB)*100)/Cr)	Cr	Cr_CFB
Total:			526,024.7121576		
Average:			103.9163793		
Count:			5062		
Standard Deviation:			18.1533807		

Urinary pH Change from Baseline (1)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
D	A	3.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	0.000
		Average:	0.000
		Count:	18
		Standard Deviation:	0.667
		5.0	
		Total:	2.000
		Average:	0.118
		Count:	17
		Standard Deviation:	0.676
		5.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-4.000
		Average:	-0.160
		Count:	25
		Standard Deviation:	0.833
		6.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	4.000
		Average:	0.143
		Count:	28
		Standard Deviation:	0.693
		8.0	
		Total:	3.000
		Average:	0.176
		Count:	17
		Standard Deviation:	0.617
		8.1	

Urinary pH Change from Baseline (2)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	0.000
		Average:	0.000
		Count:	29
		Standard Deviation:	0.788
	Total:		5.000
	Average:		0.036
	Count:		138
	Standard Deviation:		0.726
	B	3.1	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	5.000
		Average:	0.313
		Count:	16
		Standard Deviation:	0.916
		5.0	
		Total:	-4.000
		Average:	-0.190
		Count:	21
		Standard Deviation:	0.663
		6.0	
		Total:	1.000
		Average:	0.040
		Count:	25
		Standard Deviation:	0.720
		7.0	
		Total:	-1.000
		Average:	-0.048
		Count:	21
		Standard Deviation:	0.722
		8.0	
		Total:	0.000
		Average:	0.000
		Count:	19

Urinary pH Change from Baseline (3)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
		Standard Deviation:	0.725
		9.0	
		Total:	5.000
		Average:	0.238
		Count:	21
		Standard Deviation:	0.971
	Total:		7.000
	Average:		0.056
	Count:		124
	Standard Deviation:		0.806
Total:			12.000
Average:			0.046
Count:			262
Standard Deviation:			0.765
87-2D	A	1.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-1.000
		Average:	-1.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-5.000
		Average:	-0.128
		Count:	39
		Standard Deviation:	0.723
		6.1	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		7.0	

Urinary pH Change from Baseline (4)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
		Total:	4.000
		Average:	0.114
		Count:	35
		Standard Deviation:	0.919
		8.0	
		Total:	-3.000
		Average:	-0.071
		Count:	42
		Standard Deviation:	0.768
		8.1	
		Total:	-1.000
		Average:	-1.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-1.000
		Average:	-0.027
		Count:	37
		Standard Deviation:	0.753
		10.0	
		Total:	4.000
		Average:	0.125
		Count:	32
		Standard Deviation:	0.781
		11.0	
		Total:	2.000
		Average:	0.045
		Count:	44
		Standard Deviation:	0.796
	Total:		0.000
	Average:		0.000
	Count:		234
	Standard Deviation:		0.795
	C	6.0	
		Total:	9.000
		Average:	0.333
		Count:	27
		Standard Deviation:	0.770
		6.1	
		Total:	-2.000
		Average:	-2.000
		Count:	1

Urinary pH Change from Baseline (5)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
		Standard Deviation:	0.000
		7.0	
		Total:	3.000
		Average:	0.111
		Count:	27
		Standard Deviation:	0.786
		8.0	
		Total:	7.000
		Average:	0.318
		Count:	22
		Standard Deviation:	0.819
		9.0	
		Total:	3.000
		Average:	0.111
		Count:	27
		Standard Deviation:	1.066
		10.0	
		Total:	3.000
		Average:	0.107
		Count:	28
		Standard Deviation:	0.618
		11.0	
		Total:	0.000
		Average:	0.000
		Count:	25
		Standard Deviation:	0.632
	Total:		23.000
	Average:		0.146
	Count:		157
	Standard Deviation:		0.820
	D	1.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	5.000
		Average:	0.179
		Count:	28
		Standard Deviation:	0.804
		7.0	

Urinary pH Change from Baseline (6)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
		Total:	2.000
		Average:	0.091
		Count:	22
		Standard Deviation:	0.793
		8.0	
		Total:	8.000
		Average:	0.250
		Count:	32
		Standard Deviation:	0.707
		8.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	8.000
		Average:	0.286
		Count:	28
		Standard Deviation:	0.881
		9.1	
		Total:	-1.000
		Average:	-1.000
		Count:	1
		Standard Deviation:	0.000
		10.0	
		Total:	6.000
		Average:	0.231
		Count:	26
		Standard Deviation:	0.846
		11.0	
		Total:	5.000
		Average:	0.116
		Count:	43
		Standard Deviation:	0.784
		11.1	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		11.2	
		Total:	0.000

Urinary pH Change from Baseline (7)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF14_CFB
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
	Total:		34.000
	Average:		0.185
	Count:		184
	Standard Deviation:		0.800
Total:			57.000
Average:			0.099
Count:			575
Standard Deviation:			0.808
Total:			69.000
Average:			0.082
Count:			837
Standard Deviation:			0.795

Potassium Changes from Baseline (1)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
D	A	3.1	
		Total:	-0.100
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	0.500
		Average:	0.026
		Count:	19
		Standard Deviation:	0.319
		5.0	
		Total:	1.900
		Average:	0.112
		Count:	17
		Standard Deviation:	0.476
		5.1	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		5.2	
		Total:	-0.100
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-0.200
		Average:	-0.007
		Count:	27
		Standard Deviation:	0.357
		6.1	
		Total:	-0.100
		Average:	-0.050
		Count:	2
		Standard Deviation:	0.450
		7.0	
		Total:	0.100
		Average:	0.003
		Count:	30
		Standard Deviation:	0.512
		7.1	

Potassium Changes from Baseline (2)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
		Total:	-0.400
		Average:	-0.400
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-0.800
		Average:	-0.044
		Count:	18
		Standard Deviation:	0.398
		8.1	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-3.500
		Average:	-0.121
		Count:	29
		Standard Deviation:	0.394
	Total:		-2.400
	Average:		-0.016
	Count:		147
	Standard Deviation:		0.418
	B	3.1	
		Total:	-0.900
		Average:	-0.450
		Count:	2
		Standard Deviation:	0.250
		4.0	
		Total:	-1.900
		Average:	-0.119
		Count:	16
		Standard Deviation:	0.472
		5.0	
		Total:	-2.200
		Average:	-0.100
		Count:	22
		Standard Deviation:	0.378
		6.0	
		Total:	-1.800
		Average:	-0.072
		Count:	25

Potassium Changes from Baseline (3)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
		Standard Deviation:	0.241
		7.0	
		Total:	1.500
		Average:	0.068
		Count:	22
		Standard Deviation:	0.304
		8.0	
		Total:	1.600
		Average:	0.084
		Count:	19
		Standard Deviation:	0.369
		9.0	
		Total:	-0.400
		Average:	-0.017
		Count:	23
		Standard Deviation:	0.463
	Total:		-4.100
	Average:		-0.032
	Count:		129
	Standard Deviation:		0.383
Total:			-6.500
Average:			-0.024
Count:			276
Standard Deviation:			0.402
87-2D	A	1.0	
		Total:	-0.600
		Average:	-0.600
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	-0.400
		Average:	-0.400
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	1.100
		Average:	0.026
		Count:	42
		Standard Deviation:	0.387
		6.1	

Potassium Changes from Baseline (4)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	-0.300
		Average:	-0.300
		Count:	1
		Standard Deviation:	0.000
		6.5	
		Total:	1.300
		Average:	1.300
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	5.400
		Average:	0.150
		Count:	36
		Standard Deviation:	0.443
		7.1	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-3.300
		Average:	-0.077
		Count:	43
		Standard Deviation:	0.292
		8.1	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-0.300
		Average:	-0.008
		Count:	39
		Standard Deviation:	0.293
		10.0	
		Total:	-1.700
		Average:	-0.053

Potassium Changes from Baseline (5)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
		Count:	32
		Standard Deviation:	0.360
		10.1	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard iation:	0.000
		11.0	
		Total:	-3.400
		Average:	-0.077
		Count:	44
		Standard Deviation:	0.350
		11.1	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
	Total:		-2.200
	Average:		-0.009
	Count:		245
	Standard Deviation:		0.371
	C	2.1	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	0.100
		Average:	0.004
		Count:	27
		Standard Deviation:	0.256
		6.1	
		Total:	-0.100
		Average:	-0.050
		Count:	2
		Standard Deviation:	0.550
		7.0	
		Total:	2.900
		Average:	0.107
		Count:	27
		Standard Deviation:	0.261

Potassium Changes from Baseline in Patients with >20% Drops in GFR (6)

Study_ID	Group	Visit_No	SAF11_CFB
D	C	8.0	
		Total:	-0.700
		Average:	-0.032
		Count:	22
		Standard Deviation:	0.236
		8.1	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	3.100
		Average:	0.115
		Count:	27
		Standard Deviation:	0.245
		10.0	
		Total:	2.100
		Average:	0.075
		Count:	28
		Standard Deviation:	0.286
		10.2	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	0.600
		Average:	0.024
		Count:	25
		Standard Deviation:	0.330
	Total:		7.800
	Average:		0.048
	Count:		161
	Standard Deviation:		0.281
	D	1.0	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-0.100

Potassium Changes from Baseline (7)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	-0.100
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-2.400
		Average:	-0.083
		Count:	29
		Standard Deviation:	0.455
		6.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	0.500
		Average:	0.500
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-2.600
		Average:	-0.113
		Count:	23
		Standard Deviation:	0.456
		8.0	
		Total:	-3.300
		Average:	-0.100
		Count:	33
		Standard Deviation:	0.459
		8.1	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-0.300
		Average:	-0.011
		Count:	28

Potassium Changes from Baseline (8)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF11_CFB
		Standard Deviation:	0.441
		9.1	
		Total:	-0.200
		Average:	-0.050
		Count:	4
		Standard Deviation:	0.087
		10.0	
		Total:	1.600
		Average:	0.062
		Count:	26
		Standard Deviation:	0.389
		11.0	
		Total:	-2.500
		Average:	-0.058
		Count:	43
		Standard Deviation:	0.412
		11.2	
		Total:	-0.100
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
	Total:		-9.200
	Average:		-0.048
	Count:		193
	Standard Deviation:		0.428
Total:			-3.600
Average:			-0.006
Count:			599
Standard Deviation:			0.371
Total:			-10.100
Average:			-0.012
Count:			875
Standard Deviation:			0.382

Sodium Changes from Baseline in Patients with >20% Drops in GFR (1)

Study_ID	Group	Visit_No	SAF12_CFB
3	A	3.1	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	6.000
		Average:	0.316
		Count:	19
		Standard Deviation:	2.811
		5.0	
		Total:	-5.000
		Average:	-0.294
		Count:	17
		Standard Deviation:	2.782
		5.1	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		5.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-14.000
		Average:	-0.519
		Count:	27
		Standard Deviation:	2.394
		6.1	
		Total:	0.000
		Average:	0.000
		Count:	2
		Standard Deviation:	3.000
		7.0	
		Total:	4.000
		Average:	0.133
		Count:	30
		Standard Deviation:	3.085
		7.1	

Sodium Changes from Baseline (2)
in Patients with >20% Drops in GFR

tudy_ID	Group	Visit_No	SAF12_CFB
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-18.000
		Average:	-1.000
		Count:	18
		Standard Deviation:	2.236
		8.1	
		Total:	2.000
		Average:	2.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-18.000
		Average:	-0.621
		Count:	29
		Standard Deviation:	2.552
	Total:		-41.000
	Average:		-0.279
	Count:		147
	Standard Deviation:		2.677
	B	3.1	
		Total:	0.000
		Average:	0.000
		Count:	2
		Standard Deviation:	1.000
		4.0	
		Total:	-15.000
		Average:	-0.938
		Count:	16
		Standard Deviation:	2.358
		5.0	
		Total:	-10.000
		Average:	-0.455
		Count:	22
		Standard Deviation:	2.251
		6.0	
		Total:	-28.000
		Average:	-1.120
		Count:	25

Sodium Changes from Baseline in Patients with >20% Drops in GFR (3)

udy_ID	Group	Visit_No	SAF12_CFB
		Standard Deviation:	2.776
		7.0	
		Total:	-29.000
		Average:	-1.318
		Count:	22
		Standard Deviation:	2.419
		8.0	
		Total:	-6.000
		Average:	-0.316
		Count:	19
		Standard Deviation:	2.576
		9.0	
		Total:	-44.000
		Average:	-1.913
		Count:	23
		Standard Deviation:	3.216
	Total:		-132.000
	Average:		-1.023
	Count:		129
	Standard Deviation:		2.681
Total:			-173.000
Average:			-0.627
Count:			276
Standard Deviation:			2.704
87-2D	A	1.0	
		Total:	-5.000
		Average:	-5.000
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	-3.000
		Average:	-3.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-46.000
		Average:	-1.095
		Count:	42
		Standard Deviation:	3.859
		6.1	

ITEM 2 — NDA SUMMARY

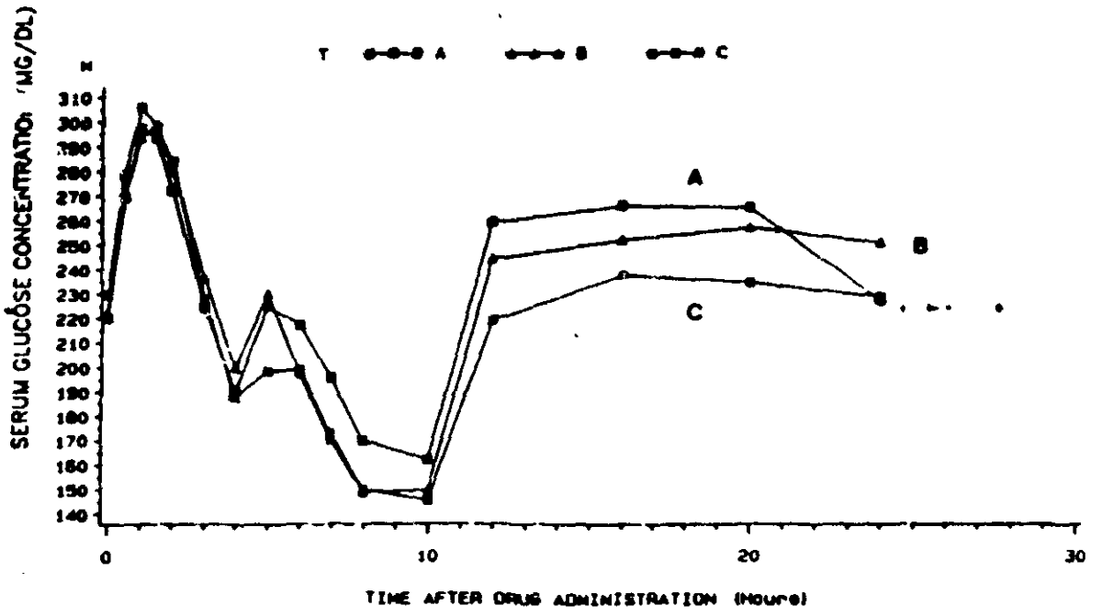

Figure 15. U.S. Study No. 89-2B-6023: *Serum Glucose Levels* Following the Administration of (A) Glucophage, 850 mg Tablet or (B) Micronase, 5 mg Tablet or (C) Glucophage + Micronase (Average Results for 14 NIDDM Subjects)

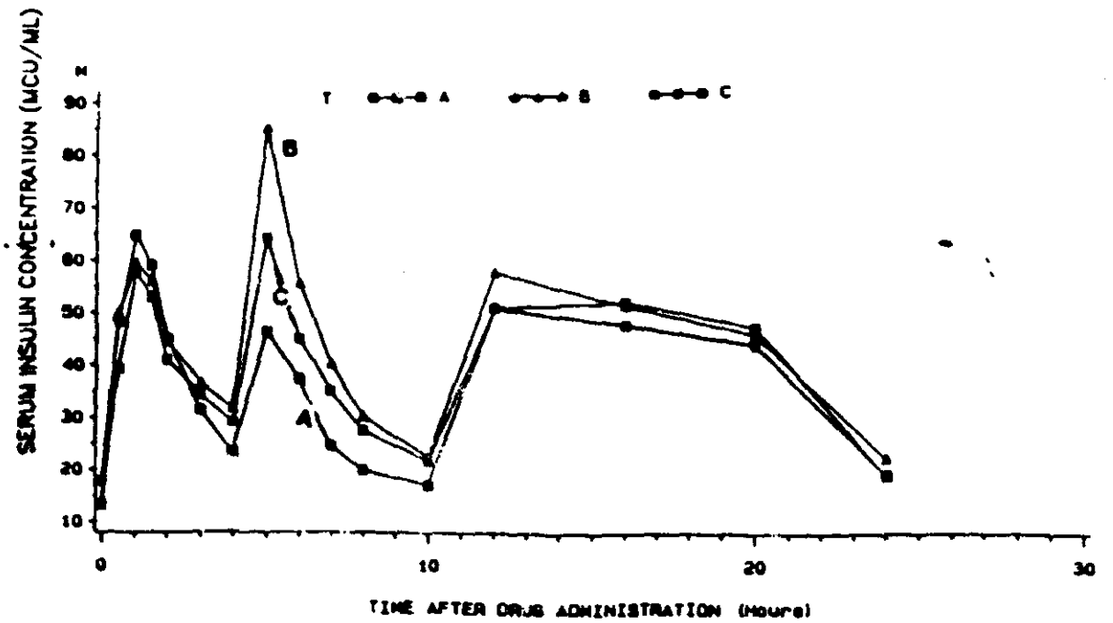

Figure 16. U.S. Study No. 89-2B-6023: Serum Insulin Levels Following the Administration of (A) Glucophage, 850 mg Tablet or (B) Micronase, 5 mg Tablet or (C) Glucophage + Micronase (Average Results for 14 NIDDM Subjects)

2.8.2.3.3 Conclusions Regarding Metformin Dose-Response

These results, derived, in part, from recently conducted, U.S. double-blind, controlled clinical trials in well-defined, relatively homogeneous diabetic populations suggest both a stepwise dose-response of blood glucose to metformin (with multiple dosing and under steady state conditions), but also confirm the empirically derived and now well-established concept that the effective therapeutic range for metformin lies between 1 - 3 g/day (albeit that this dose must be individually tailored, according to glycemic response, tolerance, and concomitant use of other glucose-lowering drugs).

The pharmacodynamic findings of U.S. Study No. 89-12-6023 additionally confirm and illustrate several points, as follows.

Metformin does not result in lowering of plasma glucose levels in non-diabetic subjects without fasting hyperglycemia, even when multiple doses are administered over the course of one week at the maximum recommended therapeutic dose and steady-state metformin levels have been achieved.

The lack of a consistent dose-response effect on fasting or postprandial plasma glucose levels in NIDDM following *single* doses of metformin in the therapeutic dose range in various pharmacodynamic studies summarized above, coupled with the significant decrease in glucose levels after the Multiple Dose Phase in U.S.

Study No. 89-12-6023, when steady state had been achieved, suggests that there has to be sufficient concentration of metformin concentration in tissue and/or at blood binding sites in order for a predictable and sustained glucose-lowering action to occur. This concept is supported by the analysis of the glucose-lowering effects during the metformin Titration Phase of Phase III U. S. Studies 87-1D-6023 and 87-2D-6023, during which time incremental metformin dose escalations were made at one or two week intervals and significant step-wise lowering of fasting plasma glucose occurred.

In Study No. 89-12-6023, the statistically significant postprandial glucose-lowering effect, seen during the two-hour postprandial period following the 1700 mg dose in NIDDM subjects, as well as the observation that plasma glucose levels during all analyzed postprandial periods following single dose administration were lower than with placebo, (even though not statistically significant) suggests that a pharmacologic effect was, however, occurring. This interpretation is supported by results from non-U.S. Study No. MET/GB/89/HOCKA.

Within one week of daily multiple doses of metformin in NIDDM subjects in U.S. Study No. 89-12-6023, there was a consistent, relevant and statistically significant lowering of fasting and postprandial plasma glucose levels which occurred without any increase in fasting plasma insulin levels. In fact, there was a statistically significant decrease in fasting plasma insulin, as well as decreases in postprandial insulin levels, which did not, however, achieve statistical significance. This, as well

as the lack of effect on plasma glucose levels in non-diabetics accompanied by decreases in insulin levels, confirms the axiom that metformin does not lower plasma glucose by stimulation of insulin secretion. (These observations on the effects of metformin dosing on insulin levels, following administration of a standard meal, are also probably more clinically relevant than plasma insulin response following administration of a pure glucose load, as in an oral glucose tolerance test). This is further substantiated by data from U.S. Study No. 89-2B-6023, showing postprandial stimulation of insulin levels by glyburide to levels statistically significantly greater than with metformin and from data of non-U.S. Study No. MET/GB/89/HOCKA, wherein a significant lowering of plasma glucose levels, post-glucose load, was seen, but accompanied by decreases in insulin over this period of time, relative to placebo.

2.8.3 Controlled Clinical Studies

2.8.3.1 Listing of Controlled Clinical Studies Related to Claims of Effectiveness (Categories I and II)

A. Studies with a Concurrent Placebo (or Placebo + Active) Control

1. Completed Domestic Studies
2. Completed Non-U.S. Studies

B. Studies with a Concurrent Active Treatment Control

1. Completed Domestic Studies
2. Completed Non-U.S. Studies

C. Studies with a Concurrent Diet-Alone Control

1. Completed Non-U.S. Studies

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS[1]
A. STUDIES WITH A CONCURRENT PLACEBO (OR PLACEBO + ACTIVE) CONTROL
1. Completed Domestic Studies with Full CRFs Available (Category I Studies)

Study #, Principal Investigator, Country, (Publications)[1]	Status (Start Date)	Location (Item #/Starting) Vol. #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs. (CRF)[1]		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex: M/F (%)	Race * B/W /H/O (%)
87-1D-6023 Multicenter (13) U S A	C (03/88)	8/1.104/ 08B 00001	8/1.107/ 08B 00467	11/1.305/ 11 000C10 (12/1.369/ 12 000012)	Pro,R,DB,PC, PG(2 M vs P), 2 mos diet run in phase, randomized if weight ± 3% of pre-enrollment weight & FPG >140 mg/dL (29 weeks)	M,tab,850 mg (U K 3 850, Lot #706,707)	85C 2550	Up to 1 tab t i d , with meals	M 143 obese NIDDM (112)	31 /0 (52 8)	82/61 (43/57)	27/102/ 12/2 (19/71 /8/2)
						P,tab	N/A	Up to 1 tab t i d , with meals	P 146 obese NIDDM (105)	33 /0 (53 0)	82/64 (42/58)	29/103/ 14/0 (20/71 /10/0)

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS
A. STUDIES WITH A CONCURRENT PLACEBO (OR PLACEBO + ACTIVE) CONTROL
2. Completed Non-U.S. Studies with Full CRFs Available (Category II Studies)

Study #, Principal Investigator, Country, (Publications)	Status (Start Date)	Location (Item #/StartingVol #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs (CRFs)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex: M/F (%)	Race B/W /H/O (%)
MET/AM/84/DORF1 G Dart H Caporal FRANCE (BCA 1229)	C (05/84)	8/1 157/ 088 18605	8/1 157/ 088 18605	11/1 357/ 11 016940 (12/1 395/ 12 010156)	Pro,R,DB,PC, PG(2 M vs P) (60 days)	M,tab,850 mg (R F 2 850 Lot #20042, 20490,20400)	850 2550	850 mg t i d . with meals	M 25 obese NIDDM (20)	29 73 (51 2)	13/12 (52/48)	N/A
						P,tab	1 3 tabs	1 tab. t i d . with meals	P 26 obese NIDDM (15)	29 /3 (56 3)	9/17 (35/65)	N/A
MET/GB/85/DORNA T Dornan UNITED KINGDOM (BCA 964, BCA 1232)	C (02/85)	8/1 159/ 088 19194	8/1 159/ 088 19194	11/1 359/ 11 017445 (12/1 395/ 12 010236)	Pro,R,DB,PC, PG(2 M vs P) (8 months)	M,tab,500 mg (U K,2 500, Lot #880)	500 2000	Up to 2 tabs b i d	M 30 obese NIDDM (30)	38 67 (54 3)	16/14 (53/47)	N/A
						P,tab	1 4 tabs	Up to 2 tabs b i d	P 32 obese NIDDM (30)	38 65 (54 8)	10/22 (31/69)	N/A

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS
A. STUDIES WITH A CONCURRENT PLACEBO (OR PLACEBO + ACTIVE) CONTROL
2. Completed Non-U.S. Studies with Full CRFs Available (Category II Studies)

Study #, Principal Investigator, Country, (Publications)	Status (Start Date)	Location (Item #/StartingVol #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs (CRFs)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex: M/F (%)	Race: B/W ::O (%)
MET/AM/86/DORF 2 G. Dorf R. Caporal FRANCE	C (01/86)	8/1 158/ 088 18921	8/1 158/ 088 18921	11/1 358/ 11 017195 (12/1 395/ 12 010213)	Pro,R,DB,PC, PG(2 M vs P) (60 days)	M,tab 850 mg (R F 2 850 Lot #20490 274)	850 2550	850 mg t.i.d. with meals	M 25 obese IGT (18)	24 66 (41 6)	4/21 (16/84)	N/A
						P,tab	1 3 tabs	1 tab t.i.d with meals	P 25 obese IGT (23)	18 78 (39 5)	7/18 (28/72)	N/A

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS
B. STUDIES WITH A CONCURRENT ACTIVE TREATMENT CONTROL
1. Completed Domestic Studies with Full CRFs Available (Category I Studies)

Study #, Principal Investigator, Country, (Publications)	Status (Start Date)	Location (Item #/Starting Vol #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs. (CRF)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex M/F (%)	Race B/W /H/O (%)
87-2D-6023 Multicenter (20) U S A	C (09/88)	8/1 120/ 088 05357	8/1 123/ 088 05031	11/1 321/ 11 004926 (12/1 378/ 12 003294)	Pro R DB PC AC, PG(3 M (+P) vs G (+P) vs M + G) 1 mo run in on max dose G (20 mg/day), randomized if FPG >140 mg/dL (29 weeks)	M,tab,500 mg (U K 3 500, Lot #309,310 391)	500 2500	M (and P for M) tablets taken with meals 0 0 1, 1 0 1, 1 1 1, 1 1 2, 2 1 2	M 210 obese NIDDM (157)	40 70 (54 5)	96/114 (46/54)	28/1?4 /2?/1 (13/73 /13/1)
						P (for M) tab	1 5 tabs		G 208 obese NIDDM (174)	40 70 (56 2)	103/105 (49/51)	30/157 /2?/1 (14/77 /8/1)
						G,tab,5 mg	20	G (and P for G) Tablets taken with meals 2-0-2	M + G 213 obese NIDDM (192)	40 70 (54 8)	98/115 (46/54)	30/150 /29/4 (14/70 /13/2)
						P (for G),tab	4 tabs					

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS
B. STUDIES WITH A CONCURRENT ACTIVE TREATMENT CONTROL
2. Completed Non-U.S. Studies with Full CRFs Available (Category II Studies)

Study #, Principal Investigator, Country, (Publications)	Status (Start Date)	Location (Item #/Starting Vol. #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs. (CRF)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex M/F (%)	Race B/W /H/O (%)
MET/GB/86/CAMP1 I W Campbell UNITED KINGDOM (BCA 1354, RCA 969)	C (03/85)	8/1 185/ 08B 21386	8/1 165/ 08B 21472	11/1 366/ 11 019347 (12/1 398/ 12 011670)	Pro,R,OL, PG(2 M vs Glip) (52 weeks)	M,tab 500 mg (N/A commercial)	1000 3000	500 1500 mg b i d	25 NIDDM, diet failures (20)	40 70 (58 1)	9/16 (36/64)	N/A
						Glip tab 5 mg (Glibenese)	5 30	N A	25 NIDDM, diet failures (23)	40 68 (57 1)	7/18 (28/72)	N A
MET/AM/86/DUCHI J Duchier FRANCE (BCA 1086)	C (12/86)	8/1 187/ 08B 21838	8/1 187/ 08B 21320	11/1 367/ 11 019497 (12/1 398/ 12 011679)	Pro,R,OL, PG(2 M vs Gliclazide) (13 weeks)	M,tab 850 mg (R F 2 850 Lot #425)	850 2550	1 tab/day, 1 tab b i d 1 tab t i d	33 NIDDM, diet or SU failures (30)	37 85 (55)	17/16 (52/48)	N A
						Gliclazide tab 80 mg (Diamicron)	80 240	1 tab/day, 1 tab b i d, 1 tab t i d	28 NIDDM, diet or SU failures (27)	31 85 (54 1)	13/15 (46/54)	N/A

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS
B STUDIES WITH A CONCURRENT ACTIVE TREATMENT CONTROL
2. Completed Non-U.S. Studies with Full CRFs Available (Category II Studies)

Study #, Principal Investigator, Country, (Publications)	Status (Start Date)	Location (Item #/Starting Vol #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs. (CRF)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex M/F (%)	Race B,W /H/O (%)
MET/S/86/HERMA Multicenter (5) I. Hermann SWEDEN (BCA 1161, BCA 1094, BCA 1198)	C (01/86)	8/1 160/ 088 19555	8/1 161/ 088 19815	11/1 360/ 11 017693 (12/1 395/ 12 010250)	Pro,DB,DP (for M & Glb), R (3 way,1 1 2), PG[3 M [+ P for Glb] vs Glb [+ P for M] vs M + Glb [low dose]) *(All pts could eventually be on high-dose combination therapy)* (Up to 46 wks 6 wk diet run in phase, followed by 2 wk P run in, prior to R, Titration phase of up to 12 wks, Maintenance phase of 24 wks, 2 wk P close out phase at end of maintenance period)	M,tab,500 mg (U K 2 500, Lot #102)	500 3000	1 3 tabs b i d before breakfast & supper	M 38 NIDDM, diet failure or prior SU (28)	38 /3 (59 2)	23/15 (61/39)	N/A
						Glb tab 1 75 mg 3 5 mg (Euglucon)	1 75 14	1 2 tabs b i d , before breakfast & supper	G 34 NIDDM, diet failure or prior SU (28)	44 /3 (61 4)	21/13 (62/38)	N/A
									M + G 72 NIDDM, diet failure or prior SU (68)	34 74 (60 4)	47/24 (66/34)	N/A

2.8.3.1 TABULAR SUMMARY OF CONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS
C. STUDIES WITH A CONCURRENT DIET-ALONE CONTROL
1. Completed Non-U.S. Studies with Full CRFs Available (Category II Studies)

Study #, Principal Investigator, Country, (Publications)	Status (Start Date)	Location (Item #/Vol #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs. (CRFs)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex M/F (%)	Race B,W /H/O (%)
MET/DIB/BERGI K Berge GERMANY (BCA 1689, BCA 1342)	C (09/86)	9/1 169/ 088 22381	9/1 169/ 088 22381	11/1 368/ 11 079863 (N/A)	Pro,R,OI, PG(2 M + diet vs diet alone) (10! wks)	M tab 850 mg	#50 1/30	Up to 1 tab b i d	M 46 obese NIDDM (2%)	24 69 (51 1)	18/28 (39/61)	N A
									Diet 31 obese NIDDM (2%)	38 66 (56 1)	21/30 (41/59)	N/A

BCA numbers are Lipha's internal reference numbers for published/unpublished reports

The following abbreviations are used throughout:

NR	= Non-randomized	M	= Metformin	B	= Black
R	= Randomized	G	= Glyburide	W	= White
Pro	= Prospective	SU	= Sulfonylurea	H	= Hispanic/Mex Amer
OL	= Open label	C	= Completed	O	= Other (incl Oriental)
NA	= Not available (applicable)				
NIDDM	= Non insulin dependent diabetes				

2.8.3.2 Summaries of U.S. Phase III Controlled Clinical Trials (Category I Studies)

2.8.3.2.1 U.S. Study No. 87-1D-6023

U.S. Study No. 87-1D-6023, conducted from March, 1988 through May, 1991, was a randomized, parallel-group (two), double-blind, multi-center (13 centers) study comparing the safety and efficacy of 29 weeks treatment with either metformin (up to 2,550 mg/day) or placebo in 289 obese (120-170% of ideal body weight) NIDDM outpatients who had either never received pharmacologic antidiabetic therapy or had not received such treatment for the two months preceding randomization. Potentially eligible patients were randomized (143 to metformin; 146 to placebo) if body weight remained within ± 3% of entry body weight and FPG remained >140 mg/dL, despite two months on a weight-reduction diet. The 850 mg dosage strength of metformin was used in this study.

All laboratory analyses were performed by central laboratories. Primary efficacy parameters included: (a) glycemic control as measured by FPG, hemoglobin A_{1c} (HbA_{1c}), and plasma glucose response during a 3-hour oral glucose tolerance test [OGTT]); (b) lipid profile effects as measured by total cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL) cholesterol, HDL subfractions and apolipoproteins; and (c) body weight changes. Secondary efficacy parameters were blood pressure and insulin and C-peptide effects

(measured as part of the 3-hour OGTT). Adverse experiences and intercurrent medical events (AE/IMEs) were recorded at each visit.

The population of interest was the intent-to-treat population. For the efficacy analysis this was defined as any patient who took study medication and completed at least one post-baseline visit. For the safety analysis this was defined as any patient who took study medication and was assessed for safety. Observed values and change from baseline values were compared for all efficacy and safety laboratory measures to determine if significant differences existed among the metformin and placebo treatment groups, based on a visit-wise analysis and a last observation carried forward analysis. The primary analyses were the within- and between-treatment comparisons of change from baseline values. The incidence of AE/IMEs were tabulated and compared between treatment groups using the Fisher's Exact test.

Subsequent to the two month dietary run-in phase, eligible patients were randomized and began a five week metformin dose titration phase (biweekly increases of metformin [or placebo] by 850 mg increments [based on FPG levels and tolerance], starting with 850 mg/day and increasing to a maximum of 850 mg t.i.d., with meals), followed by a 24 week treatment phase, while on the maintenance dose of metformin (or placebo).

Patient disposition during the study is shown in intext Table 21, page 298.

Table 21. U.S. Study No. 87-1D-6023
Patient Disposition, Post-Randomization

	METFORMIN	Placebo
Randomized	143	146
Completed	112	105
Withdrew	31	41
Withdrawals Due to:		
Adverse Experience/Intercurrent Medical Event	14 (15)	2
Treatment Failure	2	18 (19)
Intercurrent Illness	3 (3)	3
Abnormal Laboratory Result	2	1
Patient Decision	2	5
Lost to Follow-up	3	4
Never Dispensed Medication	1	1
Received Study Medication but Never Took Any	1	0
Protocol Violation	0 (1)	2
Noncompliance	1	1
Other	2 (0)	4 (3)

*NOTE: Numbers in parentheses reflect sponsor-made changes in primary reason for premature termination. In some instances, no net change occurred in categories.

Patient groups were well-matched for all demographic features, as well as for baseline values of efficacy parameters, as shown in intext Table 22, page 299. As shown in intext Table 23, page 299, at final visit, metformin had produced statistically significantly superior metabolic control compared to placebo ($p=0.001$) as evidenced by reductions in fasting plasma glucose, HbA_{1c}, post-glucose load plasma glucose and glucosuria.

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Table 22. U.S. Study No. 87-1D-6023
Mean Baseline Efficacy Parameters

	METFORMIN	Placebo	P-Value
FPG (mg/dL)	241.5	237.7	0.656
HbA_{1c} (%)	8.4	8.2	0.219
2-hr Post-Glucose (mg/dL)	383.5	368.2	0.200
Fasting Insulin (ulU/mL)	13.4	15.0	0.286
Fasting C-Peptide (ng/mL)	2.70	2.71	0.942
Total Cholesterol (mg/dL)	211.0	212.3	0.801
Triglycerides (mg/dL)	236.1	203.5	0.484
LDL (mg/dL)	135.4	138.5	0.507
HDL (mg/dL)	39.0	40.5	0.287
Apolipoprotein A_1 (mg/dl)	119.2	119.7	0.870
Apolipoprotein B (mg/dl)	101.8	104.8	0.457
Total Cholesterol/HDL Ratio	5.9	5.7	0.255
LDL/HDL Ratio	3.6	3.6	0.984
Body Weight (lbs)	201.0	206.0	0.200

Table 23. U.S. Study No. 87-1D-6023
Mean Change from Baseline at Final Visit for Key Efficacy Parameters

	METFORMIN	Placebo	P-Value
Fasting Plasma Glucose, mg/dL	-53.0	6.3	0.001**
HbA_{1c}, %	-1.4	0.4	0.001**
2-Hour Post-Glucose Load Plasma Glucose, mg/dL	-77.2	5.6	0.001**
Body Weight, lb	-1.4	-2.4	0.332
Total Cholesterol, mg/dL	-9.5	1.8	0.024*
LDL, mg/dL	-11.1	-2.0	0.021*
HDL, mg/dL	0.8	-0.3	0.303
Triglycerides, mg/dL	-38.7	1.9	0.085
Total Cholesterol/HDL Ratio	-0.4	0.2	0.043*
LDL/HDL Ratio	-0.3	-0.1	0.087

* = P-Value >0.01 but ≤0.05; ** = P-Value ≤0.01

Table 39. Duration of Metformin Treatment in U.S. and Non-U.S. Placebo-controlled Studies

	Number of Patients Treated with Metformin Vs. Time						
STUDY NO.	Baseline	≥ 1 ≥ 4	≥ 2 ≥ 8	≥ 3 ≥ 12	≥ 6 ≥ 24	≥ 12 ≥ 52	> 13 Months > 52 Weeks
87-1D-6023	143	137	134	127	114	NA	NA
MET/AM/84/DORF1	25	25	20	NA	NA	NA	NA
MET/AM/86/DORF2[1]	25	25	18	NA	NA	NA	NA
MET/GB/85/DORNA	30	30	30	30	30	NA	NA
MET/D/83/BERGI	46	-	-	43	40	31	25

[1] Patients with impaired glucose tolerance and fasting normoglycemia.

Table 40. Dosage Summary in U.S. and Non-U.S. Placebo-controlled Studies

		Daily Dose of Metformin at Final Visit[1] of Treatment Period in mg/day		
STUDY NO.	No. of Patients at Baseline	500-1000	>1000-2000	>2000-3000
87-1D-6023	143	10 (7%)	20 (14%)	110 (79%)
MET/AM/84/DORF1	25	0	0	24 (100%)
MET/AM/86/DORF2[2]	25	0	3 (14%)	18 (86%)
MET/GB/85/DORNA	30	5 (17%)	17 (57%)	8 (27%)
MET/D/86/BERGI	46	0	44 (100%)	0

[1] "Final Visit" is the observation at the last scheduled visit for patients completing the study or the last observation during the treatment period for patients withdrawing prematurely.
[2] Patients with impaired glucose tolerance and fasting normoglycemia.

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For the U.S. Category I and non-U.S. Category II active treatment comparison studies, duration of metformin treatment and dosage are respectively summarized in intext Table 41, below, and Table 42, page 352. Comparable information for non-U.S. Study No. MET/S/86/HERMA, is provided in Tables 43A and 43B, pages 353 and 354, respectively.

Table 41. Duration of Metformin Treatment:
U.S. and Non-U.S. Active Treatment Comparison Studies

STUDY NO.	No. of Patients at Baseline	Number of Patients Treated with Metformin vs. Time					
		≥ 1 ≥ 4	≥ 2 ≥ 8	≥ 3 ≥ 12	≥ 6 ≥ 24	≥ 12 ≥ 52	> 13 Months > 52 Weeks
87-2D-6023							
Monotherapy	210	202	199	190	161	NA	NA
MET + SU	213	209	208	205	196	NA	NA
MET/GB/CAMP1	25	24	24	24	23	20	NA
MET/AM/86/DUCHI	33	32	-	30	NA	NA	
MET/S/86/HERMA							
Monotherapy	- See additional intext Tables 43A and 43B -						
MET + SU	- See additional intext Tables 43A and 43B -						

ITEM 2 — NDA SUMMARY

Table 42. Dosage Summary
U.S. and Non-U.S. Active Treatment Comparison Studies

STUDY NO.	No. of Patients at Baseline	Daily Dose of Metformin at Final Visit' of Treatment Period in mg/day 500-1000	>1000-2000	>2000-3000
87-2D-8023				
Monotherapy	210	7 (3%)	15 (7%)	182 (89%)
MET + SU	213	23 (11%)	46 (22%)	142 (67%)
MET/GB/86/CAMP1	25	10 (40%)	8 (32%)	7 (28%)
MET/AM/88/DUCHI	33	0	32 (100%)	0
MET/S/86/HERMA				
Monotherapy		- See additional intext Tables 43A and 43B -		
MET + SU		- See additional intext Tables 43A and 43B -		

' "Final Visit" is the observation at the last scheduled visit for patients completing the study or the last observation during the treatment period for patients withdrawing prematurely.

Table 43A. MET/S/86/HERMA

Drug Exposure and Dosage Summary for Dose Titration Phase of Study Patient Frequency - All Patients

Treatment	Daily Dose Level	Baseline	Dose Titration Phase of Study Prescribed Doses at Week: 2	4	6	8	10	12
Metformin[1]	0 (0.5 g)	0	1	0	0	0	0	0
	1 (1 g)	38	5	1	1	1	1	0
	2 (2 g)	0	30	10	3	3	0	0
	3 (3 g)	0	1	16	6	1	0	0
Glibenclamide[2]	0 (1.75 mg)	0	3	1	0	0	0	0
	1 (3.5 mg)	34	10	1	2	1	0	0
	2 (7 mg)	0	20	8	1	1	1	1
	3 (10.5 mg)	0	0	13	2	1	1	0
Combination (M + G)[3]	0 (Placebo)	0	4	7	3	1	0	0
	1 (0.5 mg + 1.75 mg)	72	25	4	0	2	1	1
	2 (1 g + 3.5 mg)	0	43	13	9	5	3	2
	3 (1.5 g + 5.25 mg)	0	0	31	9	4	4	0

[1] Number of patients receiving METFORMIN monotherapy during dose titration phase of study.
[2] Number of patients receiving Glibenclamide monotherapy during dose titration phase of study.
[3] Number of patients receiving low dose combination therapy during dose titration phase of study.

Table 43B. MET/S/86/HERMA

Drug Exposure and Dosage Summary for Treatment Phase of Study
Patient Frequency - All Patients

Treatment		Daily Dose Level	Treatment Phase of Study Prescribed Dose(s) at: Baseline	2 Months	4 Months
Metformin	Group MM	0 (0.5 g)	0	0	0
		1 (1 g)	38	7	6
		2 (2 g)	0	8	8
		3 (3 g)	0	2	2
	Group M/G	4 (3 g + 3.5 mg)*	0	5	5
		5 (3 g + 7 mg)	0	4	4
		6 (3 g + 14 mg)	0	3	3
Glibenclamide	Group GG	0 (1.75 mg)	0	1	2
		1 (3.5 mg)	34	11	10
		2 (7 mg)	0	5	5
		3 (10.5 mg)	0	1	1
	Group G/M	4 (1 g + 10.5 mg)	0	2	2
		5 (2 g + 10.5 mg)	0	3	4
		6 (3 g + 14 mg)	0	6	5
Combination (M + G)	Group MGL	0 (Placebo)	0	7	8
		1 (0.5 mg + 1.75 mg)	72	22	22
		2 (1 g + 3.5 mg)	0	17	18
		3 (1.5 g + 5.25 mg)	0	7	6
	Group MGH	4 (2 g + 7 mg)	0	5	5
		5 (2.5 g + 8.75 mg)	0	2	2
		6 (3 g + 14 mg)	0	10	8

* First dosage refers to metformin and the added dosage refers to glibenclamide.

2.8.3.5 Analysis and Conclusions

The controlled clinical trials analyzed within this section, utilizing doses of metformin which have been shown to be maximally effective, include two pivotal multi-center U.S. studies, U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023, which rigorously fulfill the U.S. FDA statutory requirements for adequate and well-controlled studies (Category I). In addition, seven non-U.S. controlled clinical trials, which although not initiated for the purpose of supporting the U.S. registration of metformin and which were conducted in countries where metformin is already commercially available, also adhere to U.S. requirements, are included (Category II). Furthermore, these non-U.S. studies were re-analyzed according to the same general statistical plan developed for the U.S. Category I studies.

Studies within these two categories comprise the pooled database for metformin's efficacy and safety evaluation.

The primary efficacy variables used to assess the effects of metformin in target patient populations were:

- Fasting plasma glucose (FPG)
- Postprandial plasma glucose (PPG) or Oral glucose tolerance test (2-hour) plasma glucose (OGTT [2-hour] PG)
- Glycosylated hemoglobin (HbA_{1c} or HbA_1)

- Body weight (in lbs. for U.S. studies; in kg for non-U.S. studies)
- Total serum cholesterol (CHOL)
- Plasma triglycerides (TRIG)

Intext Table 44, page 357, presents a composite of results for all controlled studies in the pooled data base, showing mean changes from baseline at final visit for the key efficacy parameters.

TABLE 44.
Tabular Summary of Controlled Clinical Trials Included in the Integrated Summary of Efficacy

Protocol No., Country, (No. of Invest.)	Study Design (Max. Daily Dose of M and Study Duration in Wks.)	Treatment Groups	No. Patients per Treatment Group (withdrawals)	Major Outcomes of Primary Efficacy Variables — Mean Change from Baseline at Final Visit					
				FPG (mg/dL)	PPG[1] (mg/dL)	HbA_{1c}[2] (%)	BW[3] (kg)	Chol (mg/dL)	Trig (mg/dL)
87-10-8023, U S (13)	DB, PC, PG (2550 mg for 29 wks)	M P	143 (31) 146 (41)	-53.04 6 27	-74.77 11 89	-1.37 0 42	-1.44 -2.38	- 9.45 1 81	-38.74 1 93
87-20-8023, U S (20)	DB, AC, PG (2500 mg for 29 wks)	M G M+G	210 (53) 209 (35) 213 (21)	- 0.96 13 73 -63.47	- 1.27 2 20 -58.72	-0.38 0 24 -1.69	-0.43 -0.66 0.91	- 4.00 2 81 - 9.25	-22.56 -26 15 1.42
MET/AM/84/DORF1, France (2)	DB, PC, PG (2550 mg for 8 wks)	M P	25 (5) 26 (11)	-58.87 -19 09	-48.84 0 85	-1.09 -1 33	-3.89 -4.01	-17.31 -13 09	-37.77 -21 97
MET/AM/86/DORF2, France (2)	DB, PC, PG (2550 mg for 8 wks)	M P	25 (7) 25 (2)	2.34 - 2 09	-39.62 33 82	-0.29 0 34	-6.76 -5.50	-17.48 -12 97	-14.18 -17 21
MET/GB/85/DORNA, England (1)	DB, PC, PG (3000 mg for 32 wks)	M P	30 (0) 32 (2)	-57.01 50 14	-	-1.50 1 73	0.02 -1 08	-17.68 5 93	-29 85 32 57
MET/D/86/BERGI, W Germany (2)	OL, PG (1700 mg for 104 wks)	M Diet alone	46 (21) 51 (22)	-	-	-0.24 0 03	-2.77 -3 50	17.13 43 97	30.13 63 16
MET/GB/86/CAMP1, Scotland (1)	OL, AC, PG (3000 mg for 52 wks)	M Glip	25 (5) 25 (2)	-74.87 -60 93	-	-2 77 -1 77	-1.93 2.43	20.88 19 88	5.08 16 83
MET/AM/88/DUCHI, France (13)	OL, AC, PG (1700 mg for 12 wks)	M Gliclazide	33 (3) 28 (1)	-20.81 -30 04	-26.69 -52 89	-0.82 -0 74	-2.38 -0.09	-10.17 - 9 21	- 4.61 30 01

ITEM 2 — NDA SUMMARY

Among the two U.S. pivotal Category I studies and the seven non-U.S. supportive Category II studies, fasting plasma glucose (FPG) was measured as a primary efficacy parameter in all but non-U.S. Study No. MET/D/86/BERGI, a diet-controlled study. In addition, FPG was not a relevant endpoint in non-U.S. Study No. MET/AM/86/DORF2, since these subjects with impaired glucose tolerance did not have fasting hyperglycemia.

Of the seven remaining studies, metformin, as a monotherapeutic agent, lowered FPG at final visit, relative to baseline, in a highly statistically significant fashion in six of the seven studies, comprised of populations of obese NIDDM patients considered to be diet failures (two studies: U.S. Study No. 87-1D-6023 and MET/GB/85/DORNA) and heterogeneous, primarily obese, NIDDM populations with possible prior exposure to oral hypoglycemic agents (four studies). In U.S. Study No. 87-2D-6023, conducted in NIDDM patients considered to be sulfonylurea failures, the within-treatment group decrease in FPG in patients randomized to metformin monotherapy was not statistically significant. However, since patients randomized to glyburide in this study had an *increase* in FPG at final visit, the difference between these monotherapy arms was statistically significant, in favor of metformin monotherapy.

Metformin was statistically superior to placebo in its effect on FPG in two of three placebo-controlled studies ($p < 0.001$), including pivotal U.S. Study No. 87-1D-6023. In the remaining placebo-controlled study (MET/AM/84/DORF1), the

between-treatment difference bordered on statistical significance (p = 0.108) although in this study, almost one-third of patients randomized to metformin had been on metformin (alone or with sulfonylurea) at baseline, compared to one-fifth of placebo patients, thereby perhaps accounting for the less marked difference.

Metformin was comparable to the oral sulfonylureas, gliclazide (Non-U.S. Study No. MET/AM/88/DUCHI), glipizide (Non-U.S. Study No. MET/GB/86/CAMP1) and glibenclamide (Non-U.S. Study No. MET/S/86/HERMA) in its FPG-lowering effect in three of four active-controlled studies and was superior to glyburide ($p < 0.05$) in U.S. Study No. 87-2D-6023 (see above), conducted in patients considered to be sulfonylurea failures, which included at least one month of maximum dose glyburide.

Metformin, when added to continued sulfonylurea therapy in patients considered to be sulfonylurea failures (or suboptimally responding to sulfonylureas), had a highly significant and relevant lowering effect on FPG (U.S. Study No. 87-2D-6023), both within the treatment group and in comparison to monotherapy with either continued glyburide or metformin. This effect was also seen in non-U.S. Study No. MET/S/86/HERMA in patient subgroups beginning on glibenclamide monotherapy and requiring the addition of metformin for optimal glycemic control. In addition, combined metformin/glibenclamide therapy, at low dose, was as effective as metformin monotherapy or glibenclamide monotherapy in lowering FPG in patients with apparently less marked baseline hyperglycemia in this study.

ITEM 2 — NDA SUMMARY

Among the two U.S. pivotal Category I studies and the seven non-U.S. supportive Category II studies, the level of postprandial or post-glucose load plasma glucose (PPG) was a primary efficacy variable in both U.S. studies (placebo- and active-controlled), as well as in two placebo-controlled non-U.S. studies, (one of which was conducted in patients with abnormal glucose tolerance but fasting normoglycemia) and two active-controlled studies.

Metformin, as monotherapy, significantly lowered PPG at final visit, relative to baseline values, in one of the two placebo-controlled studies conducted in NIDDM subjects (pivotal U.S. Study No. 87-1D-6023). In the other study (non-U.S. Study No. MET/AM/84/DORF1), there was a decrease in the metformin group which approached statistical significance ($p = 0.062$). Between treatment comparisons (metformin vs. placebo) were statistically significant only in U.S. Study No. 87-1D-6023, wherein the metformin group had a mean decrease in PPG of 75 mg/dL compared to a mean increase of 12 mg/dL in the placebo group (p-value = 0.001). In non-U.S. Study No. MET/AM/84/DORF1, the metformin group experienced a mean decrease in PPG of 49 mg/dL compared to a mean increase of 1 mg/dL in the placebo group, but this difference did not achieve statistical significance ($p = 0.169$). In the remaining placebo-controlled study measuring

normoglycemia and impaired glucose tolerance. (Since mean *baseline* values for PPG were normal in both the metformin and placebo groups [140 and 130 mg/dL, respectively], minimal change would have been predicted in the metformin group, since metformin does not affect plasma glucose levels in normoglycemic subjects).

Among the three active-treatment comparison studies, metformin as monotherapy significantly lowered PPG at final visit, relative to baseline, in one study (non-U.S. Study No. MET/S/86/HERMA), with a mean decrease of 51 mg/dL. In U.S. Study No. 87-2D-6023, carried out in a population considered to be sulfonylurea failures (including maximum dose glyburide, administered until randomization), metformin monotherapy had no significant effect on PPG (mean decrease of 1 mg/dL), however, neither did maximum dose glyburide (mean increase of 2 mg/dL)($p = 0.731$, between treatment comparison). In non-U.S. Study No. MET/AM88/DUCHI, comparing metformin to gliclazide, the metformin group had a mean decrease in PPG of 27 mg/dL compared to a mean decrease in PPG of 53 mg/dL with gliclazide ($p = 0.226$, between treatment comparison). (The metformin group decrease from baseline approached statistical significance [$p = 0.067$] whereas the gliclazide group decrease was statistically significant [$p = 0.001$]). However, it should be noted that in this study, the maximum dose of metformin was set at /day, in contrast to a maximum dose of up to 2,550 mg/day in U.S. studies, and up to 3,000 mg/day in British studies.

ITEM 2 — NDA SUMMARY

Metformin, when added to continued sulfonylurea therapy in patients considered to be sulfonylurea failures (or suboptimally responding to sulfonylureas) (pivotal U.S. Study No. 87-2D-6023), had a highly significant and relevant lowering effect on PPG (a decrease of 59 mg/dL, p = 0.001), both within the treatment group and in comparison to monotherapy with either metformin or glyburide (MG vs. M, p = 0.001, MG vs. G, p = 0.001). As was the case for FPG, this effect was also seen in non-U.S. Study No. MET/S/86/HERMA, in patient subgroups beginning on glibenclamide monotherapy and requiring the addition of metformin for optimal glycemic control. This group, with apparently more severe NIDDM, experienced a mean decrease in PPG of 79 mg/dL, relative to baseline. In fact, the three patient subgroups in this study which ultimately required high dose combination therapy of metformin plus glibenclamide (those starting on glibenclamide and then having metformin added; those starting on metformin and then having glibenclamide added; and those starting on low dose combination therapy and requiring high dose combination therapy for glycemic control) experienced substantial decreases in PPG, (average decrease of 91 mg/dL, range: 77-116 mg/dL). In addition, in this same study, combined metformin/glibenclamide therapy, at low dose, significantly decreased PPG (a decrease of 36.7 mg/dL, p = 0.006, compared to baseline) in patients with less marked baseline hyperglycemia.

Glycosylated hemoglobin was a primary efficacy variable in all nine studies: both U.S. pivotal studies as well as all seven non-U.S Category II studies.

Because of methodology considerations, the greatest reliability concerning the impact of metformin on this parameter should be placed on U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023, large multicenter studies wherein all HbA_{1c} determinations were performed by a central laboratory (SciCor, Inc.) with a defined normal (non-diabetic) range for HbA_{1c} of 3.3-6.8%.

Metformin as monotherapy decreased HbA_{1c} in all three placebo-controlled studies performed in patients with NIDDM. In U.S. Study No. 87-1D-6023, there was a mean decrease in HbA_{1c} of 1.4% ($p = 0.001$) compared to a mean increase with placebo of 0.4% (M vs. P, $p = 0.001$). In non-U.S. Study No. MET/GB/85/DORNA, there was a mean decrease of HbA_1 of 1.5% in the metformin group ($p = 0.002$) compared to a mean increase of 1.7% in the placebo group ($p = 0.001$)(M vs. P, $p = 0.001$). In non-U.S. Study No. MET/AM/84/DORF1, there was a mean decrease of 1.1% in HbA_{1c} in the metformin group ($p = 0.032$) while the placebo group also had a mean decrease of 1.3% ($p = 0.052$) (M vs. P, $p = 0.759$). However, in this latter study, a relatively high proportion of patients in the metformin group were already on metformin (alone or with sulfonylurea) at baseline, thereby casting a note of unreliability on the baseline HbA_{1c} values and making comparison of changes difficult. In the single diet-controlled study (non-U.S. Study No. MET/D/86/BERGI), there was a small decrease in HbA_1 with metformin of 0.2% compared to no change with placebo (M vs. P, $p = 0.482$). (Note: The reason for this small effect is not clear although there was a very high drop out rate in both arms in this study and compliance information is lacking).

Among the four studies with an active treatment comparison, metformin, as monotherapy, caused a small but significant decrease in HbA_{1c} (0.4%) at final visit in U.S. Study No. 87-2D-6023 ($p = 0.004$), conducted in patients considered to be *sulfonylurea failures*. All patients had been on glyburide up until the time of randomization. (The glyburide monotherapy group in this study had a mean increase in HbA_{1c} of 0.2% at final visit. M vs. G, $p = 0.001$). In non-U.S. Study No. MET/GB/86/CAMP1, conducted in NIDDM patients considered to be *diet failures*, there was a highly significant decrease in HbA_1 in the metformin group of 2.8% ($p = 0.001$), relative to a decrease of 1.8% in the glipizide group ($p = 0.003$), without any statistically significant difference between treatment groups (M vs. G, $p = 0.166$). In non-U.S. Study No. MET/AM/88/DUCHI, which included NIDDM patients with *prior exposure to oral hypoglycemic agents*, the metformin group had a mean decrease from baseline in HbA_{1c} of 0.8% ($p = 0.032$), compared to a mean decrease of 0.7% in the gliclazide group ($p = 0.237$), although between treatment group differences were not significant. (*In this study, the maximal dose of metformin was 1700 mg/day, in contrast to most of the other studies, using between 2.5 and 3.0 g/day, as maximum*). In patients maintained on metformin monotherapy in non-U.S. Study No. MET/S/88/HERMA (patients *poorly controlled on diet or prior sulfonylurea therapy*), there was a mean decrease in HbA_{1c} of 0.9%, compared to a 1.3% decrease in patients maintained on glibenclamide monotherapy and a 1.2% decrease in those continued on low dose combination therapy.

Metformin, when added to continued sulfonylurea therapy in patients considered to be sulfonylurea failures (or suboptimally responding to sulfonylureas) (pivotal U.S. Study No. 87-2D-6023), had a highly significant and relevant lowering effect on HbA_{1c} of 1.7% ($p = 0.001$), compared to the previously mentioned decrease of 0.4% with metformin monotherapy (M vs. MG, $p = 0.001$) and the increase in HbA_{1c} of 0.2% in the glyburide group (G vs. MG, $p = 0.001$). As was the case for other parameters of glycemic control, this effect was also seen in non-U.S. Study No. MET/S/86/HERMA with combined metformin/glibenclamide therapy. All three patient subgroups in this study, ultimately requiring high dose combination therapy of metformin plus glibenclamide, experienced substantial decreases in HbA_{1c}, averaging 2.2%. In addition, in this same study, combined metformin/glibenclamide therapy, at low dose, also significantly decreased HbA_{1c} by 1.2%, compared to baseline ($p = 0.001$), in patients with less marked baseline glucose abnormalities.

Effects on **body weight** were sought in all nine studies, including the two U.S. pivotal studies and the seven non-U.S. Category II studies. Both the U.S. studies and the non-U.S. studies were conducted in predominantly obese NIDDM populations and, in accord with general principles of management of diabetes mellitus, included emphasis on dietary control.

In the three placebo-controlled studies performed in patients with NIDDM, metformin monotherapy resulted in a statistically significant decrease in body weight at final visit, compared to baseline, in two of the three studies, including U.S. Study No. 87-1D-6023. The magnitude of this weight loss was 0.6 kg in U.S. Study No. 87-1D-6023 and 3.5 kg in non-U.S. Study No. MET/AM/84/DORF1. In the third study (non-U.S. Study No. MET/GB/85/DORNA), patients in the metformin group had no change from baseline body weight. In these three studies, patients in the placebo group lost comparable amounts of weight (1.1 kg in U.S. Study No. 87-1D-6023 of 6 months' duration, 4.0 kg in non-U.S. Study No. MET/AM/84/DORF1 of 2 months' duration, 1.1 kg in non-U.S. Study No. MET/GB/85/DORNA of 8 months' duration) and there was no statistically significant differences between response to metformin or placebo. Thus, the differences in the glycemic control achieved with metformin cannot be attributed to body weight loss in these studies, since changes of the same magnitude in this parameter occurred with metformin and placebo. In the diet-controlled study (non-U.S. Study No. MET/D/86/BERGI of 2 years' duration), both groups also lost statistically significant and comparable amounts of weight (2.8 kg with metformin compared to 3.5 kg with diet alone). In non-U.S. Study No. MET/AM/86/DORF2 of 2 months' duration, conducted in obese subjects with impaired glucose tolerance, and with a strong emphasis on diet, both metformin and placebo groups lost comparable amounts of weight, which were statistically significant (5.8 kg for the metformin group and 5.5 kg for the placebo group).

ITEM 2 — NDA SUMMARY

Four studies compared metformin monotherapy to various sulfonylurea treatments. In U.S. Study No. 87-2D-6023 of 6 months' duration, metformin resulted in a significant decrease in body weight at final visit, relative to baseline (3.8 kg decrease), compared to a 0.3 kg decrease in patients continuing on glyburide (M vs. G, p = 0.001). In non-U.S. Study No. MET/GB/86/CAMP1 of 12 months' duration, conducted in NIDDM not previously exposed to oral hypoglycemic agents, metformin resulted in a weight loss of 1.9 kg (p = 0.008) compared to a weight gain of 2.4 kg in the glipizide treatment group (p = 0.013) (M vs. G, p = 0.001). In non-U.S. Study No. MET/AM/88/DUCHI of 3 months' duration, patients in the metformin group lost a mean of 2.4 kg at final visit, compared to no change in the gliclazide group (M vs. G, p = 0.112). In non-U.S. Study No. MET/S/86/HERMA, in patients continuing on metformin monotherapy (group MM), there was a mean weight loss of 0.4 kg, compared to a mean weight gain of 2.3 kg in the group continuing on glibenclamide monotherapy (group GG) (MM vs. GG, p = 0.001). Thus, these studies serve to illustrate a key difference between responses in body weight with metformin vs. sulfonylureas in NIDDM subjects, in that metformin patients tended to lose weight or maintain stable weight, whereas patients on sulfonylureas tended to gain weight, often significant in degree.

Addition of metformin to ongoing sulfonylurea (glyburide) therapy in U.S. Study No. 87-2D-6023 of 6 months' duration, resulted in a slight increase in body weight (0.5 kg, p = 0.048). In non-U.S. Study No. MET/S/86/HERMA, patient groups requiring high doses of both metformin and glibenclamide (patient groups M/G,

G/M and MGH) all tended to have gained weight by the end of the 6 month treatment phase (0.8 kg for group M/G, 1.9 kg for group G/M and 0.2 kg for group MGH). There was no statistically significant differences in body weight response between these treatment subgroups.

Thus, it seems that the magnitude of body weight effects for patients receiving both metformin plus a sulfonylurea is intermediate between the slight weight loss or stable weight seen with metformin alone and the weight gain seen with sulfonylurea alone.

The level of **total serum cholesterol** was a primary efficacy parameter in all nine studies, both the two U.S. pivotal studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) and the seven non-U.S. Category II studies.

Metformin, as monotherapy, resulted in modest decreases in total cholesterol in all four placebo-controlled studies (including non-U.S. Study No. MET/AM/86/DORF2, conducted in patients with impaired glucose tolerance) ranging from decreases of 9 to 18 mg/dL (an average decrease of 6.5% from baseline values), and all within-treatment changes being statistically significant or borderline significant (non-U.S. Study No. MET/GB/85/DORNA, $p = 0.075$). Between treatment comparisons of metformin to placebo were significant in U.S. Study No. 87-1D-6023 and non-U.S. Study No. MET/GB/85/DORNA ($p = 0.024$ and 0.046, respectively). In the single diet-controlled study (non-U.S. Study No.

MET/D/86/BERGI), metformin and diet both caused modest but statistically significant increases in total cholesterol, compared to baseline values, but the study suffered from a high dropout rate as well as inability to assess compliance.

Metformin, as monotherapy, resulted in decreases in mean total cholesterol levels at final visit in three of the four active treatment comparison studies, although the magnitude of the decreases was modest, ranging from decreases of 4 to 10 mg/dL. In non-U.S. Study No. MET/GB/86/CAMP1, both the metformin and the glipizide treatment groups experienced mean increases in total cholesterol (21 and 20 mg/dL, respectively), significantly different from baseline. The reason for this result is unclear.

The addition of metformin to ongoing sulfonylurea therapy resulted in a decrease in total serum cholesterol of 9 mg/dL ($p = 0.001$) in U.S. Study No. 87-2D-6023. In this same study, patients continuing on glyburide alone, had a mean increase in total cholesterol at final visit of 3 mg/dL. In non-U.S. Study No. MET/S/86/HERMA, the addition of metformin to ongoing sulfonylurea therapy (group G/M) resulted in an increase in total serum cholesterol of 11 mg/dL, although, in the same study, low dose and high dose combination therapy with metformin and glibenclamide (groups MGL and MGH) had decreases in total cholesterol at final visit of 4 and 27 mg/dL, respectively.

From subgroup analyses performed on data generated in U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023, it appears that metformin has its greatest effect on total serum cholesterol levels when the levels are higher than normal at initiation of metformin therapy.

The level of total serum triglyceride was a primary efficacy variable in all nine studies, including the two U.S. pivotal studies and the seven non-U.S. Category II studies. Metformin, as monotherapy, resulted in modest decreases in total triglyceride in all four placebo-controlled studies (including non-U.S. Study No. MET/AM/86/DORF2, conducted in patients with impaired glucose tolerance but normal fasting glycemia), ranging from decreases of 14 to 39 mg/dL (average of 30 mg/dL, representing an average decrease of 14.3% from baseline values). Within-treatment changes were statistically significant in U.S. Study No. 87-1D-6023 and in Non-U.S. Study No. MET/AM/86/DORF2. Between treatment (metformin vs. placebo) comparisons approached statistical significance in U.S. Study No. 87-1D-6023 ($p = 0.065$) and in non-U.S. Study No. MET/GB/85/DORNA ($p = 0.051$), wherein the placebo group experienced a mean increase in triglyceride levels of 33 mg/dL. In the single diet-controlled study (non-U.S. Study No. MET/D/86/BERGI), metformin and diet both caused increases in total triglycerides (30 mg/dL with metformin [$p = 0.057$] and 63 mg/dL with diet alone [$p = 0.001$]) and the between treatment comparison approached statistical significance, in favor of metformin ($p = 0.130$).

Metformin, as monotherapy, resulted in decreases in mean total triglyceride levels at final visit in three of the four active treatment comparison studies. In U.S. Study No. 87-2D-6023, the metformin group had a mean decrease from baseline of 23 mg/dL ($p = 0.011$) compared to a mean decrease of 26 mg/dL in the group continuing on glyburide ($p = 0.444$). Comparison of median values at final visit revealed a decrease of 7 mg/dL for the metformin group compared to a median increase of 7 mg/dL for the glyburide group. In non-U.S. Study No. MET/S/86/HERMA, the treatment group maintained on metformin monotherapy (group MM) had a mean decrease in serum triglyceride levels at final visit of 8 mg/dL compared to an increase of 8 mg/dL in the group maintained on glibenclamide monotherapy. This difference between groups was not statistically significant, however ($p = 0.512$). In non-U.S. Study No. MET/AM/88/DUCHI, the metformin treatment group had a mean decrease of 5 mg/dL in total serum triglyceride level at final visit compared to a mean increase of 30 mg/dL in the gliclazide group. This difference between groups was, again, not statistically significant, however ($p = 0.421$). In non-U.S. Study No. MET/GB/86/CAMP1, in contrast, the metformin group as well as the glipizide group both had increases in total serum triglyceride levels at the end of the study, 5 mg/dL for the metformin group and 17 mg/dL for the glipizide group. (In this study, both groups also had mean increases in total serum cholesterol level at study end).

METFORMIN HYDROCHLORIDE

ITEM 2 — NDA SUMMARY

The addition of metformin to ongoing sulfonylurea (GR) therapy

[illegible] glyburide treatment groups in U.S. Study No. [illegible], [illegible]

a mean increase of 1 mg/dL in total serum triglyceride level at final visit. However, in

contrast, this median value showed a decrease of 14 mg/dL from baseline

(Median change from baseline values for the metformin monotherapy and

glyburide monotherapy groups were, respectively, -7 mg/dL and 0.5 mg/dL

in non-U.S. Study No. MET/SU66/NEPMA, patients maintained on [illegible]

combination therapy (metformin + glibenclamide) had [illegible]

serum triglyceride levels of 6 mg/dL at final visit. The [illegible]

groups (M/G, G/M, and M/GH) varied [illegible]

Group M/G had a mean decrease of 47 mg/dL, [illegible]

increase of 11 mg/dL and the M/GH group had [illegible]

In addition to the primary efficacy [illegible]

variables (fasting plasma [illegible]

were also assessed. In all [illegible]

significant increases [illegible]

of increase in FPG [illegible]

populations.

its antihyperglycemic

C-peptide [illegible]

dose-dependent

ITEM 2 — NDA SUMMARY

2.8.4 Uncontrolled Clinical Studies

2.8.4.1 Listing of Uncontrolled Clinical Studies Related to Claims of Effectiveness

A. Domestic Studies

B. Non-U.S. Studies

2.9.4.1 TABULAR SUMMARY OF UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS

1. Completed Domestic Studies with Full CRFs Available

Study #, Principal Investigator, Country, (No. of Centers)	Status (Start Date)	Location (Item #/Vol. #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs. (CRF)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex: M/F (%)	Race: B/W /H/O (%)
88-1C-8023 Multicenter (29) USA	C (01/90) (Note: Clinical portion of this study was completed 12/92 analysis currently underway)	9/1 169/ 088-28332	N/A	N/A	Pro,NR,OL,uncontrolled study of M (or M + G) involving patients completing either Study No 87-1D-8023 or 87-2D-8023 (Up to 116 weeks)	M,tab,850 mg (U K 3 050, Lot #764,791 803, 804,815,816,82 3,824,825,839, 886,888)	850-2550	Up to 1 tab t i d , with meals	604 obese NIDDM subjects, all previous participants in Ph III double-blind, placebo cont trials (87-1D-8023, 87-2D-8023)	32-71 (55 5)	277/327 (46/54)	87/444/ 69/4 (14/74/ 11/1)
						G,tab,5 mg	5 20	Up to 2 tabs-b i d , with breakfast & supper				

2.8.4.1 TABULAR SUMMARY OF UNCONTROLLED CLINICAL TRIALS RELATED TO CLAIMS OF EFFECTIVENESS

2. Completed Non-U.S. Studies with Full CRFs Available (Category II Studies)

Study #, Principal Investigator, Country, (No. of Centers) (Publications)	Status (Start Date)	Location (Item #/Vol #/ Starting Page)			Study Design (Drug Treatment Duration)	Treatment Groups				Demographics		
		Full Report	Data Listings	CRF Tabs (CRF)		Drug, Dosage Form, Strength (Formulation, Lot #)	Dose Range in mg	Regimen	#,Type of Patients Entered Per Group (completed)	Age Range (Mean)	Sex: M/F (%)	Race: B/W /H/O (%)
MET/DIB/HAUPT Multicenter, private pract (326) (BCA 979, BCA 1150, BCA 1341)	C (01/86)	8/1 170/ 088 22672	8/1 170/ 088 22647	N/A	Pro,NR,OL,uncontrolled Ph IV study of M + SU (12 weeks)	M,tab,850 mg (RF 2 850, commercial lots) SU,tab,variable	850 2550 Variable	Up to 1 tab t i d , with meals Variable	3,724 NIDDM, not well controlled on SU alone (3,452)	20 86 (61 3)	1496/ 2228 (40/60)	N/A
MET/AM/87/PHASE Multicenter, private pract (>500) FRANCE	C (01/86	8/1 180/ 088 26196	8/1 180/ 088 26284		Pro,NR,OL,uncontrolled Ph IV study of M (or M + SU) (24 weeks)	M,tab,850 mg (RF 2 850, commercial lots) SU,tab,variable	1700 Variable	1 tab b i d, with breakfast & supper Variable	4,374 NIDDM, either recently diagnosed diet failures or not adequately controlled with SU (4,158)	18 104 (60 0)	2319/ 2043 (53/47)	N/A

BCA numbers are Lipha's internal reference numbers for published/unpublished reports

The following abbreviations are used throughout

NR	= Non randomized	M	= Metformin	B	= Black
R	= Randomized	G	= Glyburide	W	= White
Pro	= Prospective	SU	= Sulfonylurea	H	= Hispanic/Mex Amer
OL	= Open label	C	= Completed	O	= Other (incl Orientals)
N/A	= Not available (applicable)				
NIDDM	= Non insulin dependent diabetics				

2.8.4.2 Summaries of U.S. and Non-U.S. Uncontrolled Clinical Trials

2.8.4.2.1 U.S. Study No. 89-1C-6023

U.S. Study No. 89-1C-6023, conducted from January, 1990 through December, 1992, was a non-randomized, open-label, multicenter (23 centers with 25 investigators), long-term (up to 116 weeks) study of the continued safety and efficacy of metformin, involving 604 NIDDM patients who had completed all visits of the previous double-blind Phase III studies (U.S. Study No. 87-1D-6023 and Study No. 87-2D-6023). (Data from this study are currently under analysis and will be reported in full in the first safety update to this NDA). The 850 mg dosage strength of metformin was used in this study and, in addition, in applicable patients, the 5 mg dosage strength of glyburide.

Safety assessments included a review of tolerance and AE/MEs at each visit as well as an evaluation of laboratory parameters.

Primary efficacy parameters included: (a) glycemic control as measured by FPG, HbA_{1c} and two-hour postprandial plasma glucose; (b) lipid profile effects as measured by total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, HDL subfractions and apolipoproteins; and (c) body weight effects. The secondary efficacy parameters were blood pressure and fasting and postprandial plasma insulin and C-peptide effects.

Since the majority of patients went directly from the previous double blind study (and which remained blinded to both patients, investigators and sponsor) into this open-label study, their previous drug exposure was heterogeneous and could have been either metformin, glyburide, metformin plus glyburide or placebo. As a consequence, all patients were assumed to have never been exposed to metformin and, therefore, the study consisted of two phases: a) a metformin dose titration phase of four weeks and 2) a long-term treatment phase up to 116 weeks or until December 1, 1992, whichever came first. All laboratory studies were performed by a centralized laboratory (SciCor, Inc., Indianapolis, Indiana) or, when performed locally, were confirmed by the central laboratory.

Following baseline evaluation, patients were started on 850 mg/day of metformin, with biweekly increases in 850 mg increments, based on considerations of efficacy and tolerance, to the maximum dose of 2.55 g/day or optimal dose, if less. Metformin was administered with meals. If after one month at the maximum dose of metformin, glycemic control was considered inadequate (FPG >140 mg/dL), the option existed to add glyburide to ongoing metformin therapy, beginning with 5 mg/day and increasing to a maximum of 20 mg/day (two tablets b.i.d., with breakfast and supper).

Out of 740 potentially eligible subjects (i.e., patients completing all visits of either Study No. 87-1D-6023 [217 subjects] or of Study No. 87-2D-6023 [523 subjects]), 604 were enrolled in this study. Intext Table 45, page 379, summarizes total

duration of exposure to metformin of the study population, as well as exposure during the preceding double-blind study and during Study 89-1C-6023 itself.

Table 45. U.S. Study No. 89-1C-6023
Summary of Exposure to Metformin

Previous Treatment During Double Blind Study	Duration of Metformin Treatment (weeks)		
	Study No. 87-1D-6023 or 87-2D-6023	Study No. 89-1C-6023	Total Exposure to Metformin (min.,max.)
Metformin (n = 217)	29.7 ± 0.1	71.0 ± 2.0	100.7 ± 1.9 (34.7, 142.6)
Glyburide (n = 142)	0	71.5 ± 2.5	71.5 ± 2.5 (2.0, 111.9)
Metf/Glyb (n = 168)	29.0 ± 0.1	71.0 ± 2.3	100.1 ± 2.3 (33.9, 140.3)
Placebo (n = 75)	0	66.2 ± 3.6	66.2 ± 3.6 (0, 108.3)

Of the 604 patients enrolled in this study, preliminary data review indicates that 164 patients were terminated from the study prior to the potential termination time. A complete analysis of patient disposition will be provided with the complete study report (to be submitted with the first safety update of this NDA). Included in Item 8 of this NDA is a summary of the 74 patients who terminated prematurely for either an AE/IME, significantly abnormal laboratory result or because of patient death. (***NOTE:*** *Detailed individual narratives, based on review of unedited case report forms, on all such patients are provided in Section 8.8.15.6.1, Volume 1.81, beginning on Page 08A-03285*).

Intext Table 46, below, summarizes the distribution of the 74 patients, according to reason for premature study termination (as indicated by the principal investigator) and treatment at the time of termination (either metformin alone or metformin plus glyburide).

Table 46. U.S. Study No. 89-1C-6023
Distribution of Patients According to Primary Reasons for Termination
(Adverse Experience, Intercurrent Medical Illness,
Abnormal Laboratory Result, Death)

Reason for Withdrawal	Treatment at the Time of Premature Termination	
	Metformin alone	Metformin + Glyburide
Patient Death	2	4
Adverse Experience	9	5
Intercurrent Illness	13	18
Significant Laboratory Abnormality	3	20

Of the six patient deaths occurring during participation in this study, four were cardiovascular in nature: two patients were on metformin alone (cardiogenic shock, post-myocardial infarction and cardiac arrest); two patients were on metformin/glyburide (both with arteriosclerotic cardiovascular disease). One patient had lung cancer (metformin/glyburide) and another patient, without any history of psychiatric problems, committed suicide (metformin/glyburide).

Gastrointestinal adverse experiences were the reasons for 13 subjects to terminate prematurely. Eleven patients (three on metformin/glyburide, eight on metformin

alone) had a primary complaint of diarrhea. One patient had "gastrointestinal complaints" (metformin/glyburide) and one patient had abdominal pain (metformin only).

One patient terminated prematurely because of pain and weakness (metformin/glyburide).

Twenty-three patients were terminated due to abnormal laboratory results. Of this total, nineteen were discontinued due to abnormal renal function tests (since this precluded continued study eligibility). One subject, on metformin/glyburide, was terminated because of an elevated fasting plasma lactate level and three patients were terminated due to abnormal liver function tests (all on metformin plus glyburide).

2.8.4.2.2 Non-U.S. Category II Study No. MET/D/86/HAUPT

Non-U.S. Category II Study No. MET/D/86/HAUPT, conducted in Bad Kissingen, Germany from January, 1986 to February, 1989, was a 3 month, prospective, open-label, uncontrolled Phase IV, multicenter (326 physicians in private practice) study of the efficacy of metformin when added to ongoing sulfonylurea therapy in 3,724 NIDDM outpatients. The 850 mg dosage strength of metformin was used in this study, of commercial source.

Primary efficacy parameters consisted of fasting blood glucose (FBG) (available, however, in only about 15% of patients), post-prandial blood glucose (PPG) (available for the majority of patients), HbA_{1c} or HbA_1, total cholesterol, triglycerides, body weight and blood pressure. AE/IMEs were recorded before therapy onset and at each visit. Serum creatinine was measured at baseline and after 12 weeks of treatment.

Observed values and change from baseline values were tabulated for all patients at each visit. In addition, the changes from baseline values were tabulated at final visit for seven subgroups to see if any one particular subgroup reacted better or worse to treatment with metformin. Two subgroups included breakdowns by sex and age. Other subgroups were formed by taking five efficacy variables and categorizing their values into two or three categories according to the quality of diabetes control as it was defined by their value at baseline. The frequency of patients within each subgroup at baseline was compared to the frequency at final visit. The incidence of AE/IMEs were computed overall by severity, by outcome, by sex, and by age.

Metformin was introduced in gradually increasing doses (850 to 2550 mg/day), at biweekly intervals, depending on glycemic response and tolerance. Tablets were taken with meals. Sulfonylurea drug dosages for all patients were continued unchanged throughout the study.

A total of 3724 patients entered the study. Of these, 3452 patients (93%) completed the 12-week study.

Changes from baseline for key efficacy parameters are shown in intext Table 47, below.

Table 47. Non-U.S. Study No. MET/U/86/HAUPT
Changes from Baseline at Final Visit for Key Efficacy Parameters

Parameter	Mean Decreases at Final Visit
Fasting Blood Glucose (mg/dL)	-62.13
Post-Prandial Blood Glucose (mg/dL)	-80.24
HbA_{1c} (%)	-1.77
HbA_1 (%)	-1.81
Total Cholesterol (mg/dL)	-22.05
Triglycerides (mg/dL)	-36.32
Body Weight (kg)	-1.91
Systolic Blood Pressure (mm Hg)	-4.08
Diastolic Blood Pressure (mm Hg)	-1.87

Of the 3,724 enrolled patients, 272 patients (7%) discontinued from the study before the end of the study, 113 (3%) for digestive system symptoms. Of those patients who withdrew due to an adverse event/intercurrent medical event (AE/IME), the three major events were diarrhea, nausea and epigastric distress. Intext Table 48, page 384, indicates patient disposition, post-enrollment.

Table 48. Non-U.S. Study No. MET/D/86/HAUPT
Patient Disposition, Post-Enrollment

Total Number of Patients	3724
Total Number of Withdrawals	272 (7.3%)
Reason for Withdrawal:	
Adverse experience/Intercurrent medical event	146 (3.9%)
Lost to follow-up	58
Lack of effectiveness	33
Hospitalization	19
Switched to insulin	9
Lack of compliance	7

Metformin was well tolerated throughout the course of the study. Six hundred forty-three patients (17%) reported a total of 1096 AE/IMEs. Patients reporting AE/IMEs affecting the digestive system (13% of the patients) outnumbered those reporting AE/IMEs affecting other body systems. Within this body system, the most frequently reported AE/IMEs were diarrhea (250 patients, 7%), nausea (168 patients, 5%), epigastric distress (112 patients, 3%), and vomiting (47 patients, 1%). As noted above, 3% of patients withdrew for digestive system complaints.

Of note, there were only nine AE/IMEs identified as "hypoglycemia" (<1%). Of these, 3 were considered to be "slight" in severity, 4 "moderate" and 2 "severe". (It should be recalled that all patients were concomitantly taking oral sulfonylureas.) Sixty-four patients (2%) complained of metallic taste.

Specific AE/IME frequencies were similar across sex, age and severity subgroups. No deaths were reported. Serious and/or potentially serious AE/IMEs were seen in only 1% of patients. Twenty-two patients were hospitalized (19 before Week 12). Two patients were noted to have had myocardial infarctions during the study. A total of 182 patients (174 patients before Week 12 [≤84 days] and 8 patients after Week 12) were withdrawn from study medication due to medical events which included AE/IMEs, hospitalization, and insulin treatment.

2.8.4.2.3 Non-U.S. Category II Study No. MET/AM/87/PHASE

Non-U.S. Category II Study No. MET/AM/87/PHASE, conducted in France from January, 1986 to January, 1990, was a six month, Phase IV, open-label, multicenter (>500 private practice-based physicians) study of the efficacy and safety of metformin monotherapy or metformin in addition to continued sulfonylurea therapy in 4,374 NIDDM outpatients. The 850 mg dosage strength of metformin was used in this study.

The primary objective of this study was to assess efficacy and tolerance of six-month's treatment with metformin in NIDDM patients (either recently diagnosed diabetics who failed diet therapy, or known diabetics not adequately controlled by their current treatment). Each of the approximately 500 physicians was to recruit between 5-10 NIDDM patients.

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Primary efficacy parameters consisted of FPG, PPG, total cholesterol, triglycerides, body weight, blood pressure, and investigator determination of efficacy. Serum creatinine was measured and digestive tolerance assessed at each visit. AE/IMEs were recorded as general comments.

Means of observed values and change from baseline values were computed for all efficacy and safety parameters to evaluate metformin. Frequencies were provided for categorical parameters. The primary analysis was within-treatment comparisons of change from baseline values.

Metformin was administered as one tablet per day (850 mg per day) for one week, then two tablets per day (1700 mg per day) for the remainder of the study. Metformin was administered as monotherapy for recently diagnosed diabetics. For more long-standing diabetics, metformin was administered with continued sulfonylurea therapy.

As can be seen in intext Table 49, page 387, all efficacy variables improved over the course of the study.

Table 49. Non-U.S. Study No. MET/AM/67/PHASE
Mean Change from Baseline at Final Visit in Key Efficacy Parameters

Mean Change From Baseline	
Parameter	Final Visit
Fasting Plasma Glucose (mg/dL)	-55.88
Post-Prandial Plasma Glucose (mg/dL)	-84.30
Body Weight (kg)	-2.75
Total Cholesterol (mg/dL)	-21.47
Triglycerides (mg/dL)	-39.67
Systolic Blood Pressure (mm Hg)	-5.21
Diastolic Blood Pressure (mm Hg)	-2.47

Upon initiation or addition of metformin treatment, there was a steady decrease over time in plasma glucose, total cholesterol, triglycerides, body weight and blood pressure. All patient subgroups analyzed showed similar improvement, suggesting that metformin was equally efficacious both in Type II NIDDM patients with recently diagnosed diabetes, failing diet therapy and in long-term diabetics not adequately controlled by their current treatment. There was a greater blood glucose-lowering effect in patients with more marked hyperglycemia at baseline. Response of patients >65 years of age was comparable to younger subjects, both with regard to efficacy and safety.

Of the 4,374 enrolled patients, 144 (3.3%) were discontinued from the study due to digestive intolerance, 24 for other adverse experiences/intercurrent medical events (AE/IMEs), and 48 for other unspecified reasons, as shown in intext Table 50, below (total of 4.9% withdrawals). Less than 4% of the patients reported "severe" or "very severe" levels of digestive intolerance at any point in the study.

Table 50. Non-U.S. Study No. MET/AM/87/PHASE
Patient Disposition, Post-Enrollment

Patient Disposition	
Total Number of Patients	4374
Total Number of Withdrawals	216 (4.9%)
Reason for Withdrawal:	
Digestive intolerance	144 (3.3%)
Other adverse experience/ intercurrent medical event	24
Other	48

Among 84 patients considered to have serious or potentially serious AE/IMEs, were eight patients identified as having neoplasms during or subsequent to the study: bowel cancer (two patients); and single patients with: esophageal cancer; pharyngeal cancer; pancreatic cancer; brain tumor; insulinoma; and pheochromocytoma.

Ten patients (four before the end of the study and six after their Month 6 visit) died due to AE/IMEs as follows: myocardial infarction (two patients); cerebrovascular disease (two patients); pulmonary embolism; pulmonary edema;

post-coronary artery bypass surgery; cranial trauma; esophageal cancer; and decompensation of alcoholic cirrhosis. One additional patient died as the result of an automobile accident.

2.8.4.2.4 Analysis and Conclusions

The available data from these two non-U.S. Phase IV uncontrolled clinical trials, involving 8,098 NIDDM patients (7,950 patients who completed all visits), revealed strong improvement in all glycemic control parameters (fasting blood glucose, postprandial blood glucose and glycosylated hemoglobin). Data from non-U.S. Study No. MET/D/86/HAUPT support the efficacy of metformin in lowering blood glucose levels in a diabetic population for whom sulfonylurea therapy alone has not produced (or has ceased to produce) satisfactory results. The addition of metformin to the sulfonylurea therapy (mainly glibenclamide) resulted in an average reduction of two percent in HbA_1 and HbA_{1c} levels, and a mean reduction of 80 mg/dL in post-prandial blood glucose level. The magnitude of change appeared to be related to the degree of baseline abnormality of such parameters, with globally greater improvement occurring in patients with more severe diabetes at baseline. This evidence supports similar conclusions regarding parameters of glycemic control made in the controlled clinical trials summarized above. In addition, these large clinical trials demonstrated clear improvement in lipid profiles (an average reduction in total serum cholesterol and triglyceride levels on the order of 9% and 15%, respectively in MET/D/86/HAUPT and 9% and 22%,

respectively, in MET/AM/87/PHASE) and weight reduction, again, consistent with data from the controlled studies summarized above. There were also decreases in systolic and diastolic blood pressure in these large Phase IV studies.

Finally, serious and/or potentially serious AE/IMEs were seen in only 1% of the patients. Moreover, only 146 patients (3.9%) were withdrawn from metformin therapy because of AE/IMEs. The relationship of adverse experiences to other concomitant diseases and to concomitant medication (including sulfonylureas) was not explored in this study.

The combined three studies (89-1C-6023, MET/D/86/HAUPT and MET/AM/87/PHASE) reported a total of 359 withdrawals due to AE/IMEs out of a total of 8,702 initially enrolled patients (4%). The two non-U.S. studies (MET/D/86/HAUPT and MET/AM/87/PHASE), with a combined enrollment of 8098 subjects, reported 121 patients with AE/IMEs defined as "serious" (1.5%).

The results of Study No. MET/D/86/HAUPT with 3,724 subjects did not reveal any significant problems with patient tolerance of metformin. A total of 1,096 AE/IMEs were reported by 643 patients (17%). The majority of patients (484 of 643 patients or 71%) reported AE/IMEs related to the digestive tract. Only 146 patients terminated the study due to AE/IMEs (3.9%), with 113 (3%) of these prematurely terminating patients doing so because of digestive system AE/IMEs. The premature termination rate was very similar in MET/AM/87/PHASE, with 168

withdrawals (3.8%) for AE/IMEs and 144 (3.3%) of these being for digestive system symptoms. Subgroup analysis in the MET/D/86/HAUPT study indicated that AE/IME frequencies were similar across sex, age and diabetes severity subgroups.

2.8.5 Other Studies and Information

2.8.5.1 Other Clinical Studies

In addition to the controlled U.S. Category I and non-U.S. Category II studies and the non-U.S. Category II Phase IV studies summarized above, 100 non-U.S. Category III studies, with deficiencies as defined on Page 184, are included in this NDA and integrated, as possible and appropriate in the clinical pharmacology and clinical sections. All these studies were carefully reviewed for safety-related information.

Fifty-one of these 100 non-U.S. Category III studies were clinical pharmacology studies (35 completed, 11 ongoing, 3 incomplete, 2 never initiated). A tabular summary of these studies is located in Section 8.3.1.5, Volume 1.67, beginning on Page 08A-00092. Synopses of these studies are located in Section 8.20.1, Volume 1.202, beginning on Page 08B-32812. Where pertinent, publications related to these studies immediately follow the synopses.

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Forty-nine of the 100 non-U.S. Category III studies were clinical trials. There were 24 controlled studies, related to claims of effectiveness sought in this NDA. Five of these were placebo-controlled (2 completed, 1 ongoing, 2 incomplete) and 18 were with an active-treatment comparator (9 completed, 2 ongoing, 7 incomplete) and one was a completed dose-comparison study. A tabular summary of these studies is presented in Section 8.4.1.1, Volume 1.69, beginning on Page 08A-00448. Synopses of these studies are located in Sections 8.20.2 (placebo-controlled), 8.20.3 (active-controlled) and 8.20.4 (dose-comparison), Volume 1.204, beginning on Pages 08B-33306, 08B-33337 and 08B-33444, respectively. There were seven uncontrolled studies, related to claims of effectiveness sought in this NDA (4 completed, 3 incomplete). A tabular summary of these studies is presented in Section 8.5.2.1, Volume 1.69, beginning on Page 08A-00596. Synopses of these studies are located in Section 8.20.7, Volume 1.204, beginning on Page 08B-33542. Where pertinent, publications related to these studies immediately follow the synopses.

There were 18 studies (15 controlled and 3 uncontrolled) related to uses of metformin other than those related to claims of effectiveness. The controlled studies are presented in tabular form in Section 8.6.2.1, Volume 1.69, beginning on Page 08A-00633, with synopses of these studies located in Section 8.20.5, Volume 1.204, beginning on Page 08B-33452. The uncontrolled studies are presented in tabular form in Section 8.6.4.1, Volume 1.69, beginning on Page 08A-00659, with synopses of these studies located in Section 8.20.6, Volume 1.204,

beginning on Page 06B-33528. Where pertinent, publications related to these studies immediately follow the synopses.

2.8.5.2 Metformin Published Reports

In Item 15, a listing of more than 2,000 citations involving metformin (primarily published but also including unpublished reports, theses, etc.) is provided as a numerical listing (according to Lipha's BCA internal referencing system) in Section 15.2, Volume 1.403, beginning on Page 15 000004, and as an alphabetical listing in Section 15.4, Volume 1.411. All citations have been reviewed for safety-related information and are integrated into this NDA as appropriate (see below, Section 2.8.5.3). An abstract of each citation is provided in Section 15.3, Volumes 1.404 through 1.410.

2.8.5.3 Post-Marketing Surveillance Information and Relevant Published Information

During at least ten years of adverse event reporting to the parent company Lipha S.A., Lyon, France, from within France and from its subsidiaries and licensees of Glucophage® brand of metformin hydrochloride, including subsidiaries in the United Kingdom, Germany, Belgium, Italy, Switzerland and Portugal and licensees in Australia, Austria, Canada, Denmark, Holland, Japan, New Zealand, South Africa and Sweden, there have been 279 adverse events reported, consistent with

the reporting requirements of the respective countries. Intext Table 51, page 395, provides an alphabetical listing of these events, including, for each event, the total number of events as well as the number of events by country. Following the table, is a discussion of some of the more noteworthy adverse events and, where relevant, related published reports.

Table 51. Alphabetical Listing of Adverse Events Reported to Lipha S.A. by Subsidiaries and Licensees (1982-1992)

Adverse Event (Total Events)	Country (No. of Events Reported)
Abdominal Pain (2)	United Kingdom (2)
Alcohol Intolerance (1)	United Kingdom (1)
Alopecia (6)	France (6)
Anemia (9)	
Aplastic (1)	United Kingdom (1)
Iron-deficiency (1)	Canada (1)
Macrocytic (2)	France (2)
Macrocytosis (1)	France (1)
Megaloblastic (1)	France (1)
Unspecified (3)	Austria (1)
	Denmark (1)
	France (1)
Asthenia (1)	Norway (1)
Back Pain (2)	France (1)
	United Kingdom (1)
Breast Pain (1)	Canada (1)
Bronchospasm (1)	United Kingdom (1)
Cholecystitis (1)	Germany (1)
Circulatory Failure (1)	France (1)
Decreased Therapeutic Response (4)	Canada (3)
	Australia (1)

Table 51. Alphabetic Listing of Adverse Events Reported to Lipha S.A. by Subsidiaries and Licensees (1983-1992) (cont'd)

Adverse Event (Total Events)	Country (No. of Events Reported)
Dermatologic Disorders (21):	
Allergic eczema (2)	Germany (2)
Cutaneous eruption (7)	Australia (3)
	Germany (3)
	France (1)
Dermatitis (1)	France (1)
Erythema multiforme (2)	France (1)
	Canada (1)
Erythematous skin eruption (1)	France (1)
Maculopapular skin eruption (3)	France (3)
Nail abnormality (1)	France (1)
Photosensitivity reaction (1)	United Kingdom (1)
Pruritus (3)	France (2)
	Germany (1)
Diarrhea (8)	United Kingdom (3)
	Australia (1)
	Denmark (1)
	France (1)
	Germany (2)
Drug interaction with warfarin (1)	Canada (1)
Dyspepsia (2)	Denmark (1)
	United Kingdom (1)
Dysuria (1)	New Zealand (1)
Edema of the legs (1)	United Kingdom (1)
Elevated lactate level (11)	France (9)
	Austria (1)
	Germany (1)

Table 51. Alphabetic Listing of Adverse Events Reported to Lipha S.A. by Subidiaries and Licensees (1982-1992) (cont'd)

Adverse Event (Total Events)	Country (No. of Events Reported)
Ketoacidosis (6)	France (5) Canada (1)
Lactic acidosis (99)	France (73) Belgium (5) Canada (4) Germany (5) United Kingdom (4) New Zealand (3) Australia (1) Denmark (1) Austria (1) Sweden (1) Switzerland (1)
Malaise (2)	Denmark (1) France (1)
Menstrual disorders (2):	
Amenorrhea (1)	New Zealand (1)
Unspecified (1)	United Kingdom (1)
Metabolic acidosis (6)	France (5) Germany (1)
Myalgia (1)	United Kingdom (1)
Nausea (1)	Germany (1)
Neuropathy (1)	United Kingdom (1)
Nightmares (1)	United Kingdom (1)
Numbness of mouth and throat (1)	Canada (1)
Pain (1)	United Kingdom (1)

Table 51. Alphabetic Listing of Adverse Events Reported to Lipha S.A. by Subidiaries and Licensees (1982-1992) (cont'd)

Adverse Event (Total Events)	Country (No. of Events Reported)
Pancreatitis (2)	France (1) United Kingdom (1)
Paresthesias (1)	Sweden (1)
Prothrombin abnormalities (3):	
Increased prothrombin activity (2)	Australia (1) Canada (1)
Prolonged prothrombin time (2)	Germany (1)
Renal disorders (4):	
Acute renal insufficiency (2)	France (2)
Renal failure (1)	New Zealand (1)
Renal tubular necrosis (1)	United Kingdom (1)
Suicide attempt/voluntary overdose (15)	France (14) Germany (1)
Sweating disorders (2)	
Excess sweating (1)	France (1)
Increased sweating (1)	Canada (1)
Thrombocytopenia (5)	France (3) Canada (1) Germany (1)
Transplacental metformin transfer (1)	France (1)
Vasculitis (1)	United Kingdom (1)
Vision abnormality (1)	United Kingdom (1)
Vomiting (4)	Australia (3) United Kingdom (1)
Vitamin B_{12} and folic acid deficiency (2)	Sweden (1) Switzerland (1)

Table 51. Alphabetic Listing of Adverse Events Reported to Lipha S.A. by Subidiaries and Licensees (1982-1992) (cont'd)

Adverse Event (Total Events)	Country (No. of Events Reported)
White blood cell disorders (3):	
Agranulocytosis (1)	France (1)
Granulocytopenia (1)	France (1)
Leukopenia (1)	France (1)
Xerophthalmia (1)	United Kingdom (1)

Lactic Acidosis:

Included in this group are 99 cases of lactic acidosis, the majority of which (73) are from France. For a number of the 99 cases, the diagnosis of lactic acidosis is a presumed diagnosis, since the necessary laboratory documentation to substantiate the relationship between metformin and the acidosis (metformin plasma or red blood cell levels) or to ascertain that the acidosis was, indeed, "lactic acidosis" are lacking. Furthermore, in many countries (with the exception of France, for which considerable detail on individual cases is available) very little information could be obtained, despite much effort on the part of the subsidiaries and licensees, primarily based on individual country reporting systems and considerations of patient confidentiality.

Of note is the observation that, in those cases for which sufficient information is provided, lactic acidosis has occurred in patients in whom the use of metformin, acutely or long-term, was contraindicated. Diabetic patients in whom lactic

acidosis occurred tended to be older (average age of 67, range 21 to 87), to have multiple associated medical or surgical problems (particularly chronically or acutely impaired renal function, chronic hepatic disease, chronic ethanol abuse, chronic cardiovascular disease with acute event, sepsis, or dehydration) and to be on multiple medications.

Nine cases (9% of 99) followed an intravascular radiographic contrast study, prior to which metformin was not discontinued. The use of iodinated contrast materials in diabetic patients is a diagnostic intervention with known risk, in and of itself, for precipitation of acute renal failure in diabetics: metformin accumulation under such circumstances, with resultant lactic acidosis, has been been reported. Contrast studies represent a temporary contraindication to the use of metformin and require cessation of metformin therapy for at least 48 hours prior to such a study.

In addition, one fatal case of lactic acidosis, reported from Canada, involved a patient who had been on a week-long acute alcoholic binge, while continuing to take his metformin and glyburide, and who had marked dehydration and evidence both of toxic levels of ethanol and lactic acidosis. Cases of lactic acidosis, triggered by an excessive intake of alcohol in patients taking metformin, have been previously reported. Experimentally, it has been shown that ethanol itself increases lactate levels and metformin further enhances this increase. Sixteen additional cases of lactic acidosis, reported herein, had chronic ethanolism and chronic hepatic disease as contributory factors (17% of 99 cases).

Among 53 of the 73 cases reported from France with plasma metformin level measurements available (often with erythrocyte metformin levels, in addition), levels were elevated (≥5 μg/mL) in 34 or 64% of cases, with 28 (53% of 53) having plasma metformin levels ≥10 μg/mL. Conversely, 19 patients (or 35% of 53) had either non-detectable metformin levels or levels that were within the expected therapeutic range.

In France, where detailed information was available on the majority of cases and where, also, use of metformin is, relatively speaking, very high and accurate information concerning metformin sales is available, the incidence of lactic acidosis over at least the past eight years has remained very constant, at approximately 0.03 cases/1,000 patient-years. The fatality rate for such cases has also remained relatively constant at approximately 50%, or 0.015 fatal cases/1,000 patient-years.

Voluntary Overdose:

Fifteen cases of intentional overdosage were reported (14 from France and one from Germany), often with multiple medications (including unknown medications and unknown quantities) being ingested in great excess. The amount of metformin ingested varied from 7.65 to 76.5 grams, as a single dose.

Of the nine patients for whom information is available regarding plasma glucose levels, there was only one patient with hypoglycemia (#614 from France), who was *presumed* to have taken metformin but, who, in fact, did not have detectable metformin in either plasma or erythrocytes and who had also taken glibenclamide.

Eight of the 14 patients, for whom there is available information, had an associated lactic acidosis at the time of hospital presentation. Five of the eight recovered completely, as did all of the remaining patients (including the patient from France, #759, for whom no other information is available). Thus, the overall mortality of the 15 patients was 20%. For those with lactic acidosis it was 37.5%.

Significant Hematologic Abnormalities:

With regard to significant reported hematologic abnormalities, the single case of reversible aplastic anemia (reported from the United Kingdom) occurred in an elderly woman who had simultaneously started six other medications, in addition to metformin. Causality is, therefore, difficult to assess and the patient recovered.

The single case of megaloblastic anemia reported from France (#339) provides no information except that the patient had been on metformin and the sulfonylurea glibenclamide for two years. One case of macrocytic anemia reported from France occurred in a chronic alcoholic with lactic acidosis (#433) who was found to have decreased serum iron, vitamin B_{12} and folic acid levels and who recovered with conservative management and whose diabetes was later controlled with diet

alone. The second case of macrocytic anemia reported from France (#1168) appeared to be due to decreased vitamin B_{12} without evidence of hypochlorhydria or intrinsic factor deficiency. The anemia reversed with oral vitamin B_{12} and discontinuation of metformin. This case appears to be causally related to metformin although the duration of metformin treatment is not provided. The patient with macrocytosis reported from France was also a chronic alcoholic (#554), with normal serum vitamin B_{12} levels and decreased serum folic acid. The macrocytosis was attributed to ethanol abuse. (***NOTE:*** *To date, three cases of megaloblastic anemia, related to metformin use, have been reported in the literature. In no instance has there been associated neurologic problems*).

Five cases of thrombocytopenia have been reported. In the case reported from Germany, the patient had been started on metformin two months prior to detection of thrombocytopenia. Metformin was discontinued and, simultaneously, the patient was treated with anabolic- and cortico-steroids, with gradual increase in platelets. No additional information is available. The case of thrombocytopenia reported from Canada, provides no additional information whatsoever. The three cases reported from France included a case (#686) of thrombocytopenia in the setting of chronic alcoholism and hyperuricemia (the patient was also on other medications). All medications were discontinued but the moderate thrombocytopenia persisted. (The possible role of hypersplenism on the basis of cirrhosis and portal hypertension was not addressed). The second case of moderate thrombocytopenia reported from France (#1256) occurred in a

hypertensive patient treated intermittently with metformin over a three year period. When metformin was discontinued the platelet count gradually returned to normal. The third case reported from France (#1263) appeared to be more clearly causally related to metformin, in that the platelet count increased with metformin withdrawal and then decreased again to moderate levels when the patient was re-challenged with metformin. Thus, it is possible that metformin, on rare occasions, can cause mild thrombocytopenia.

Three cases of leukopenia have been reported. The case of "leukopenia" (WBC 2400/mm^3) reported from France occurred in an elderly patient on metformin for 5-6 years (#484). The leukopenia disappeared when metformin was discontinued. The case of "agranulocytosis" reported from France occurred in an alcoholic patient (#606) and disappeared without treatment, after discontinuation of metformin. (The possible role of hypersplenism in this case or transient bone marrow depression due to nutritional deficiency was not addressed). The case of "granulocytopenia" occurred in the context of a febrile illness in a patient with thalassemia (#810) who had started metformin one month earlier. The granulocytopenia disappeared when metformin was discontinued. (Transient bone marrow depression due to an aplastic crisis in this thallassemic patient with fever and possible infection was not addressed). Although in all three cases the depression in white blood cell counts disappeared with discontinuation of metformin, all three cases had other possible etiologic factors present and thus, causality is difficult to assess or definitively attribute to metformin administration.

Hyponatremia:

Two cases of hyponatremia were reported, both from France (#524 and #761). The former case, involving a mean decrease in serum sodium levels of 3 mEq/L upon the addition of metformin to continued chlorpropamide therapy, was reported in a publication by Gin et al. The possibility of the hyponatremia being due to metformin-related inhibition of catabolism of antidiuretic hormone was raised, which was also suggested by published work of Katsuki and Ito in patients with diabetes insipidus, in whom metformin alone reduced diuresis by 30%.

The second case (#761) involved an elderly diabetic woman, taking multiple medications, who presented with somnolence, muscular weakness and dehydration and who was found to be hyponatremic, hypokalemic, moderately hyperlactatemic and to have hemoconcentration. She responded to fluid replacement.

Possible Drug Interactions:

A single case was reported from Germany of prolongation of the prothrombin time in a metformin-treated patient on the oral anti-coagulant, phenprocouman, for treatment of a pulmonary embolus. The patient was also on glibenclamide, and prazosin. The phenprocouman was discontinued. (Prolongation of the prothrombin time would be contrary to the expectations of decreased effectiveness of phenprocoumon during metformin co-administration, based on the published study of Ohnhaus et al, showing that metformin increased the

elimination of phenprocouman through reduction of its enterohepatic cycle).

From Canada comes a case of an "interaction with warfarin", without further available information.

Metformin in Pregnancy:

Two cases involved the use of metformin during pregnancy. From France came a report (#s 718 and 719) which provided evidence of transplacental transport of metformin. The case was that of a pregnant diabetic who took metformin and sulfonylurea until parturition and gave birth to a profoundly hypoglycemic, acidotic infant, who, however, recovered and subsequently appeared normal. At parturition, both mother and newborn had detectable but very low metformin plasma levels (0.34 mg/L and 0.1 mg/L, respectively), with higher concentrations in the maternal plasma compared to the newborn. Levels of metformin in milk could not be measured because lactation had been artificially suppressed. *(This case was reported at the Association Française des Centres de Pharmacovigilance meeting held in Nice, France, Oct. 28-29, 1991).*

Detectable metformin levels in human amniotic fluid have been prevously reported. Animal studies are consistent with the above case and have suggested that the placenta is a partial barrier to metformin transmission from maternal to fetal circulation, but with a more complete barrier in terms of fetal to maternal circulation. Animal studies have shown that metformin is excreted into milk.

There was one case of fetal malformation (malformed hand in a normal weight infant without other abnormality) reported from France (#1199), occurring in the offspring of a diabetic mother who had taken metformin and alphamethyldopa through the first two trimesters of her pregnancy. (There had been a prior history of multiple spontaneous abortions and an in utero death for this mother).

The use of metformin in human pregnancy has not been studied in a systematic fashion, although there are a number of anecdotal reports of women receiving metformin throughout pregnancy and delivering normal children.

The largest published series is that of Coetzee and Jackson from South Africa, involving 60 pregnant diabetics treated with metformin. Thirty-three of the diabetics (established or gestational diabetes) were treated to term with metformin alone. An additional 27 pregnant diabetics received metformin for part of their pregnancy but were considered to have responded inadequately to metformin monotherapy and, therefore, were either treated with metformin plus glibenclamide or insulin alone.

Among the total group of 60 patients who received metformin at some time during their pregnancy, there were no stillbirths and there were two neonatal deaths, giving a perinatal mortality for all patients receiving metformin of 61/1000. One of the neonatal deaths occurred in the setting of premature rupture of the membranes, with delivery of a premature infant who died of immaturity and

hyaline membrane disease. The second neonatal death occurred in an infant with multiple congenital anomalies (hare-lip, cleft palate and heart defect). The mother had not received any treatment during the first trimester and only metformin (500 mg t.i.d.) during the last three weeks of her pregnancy. (There were three other infants with congenital abnormalities [two heart defects, one sacral agenesis] but in all cases the mother had *not* taken metformin during the first 28 weeks of pregnancy and these were not attributed to metformin. Of the 12 diabetic mothers who had taken metformin during the first trimester, none had offspring with congenital abnormalities).

Neonatal morbidity was very low with a mean 5 minute Apgar score of 9.7 out of a possible 10. With regard to the newborns, the authors note that "hypoglycemia was not a problem". Three neonates had a Dextrostix reading below 45 mg/dL but without symptoms of hypoglycemia and were easily treated with intravenous glucose (it is not indicated as to whether or not these were newborns of mothers treated with metformin alone or with metformin plus sulfonylurea).

Metformin was well-tolerated by these pregnant diabetics, with only 3% requiring change in medication because of nausea and vomiting. No diarrhea was reported in this published series of 60 women.

ITEM 2 – NDA SUMMARY

Hypoglycemia:

Eight cases of hypoglycemia were reported (three from Australia, two from Holland, two from France [#350 and #523] and one from Sweden). (*NOTE: No information whatsoever is available on the Australian cases except that causality was assessed as "definite" in one case and "possible" in the other two*). Four of the five patients for which some information is available were also taking a sulfonylurea (three cases with glibenclamide; one case with gliclazide) and the remaining patient had been on a low calorie diet and was only taking 1 g/day of metformin.

Hypoglycemia with metformin monotherapy is not a recognized risk, as is supported by data contained within this submission on both diabetic and non-diabetic subjects. Hypoglycemia, occurring when metformin and a sulfonylurea are used together therapeutically, has an incidence rate similar to that of sulfonylurea alone, as is also supported by data provided in this NDA and as confirmed by the observation that 80% of "hypoglycemia" adverse events reported in this section (for which there is information), occurred with co-administration of metformin and a sulfonylurea.

The risk of hypoglycemia may be increased when other agents, also capable of lowering blood glucose, are co-administered with metformin and a sulfonylurea, e.g., angiotensin-converting enzyme inhibitors or alcohol. Alcohol itself can cause hypoglycemia and may potentiate the blood glucose-lowering effect of metformin.

Dermatologic Disorders:

There were 21 cases of skin eruption or other dermatologic disorder, a number of which were more likely to be related to a concomitantly taken medication.

Two cases of erythema multiforme were reported (one from France [#625] and one from the United Kingdom). No further information is available on the latter case. Case #625, from France, was attributed to the concomitant medication, enalapril.

There was one photosensitivity reaction reported from the United Kingdom, involving a patient also taking naproxen, indomethacin, glibenclamide and atenolol + chlorthalidone. An erythematous skin eruption, involving light-exposed areas of the skin in a patient from France (#1235), was attributed to metformin by a consulting dermatologist.

Miscellaneous:

One case of *vasculitis* was reported from the United Kingdom, in a patient who had been on metformin for four years, in addition to cyclopenthiazide and potassium chloride. The latter two products were discontinued but no further information is available as to outcome.

A published report has attributed a case of *perivasculitis* to metformin. This diabetic patient, on long-term glibenclamide treatment, developed a diffuse

purpuric eruption, accompanied by fever and arthralgias, four months after metformin, 2.55 g/day, was added to her diabetic treatment program. She also had X-ray evidence of pneumonitis. On skin biopsy, an intense perivascular polymorphonuclear infiltrate was seen, with fibrinoid deposits in the small dermal vessels and fragmented neutrophils, considered to be compatible with leucocytoclastic vasculitis. Other causes of the latter condition were excluded, based on negative or normal results of: immunofluorescent study of biopsy material for immunoglobulins; antinuclear factor; latex fixation, Rose-Waaler, C3, hepatitis B surface antigen, protein electrophoresis and cryoglobulin tests. The eruption improved rapidly after glibenclamide and metformin were discontinued and the patient was treated with prednisone. Two weeks after discontinuation of prednisone, the patient was re-admitted to the hospital and challenged with metformin. Two days later, an identical purpuric eruption developed, according to the report.

There were six cases of diffuse *alopecia* in female patients, reported from France (#s 733, 734, 735, 736, 737 and 738), but all were reported by the same practitioner.

There were four cases of *abnormal liver function tests* reported: (France: #s 812, 1151, 1269; Germany, reported 10/90 [67 yo M]). Case #812, on metformin and other medications for several years, had return of abnormally elevated SGPT and SGOT with discontinuation of metformin; Case #1151 had bowel obstruction and

abnormal liver function tests (SGOT, SGPT and GGT), which returned to normal with discontinuation of metformin. However, there was also a suspicion of excess ethanol intake in this case. Case #1269 had an isolated increase in GGT, but it was concluded that fluctuations in this enzyme reflected fluctuations in glycemic control. Both Case #812 and 1269 had past histories of viral hepatitis. The case from Germany was that of a male patient with carcinoma, on other medications, with markedly abnormal liver function tests, which normalized. No other information is available. Recently, a published case of jaundice and abnormal liver function tests, with onset four weeks after starting metformin, was reported as occurring in a 57 year old diabetic woman, also on gliclazide, isosorbide dinitrate and calcium antagonists. Within four days of discontinuation of metformin, the liver function tests had returned to normal and the jaundice had subsided. The patient was also found to have cholelithiasis. Liver biopsy, however, was interpreted as being consistent with drug-induced hepatitis. No drug re-challenge was undertaken.

A single case of "*nightmares*" was reported in an elderly woman from the United Kingdom, who was also taking multiple other medications, including benzodiazepines and codeine. The only mental disturbance, remotely similar, reported in the literature is a case report of an obsessive-compulsive and depressive psychiatric patient who developed *panic attacks* while on metformin and, in whom, such attacks disappeared when metformin was discontinued. The authors speculated that the panic attacks may have been related to plasma lactate

excursions brought on with metformin, since, experimentally, intravenous lactate infusion has been associated with precipitation of panic attacks in susceptible individuals (those with prior attacks).

2.8.6 Safety Summary — General Safety Conclusions

2.8.6.1 Metformin Exposure and Adverse Experiences During Controlled and Uncontrolled Clinical Studies Included in the NDA Data Base

The summarized assessments in this section are based on data from three sources:

a) ***U.S. Randomized, Controlled Studies (Category I):***
Study No. 87-1D-6023 and Study No. 87-2D-6023)

b) ***Non-U.S. Randomized, Controlled Studies (Category II):***
Study No. MET/AM/84/DORF1, Study No. MET/AM/86/DORF2, Study No. MET/GB/85/DORNA, Study No. MET/D/86/BERGI, Study No. MET/GB/86/CAMP1, Study No. MET/AM/88/DUCHI and Study No. MET/S/86/HERMA

c) ***Non-U.S. Uncontrolled Studies - Phase IV:***
Study No. MET/D/86/HAUPT and Study No. MET/AM/87/PHASE

2.8.6.1.1 Extent of Exposure to Metformin

Metformin drug exposure data from the aforementioned eleven studies, comprising the integrated safety database, are summarized in intext Table 52.

page 417. The table shows the extent of drug exposure in terms of the number of patients in each study and the length of time subjects were exposed to metformin (i.e., duration of the treatment period for each study). Dosage exposure is discussed in terms of number (percent) of each study population, treated within a specific dose range of metformin (i.e., 500-1000 mg/day; >1000-2000 mg/day; >2000-3000 mg/day).

For the U.S. studies, mean total daily dosages of metformin are also available. The mean total daily dose of metformin for U.S. Study No. 87-1D-6023 (placebo-controlled) was 1980 mg/day and the mean duration of treatment was 27 weeks (out of a possible 29 weeks). The mean total daily dose of metformin for U.S. Study No. 87-2D-6023 (active treatment-controlled) was 2050 mg/day for the monotherapy treatment group with a mean duration of treatment of 25 weeks. For the metformin/glyburide combination therapy treatment group, the mean total daily dose of metformin was 1894 mg/day and the mean duration of treatment was 28 weeks (out of a possible 29 weeks).

Precise drug compliance data was unavailable for most of the non-U.S. studies and, therefore, calculations of mean daily doses were not possible. Thus, information relative to the dosage of medication *prescribed*, rather than actually *taken*, for individual patients is presented.

Table 52. Dosage Summary -- All Studies in Integrated Data Base

Protocol	Duration of Treatment Period (Weeks)	Number of Patients from METFORMIN Groups	Statistic	Daily Dose of METFORMIN at Final Visit of Treatment Period			
				500-1000 mg/day	>1000-2000 mg/day	>2000-3000 mg/day	>3000 mg/day
BJ-ID-6023	29	143	n (%)	10 (7%)	20 (14%)	110 (79%)	0
BJ-2D-6023							
Monotherapy	29	210	n (%)	7 (3%)	15 (7%)	182 (89%)	0
METFORMIN-Glyb	29	213	n (%)	23 (11%)	46 (22%)	142 (67%)	0
MET/AM/84/DBMF1	8	25	n (%)	0	0	24 (100%)	0
MET/AM/84/DBMF2	8	25	n (%)	0	3 (14%)	18 (86%)	0
MET/GB/85/DBMA	32	30	n (%)	5 (17%)	17 (57%)	8 (27%)	0
MET/GB/86/BERG1	104	46	n (%)	0	44 (100%)	0	0
MET/GB/86/CAMP1	52	25	n (%)	10 (40%)	8 (32%)	7 (28%)	0
MET/AM/88/DBCH1	12	33	n (%)	0	32 (100%)	0	0
MET/S/86/MEMA							
Monotherapy	30	30	n (%)	8 (22%)	12 (32%)	17 (46%)	0
METFORMIN-Glib	30	72	n (%)	32 (44%)	18 (25%)	22 (31%)	0
MET/B/86/MAMP1[1]	12	3724	n (%)	1931 (54%)	1450 (40%)	211 (6%)	1 (<1%)
MET/AM/87/PHASE[2]	26	4374	n (%)	355 (11%)	2956 (89%)	0	0

[1] Predominantly METFORMIN in combination with Glibenclamide.
[2] Predominantly METFORMIN alone or in combination with sulfonylurea.

2.8.6.1.2 Adverse Experiences

General Considerations: Adverse Experiences/Intercurrent Medical Events (AE/IMEs) included adverse experiences, treatment-emergent signs and symptoms, and new intercurrent illnesses. All events were coded by preferred terms using a sponsor-modified COSTART dictionary. Events coded with a preferred term of "intercurrent illness" were excluded from adverse experience analyses.

All AE/IMEs considered here were treatment emergent AE/IMEs (i.e. new AE/IMEs or AE/IMEs whose severity increased during a study). The number of patients who reported AE/IMEs has been summarized by presenting incidence rates (i.e., numbers of patients with one of more occurrences of each AE/IME). Incidence of AE/IMEs were summarized by body system and individual event (preferred terms). A patient having the same AE/IME more than once over the course of a study was counted only once in the incidence calculation for that AE/IME. Similarly, if a patient had more than one AE/IME in a single body system, the patient was counted only once in the total number of patients with AE/IMEs within that body system.

Within each grouping, data from U.S. studies are presented first, followed by supportive data from non-U.S. randomized studies, and, finally, data from non-U.S. post-marketing studies. The discussion of active treatment comparison studies

includes comparisons of metformin monotherapy and vs. metformin/sulfonylurea (i.e., glyburide, glipizide, gliclazide or glibenclamide) combination therapy in target patient populations.

2.8.6.1.2.1 Adverse Experiences by Body System

As can be seen in intext Table 53, page 420, overall incidence of AE/IMEs by body system for the pooled U.S. studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023), revealed substantial differences among treatment groups only for the Digestive System. In the metformin and metformin/glyburide treatment groups, 69% and 65% of the patients, respectively, reported at least one AE/IME in this body system vs. 43% of the patients in the placebo group and 38% of the patients in the glyburide group with at least one AE/IME in this body system. Differences among any two of the treatment groups for all other body systems did not exceed 7% except for Metabolic and Nutritional Disorders, wherein the metformin/glyburide group had a higher incidence (24%) AE/IMEs, which were accounted for by an increased incidence of hypoglycemia in this treatment group.

Overall incidence of AE/IMEs by body system for the pooled non-U.S. randomized studies (Studies MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/88/CAMP1, MET/GB/85/DORNA, MET/AM/88/DUCHI and MET/S/86/-HERMA) (intext Table 54, page 421) revealed treatment group differences that were generally consistent with the pattern noted for the pooled U.S. Phase III studies, as described above.

Table 53.
Number of Patients Reporting AE/IMEs by Body System:
U.S. Controlled Phase III Studies (Pooled)[1]

Body System	Metformin	Placebo	Glyburide	Met+Glyb
Total Number of Patients	n=351	n=145	n=209	n=213
Any AE/IME	303 (86%)	114 (79%)	171 (82%)	188 (88%)
Body as a Whole	152 (43%)	59 (41%)	80 (38%)	95 (45%)
Cardiovascular	42 (12%)	13 (9%)	26 (12%)	21 (10%)
Digestive	242 (69%)	62 (43%)	80 (38%)	138 (65%)
Endocrine	1 (<1%)	1 (<1%)	0	0
Hemic and Lymphatic	5 (1%)	1 (<1%)	4 (2%)	2 (<1%)
Metabolic and Nutritional Disorders	41 (12%)	19 (13%)	32 (15%)	51 (24%)
Musculoskeletal	79 (23%)	32 (22%)	51 (24%)	51 (24%)
Nervous	52 (15%)	27 (19%)	31 (15%)	44 (21%)
Respiratory	116 (33%)	51 (35%)	80 (38%)	85 (40%)
Skin and Appendages	57 (16%)	19 (13%)	27 (13%)	27 (13%)
Special Senses	45 (13%)	16 (11%)	28 (13%)	25 (12%)
Urogenital	63 (18%)	33 (23%)	38 (18%)	32 (15%)
Intercurrent Illness	9 (3%)	6 (4%)	3 (1%)	7 (3%)

[1] Studies: U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023.

Table 54.
Number of Patients Reporting AE/IMEs by Body System:
Non-U.S. Randomized Studies (Pooled)[1]

Body System	Metformin	Placebo	Sulfonylurea	Met + Sulf[2]
Total Number of Patients	n=176	n=83	n=87	n=72
Any AE/IME	110 (63%)	32 (39%)	50 (57%)	61 (85%)
Body as a Whole	24 (14%)	9 (11%)	17 (20%)	33 (46%)
Cardiovascular	11 (6%)	3 (4%)	7 (8%)	9 (13%)
Digestive	81 (46%)	25 (30%)	18 (21%)	28 (39%)
Hemic and Lymphatic	0	0	0	1 (1%)
Metabolic and Nutritional Disorders	15 (9%)	2 (2%)	17 (20%)	36 (50%)
Musculoskeletal	6 (3%)	1 (1%)	3 (3%)	4 (6%)
Nervous	15 (9%)	4 (5%)	21 (24%)	33 (46%)
Respiratory	16 (9%)	2 (2%)	13 (15%)	15 (21%)
Skin and Appendages	13 (7%)	3 (4%)	8 (9%)	12 (17%)
Special Senses	14 (8%)	1 (1%)	8 (9%)	8 (11%)
Urogenital	7 (4%)	2 (2%)	7 (8%)	16 (22%)

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/85/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA.
[2] Consists of data from one study only: Non-U.S. Study No. MET/S/86/HERMA. The sulfonylurea used in this study was micronized glibenclamide.

Consistent with results from the U.S. and non-U.S. randomized studies, data from non-U.S. Phase IV Study No. Study MET/D/86/HAUPT also show that the body system with the highest incidence of AE/IMEs (i.e., number of patients reporting at least one AE/IME) was the Digestive System (14%), as shown in Intext Table 55, below.

Table 55.
Number of Patients Reporting AE/IMEs by Body System:
Non-U.S. Study No. MET/D/86/HAUPT (Phase IV)

Body System	Metformin+Sulf
Total Number of Patients	n=3724
Any AE/IME	684 (18%)
Body as a Whole	107 (3%)
Cardiovascular	19 (<1%)
Digestive	504 (14%)
Metabolic & Nutritional Disorders	28 (<1%)
Musculoskeletal	14 (<1%)
Nervous	96 (3%)
Respiratory	2 (<1%)
Skin & Appendages	37 (1%)
Special Senses	67 (2%)
Urogenital	1 (<1%)

2.8.6.1.2.2 Adverse Experiences by Symptom

For the pooled U.S. studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) and for the randomized non-U.S. studies (Studies MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/86/CAMP1, MET/GB/85/DORNA, MET/AM/88/DUCHI and MET/S/86/-HERMA), intext Tables 56 and 57, pages 425 and 426, respectively, list individual AE/IMEs reported by at least 9% of the patients in one or more treatment groups. In addition, these listings include AE/IMEs that had differences in incidence between any two treatment groups of at least 5%.

As can be seen, Digestive System symptoms, consisting of diarrhea, nausea/vomiting and abdominal discomfort were the most frequent AE/IMEs reported in both groups of pooled randomized studies in the metformin-containing treatment arms. In non-U.S. Phase IV Study No. MET/D/86/HAUPT, involving 3724 patients treated with metformin/sulfonylurea, the incidence of individual AE/IMEs as shown in intext Table 58, page 427, reflects the higher incidence of Digestive System AE/IMEs, such as diarrhea (7%), nausea/vomiting (5%) and abdominal discomfort (4%).

Hypoglycemia was comparably infrequent in the metformin, placebo and glyburide arms (2%, <1% and 3%, respectively) of the U.S. pooled Phase III studies, although it should be recalled that the glyburide-treated patients (from U.S. Study No. 87-2D-6023) had been on the same dose of glyburide for at least one month,

prior to study entry, without dosage changes during the course of the study. In contrast, the incidence of hypoglycemia was increased in the metformin/glyburide treatment group (18%), although this was never severe (see below, intext Table 61, page 431). In the pooled randomized non-U.S. studies, the incidence of reported hypoglycemia by treatment group was 5% for metformin, 0 for placebo, 14% for sulfonylurea and 33% for metformin/sulfonylurea (the latter from a single study, MET/S/86/HERMA, and including patients on both low dose and high dose combination therapy). In these studies, the sulfonylurea monotherapy group, for the most part, was comprised of patients in whom sulfonylurea therapy was being newly initiated and thus, more accurately than in the U.S. study, reflects the incidence of hypoglycemia in sulfonylurea-treated patients. In non-U.S. Phase IV Study No. MET/D/86/HAUPT, the incidence of hypoglycemia in metformin/sulfonylurea-treated patients was <1%.

ITEM 2 — NDA SUMMARY

Table 56.
Frequently Reported AE/IMEs by Symptom:
U.S. Controlled Phase III Studies (Pooled)

AE/IME	Metformin	Placebo	Glyburide	Met+Glyb
Total Number of Patients	n=351	n=145	n=209	n=213
Any AE/IME	303 (86%)	114 (79%)	171 (82%)	188 (88%)
Diarrhea	177 (50%)	21 (14%)	25 (12%)	95 (45%)
Nausea/Vomiting	98 (28%)	14 (10%)	17 (8%)	54 (25%)
URI	75 (21%)	32 (22%)	46 (22%)	67 (31%)
Asthenia	44 (13%)	16 (11%)	20 (10%)	24 (11%)
Headache	43 (12%)	18 (12%)	17 (8%)	29 (14%)
Abdominal Discomfort	40 (11%)	8 (6%)	22 (11%)	27 (13%)
Accidental Injury	32 (9%)	8 (6%)	16 (8%)	18 (8%)
Flatulence	32 (9%)	8 (6%)	15 (7%)	22 (10%)
Flu Syndrome	30 (9%)	8 (6%)	16 (8%)	18 (8%)
Back Pain	29 (8%)	10 (7%)	20 (10%)	13 (6%)
Arthralgia	26 (7%)	15 (10%)	15 (7%)	22 (10%)
Indigestion	25 (7%)	8 (6%)	8 (4%)	25 (12%)
Urinary Tract Infection	23 (7%)	13 (9%)	12 (6%)	18 (8%)
Myalgia	23 (7%)	12 (8%)	20 (10%)	13 (6%)
Pharyngitis	20 (6%)	7 (5%)	10 (5%)	19 (9%)
Vaginitis	12 (3%)	11 (8%)	16 (8%)	5 (2%)
Paresthesia	9 (3%)	12 (8%)	8 (4%)	10 (5%)
Thirst	7 (2%)	8 (6%)	8 (4%)	3 (1%)
Hypoglycemia	7 (2%)	1 (<1%)	7 (3%)	38 (18%)

[1] Studies U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023.

ITEM 2 — NDA SUMMARY

Table 57.
Frequently Reported AE/IMEs by Symptom:
Non-U.S. Randomized Studies (Pooled)[1]

AE/IME	Metformin	Placebo	Sulfonylurea	Met+Sul[2]
Total Number of Patients	n=176	n=83	n=87	n=72
Any AE/IME	110 (63%)	32 (39%)	50 (57%)	61 (85%)
Diarrhea	57 (32%)	12 (14%)	1 (1%)	12 (17%)
Nausea/Vomiting	30 (17%)	4 (5%)	4 (5%)	3 (4%)
Abdominal Discomfort	23 (13%)	5 (6%)	3 (3%)	9 (13%)
Indigestion	12 (7%)	3 (4%)	2 (2%)	3 (4%)
Asthenia	12 (7%)	1 (1%)	7 (8%)	22 (31%)
URI	8 (5%)	2 (2%)	7 (8%)	9 (13%)
Hypoglycemia	8 (5%)	0	12 (14%)	24 (33%)
Taste Disorder	8 (5%)	0	2 (2%)	2 (3%)
Constipation	7 (4%)	7 (8%)	3 (3%)	5 (7%)
Headache	7 (4%)	3 (4%)	2 (2%)	11 (15%)
Sweating Increased	7 (4%)	0	5 (6%)	5 (7%)
Dizziness	6 (3%)	3 (4%)	8 (9%)	17 (24%)
Lower Respiratory Tract Infection	4 (2%)	0	3 (3%)	4 (6%)
Urinary Tract Infection	4 (2%)	0	2 (2%)	4 (6%)
Thirst	3 (2%)	1 (1%)	1 (1%)	8 (11%)

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DOHF2, MET/GB/85/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA.
[2] Consists of data from one study only: Non-U.S. Study No. MET/S/86/HERMA. The sulfonylurea used in this study was micronized glibenclamide.

Table 57. (cont'd)
Frequently Reported AE/IMEs by Symptom:
Non-U.S. Randomized Studies (Pooled)[1]

AE/IME	Metformin	Placebo	Sulfonylurea	Met+Sulf[2]
Abnormal Vision	3 (2%)	0	3 (3%)	5 (7%)
Pruritus	2 (1%)	1 (1%)	0	4 (6%)
Tremulousness	2 (1%)	0	14 (16%)	23 (32%)
Polyuria	2 (1%)	0	4 (5%)	5 (7%)
Appetite Increased	1 (<1%)	0	11 (13%)	6 (8%)
Anxiety/Tension	1 (<1%)	0	1 (1%)	4 (6%)
Angina Pectoris	1 (<1%)	0	0	3 (4%)

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/85/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA.
[2] Consists of data from one study only: Non-U.S. Study No. MET/S/86/HERMA. The sulfonylurea used in this study was micronized glibenclamide.

Table 58.
Frequently Reported AE/IMEs by Symptom:
Non-U.S. Study No. MET/D/86/HAUPT (Phase IV)

AE/IME	Metformin+Sulf
Total Number of Patients	n=3724
Any AE/IME	684 (18%)
Diarrhea	250 (7%)
Nausea/Vomiting	197 (5%)
Abdominal Discomfort	164 (4%)

Available data on incidence of AE/IMEs for non-U.S. Study No. MET/AM/87/PHASE are summarized in intext Table 59, below. Although the CRF for this study was not designed to collect comprehensive AE/IME data, limited AE/IME information was collected on the CRF relative to gastrointestinal complications/events under the heading "Digestive Intolerance". Although specific AE/IMEs were not recorded, an assessment of the severity of the digestive intolerance for each patient was made (no intolerance, mild, moderate, severe, very severe).

Table 59.
Number of Patients Reporting Digestive Intolerance:
Non-U.S. Study No. MET/AM/87/PHASE (Phase IV)

	Digestive Intolerance		
Level of Intolerance	Month 1	Month 3	Month 6
Total Number of Patients	n=4252	n=4201	n=4158
No Intolerance	3282 (78%)	3376 (85%)	3412 (89%)
Mild	455 (11%)	419 (11%)	301 (8%)
Moderate	277 (7%)	134 (3%)	94 (2%)
Severe	188 (3%)	36 (1%)	11 (<1%)
Very Severe	51 (1%)	15 (<1%)	7 (<1%)

2.8.6.1.2.3 AE/IMEs Analyzed with Respect to Severity

These analyses do not employ any universal, standardized or objective criteria defining a "severe" AE/IME, but rather reflect the subjective judgements of the investigator/patient as to what constitutes a "severe" AE/IME.

Incidence of AE/IMEs by body system and severity and specific AE/IMEs and severity for the pooled U.S. studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) are summarized in intext Tables 60 and 61, pages 430 and 431. Intext Table 60, page 430, gives the number of patients that reported severe AE/IMEs versus the total number of patients that reported any AE/IMEs for that body system.

It was shown above that there were substantial differences among treatment groups with regard to the percentage of patients reporting AE/IMEs for the Digestive System with higher percentages in the metformin and metformin/glyburide treatment groups. Generally, the body systems which had the highest percentages of patients reporting any AE/IMEs also tended to have the highest percentage of patients reporting *severe* AE/IMEs. The exception is the lack of any *severe* hypoglycemia in any treatment group in the pooled U.S. Phase III studies.

Table 60.
Number of Patients Reporting AE/IMEs by Body System and Severity: U.S. Studies (Pooled)[1]

	Patients Reporting Severe AE/IMEs/. Patients Reporting AE/IMEs (%)			
Body System	**Metformin**	**Placebo**	**Glyburide**	**Met+Glyb**
Total Number of Patients	**n=351**	**n=145**	**n=209**	**n=213**
Body as a Whole	15/152 (10%)	7/59 (12%)	6/80 (8%)	7/95 (7%)
Cardiovascular	7/42 (17%)	0/13	4/26 (15%)	2/21 (10%)
Digestive	32/242 (13%)	4/62 (6%)	3/80 (4%)	12/138 (9%)
Endocrine	0/1	0/1	0	0
Hemic & Lymphatic	0/5	0/1	0/4	0/2
Metabolic & Nutritional Disorders	5/41 (12%)	2/19 (11%)	2/32 (6%)	2/51 (4%)
Musculoskeletal	7/79 (9%)	3/32 (9%)	2/51 (4%)	4/51 (8%)
Nervous	4/52 (8%)	0/27	2/31 (6%)	1/44 (2%)
Respiratory	4/116 (3%)	0/51	2/80 (3%)	3/85 (4%)
Skin & Appendages	3/57 (5%)	1/19 (5%)	0/27	3/27 (11%)
Special Senses	2/45 (4%)	0/16	0/28	1/25 (4%)
Urogenital	1/63 (2%)	2/33 (6%)	0/38	2/32 (6%)
Intercurrent Illness	3/9 (33%)	0/6	0/3	1/7 (14%)

[1] Studies: 87-1D-6023 and 87-2D-6023

Intext Table 61, page 431, lists individual AE/IMEs, according to incidence of "severe" events, for those AE/IMEs reported by at least 9% of the patients in one or more treatment groups. In addition, this listing includes AE/IMEs that had differences in incidence between any two treatment groups of at least 5%.

Table 61.
Frequently Reported AE/IMEs by Severity:
U.S. Studies (Pooled)[1]

	Patients Reporting Severe AE/IMEs/ Patients Reporting AE/IMEs			
AE/IME	Metformin	Placebo	Glyburide	Met+Glyb
Diarrhea	21/177 (12%)	2/21 (10%)	0/25	8/95 (8%)
Nausea/Vomiting	9/98 (9%)	1/14 (7%)	0/17	1/54 (2%)
URI	0/75	0/32	1/46 (2%)	1/67 (1%)
Asthenia	4/44 (9%)	0/16	0/20	2/24 (8%)
Headache	0/43	2/18 (11%)	0/17	2/29 (7%)
Abdominal Discomfort	4/40 (10%)	0/8	2/22 (9%)	1/27 (4%)
Accidental Injury	4/32 (13%)	0/8	0/16	1/18 (6%)
Flatulence	2/32 (6%)	0/8	0/15	0/22
Flu Syndrome	2/30 (7%)	0/8	1/16 (6%)	1/18 (6%)
Back Pain	4/29 (14%)	2/10 (20%)	2/20 (10%)	0/13
Arthralgia	4/26 (15%)	0/15	1/15 (7%)	3/22 (14%)
Indigestion	2/25 (8%)	1/8 (13%)	0/8	0/25
Urinary Tract Infection	0/23	0/13	0/12	1/18 (6%)
Myalgia	1/23 (4%)	1/12 (8%)	0/20	0/13
Pharyngitis	0/20	0/7	1/10 (10%)	1/19 (5%)
Vaginitis	0/12	1/11 (9%)	0/16	0/5
Paresthesia	2/9 (22%)	0/12	0/8	0/10
Thirst	0/7	0/8	0/8	0/3
Hypoglycemia	0/7	0/1	0/7	0/38

[1] Studies: 87-1D-6023 and 87-2D-6023.

Since the genetic/concordance data are much stronger for NIDDM, than for IDDM[10,11], investigators are feverously searching for the molecular basis of the defect [or defects] in NIDDM. Obesity itself, though, has also been shown to have a very strong genetic predisposition,[12,13] Given the above data relating obesity to NIDDM, perhaps a significant genetic link which has been observed in nondiabetic offspring of NIDDM patients might associate more closely with obesity [which in turn correlates with hyperinsulinemia] than with glycemia, per se (Haffner et al, Table 1, loc.cit[9]).

What might make a particular obese individual predisposed to NIDDM? In addition, is it possible that the route to NIDDM could represent a normal physiologic escape from what otherwise might develop into the pathophysiologic state of "morbid obesity?" Are there any lines of evidence which might lend support to such a hypothesis? What is the nature of the relationships which exist between insulin resistance, hyperinsulinemia, and obesity? Is there a form of nutritional saturation present at the cellular [and sub-cellular] level which may be operative in these inter-relationships? If so, can this kind of pathophysiology be safely and appropriately rectified?

Watanabe[14] first noted the hypoglycemic effect of guanidines early this century. Since guanidine was quite toxic, substituted guanidines (Synthalin A and B) were synthesized around 1928 and utilized. These, too, proved very toxic. This led to the synthesis of biguanides in 1929. However, some initial investigators believed even the most active of these biguanides (N1,N1-dimethylbiguanide or metformin) to be not indicated for use as an insulin substitute in humans[15]. Phenformin (phenylethylbiguanide) was synthesized by USV in 1956, developed and then widely used until the latter 1970's when its lethal association with lactic acidosis forced its elimination from the market in most of the civilized world. Metformin, however, is still fairly widely marketed and used in the treatment of NIDDM.

Prof. Med. Günter Schäfer of the Department of Biochemistry at the Medizinische

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10Newman B, Selby JV, King MC, Slemenda C, Fabsitz R, and Friedman GD, *Diabetologia* 30:763, 1987

11Barnett AH, Eff C, Leslie RD, and Pyke DA, *Diabetologia* 20:87, 1981

12Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G, Dussault J, Moorjani S, Pinault A, and Fournier G, *NEJM* 322:1477, 1990

13Stunkard AJ, Harris JR, Pedersen NL, and McClearn GE, *NEJM* 322:1483, 1990

14 Watanabe Studies in the metabolic changes by administration of guanidine bases - I. Influence of injected guanidine hydrochloride upon blood sugar content. *J. Biol. Chem.* 33:253-265, 1918

15Hesse E; Taubman G. *Arch. Exp. Pathol. Pharmacol. Naunyn-Schmiedberg's* 142: 290, 1929.

Hochschule in Hannover, Germany described how biguanides intercalate into all lipid membranes.[16] Pursuant to this activity, biguanides appear to (1) inhibit shuttling of reducing equivalents(Ibid.) [at pharmacologic, non-toxic levels-see **Figure 0**] and also possibly via glyceraldehyde-3-phosphate/dihydroxyacetone phosphate or malate/aspartate conversions thereby resulting in increased cytoplasmic NADH[H+]:NAD+ ratios and (2) inhibit fatty acid ß-oxidation by limiting mitochondrial expansion thereby diminishing the mitochondrial flux coefficient while inhibiting gluconeogenesis[17,18];

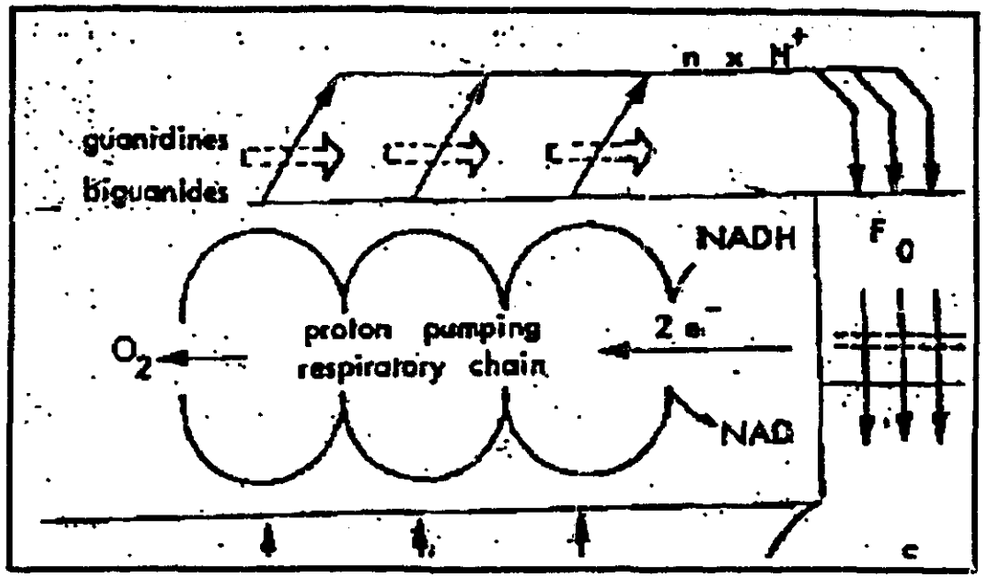


Figure 0 (from Schäfer[16], p.28)

16 Schäfer G. "Biguanides:molecular mode of action" *Research and Clinical Forums* 1:22-32 [NDA Vol 1.99 Section 8.12.2.284]

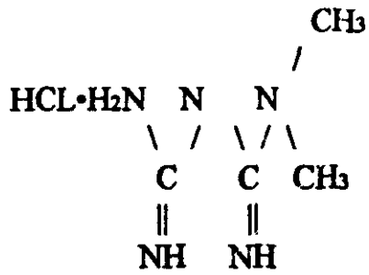
17 Muntoni S: Inhibition of fatty acid oxidation by biguanides: implications for metabolic physiopathology. *Adv Lip Res* 12:311-377, 1974

18 Pryor HJ; Smyth JE; Quinlan PT; Halestrap AP; Evidence that the flux control coefficient of the respiratory chain is high during gluconeogenesis in hepatocytes from starved rats: implications for the hormonal control of gluconeogensis and action of hypoglycaemic agents. *Biochem J.* 247:449-457, 1987

18 Owen MR; Halestrap AP; The mechanisms by which mild respiratory chain inhibitors inhibit hepatic gluconeogenesis. *Biochim Biophys Acta* 1142:11-22, 1993

Is the toxicity profile of these biguanides a manifestation of their mechanism of action? In his review "Biguanides:molecular mode of action" [16] Prof. Schäfer also concluded:- "We have to assume that no different molecular mechanisms underlie the desirable drug effects, or their toxic effects, respectively. We may consider this point ainly as a matter of biguanide concentration in the specific tissues....Of course, the dominating toxic reaction which may lead to lactic acidosis is an inhibition of cellular respiration and of ATP production. Unfortunately, two unfavourable circumstances coincide, if respiratory inhibition causes a stimulation of glycolysis and of peripheral lactate production, while theremoval of lactate by hepatic and renal gluconeogenesis is also inhibited; lactic acidosis will be the result."

2. CHEMISTRY:



Metformin is a white to off-white crystalline compound whose molecular weight is 165.63. It is the hydrochloride salt of N,N-dimethylimidodicarbonimidic diamide. It is very hydrophilic and virtually insoluble in acetone, ether, and chloroform, but is readily dialyzable. Its pKa is 12.4 and a 1% aqueous solution of metformin hydrochloride has a pH of 6.68. (See also **Chemistry Officer Review** of Dr. Xavier Ysern.)

3. PRECLINICAL TOXICOLOGY:

3.1 Acute toxicity:-

Oral LD50 for the dog was ~375 mg/kg and for the mouse was ~2400 mg/kg. Sensitivity was greatest in rabbits and dogs and least in mice or rats. Major clinical signs were decreased activity, ataxia, and diarrhea. Convulsions were seen prior to death. In primates (monkeys) a single metformin dose of 250 mg/kg showed "no clinical signs." However, higher doses produced vomiting. The lethal dose of 693.75 mg/kg led to a "subconvulsive state" with loss of righting reflex, decreased respiration, decreased activity, and ptosis.

3.2 Multidose Toxicity:-

A 1-year study in mice showed no adverse effects up to and including the 450 mg/kg dose level. The highest dose of 1500 mg/kg showed decreased weight and some renal tubular abnormalities. According to the **Pharmacology Officer Review** of Dr. David Hertig :

> **The incidence and severity of Gp4 [1500mg/kg/day] male and female kidney cystic tubular dilation and Gp4 male kidney tubular vacuolization showed a drug-related increase.**

A 91-week study showed no carcinogenicity but an increased mortality in males treated at the 450 and 1500 mg/kg/day levels. This death rate was ascribed to "an increase in urogenital lesions resulting from the renal toxicity." Again, according to the **Pharmacology Officer Review**:

> **Amyloid cystic nephropathy caused deaths (Gps 1-4: 0, 150, 450, 1500mg/kg/day) in 0, 0, 7, 11 males and 0, 0, 5, 10 females....**
>
> **Kidneys however, showed treatment related changes. Cystic nephropathy (cystic tubular dilation)...showed a dose related increase....**
> **All male treatment groups and intermediate and high dose females showed an increased incidence and severity of cystic nephropathy. A polycystic appearance (usually present at necropsy), often accompanied by a shortening of the renal papilla and dilation of the renal pelvis (hydronephrosis) was present in the more extensive cases. Cystic nephropathy was frequently associated with amyloidosis. Deaths of several were attributed to amyloid/cystic nephropathy and renal papillary necrosis.**

Other rodent studies showed only reductions in weight gain. A 99-week study in female rats showed no hormonal effects of metformin.

A 6-month study in dogs showed toxicity at 100 or 500 mg/kg/day levels with salivation, emesis, diarrhea, and CNS "effects, including convulsions." Although no clinical signs were seen at the 50 mg/kg/day dose, gross and tissue changes were noted in brain, heart, kidney, stomach, and small intestine. The high dose group manifested cerebral edema and "neuronal necrosis" questionably secondary to some form of vascular hyperplasia.

There was no apparent mutagenic or teratologic disposition uncovered. (See also **Pharmacology Officer Review** of Dr. David Hertig.)

4. PHARMACOLOGY:

4.1 ADME:-
Although the dog excretes an oral dose primarily in the urine, monkeys excrete almost equal amounts in urine and stool. Apparently absorbed drug is excreted primarily via the kidneys (79-98% of an IV dose) in all species tested. Only one metabolite has been found (N-desmethyl metformin) and that only in rabbits.

Favorable anti-atherogenic effects were seen in cholesterol-fed animals. (See also **Pharmacology Officer Review** of Dr. David Hertig.)

5. HUMAN PHARMACOKINETICS:

Although most single dose studies show a half life of ~2-4 hours, multiple dosing significantly and reproducibly increases the t½ to 5-21 hours after 6 days. This increase in half-life after multiple dosing also occurs in animals. Most of the variability appears to be a function of delayed gastrointestinal absorption.

Dose proportionality above 500mg was not observed in humans or in animals. Glybenclamide seemed to increase metformin levels especially at the lower metformin doses in the long-term clinical trials - but not in single dose PK studies.

Metformin, once absorbed, is primarily excreted. The renal clearance is in excess of 500 ml/min (greater than 4x the mean glomerular filtration rates) implying significant tubular secretion via the cationic pathway. Not unexpectedly, therefore, the similarly cationically-secreted cimetidine significantly interacts with metformin resulting in elevated metformin levels. (See also **Biopharmaceutical Officer Review** of Drs. Dan Gordin and John Hunt.)

6. EFFICACY REVIEW

6.1 DCCT
The DCCT has demonstrated that tight control of IDDM reduces microvascular complications. These microvascular complications are predominantly renal, retinal, and neurologic. Review of the DCCT data suggests that the error would be suitably small in predicting that none of these complications would arise within a range of glycohemoglobins of less than 7%[25].

Most of the morbidity and mortality (~80%) from NIDDM is macrovascular and secondary to enhanced atherosclerosis or coronary heart disease (CHD) seen in this population. **There is no data that suggests any correlation of CHD with**

glycemia.[19] The primary microvascular mortality in NIDDM, as in IDDM, derives from renal disease. It is possible, then, to assess the incidence of microvasculopathy, and, therefore also the death rate, which would accrue from a modality which would decrease the glycohemoglobin to less than 7% (see Figure 1).

6.2 End-Stage Renal Disease (ESRD)

6.2.1 There were 4535 cases of ESRD felt to be secondary to "diabetes mellitus" reported to the CDC from January-June 1988. Of these, 2,577 (56.8%) cases of ESRD were ascribed to non-insulin dependent diabetes mellitus (NIDDM), 1,836 (40.5%) cases to insulin dependent diabetes mellitus (IDDM), and 122 (2.7%) were unclassified. This equates to 5154 cases of ESRD per year from NIDDM, 3672 cases of ESRD per year from IDDM, and 9070 cases per year from diabetes mellitus as a whole.[20]

6.2.2 The estimated prevalence of NIDDM in the US was 14,400,000 DM cases in 1991[22,23] of which 5% - 720,000 - are felt to have IDDM and the remaining 95% or 13,680,000 felt to have NIDDM[21]. This figure is based on an estimate of 7,200,000 diabetic patients from the National Center for Health Statistics, Health Information Survey quoted by Harris.[22] As part of that study, a subset of responders were administered oral glucose tolerance tests. Only half of those patients with World Health Organization (WHO) OGTT criteria diagnostic for diabetes reported the diagnosis on the original survey. Therefore, the survey statistic was doubled.

6.2.3 Cowie[23] calculated the total yearly ESRD incidence in the general diabetic population of Michigan as 144.5 per hundred thousand (127.2 to 161.8) among blacks and 60.4 per hundred thousand (53.7 to 67.1) among whites. Additional data from Harris[21] would suggest that 70% of NIDDM patients are white, 20% black, 6% hispanic, and 4% "other." Since only 5% of DM is IDDM these ratios may approximate those in the general diabetic population. In that case the total US black diabetic population base would be 20% x

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19Lebovitz,HL. The DCCT and its implications for NIDDM. *Clinical Diabetes* 12(1):3-4, 1994

20 USRDS, "Incidence and Causes of Treated ESRD" (Chapter 3) 1993 Annual Data Report, pp 19-28

21Harris MI, Personal Communication, 3/7/94

22 Harris MI; Hadden WC; Knowler WC; Bennett PH. Prevalence of diabetesand impaired glucose tolerance and glucose levels in U.S. population aged 20-74 yr. *Diabetes* 36:523-34, 1987

23Cowie CC; Port FK; Wolf RA; Savage PJ; Moll PP; Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *NEJM* 321: 1074-9, 1989

14,400,000 or 2,880,000 patients. Likewise, the total US white diabetic population base would be 70% x 14,400,000 or 10,080,000 patients.

Cowie further estimated 108.2 per 100,000 black NIDDM patients (93.5 to 123.0 per 100,000 black NIDDM patients) cases of ESRD a year in black NIDDM based on the ratio observed in southeastern Michigan from 1974 through 1983. [By the 1991 NCHS-HIS statistics doubled according to Harris[22]] this should amount to 108.2 x 28.8(hundred thousand) or 3116 black NIDDM ESRD cases per year (1.082 cases per thousand black diabetics). However, this point estimate (mean) yields about a 20% under-representation of the actual reports of ESRD incidence/death rate according to the USRDS. Using the upper bound of the [Cowie] confidence interval would yield 123.3 x 28.8(hundred thousand) or 3551 black NIDDM ESRD cases per thousand black diabetics per year. This combined with the figure of 2974 derived from using the upper limits of the confidence interval for whites yields a total rate of 6525 cases per year which is more in line with actual reports particularly given the extra 10% of diabetic patients (hispanics, others) not previously accounted for. [Keep in mind that this under-representation of projected diabetic ESRD cases is even based upon the "diagnosed plus undiagnosed" population estimate ofHarris (14,400,000) and not just upon that of the "diagnosed" diabetics that resulted in Cowie's original estimates.]

6.2.4 The USRDS recorded 51,665 ESRD cases from DM from 1987 to 1990[20]. This equates to 12,916 new diabetic ESRD cases per year from DM over that 4 year period (and is 29.8% more than the 4535 cases [over 6 months in 1988 from DM] reported to the CDC, see **Section 6.2.1**). Using this larger figure to avoid underestimating the true incidence of ESRD from NIDDM, 56.8% (2° to NIDDM, see **Section 6.2.1**) of 12,916 comes out to 7336 cases of ESRD per year 2° to NIDDM.

6.2.5 **The incidence of ESRD emerging from the NIDDM population in 1991 would then be 7,336/13,680,000 or 0.53625 cases per thousand (NIDDM).**

6.2.6 The CDC suggests a [Medicare] base of 147,000 ESRD patients and USRDS[20] estimates 32.9% of those are 2° to diabetes. Based on USRDS data, the death rate from ESRD 2°.to DM would appear to be 25.8% per year.[20] This, then, calculates out to 12,478 deaths per year (approximately the incidence of new cases as might be expected at steady state).[24]

6.2.7 **The death rate from ESRD 2° to NIDDM would then appear to be** 56.8% of 12,478 or 7,087 divided by a base of 13,680,000 NIDDM patients or **0.51806 cases per thousand** (NIDDM). Again, utilizing the somewhat higher *incidence* rate (rather than the slightly lower *mortality* rate) should avoid underestimating true NIDDM ESRD mortality.

24CDC: End-stage renal disease associated with diabetes - United States. *MMWR* 38:546-548, 1988 [Based on data from January through June, 1988]

6.2.8 NDA US Data - All races

EOT	metformin	control
A1c>=7	354	294
A1c <7	212	60

Only 60 of 354 control (16.9%) patients dropped their HbA1c's to less than 7% as opposed to 212 of 566 metformin (37.5%) patients. This amounts to a drug-attributable benefit of 20.5% 99%CI(13.2 to 27.9%). Assuming that a HbA1c of less than 7% may not associate with microangiopathy[25] (See Figure 1),

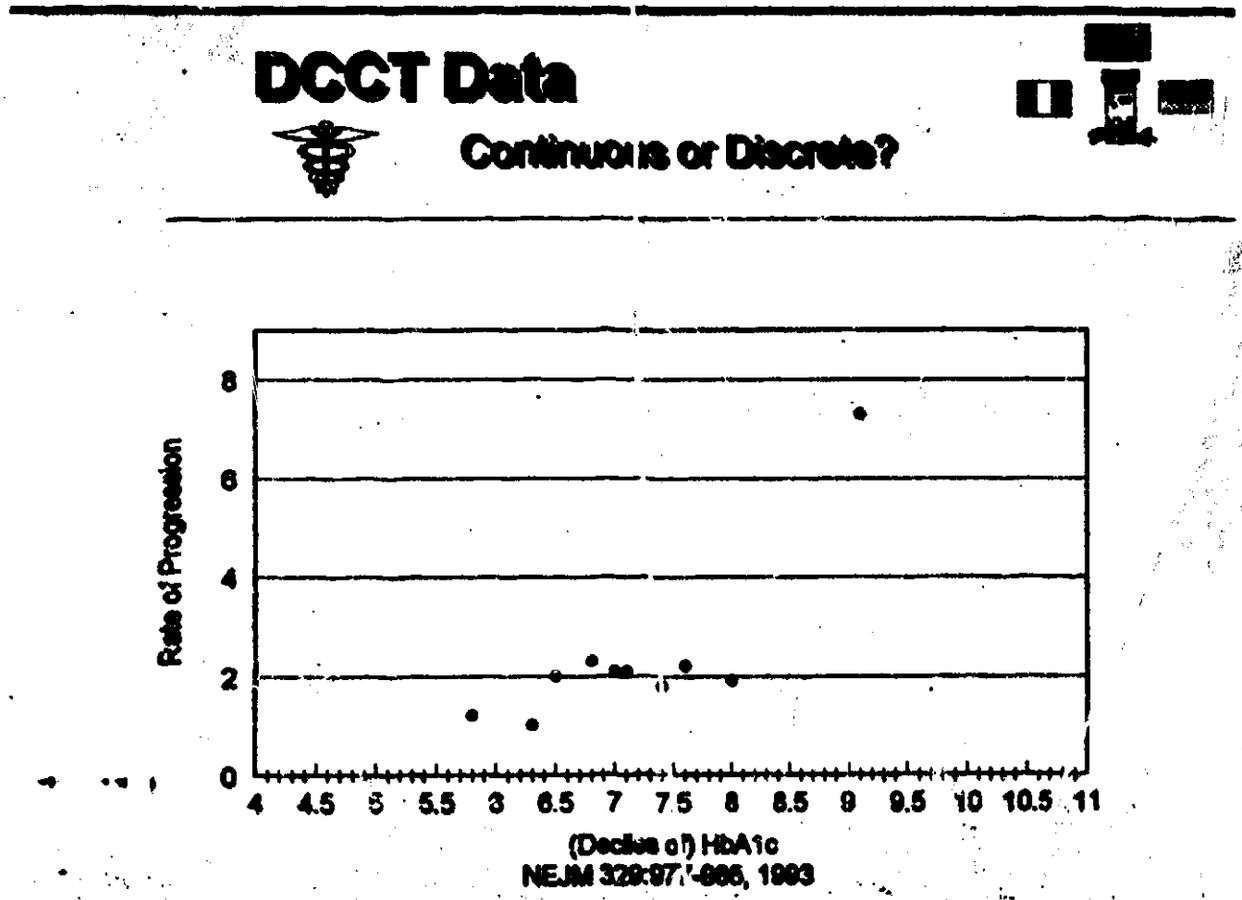


Figure 1

that 385,000 NIDDM patients will be taking metformin [as were taking phenformin in

25 DCCT Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *NEJM* 329:977-986, 1993

1976[26]], and that one-fourth of these will be switched from insulin [for which no additional glycemic benefit of metformin is to be expected], then one can calculate that the net reduction of death or incidence of ESRD from NIDDM attributable to metformin would be 385 x 0.53625 x 20.5% x 75% or about 32 (deaths or new cases) per year. **This metformin-attributable *savings* rate is 0.08 deaths/1000 PYE.**

6.2.9 **The annual death rate from ESRD in black NIDDM should approximate the incidence rate of 1.233 cases per thousand (see Section 6.2.3).**

6.2.10 NDA US Data - Blacks

EOT	metformin	control
A1c>=7	47	48
A1c <7	33	4

Only 4 of 52 black control (7.7%) patients dropped their HbA1c's to less than 7% as opposed to 33 of 80 metformin (41.2%) patients. This amounts to a drug-attributable benefit of 33.6% 99%CI(16.5 to 50.7%). Assuming that a HbA1c of less than 7% may not associate with microangiopathy[25], that 385,000 black NIDDM patients will be taking metformin [reflective of the total population taking phenformin in 1976[26]], that 100% of these will be black, and that one-fourth of these will be switched from insulin [for which no additional glycemic benefit of metformin is to be expected], then one can calculate that the net reduction of death or incidence of ESRD from NIDDM attributable to metformin would be 385 ÷ 95% (to yield the respective total diabetic population in hundreds of thousands) x 1.233 (upper bound of 95% CI for ESRD incidence in black NIDDMS per hundred thousand diabetics) x 33.6% (who get a net benefit from metformin therapy) x 75% (excluding the population that was switched from insulin) -
385 ÷ 95% x 1.233 x 33.6% x 75% - or about 126 (deaths or new cases) per year if the total population taking metformin were limited to blacks. **This metformin-attributable *savings* rate is 0.33/1000 PYE.**

6.2.11 **The death rate from ESRD in white NIDDM should approximate the incidence rate of 0.295 cases per thousand (see Section 6.2.3).**

26Lowenstein J, Presentation to 15 October 1981 DMEDP Advisory Committee on metformin

6.2.12 NDA US Data - Whites

EOT	**metformin**	**control**
A1c>=7	**238**	**198**
A1c <7	**147**	**52**

Only 52 of 250 white control (20.8%) patients dropped their HbA1c's to less than 7% as opposed to 147 of 385 metformin (38.2%) patients. This amounts to a drug-attributable benefit of 17.4% 99%CI(8.18 to 26.6%). Assuming that a HbA1c of less than 7% may not associate with microangiopathy[25], that 385,000 NIDDM patients will be taking metformin [as were taking phenformin in 1976[26]], that 100% of these will be white, and that one-fourth of these will be switched from insulin [for which no additional glycemic benefit of metformin is to be expected], then one can calculate that the net reduction of death or incidence of ESRD from NIDDM attributable to metformin would be 385 ÷ 95% (to yield the respective total diabetic population in hundreds of thousands) x 0.295 (upper bound of 95% CI for ESRD incidence in white NIDDMS per hundred thousand diabetics) x 17.4% (who get a net benefit from metformin therapy) x 75% (excluding the population that was switched from insulin) - 385 ÷ 95% x 0.295 x 17.4% x 75% - or about 16 (deaths or new cases) per year if the total population taking metformin were limited to whites. **This metformin-attributable *savings* rate is 0.04/1000 PYE.**

6.2.13 At first glance, then it would appear that by limiting the population at inference to just blacks the increase in lives saved could be almost fourfold. Treating homogeneous black populations saves more than eightfold the lives gained by treating homogeneous white populations.

Remember that this also assumes that all patients - diagnosed and undiagnosed - would be treated. If one treated only the diagnosed, as seems likely, the savings estimate is proportionately lowered.

6.2.14 *NB*: A significant treatment-by-baseline interaction elucidated by the sponsor has demonstrated more glycohemoglobin reduction the worse the baseline glycemic control. The number of black patients randomized to metformin in these studies was relatively small - 80 (15%) - and the baseline for these patients was quite significantly higher (9.65 ± 1.75%) than that of the 385 white patients (8.54 ± 1.59) exposed to metformin (mean racial difference of 1.11 ± 0.199% SED with a 99%CI around that difference of 0.596 to 1.62%).

==> In summary, therefore, the difference attributed to race may actually reflect a difference in baseline control which may be independent of race.

6.3 METFORMIN AND POSSIBLE INHIBITION OF GLYCATION:

The primary efficacy variable in the US trials was the mean change in HbA1c from baseline. There may be some reason to believe that metformin may directly inhibit glycosylation. The rationale includes:

Opportunity: Metformin has a significant life-span (half-life) within the erythrocyte which is longer than in plasma

Weaponry: As a guanidine derivative with protein-denaturant activity it has much in common with aminoguanidine which is being developed solely for its anti-glycation properties

Circumstantial data:

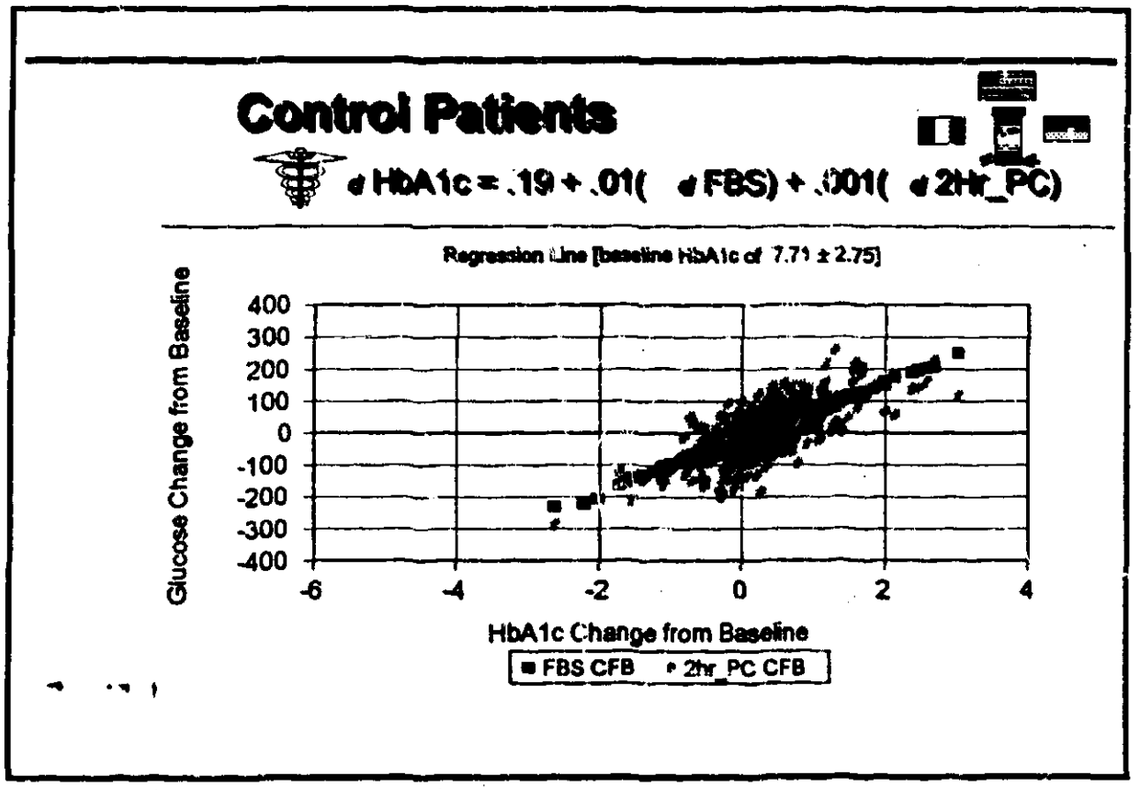


Figure 2

In control patients, the intersection of the X-axis (no change in either fasting or prandial glucose levels) with the regression curve shows that for this control population the HbA1c has increased by 0.19%. Note the basline of HbA1c for this population is 7.71%.

In metformin patients, however, the intersection of the X-axis (no change in either fasting or prandial glucose levels) with the regression curve shows that for this control population the HbA1c has decreased by 0.54%. Note the baseline of HbA1c for this population is

even higher than that of the controls at 8.14%.

What this means is that when there is no change in fasting or prandial sugars, control patients increase their glycohemoglobin while metformin patients decrease theirs for a mean treatment difference of -0.73% ± 0.186. This regression difference has a 99% CI of 0.25 to -1.21.

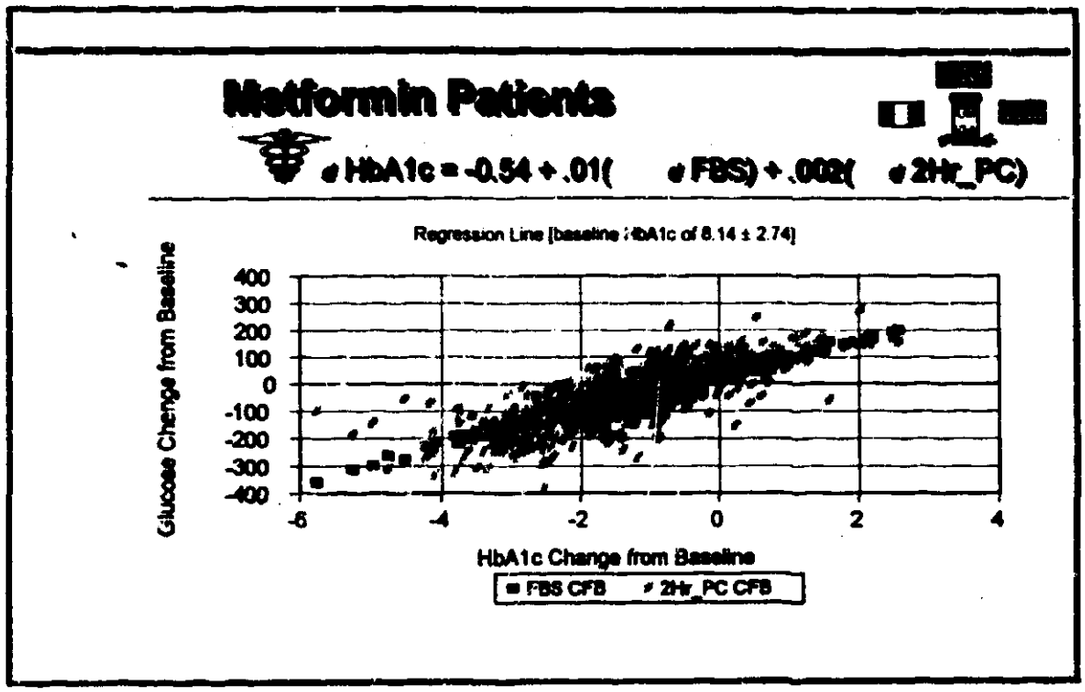


Figure 3

This evidence may appear somewhat circumstantial, however the metformin monotherapy arm of the 87-2D trial had essentially nochange in glycemia. What happened to the glycohemoglobin?

dFBS (mg/dl) from b/l	d2hr_pc (mg/dl) from b/l	dHbA1c (%Hb) from b/l	b/l HbA1c (%Hb)	n ±SD
-0.43	-4.29	*-0.38*	8.28	217
71.24	84.3	1.58	2.82	

Primary Failure with Metformin Monotherapy in the 87-2D Study

The 99%CI for HbA1c change of -.38% is from -.10 to -.66%. [This effect should be magnified when compared to control data.] Thus it may be safe to assume that at least some of the efficacy shown by metformin may be due to direct inhibition of intracorpuscular glycation independent of an effect upon glycemic control. Assuming a *net* -0.7%

contribution from inhibition of glycation, the point estimate of the net treatment difference in the 87-1D study of dietary failure would then be (+0.4)placebo -(-1.4)metformin +(-0.7)glycation or 1.1%. Assuming this very same contribution from inhibition of glycation, the point estimate of the net treatment difference in the 87-2D study of sulfonylurea failure would then be (+0.2)glybenclamide -(-1.7)metformin&glibenclamide combination +(-0.7)glycation or 1.2%. Given especially that the primary analysis was based on the intention-to-treat population, these results remain both clinically and statistically robust.

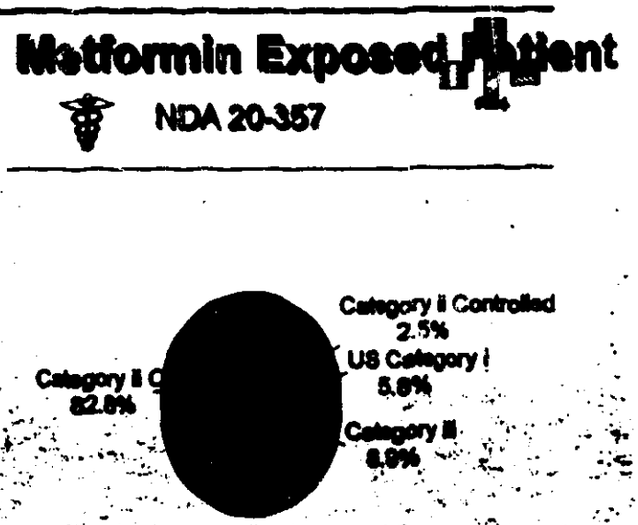
7. SAFETY REVIEW

7.1 METHODS:

This submission comes with little or no useful pooling of safety data.

Short-term [clinical trial] safety data presented in this NDA has been compartmentalized into three (3) categories. The first segregation consists of the two "pivotal" US Studies: 87-1D and 87-2D. These studies comprise 566 patients treated with metformin (213 were concomitantly on glibenclamide). Of these 566 patients, 471 (83.2%) were treated with metformin for a full 24 weeks and 434 (76.7%) received a dose higher than or equal to 2g/day at the last treatment visit.

A small portion of the patients exposed were in controlled clinical trials. **Figure 4**



There were 403 males (43%) and 454 females (57%) in controlled portions of pooled Category i and ii trials of which 814 were felt by this reviewer to be evaluable (c.f. **BERGIS STUDY**).

Only a small percentageof the 857 patients enrolled in controlled clinical trials and exposed to metformin for whom age information is available were over age 65 (15.8%). The mean age of all of these patients who were exposed to metformin was 54.5 years. In the US 87-1D trial there were143 patients randomized to metformin and 146 to placebo. In the 87-2D study, 210 were randomized to monotherapy with metformin, 209 to monotherapy with glibenclamide, and 213 to combination therapy. Pooling by exposure sults in 566 metformin patients and 355 controls. In the European (Category ii) controlled trials, safety data is available on176 were randomized to metformin monotherapy., 83 to placebo, 87 to monotherapy with sulfonylurea, and 72 to

combination sulfonylurea plus metformin. Again pooling results in 248 metformin patients and 170 controls. NDA wide pooling yields 814 metformin patients and 525 controls.

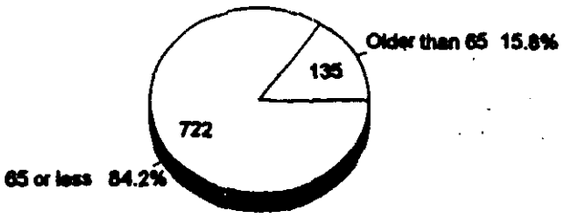


Figure 5

Only 15% of the US study population was black as opposed to at least 20% of the US NIDDM population which is black.

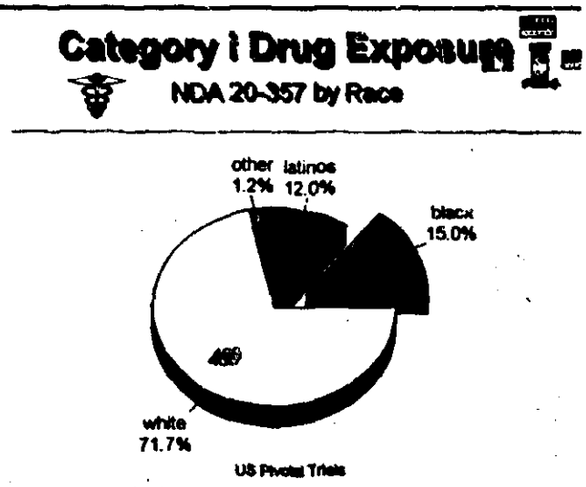
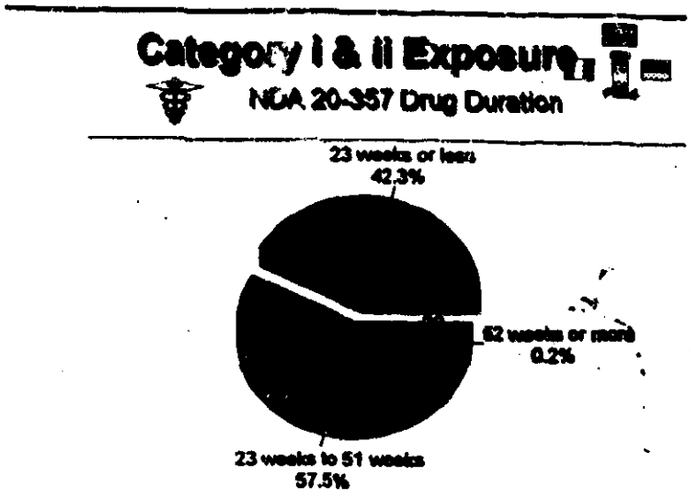


Figure 6

The second segregation ("Category II") comprises nine (9) non-US studies with "reasonable" safety data, i.e., (1) AM/84/DORF1 (2) AM/86/DORF2 (3) GB/85/DORNA (4) D/86/BERGI (5) GB/86/CAMP1 (6) AM/88/DUCHI (7) S/86/HERMA (8) D/86/HAUPT and (9) AM/87/PHASE. Study D/86/BERGI, however, was a two-year, open-labeled study at 800mg/day of metformin versus diet initiated and completed at a hospital setting in Germany but followed at primary care centers in the field. "Minimal information relative to safety was available for this study: no data on concurrent medications, adverse experiences/intercurrent medical events, or creatinine levels was collected" (NDA 8.8.6. p.1453). This study (D/86/BERGI) will therefore not be included in the subsequent summary of the non-US studies.

Most of the patients presented in the NDA had very short durations of exposure, with only 0.2% on therapy for over a year. There were 57.5% on therapy for 23-51 weeks, and 42.3% on therapy for 23 weeks or less.



There appears to be dose information available for 8992 patients exposed to metformin and included in the safety data-base:

½g-1g/day: 1532 patients
>1g-2g/day: 3844 patients
>2g-3g/day: 696 patients

Figure 7

Relatively fewer patients have been exposed to very high doses. This situation has improved with preliminary submission of data from the open enrollment 89-1C-6023 study. However, a final and complete study report is open and still pending submission to this NDA.

The third compartmentalization included studies which were non-US, poorly designed, poorly-controlled, and/or poorly-executed, and therefore not pooled in any coherent fashion in this NDA.

7.2 DEATHS:

CRF's are available for nine (9) of the 20 deaths in the Catgeory i and Category ii trials combined as well as in the open-enrollment study. One of these patients for which CRF's are available died in the US controlled study 87-2D-6023, six died in in the US (open-enrollment) study 89-1C-6023 (see also Section 7.3.3), one died in the non-US study MET/GB/86/CAMP1, and one died in the non-US study MET/S/86/HERMA. Eighteen (18) of the 20 patients were on metformin, one was on glipizide, and one on glibenclamide. Despite the lack of a complete study report for the open-enrollment trial, there have been no other deaths which have occurred in that trial (confirmed in a telephone conversation with the sponsor on 22 Mar 1994.)

Of the 11 patients who died for whom no CRF's are available - all in the non-US study MET/AM/87/PHASE) - one (M,56) died from the "result of an automobile accident", one (M,53) died of "decompensation of alcoholic cirrhosis", one (M,63) died of "esophageal cancer", one (M,58) died of "pulmonary embolism", two

(M,71; M,51) died of "myocardial infarction", one (F,78) died of "cranial trauma", one (M,70) died "during a coronary artery bypass", two (M,67; M,52) died of "cerebrovascular disease", and one (F,81) died of "pulmonary edema".

One patient on glipizide in study MET/GB/86/CAMP1 (F,61) developed carcinoma of the stomach, liver, and omentum on study day 306 and died four days later.

One patient on glibenclamide in study MET/S/86/HERMA (M,63) had a prior history of angina, myocardial infarction, and atrial fibrillation. He had mild to moderate chest pain throughout the study and died 4 months later of a "myocardial infarction." No post-mortem, however, was obtained.

7.2.1 The single patient in the controlled portion of the US trials to die (V01-20006, a 51 y.o. white male, Vignati site) had an 11-year history of NIDDM. He was enrolled onto metformin monotherapy in study 87-2D-6023. On study day 31 after having been titrated up to 2500 mg/day of metformin from 2000 mg/day he developed a "flu syndrome" which progressed into "abdominal discomfort - lower abdominal discomfort - cramps" and "lower abdominal suprapubic pain" and associated with "nausea/vomiting" on day 55. These symptoms apparently lasted until study day 61. By study day 67 he had a blood level of 629 ng/ml on 2500 mg of metformin per day. His creatinine had increased to 1.3 from 1.0, and he had proteinuria and microscopic hematuria [which had been there at baseline.] There were no associated changes in acid-base balance. He apparently developed "chest pains" on study day 97. Advised earlier to go to the emergency room, he nevertheless was later brought there in full cardiac arrest with electromechanical dissociation and pronounced after resuscitative measures had failed. Notably, this gentleman had no prior history of cardiovascular disease. The NDA describes him as "obese, diabetic, and a former smoker." His total duration of exposure to metformin was 97 days.

7.2.2 The first patient who died in the open-enrollment study (89-1C-6023) to be discussed (T01-06021, a 65 y.o. black female, Taylor site) had previously been enrolled onto metformin monotherapy in study 87-2D. Her past medical history included hypertension and arthritis. She had one episode of diarrhea on study day 124 and also developed "asthenia" and "lethargy" which lasted until study day 152. These latter reoccurred on study day 187 through the end-of-study. Her HbA1c had dropped 2.1% to from 8.5% to 6.4% during the course of therapy. On study day 97 her bicarbonate dropped transiently (2.72 SD) down to 18.3 from a baseline of 25.7 associated with an increased anion gap of 2.7 meq but a decrease in lactate of 0.3 mm/L to 0.9. These were the only abnormal acid-base disturbances during double-blind therapy. Blood metformin levels were 873 ng/ml on 2500 mg of metformin day. By the end of double-blind her FBS was 167mg/dl (up 19 mg/dl from baseline) but her HbA1c was 6.4 (down 2.1% from baseline). Persistent fatigue/lethargy continued through study 89-1C-6023 on 2500 mg metformin/day. Concomitant therapy initially included glibenclamide 10 mg bid, verapamil SR 240mg qd,

and ascorbate 1000 mg qd. Ten days before the patients demise she was seen on glibenclamide 10mg qd and 1500 mg of metformin day complaining, again, solely of "lethargy". The site apparently called "to repeat some labs and a U/A" - only to be informed that the patient had just been found dead in her apartment. The exact nature of the labs which needed repeating were not described. A slight increase in creatinine (0.2 mg/dl) and decrease in bicarbonate (2.4 meq/L) was all that was noted. No post-mortem was performed. Her total duration of metformin exposure was 754 days.

7.2.3 The second patient (G04-07026, a 60 y.o. white male, Gerich site) enrolled onto metformin monotherapy in the 87-2D-6023 study. By the end of double-blind his FBS was 285 mg/dl (up 54 mg/dl from baseline) but his HbA1c was 8.9 (down 2.0% from baseline). In the 1C-6023 extension was placed on concomitant glipizide therapy at 10 mg bid. He later died of steroid-requiring pulmonary fibrosis apparently secondary to an inoperative non-small cell carcinoma of the lung. His total duration of exposure to metformin was 510 days.

7.2.4 The third patient to die in the open-extension US study (F02-10023, a 67 y.o. hispanic female, Fischer site) had been on metformin/glibenclamide in the 2D study. Adverse experiences in that study included heel pain (SD 0-14), left deltoid shoulder pain/myalgia (SD 56-70), diarrhea (SD 89-89), and laser surgery of the left eye (SD 178-178). By the end-of-treatment (SD 201), however, her HbA1c had dropped 4.6% from 10.9 to 6.3% (!) and her FBS dropped 137 mg/dl to 148 mg/dl. She then had blood levels of 2140 ng/ml of metformin and 193 ng/ml of glibenclamide on 2500 and 20 mg/day, respectively. Her B12 had dropped 206 pg/ml to 294 pg/ml and folate 2.2 ng/ml to 6.4 ng/ml with an increase in MCV of 7 to 84 from an abnormally low baseline of 77. Lactates increased 0.3 mM/L to 1.3 mM/L. Open-enrollment was complicated by:

(V2): dental infection requiring erythromycin and penicillin
(V4): UTI requiring norfloxacin
(V8): muscle strain and ankle edema
(V10.1): URI
(V12): hand burn and hypoglycemia
(~V14): ST-T wave changes developed on routine EKG. Unbeknownst to the site she was referred to a cardiologist who performed an echocardiogram which "suggested severe coronary artery disease." [Review of the actual cardiologist's notes determined that the echo, performed on 04/08/91, "did reveal diminished LV function with evidence of multiple regional wall motion abnormalities." This echo has been requested from the site.]
(V15.1): UTI requiring TMP/SFX
(V16): dry cough requiring Tussar SF, myalgias, fatigue, head tremor
(V16.1): mid-back pain
(V17): pedal edema requiring furosemide 20 mg/qd
(V18): blurring of vision requiring laser surgery x 3
(V19.1): herpetic lesions right leg requiring acyclovir 200mg q3h x5/d x10d

(V20): "cardiac prophylaxis" with isorbide dinitrate
At V20.2 she was seen with chest pain, nausea, vomiting, and weakness x 24 hours, found to be "in extreme distress" with "profound wide-QRS arrhythmia." "Attempts were made to catheterize her...." She presented in severe lactic acidosis. [Review of the admission H&P: Admission chemistries showed a CPK of 3200, a glucose of 628, a BUN of 36, a creatinine of 2.2, a potassium of 5.7, a bicarbonate of 9, a pH of 7.05, pO2 of 203, and pCO2 of 13, and an elevated lactic acid level (actual results unavailable at the current time) that was elevated. The cardiologist did not ascribe the acidosis to circulatory causes but rather appeared to feel that the acidosis was on a diabetic basis, i.e., - "diabetic ketoacidosis." The patient's condition deteriorated and she expired. Her total duration of exposure to metformin was 825 days.

7.2.5 The fourth open-enrollment expiration (J01-13002, a 61 y.o. white male, Johnson site) had a past medical history of hypertension, aneurysm OD, redwood allergy, arthritis, and left pulmonary nodule-stable. He had a 5 year history of NIDDM complicated by neuropathy and retinopathy. He was on lisinopril 10 mg qd and ASA 2 gr qd. In the 87-2D study he was randomized to therapy with metformin and glibenclamide. By study day 63 on 2500 mg of metformin and 20 mg glibenclamide blood levels were 756 and 128 ng/ml, respectively. Creatinine had increased 0.3mg/dl to 1.4 mg/dl. By SD 91, trace proteinuria and ketonuria had appeared. On SD 93 he developed small ulcers on the right leg attributed to "spider bites." On this day metformin level was 3343 ng/ml and glibenclamide levels were non-detectable. These bites resolved by SD 104. At that time blood levels of metformin had decreased to 725 ng/ml and those of glibenclamide increased to 38.5 ng/ml. MCV had increased 9 points to 92 and Hb had dropped 1.3 to 14.8. At double-blind end-of-treatment HbA1c had decreased 2.3% to 7.1 and FBS had decreased 104 mg/dl to 132. By then, blood levels of metformin had increased to 1044 ng/ml and those of glibenclamide to 63 ng/ml. MCV had increased by 12 to 95 and B12 decreased by 124 pg/ml to 232. No acid-base changes were noted. He had eight relatively uneventful months of open-enrollment on maximum doses of metformin and glibenclamide. However, his ultimate EKG had shown "non-specific ST-T wave abnormalities, consistent with ischemia, drugs, etc." (This EKG had apparently even improved since the previous tracing!) He expired quite suddenly twelve days later without any well-documented diagnosis. The total duration of his metformin exposure had been 343 days.

7.2.6 The fifth open-enrollment expiration (F03-11024, a 68 y.o. white female, Flood site) with a BMI of 22.26 had a past medical history of renal tuberculosis s/p left nephrectomy, malignant melanoma s/p right radical neck, right hip replacements x 3, bilateral breast carcinoma/mastectomy, hypertension, osteoarthritis, retinopathy s/p laser infarction. She had had NIDDM for 11 years at one point requiring insulin therapy. She was enrolled onto metformin and glibenclamide in the 2D study also taking ibuprofen 800mg bid and enalapril maleate 5 mg qd. Baseline alkaline phosphatase was slightly elevated at 118

with a normal creatinine of 0.9. She was diagnosed with lower respiratory tract infection from SD 11-24. Hip and right thigh pains occurred on SD 28-36. On SD 73 on 2500 mg metformin and 20 mg glibenclamide she had metformin levels of 74 ng/ml and glibenclamide levels of 65.9 ng/ml. On SD 122-136 she suffered from a lacerated left hand. By SD 133 she had metformin levels of 748 ng/ml and glibenclamide levels of 131 ng/ml. Her hematocrit had fallen 4% to 34 with an MCV decrease of 7 points. Creatinine had fallen to 0.8. On SD 233 at end-of-treatment she had developed a left carotid bruit. Her HbA1c had fallen by 4.4% to 7.7 and FBS 92 mg/ml to 255. Hematocrit was 36 with an MCV of 96, an RBC count of 3,700,000, and an MCV of 192 (down 195 pg/ml). Her bicarbonate was 21.8 (down 3.3 meq/l) , but lactates had only increased by 0.3 mM/L to 1.6 with negligeable (0.8) increase in anion gap to 13. Creatinine was 0.7 at this time. However, by two months (V2) of the open-enrollment her creatinine clearance was found to be 42.7 ml/min. Lactate at V3 was apparently 0.8 mM/L. Calling to terminate the patient from the study the site was informed of the patients sudden expiration. Her total duration of metformin exposure was 252 days.

7.2.7 The sixth and final patient who expired during open-enrollment (S01-18018, a 53 y.o. white male, Saudek site) was also in the 2D study during double-blind enrolled on metformin and glibenclamide. No adverse experiences were noted, however at end-of-treatment on 2500 mg of metformin and 20 mg of glibenclamide he had an increase of 0.1% in the HbA1c to 6.7% with a 46 mg/dl drop in FBS to 130 with metformin levels of 527 ng/ml and glibenclamide levels of 89.7 ng/ml and a BMI of 26.75. Of note was a 55 pg/ml drop in B12 to 233, a 5.8 mEq/L increase in anion gap to 18.5, a 6.8 mEq/L decrease in bicarbonate to 22.5, and a 0.5 mM/L increase in lactate to 2.2. Twelve and some months into the open-enrollment phase the patient apparently committted suicide by "ingestion of chemicals." The total duration of his exposure to metformin was 461 days.

7.2.8 Summary Breakdown of Deaths in this NDA

	Suicide	Accident	Cancer	Pulm Emb	MI CABG	Sudden Death	CVD	CHF	Meta bolic
met	1	2	2	1	3	4	2	1	2
glyb			1		1				

	Total	Non_CV	Deaths	Total	CV	Deaths
met		5 (27.8%)			13 (72.2%)	
glyb		1 (50%)			1 (50%)	

7.2.9 It is true that (7%) more of the metformin patients elected to be followed in the open-extension than did glibenclamide patients. **Nevertheless, it is of no small note that all 7 of the deaths in the US trials emanated not only from the 87-2D study, but only**

from the metformin arms of that trial. On an intent-to-treat basis there were 7 deaths out of 426 patients exposed to metformin in that trial versus 0 deaths in 209 patients not originally randomized to metformin but randomized rather to monotherapy with glibenclamide. The mean treatment difference of having been randomized to metformin (alone or in combination with glibenclamide) versus having been randomized to glibenclamide alone was 1.64% - 99% CI (0.0541 to 3.23%) - i.e., significant at the $p < 0.01$ level. Considering that 1 death was due to cancer and another to suicide, then excluding these deaths from analysis reveals a mean treatment difference of 1.17% with a 95% CI of 0.151% to 2.20% and a 99% CI of -0.173% to +2.52% - i.e., still significant at the $p<0.05$ level. The same levels of significance apply to consideration of ITT evaluation of deaths in all patients in the pooled Category i trials by exposure to metformin. At any rate, all six of the deaths in the open-enrollment phase were on combination therapy at the time of death. **A Kaplan-Meier analysis revealed that the event rate was enriched at the end of observation to its maximum of 29.22 deaths/1000/year**. [Over the entire observation period the mortality rate averaged 14.58 ± 8.03 deaths/1000/year.]

7.2.9.1 Two major questions emerge from such an analysis:

1) Were patients originally randomized to metformin in the 1D study protected and, if so, by what mechanism?

2) Were patients originally randomized to glibenclamide monotherapy in the 2D study also protected and, if so, by what mechanism? Duration of exposure may not be the answer. The smallest duration of exposure to metformin in this group was 14 days. The longest was 783 days. The mean was 498.28 ± 209.70 days. These compare quite favorably to the statistics manifested by those patients from the other two groups in the 2D study who died.

The answer to the first question may have to do with lack of enough power to detect a difference in that arm.

The answer to the second question may not be so readily apparent. The major bug-a-boo relates to the notion that the glibenclamide-monotherapy patients had relatively similar and sufficient durations of metformin exposure to the other two groups and came from the same sulfonylurea-failure population at risk. The simplest solution would be to say that there was not enough power in that arm alone to warrant any conclusion of protection. Nevertheless, the difference between the glybenclamide lack of deaths and the seven deaths in the other two arms was statistically significant at a $p < 0.01$. What other possible explanations exist as to why no mortality was seen in that arm, if valid? A conceivable answer may lie in the design features of the double-blind portion of the study. The patients on metformin in the double-blind study had to be rapidly titrated up to, and, for the most part kept on, maximum doses of metformin (i.e., 2500 mg day) on top of maximum doses of glibenclamide. When glibenclamide-monotherapy patients entered the 1C study the following occurred:

1) a time lag was likely from the cessation of the 2D study
2) whatever sulfonylurea patients were taking at the time needed to be completely discontinued
3) no retitration of metformin would have been necessary
4) these patients would have been forced to discontinue sulfonylurea completely, then have metformin titrated upward in biweekly 850mg increments, and then have their previous sulfonylurea - which was not necessarily glibenclamide - retitrated upwards. This strategy is unlike the 2D combination arm in which metformin was titrated upward more gradually in weekly 500mg increments on top of maximum glybenclamide therapy (which could not be reduced.)

Another intriguing lead relates to selection bias, the argument being that glybenclamide-randomized patients who elected open-enrollment were somehow more resistant to metformin toxicity than those who opted out. There has, unfortunately, not been enough time to fully explore this mechanism. Yet, here is some preliminary analysis:

Did Glyburide-Randomized Patient Enter Open-Enrollment?	**n**	**Age**	**BMI**	**HbA1c**
==> No	**70**			
[Mean:]		**55.66**	**28.33**	***7.10***
[Standard Deviation:]		**8.86**	**3.62**	**3.56**
==>Yes	**146**			
[Mean:]		**56.51 NS**	**29.03 NS**	***8.16****
[Standard Deviation:]		**8.50**	**4.47**	**2.86**

*95% CI for 1.06 difference ± 0.451 (SED) -> 0.171 to 1.95

The (1) selective self-removal of better controlled [glibenclamide] patients from open enrollment and the (2) decreased incidence of death in that arm followed in open enrollment taken with the (3) highly significant increase in hypoglycemia seen with combination therapy suggests that hypoglycemia may be a significant contributing factor to the deaths seen in the other two arms. If this is the case than it renders somewhat less credible the sponsor's argument that the hypoglycemia seen in the double-blind phase of the trials was an ersatz function of the design which kept maximum sulfonylurea therapy fixed while only allowing titration of metformin.

All this may suggest:

a) some possible sensitization-withdrawal-rechallenge mechanism
b) some possible higher metformin dose + maximum glibenclamide dose interaction
c) some possible interaction based on hypoglycemia or,
d) some combination of the above operative in this population of sulfonylurea-failure patients.

7.2.9.2 ITT Statistics
==>: There is a highly statistically significant increase in the number of deaths in patients randomized to prescription for metformin than to prescription for glibenclamide alone or than to prescription with either glibenclamide alone or placebo alone. The predominant population at risk was patients with sulfonylurea-failure (excess risk 1.65% with 99% CI of 0.0545% to 3.26%). The earliest duration of exposure to metformin resulting in a death was 97 days. The latest was 825 days. The mean was 463.14 ± 242.26 days.

Of the metformin deaths, 72.22% were due to cardiovascular related causes, yet only 16.67% were directly attributable to coronary heart disease, which usually claims 75 to 80% of NIDDM patients[21].

7.2.10 Lactic acidosis, a known sequel to therapy with metformin was seen in one patient with sudden death (F02-10023, see **Section 7.2.4**), and renal failure which is known to predispose to lactic acidosis in patients taking metformin, was seen to develop in another patient on metformin who had a sudden, unexplained death (F03-11024, see **Section 7.2.6**).

However, considering one lactic acidosis death in the clinical trials yields a death rate of 0.88/1000 PYE. This death rate is about threefold our point estimate of 0.3/1000 PYE (see **Section 7.17.1.2**) In addition, both of these events have occurred in females. Moreover, there were no episodes of lactic acidosis ascribable to patients taking placebo or glibenclamide monotherapy in the US clinical trials.

==> The death rate estimated from metformin-associated lactic acidosis in the US clinical trials is slightly greater than one-third that of the highest FDA estimate (2.5/1000 PYE) of phenformin-associated lactic acidosis mortality at the time pheaformin was removed from the market for "imminent hazard."

7.2.11 Thirdly, at least two of the patients who died (F02-10023, and J01-13002, see

Sections 7.2.4-5) had EKG ST-T wave changes which developed on therapy with metformin. There was a statistically significant increase in "clinically-significant EKG changes from baseline" in patients exposed to metformin in the US clinical trials (see Sections 7.7, 7.12.2). It may also be that 8/18 (44.4%) metformin deaths although cardiovascular, were non-CHD, non ASCVD related. If that is the case, then: the associated increase in total (primarily cardiovascular) mortality manifested by phenformin in the University Group Diabetes Program[27] (UGDP) study may have been revalidated and operative with metformin, and, perhaps, with other biguanides as well.

==>: There appears to be an increase in sudden deaths in patients exposed to metformin. Some of these sudden deaths may be a function of hypoglycemia seen with combined metformin-sulfonylurea therapy, others may be related to conductive disturbances (see also Section 7.12.2).

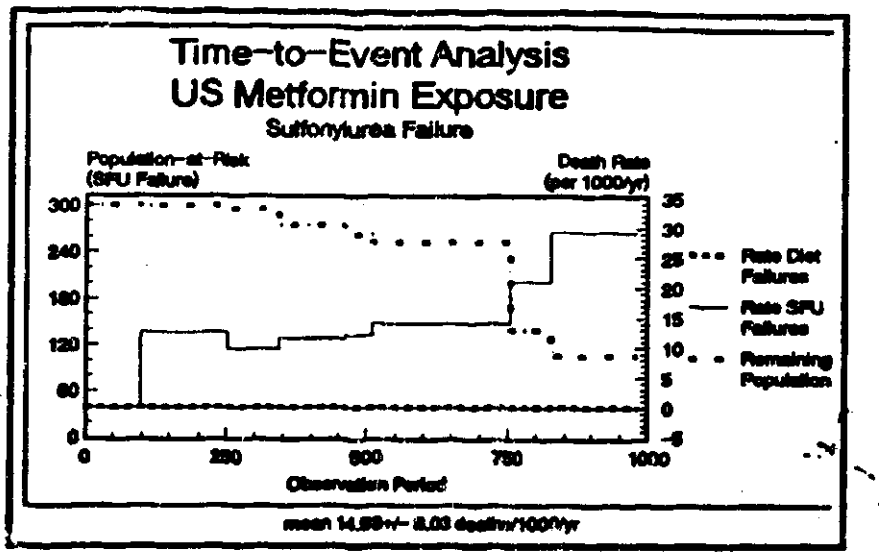
7.2.12 Sulfonylurea Failure Popuiation and Deaths

==> The patients at risk of metformin-induced mortality in the US trials appear to be solely those with sulfonylurea-failure. It is difficult to sort out the precise mechanisms which may underlie this association. The University Group Diabetes Program[27] (UGDP) showed significant excess mortality independently in both the sulfonylurea and biguanide arms - but no study was made of the potential additive effects of the two classes of medication taken simultaneously. The significant excess mortality displayed by the combination therapy among patients with sulfonylurea-failure in the comparatively well-underpowered US trials may, indeed, be a function of this additive phenomenon.

Once again, the predominant population at risk from death in these US trials was patients with sulfonylurea-failure (excess risk 1.65% with 99% CI of 0.0545% to 3.26%). A Kaplan-Meier analysis revealed that the event rate was enriched at the end of observation to its maximum of 29.22 deaths/1000/year. [Over the entire observation period the mortality rate averaged 14.58 ± 8.03 deaths/1000/year.]

27University Group Diabetes Program, A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes V. Evaluation of phenformin therapy. *Diabetes* 24 (Suppl 1):65-184, 1975

Figure 8



So far as B12 associations may be concerned, B12 abnormalities were so prevalent among metformin users that it is difficult to attribute any prognostic import to changes seen along this axis amongst the patients who died.

7.3 DROP-OUTS:

7.3.1 ALL PATIENTS

Of the total of 566 "pivotal" Category I patients on metformin, 105 patients (18.6%) withdrew from the studies. Of these 105 patients, 24 (4.2%) withdrew for lack of efficacy, and 81 (14.3%) for "non-efficacy related" reasons with 23 (4.1%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 353 patients on metformin alone, a total of 84 patients (21.4%) withdrew from the studies. Of these 84 patients, 23 (6.5%) withdrew for lack of efficacy, and 61 (17.3%) for "non-efficacy related" reasons with 19 (5.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 213 patients on metformin plus glibenclamide, a total of 21 (9.9%) patients withdrew from the study. Of these 21 patients, only 1 (0.5%) patient withdrew for lack of efficacy, and 20 (9.4%) for "non-efficacy related" reasons with 4 (1.9%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

This first compartment also had 355 comparators, i.e., 146 on placebo and 209 on glibenclamide alone. Of these 355 controlled patients a total of 76 (21.4%) patients withdrew from the study. Of these 76 patients, 24 (6.8%) patients withdrew for lack of efficacy, and 52 (14.6%) for "non-efficacy related" reasons with 7 (1.1%) of these citing definite adverse events (AE's) or

intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 146 patients on placebo alone, a total of 41 (28.1%) patients withdrew from the study. Of these 41 patients, 18 (12.3%) patients withdrew for lack of efficacy, and 23 (15.8%) for "non-efficacy related" reasons with 2 (1.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 209 patients on glybenclamide alone, a total of 35 (16.7%) patients withdrew from the study. Of these 35 patients, 6 (2.9%) patients withdrew for lack of efficacy, and 29 (12.4%) for "non-efficacy related" reasons with 5 (2.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The second segregation ("Category II") includes the other eight (8) non-US studies (excluding D/86/BERGI) and comprises 8346 patients treated with metformin (72 were concomitantly on glipizide, glibenclamide, or glicazide). Of these 8346 patients, 248 patients were in controlled clinical trials and 8,098 were uncontrolled in open-labeled trials.

Of the controlled 248 Category II patients, 20 (8.1%) were treated with metformin for a full 52 weeks (versus glipizide in GB/86/CAMP1), 23 (9.3%) patients for at least 24 weeks, and 67 (27.0%) received a dose higher than or equal to 2g/day at the last treatment visit.

Of the total of 248 controlled Category II patients on metformin, 34 patients (13.7%) withdrew from the studies. Of these 34 patients, 0 (0.0%) withdrew for lack of efficacy, and 34 (13.7%) for "non-efficacy related" reasons with 24 (9.7%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 176 patients on metformin alone, a total of 30 patients (17.0%) withdrew from the studies. Of these 30 patients, 0 (0.0%) withdrew for lack of efficacy, and 30 (17.0%) for "non-efficacy related" reasons with 20 (11.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 72 controlled Category II patients on metformin plus sulfonylureas, a total of 4 (5.6%) patients withdrew from the studies. Of these 4 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 4 (5.6%) for "non-efficacy related" reasons with 4 (5.6%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

This second compartment had 170 comparators, i.e., 83 on placebo and 87 on sulfonamides (34 on glibenclamide, 25 on glipizide, and 28 on glicazide). Of these 170 controlled patients a total of 24 (14.1%) patients withdrew from the

studies. Of these 24 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 24 (14.1%) for "non-efficacy related" reasons with 11 (6.5%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 83 patients on placebo alone, a total of 15 (18.1%) patients withdrew from the study. Of these 15 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 15 (18.1%) for "non-efficacy related" reasons with 7 (6.5%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal. Of the 87 patients on sulfonylureas alone a total of 9 (10.3%) patients withdrew from the study. Of these 9 patients, 0 (0.0%) patients withdrew for lack of efficacy, and 9 (10.3%) for "non-efficacy related" reasons with 4 (4.6%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The second compartment also had 8,098 uncontrolled patients. Of these, no patients (0.0%) were treated with metformin for a full 52 weeks, 4160 (51.8%) patients were treated for at least 24 weeks, and 4406 (5.4%) received a dose higher than or equal to 1.7g/day at the last treatment visit. One hundred fifty two patients (1.9%) received a dose higher than or equal to 2g/day and 211 patients (2.6%) received a dose higher than or equal to 2.55g/day at the last treatment visit. Of the total 8,098 uncontrolled patients on metformin, 488 patients (6.0%) withdrew from the studies. Of these 488 patients, 33 (0.4%) withdrew for lack of efficacy, and 455 (5.6%) for "non-efficacy" reasons with 170 (2.1%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

7.3.2 **POOLED PATIENTS FROM CONTROLLED TRIALS**

There were a total of 814 controlled patients on metformin. Of these 814, 139 patients (17.1%) withdrew from the studies. Of these 139 patients, 24 (2.9%) withdrew for lack of efficacy, and 115 (14.1%) for "non-efficacy related" reasons with 47 (5.8%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 529 controlled patients on metformin alone, a total of 114 patients (21.6%) withdrew from the studies. Of these 114 patients, 23 (4.3%) withdrew for lack of efficacy, and 91 (17.2%) for "non-efficacy related" reasons with 39 (7.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 285 controlled patients on metformin plus sulfonylureas, a total of 25 (8.8%) patients withdrew from the studies . Of these 25 patients, 1 (0.4%) patient withdrew for lack of efficacy, and 24 (8.4%) for "non-efficacy related" reasons with 8 (2.8%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The pooled controlled studies had 525 comparators, i.e., 229 on placebo and 296 on sulfonamides (243 on glibenclamide, 25 on glipizide, and 28 on gliclazide). Of these 525 controlled patients a total of 100 (19.0%) patients withdrew from the study. Of these 100 patients, 29 (5.5%) patients withdrew for lack of efficacy, and 71 (13.5%) for "non-efficacy related" reasons with 18 (3.4%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 229 patients on placebo alone, a total of 56 (24.5%) patients withdrew from the study. Of these 56 patients, 18 (7.9%) patients withdrew for lack of efficacy, and 38 (16.6%) for "non-efficacy related" reasons with 11 (4.8%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

Of the 296 patients on sulfonylureas alone a total of 44 (14.9%) patients withdrew from the study. Of these 44 patients, 6 (2.0%) patients withdrew for lack of efficacy, and 38 (12.8%) for "non-efficacy related" reasons with 9 (3.0%) of these citing definite adverse events (AE's) or intercurrent medical illnesses (IME's) as a reason for withdrawal.

The pooled (Category I and II controlled) relative risk of dropping out on metformin or placebo alone versus that on metformin in combination with sulfonylurea was 3.18 (99%CI of 1.90 to 5.33; $p<0.001$).

7.3.3 **PATIENTS FROM THE OPEN-ENROLLMENT TRIAL**
Concerning the 89-1C-6023 open-extension trial the sponsor states on page 08A-1669 of Volume 1.75 of this NDA:-

> **Of the 604 patients enrolled in this study, *preliminary* data review indicates that 164 patients were terminated from the study prior to the potential termination time. A complete analysis of patient disposition will be provided with the complete study report *(to be submitted with the first safety update of this NDA)*.** [Italics mine]

A "complete study report" of this trial has yet to be submitted(!) Nevertheless, it would appear that six hundred four (604) patients enrolled into the 89-1C-6023 open-extension trial to receive metformin with or without sulfonylureas. Of these, 217 were from control arms in the 87-1D or 87-2D trials with 75 emanating from placebo in the 1D trial and 142 from glybenclamide in the 2D trial. This amounts to 75/145 placebo patients, 142/209 glybenclamide patients, 217/351 metformin (monotherapy) patients, and 168/213 metformin/glybenclamide (combination) patients. This (385/564 or 68.3% of metformin patients minus 217/354 or 61.3% of control patients) amounts to a mean treatment difference of 6.96% with a 95%CI of 0.599 to 13.3% [and a $p<0.05$]. (The open-enrollment study increased the total duration of metformin exposure during all of the US open and

controlled trials to 1136 patient years.)

Of the 604 patients enrolled into 89-1C, 164 (27.15%) patients discontinued prematurely. There were 74 (12.23% of the total enrolled) discontinuations secondary to an adverse event/intercurrent medical event (AE/IME), significant laboratory abnormality, or death.

Adverse Events/Intercurrent Medical Illnesses/Significant Labs/Deaths Resulting in Withdrawal from Study 89-1C

Total		**74**
GI		**26**
Abdominal pain	**3**	
Bloody stools/diarrhea	**2**	
Diarrhea	**11**	
Colon Carcinoma	**3**	
Pancreatitis	**2**	
Cirrhosis	**1**	
Abnormal LFT's+Sx	**1**	
Abnormal LFT's..(Lab only)	**3**	
GU		**24**
Pyelonephritis	**1**	
Stones/UTI	**1**	
Increased Pcr/Decreased Ccr	**19**	
Prostate Ca/BPH	**3**	
CNS		**4**
Suicidal Deaths	**1**	
Neuropathy	**1**	
Toe infection/gangrene	**2**	
Cardiovascular		**17**
Deaths	**4**	
EKG changes/Arrhythmias/CHF	**6**	
Angina/MI	**4**	
Surgery/Catheterization	**3**	
Respiratory		**1**
Carcinoma of the lung/Deaths	**1**	
GYN		**1**
Breast Carcinoma	**1**	
Metabolic		**1**
Increased lactates/risk of lactic acidosis	**1**	

7.4 INCIDENCE OF ADVERSE EXPERIENCES

Adverse events or intercurrent medical illnesses in the US pooled Category i randomized trials either reported by at least 9% of the patients in one treatment group or for whom the mean treatment differences in incidence between any two treatment groups was at least 5% follows:

7.4.1 Category i Pooled Adverse Events/Intercurrent Medical Illnesses

AE/IME	metformin	placebo	glyburide	combination
n	*351*	*145*	*209*	*213*
any AE/IME**	86%	79%	82%	88%
diarrhea**	50%	14%	12%	45%
nausea/vomiting**	28%	10%	8%	25%
URI	21%	22%	22%	31%
asthenia	13%	11%	10%	11%
headache	12%	12%	8%	14%
abdominal discomfort	11%	6%	11%	13%
accidental injury	9%	6%	8%	8%
flatulence	9%	6%	7%	10%
flu syndrome	9%	6%	8%	8%
back pain	8%	7%	10%	6%
arthralgia	7%	10%	7%	10%
indigestion*	7%	4%	6%	12%
UTI	7%	9%	6%	8%
myalgia	7%	8%	10%	6%
pharyngitis	6%	5%	5%	9%
vaginitis++	3%	8%	8%	2%
paresthesia	3%	8%	4%	5%
thirst+	2%	6%	4%	1%
hypoglycemia##	2%	<1%	3%	18%

+p<0.05 higher in control pool than metformin pool
++p<0.01 higher in control pool than metformin pool
*p<0.05 higher in metformin pool than control pool
**p<0.01 higher in metformin pool than control pool
##p<0.01 higher in combination than SFU

Adverse events or intercurrent medical illnesses in the non-US pooled Category ii randomized trials either reported by at least 9% of the patients in one treatment group or for whom the mean treatment differences in incidence between any two treatment groups was at least 5% follows:

7.4.2 Category ii Pooled Adverse Events/Intercurrent Medical Illnesses

AE/IME	metformin	placebo	SFU	combination
n	*176*	*83*	*87*	*72*
any AE/IME**	63%	39%	57%	85%
diarrhea**	32%	14%	1%	17%
nausea/vomiting**	17%	5%	5%	4%
abdominal discomfort**	13%	6%	3%	13%
AE/IME	**metformin**	**placebo**	**SFU**	**combination**
indigestion	7%	4%	2%	4%
asthenia	7%	1%	8%	31%
URI	5%	2%	8%	13%
hypoglycemia##	5%	0%	13%	33%
taste disorder	5%	0%	2%	3%
constipation	4%	8%	3%	7%
headache##	4%	4%	2%	15%
sweating	4%	0%	6%	7%
dizziness#	3%	4%	9%	24%
bronchitis	4%	0%	3%	6%
UTI	4%	0%	2%	4%
thirst*	3%	1%	1%	8%
abnormal vision	2%	0%	3%	7%
pruritus	1%	1%	0%	6%
tremulousness#	1%	0%	16%	32%
polyuria	1%	0%	5%	7%
appetite increased	1%	0%	13%	8%
anxiety/tension	1%	0%	1%	6%
angina pectoris*	<1%	0%	0%	4%

#p<0.05 higher in combination than SFU
##p<0.01 higher in combination than SFU
*p<0.05 higher in metformin pool than control pool
**p<0.01 higher in metformin pool than control pool

With the exception of thirst the statistical tests were all confirmatory in these pooled studies separated across the wide Atlantic. In the US the significant differences favoring metformin for vaginitis or thirst undoubtedly reflect the differences in efficacy manifested. This, apparently, was not quite so profound in Europe. Note the hypoglycemic symptom complex of combination therapy versus sulfonylurea alone was highly significant for "hypoglycemia or headache" and significant for "tremulousness or dizziness."

The highly significant gastrointestinal profile of "diarrhea" or "nausea/vomiting" with "abdominal discomfort" (Non-US) or "indigestion" (US) undoubtedly reflects some portion of the mechanism of action of the drug by which it induces carbohydrate as well as

protein and B12 malabsorption[28,29,30,31,32,33,34] (see Section 7.5).

The significant treatment difference in angina pectoris (1.61% with 95% CI of 0.0451% to 3.18%,) seen in the pooled European studies must be taken particularly seriously in light of:

a) the statistically significant difference in clinically significant changes from baseline seen in EKG's during the US controlled trials (see Section 7.7) and the mandate of the 18 March 1994 DMEDP Advisory Committee to completely follow that up

b) the highly significant treatment increase in deaths reported during the US trials on an intent-to-treat basis (only among the two groups originally randomized to metformin - see Section 7.2), and

c) the significant increase in hospitalizations seen in the UK Prospective Diabetes Study (see Section 7.17.2)[35]

28Walter-Sack I. Reduction and delay in resorption as a pathogenetic and therapeutic principle. *Z Gastroenterol* [Verh] 16:54-61, 1979

28aLeroy Guerin V Acidose lactique induite par la metformine. Revue de littérature à propos de 2 cas. *THESIS MED.*:1-81, 1979 (see page 17) reprinted in *NDA 20-357*, Vol. 1.102, p 08A-08951

29Caspary WF. Effect and side effects of drugs on digestive and resorptive function of small intestine. *Dtsch Med Wochenschr* 102(5):167-73 1977

30Longstreth GF ; NewcomerAD. Drug-induced malabsorption. *Mayo Clin Proc* 50(5):284-93, 1975

31Kendall MJ ; Chan K. Drug-induced malabsorption. *Xenobiotica* 3(11):727-44, 1973

32Gray GM. Drugs, malnutrition, and carbohydrate absorption. *Am J Clin Nutr* 26(1):121-4, 1973

33Olsen WA ; Rasmussen HK. Effect of phenformin on carbohydrate absorption in man. *Diabetes* 23(8):716-8, 1974

34Tomkin GH ; Hadden DR ; Weaver JA ; Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. *Br Med J* 19;2(763):685-7, 1971

35UK Prospective Diabetes Study Group, UK Prospective Diabetes Study (UKPDS): 14. Relative efficacy of randomly allocated diet, sulfonylurea, insulin, or metformin therapy in patients with newly diagnosed type 2 diabetes followed for three years. Manuscript enclosed in *NDA Amendment #19*, 11 Feb 1994, Table 4, p 17 [slated for BMJ 20 Dec 1993]

7.5 LABORATORY ABNORMALITIES

Changes in the following safety laboratory variables were reviewed for mean changes, treatment-emergent lows or highs, and movement of at least 1 standard deviation at any time during double-blind therapy in the US trials:

Hematocrit (Hct), Red Blood Cells (RBC), Hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), White Blood Cells (WBC), Granulocytes, Stabs, Eosinophils, Lymphocytes, Basophils, Monocytes, Platelets, Creatinine, BUN, Bilirubin, Uric_Acid, ALT (SGPT), AST (SGOT), Alkaline Phosphatase, Albumin, Total Protein, Folic Acid, Vitamin B12, Anion Gap, Bicarbonate, Calcium, Chloride, Phosphate, Potassium, Sodium, Urinary Specific Gravity, Urinary pH, Urinary Glucose, Urinary Protein, Urinary Ketones, Urinary Blood, Serum Lactate, Plasma Metformin, Plasma Glybenclamide [in 87-2D Study].

There were no clinically significant differences in laboratory safety variables reviewed with the exception of the red cell series and vitamin B12 levels [or drug levels, themselves]. There did appear to be a slightly statistically significant but clinically insignificant difference in lactate levels across pooled treatment groups (0.07 mM/L with 90% CI ranging from 0.00956 to 0.130mM/L) at end-of-treatment (EOT).

Patients randomized to metformin (564) dropped their B12 levels a mean of 131.89 pg/ml from a baseline average of 530.68 pg/ml. Control patients (354) increased their B12 a mean of 12.59 from a baseline average of 518.71 pg/ml. This is a mean treatment difference of 144.48 pg/ml. There were 6.89% of metformin patients with normal B12 levels at baseline who dropped their B12 below the normal range of 200 pg/ml during double-blind therapy as opposed to 0.28% of controls. This mean treatment difference (excess risk) of 6.61% has a 99% CI of 3.77 to 9.45% or a relative risk of 24.4 with a 99%CI of 1.8 to 333. Interestingly enough this did not translate into any meaningful treatment difference in MCV (0.65 ± 4.5NS). Nevertheless, this did translate into a mean treatment difference of -1.15 in the hematocrit with a 99% CI around this difference of -0.63 to -1.67. Likewise for hemoglobin (-0.418, 99%CI -0.265 to -0.571) and RBC (-169,000/cc, 99%CI -107,000 to -231,000/cc). Looked at categorically, Hb displayed drops of over 1 gram in 126 patients on metformin but only in 32 controlled patients. This 13.3% difference had a 99%CI of 7 to 19%). Moreover, Hb displayed drops of over 2 grams in 23 patients on metformin but only in a single controlled patient. This 3.8% difference had a 99%CI of 1.5 to 6.1%). Hb displayed drops of over 3 grams in 5 patients on metformin but still only in a single controlled patient. This last difference was not statistically significant.

There were 34/564 metformin patients (6.03%) with treatment-emergent low RBC counts

as opposed to 8/354 controls (2.26%) for a mean treatment difference of 3.77 ± 1.27% SED with 99% CI of 0.462 to 7.03%. There were 18/564 metformin patients (3.19%) with treatment-emergent low hemoglobins as opposed to 4/354 controls (1.13%) for a mean treatment difference of 2.06 ± 0.93% SED with 95% CI of 0.233 to 3.87%. The difference in hematocrit (a volume parameter) was significant only at the $p<0.1$ level. Therefore significantly more patients on metformin had both meaningful hemoglobin drops and treatment-emergent anemias than did patients on controlled therapy.

"Malabsorption" was defined as the adverse event "diarrhea" in association with the laboratory change "B12 drop from baseline of over 150 pg/ml" occurring in the same patient during therapy. There were 100 pooled patients on metformin with malabsorption thus defined as opposed to 5 pooled patients on controlled treatment. This is an excess risk for malabsorption on metformin of 16.6% with a 99% CI of 12.1 to 22.2% [or a relative risk of 12.6 with a 99% CI of 3.9 to 40.4].

Cross-associations of changes in laboratory variables in particular sub-populations defined by specific adverse experiences or other laboratory abnormalities were also reviewed and are attached as appendices.

1) B12 vs lactate in all patients, by treatment group, in patients with and without diarrhea:
Conclusions: no significant findings

2) drug levels vs dose vs BMI in patient visits ± ADR's, ± diarrhea:
Conclusions: there were significantly higher drug levels of metformin ($p<0.05$) in patients also on glibenclamide at both the 1000 (MTD 195 µg/ml with 95% CI of 3.69 to 386 µg/ml) and 2500mg (MTD 112 µg/ml with 95% CI of 6.2 to 218 µg/ml) metformin dose levels when compared to patients at the same doses on metformin monotherapy (in the 87-2D study).

3) GFR-Changes vs Urinary pH vs potassium changes vs sodium changes vs phosphate changes vs anion gap changes vs treatment group:
Conclusions: no significant findings

4) hematocrit changes vs lactate changes:
Conclusions: no significant findings

5) lactate changes vs creatinine changes vs treatment group:
Conclusions: no significant findings

6) urinary pH vs lactate changes vs treatment group
Conclusions: no significant findings

7) anion gaps vs lactate changes
Conclusions: no significant correlations

8) diarrhea vs Hb drops vs treatment group
Conclusions: no significant findings

7.6 VITAL SIGNS:

Because the sponsor felt that by relieving insulin resistance in patients (putatively with "Syndrome X") that hypertension could then be ameliorated, only reductions in pressure were analyzed and not elevations (as might reasonably be expected given the phenformin experience as reported in the Federal Register, 06 April 1979.)

This analysis although requested from the sponsor in February, has not yet been received. It is to be noted, however, that in the US open-enrollment 89-1C Study there were 17 reported events of "blood pressure increased" (6 moderate) and 115 reported events of "hypertension" (2 severe/ 53 moderate) while only 3 events of "hypotension" were reported.

Nevertheless, this reviewer's analysis of patients reporting "hypertension" as a treatment-emergent AE (hypertension that occurred on treatment which was either absent or present at a lower level of severity at baseline) which was "sustained" (present at that new level or higher on two or more visits) reveals the following significant findings:

TREATMENT EMERGENT SUSTAINED HYPERTENSION

drug \study	87-1D		87-2D	
	whites	blacks	whites	blacks
metformin	3/100	0/26	5/151	4/28
placebo	5/101	2/29	—	—
glibenclamide	—	—	12/160#	1/30
combination	—	—	3/149	3/30

#p<0.05 vs metformin pool MTD +4.83% 95%CI from +1.07% to +8.6% (whites 2D)

The overall changes either pooled (metformin vs control) or in the 2D study (metformin vs

glibenclamide) showed no significant differences. However, there was a significant decrease (4.83%) in reports of sustained treatment-emergent hypertension in white patients with sulfonylurea-failure, and a trend in the opposite direction among blacks in this population.

7.7 EKG's:

On page 08A-01592 (Vol 1.74) of the NDA the sponsor noted clinically "significant EKG changes from baseline" occurred as follows (Sponsor Table 242):

		Significant Change From Baseline	
Study No.	**Treatment**	**Yes**	**No**
87-1D	**Metformin**	**19 (15%)**	**110 (85%)**
	Placebo	**9 (7%)**	**117 (93%)**
87-2D	**Metformin**	**14 (8%)**	**169 (92%)**
	Glyburide	**13 (7%)**	**175 (93%)**
	Combination	**24 (12%)**	**180 (88%)**
Pooled (Sic!)	**Metformin (Monotherapy)**	**33 (11%)**	**279 (89%)**

Only "pooling" metformin monotherapy patients does not make much sense, especially when true pooling based on exposure reveals 57 (10.1%) significantly changed EKG's in patients exposed to metformin as opposed to 22 (6.2%) in unexposed patients. This amounts to an excess risk of +3.9% which has a [significant] 95% CI around it of +0.324% to +7.3%). All of these EKG's as well as similarly significantly changed EKG's from the open-enrollment 1C study were requested from the sponsor on 22 Mar 1994 as decreed by the DMUDP Advisory Committee 4 days prior.

7.8 WITHDRAWAL PHENOMENA:

There does not appear to be any evidence for tolerance or withdrawal.

7.9 ABUSE POTENTIAL:

The only abuse potential may relate to whether or not a suicidal predisposition exists.

7.10 HUMAN REPRODUCTION:

No data is presented in this NDA

7.11 OVERDOSE EXPERIENCE:

There was 1 suicide in the US trials which was described previously and not definitely attributed to ingestion of metformin.

Review of 255 cases of lactic acidosis did reveal 12 suicides (4.71 ± 1.33%, 99% CI 1.28 to 8.13%). These comprised 5 men and 7 women whose ages ranged from 16 to 83 (44.67 ± 16.66 years) on metformin anywhere from 0.25 to 8395 days (1687.72 ± 3353.68 days) taking from 1700 to 38250 mg of metformin (15695.45 ± 10161.35 mg) with metformin blood levels ranging from 39.10 to 110 µg/ml (65.42 ± 23.4 µg/ml). Of the ensuing deaths, 2 were female and 1 was male. Of the survivors, 5 were female and 4 were male. The metformin blood levels trended lower (59.41 ± 17.05 µg/ml) in the 5/9 survivors with drug level data available than in the 2/3 deceased patients with that data available (80.45 ± 29.55 µg/ml). Most of the cases seemed to respond to alkalinization and/or hemodialysis.

(See the sections on "*LACTIC ACIDOSIS*" in "**POTENTIALLY SERIOUS DRUG-RELATED AE'S**", Section 7.12and "**OTHER HUMAN SAFETY DATA**", Section 7.17)

7.12 POTENTIALLY SERIOUS DRUG-RELATED ADVERSE EVENTS:

7.12.1 LACTIC ACIDOSIS: **(See also Section 7.17.1)**

The following metabolic, non-hypoglycemic events were noted in the US open-enrollment 89-1C study:

AE/IME	total	mild	moderate	severe
BUN increased[1]	2	2	0	0
creatinine clearance decr[1]	9	4	5	0
creatinine serum increased[1]	8	6	2	0
dehydration[1]	6	0	3	3
hyperchloremic acidosis[3]	1	1	0	0
ketoacidosis[3]	1	0	0	1
ketonuria[2]	4	1	1	2
kidney function abnormal[1]	2	1	0	1
lactate blood increased[2]	15	2	12	1
lactic acidosis[3]	1	0	0	1
renal insufficiency[1]	1	0	1	0
[1]Renal-related	28	13	11	4
[2]Lactatemia/Ketonemia	19	3	13	3
[3]Acidosis	3	1	0	2
TOTAL	50	17	24	9

Please note that there were at least 28 renal-related events all which occurred while on therapy, all but four of which were mild or moderate, and all of which could potentially predispose toward lactic acidosis. In fact 19 patients were removed from this study for this very reason (See Sections 7.3.3, 7.17.1).

Nevertheless, despite these preventive withdrawals there were at least two events which classify as lactic acidosis and at least one fatality among the 15 cases of hyperlactatemia seen in this study. The first event was imputational based upon the removal of patient 89-1C-T01-06006 from the study because of:

1) increasing lactates
2) decreasing bicarbonates
3) increased risk of developing lactic acidosis

The second case was 89-1C-F02-10023 [described in great detail earlier in the section dealing with deaths.] She was noted to have documented lactic acidosis

during her final hospitalization. That hospitalization record is pending at the this time.

Lactic acidosis, a known sequel to therapy with metformin, was therefore seen in one patient with sudden death (F02-10023), and renal failure which is known to predispose to lactic acidosis in patients taking metformin, was seen to develop in another patient on metformin who had a sudden, unexplained death (F03-11024). [If this latter case were ascribed to lactic acidosis, a not unlikely scenario, then given 781 patients exposed to metformin for a total of 1136 patient years, there would have been 3 events (see the section on premature terminations for the third patient) and 2 deaths for an event rate of 2.64/1000 PYE and a death rate of 1.76/1000 PYE. This death rate is about sixfold our point estimate of 0.3/1000 PYE and greater than 70% that of the highest FDA estimate (2.5/1000 PYE) of phenformin-associated lactic acidosis mortality at the time phenformin was removed from the market for "imminent hazard."(see Section 7.17.1.2)]

Considering two events of lactic acidosis and one death in the clinical trials yields an event rate of 1.76/1000 PYE and a death rate of 0.88/1000 PYE. This death rate is about threefold our point estimate of 0.3/1000 PYE (see Section 7.17.1.2). In addition, both of these events have occurred in females. Moreover, there were no episodes of lactic acidosis ascribable to patients taking placebo or glibenclamide monotherapy in the US clinical trials.

7.12.2 CARDIOVASCULAR EVENTS:

Several lines of evidence point to an increased association of metformin therapy and enhanced cardiovascular morbidity and mortality, particularly in patients with sulfonylurea failure:

1) the UGDP[27] noted an excess cardiovascular mortality (6.55/1000 patient years over placebo) with the related drug, phenformin

2) despite the small power and metformin exposure of the US trials in this NDA (1136 pt-years), there was a highly significant excess mortality seen here in [sulfonylurea-failure] patients originally randomized to metformin (see Section 7.2)

3) despite the small power and metformin exposure of the US controlled trials in this NDA (305 patient-years), there was a statistically meaningful excess in "significant EKG changes from baseline" seen in patients randomized to metformin (see Section 7.7)

4) the UK Prospective Diabetes Study noted an annual hospital admissions rate of 4.4% of 262 obese patients exposed to metformin versus 1.75% of 994 patients unexposed (291 on diet alone, 187 on chlorpropamide, 212 on glibenclamide, and 304 on insulin) - an excess yearly morbidity of 2.83% with 95% CI of this point estimate at 0.195% to 5.46% (see also section 7.17.2)

5) despite the small power and metformin exposure of the pooled non-US trials in this NDA, there was a significant excess of patients with angina pectoris ($p < 0.05$) in patients exposed to metformin (see Section 7.4.2).

The following cardiovascular events were noted in the 89-1C open-enrollment study:

AE/IME	total	mild	moderate	severe
angina pectoris[1]	19	11	5	3
arrhythmia[2]	7	2	4	1
arteriosclerosis[1]	1	1	0	0
atrial fibrillation[2]	4	2	1	1
bundle branch block[2]	1	0	1	0
cardiomegaly[3]	1	1	0	0
cardiomyopathy[3]	1	0	1	0
cardiovascular disorder[4]	2	0	2	0
congestive heart failure[3]	1	1	0	0
coronary artery disorder[1]	10	3	7	0
coronary artery occlusion[1]	2	0	0	2
chest discomfort[1]	6	5	0	1
chest pain[1]	30	17	8	5
chest pain - substernal[1]	3	3	0	0
chest pain -> L arm[1]	1	0	0	1
dizziness[2]	39	17	21	1
dyspnea[3]	7	3	4	0
edema[3]	8	6	2	0
edema extremities[3]	21	15	5	1
edema legs[3]	13	9	4	0
edema peripheral[3]	3	1	2	0
EKG abnormal[2]	1	0	1	0
extrasystoles[2]	1	1	0	0
fluid retention[3]	2	2	0	0
generalized edema[3]	2	0	2	0
heart fluttering[2]	1	0	1	0
infarct[1]	1	0	0	1
ischemia myocardial[1]	1	0	0	1
light-headed[2]	11	7	4	0
myocardial infarction[1]	3	0	2	1
palpitation[2]	10	6	4	0
PVC's[2]	2	1	1	0
shortness of breath[3]	13	9	3	1
SV tachycardia[2]	1	0	1	0
syncope[2]	6	1	3	2
tachycardia[2]	10	7	3	0
tachycardia ventricular[2]	1	0	1	0
tightness in chest[1]	4	3	1	0
TIA[1]	3	1	1	1
ventricular arrhythmia[2]	1	1	0	0

EVENT CLASSES (Pooled):

AE/IME	total	mild	moderate	severe
[1]Ischemic	84	44	24	16
[2]Conductive	96	45	46	5
[3]Contractile	72	47	23	2
[4]Unclassifiable	2	0	2	0
TOTAL:	254	136	95	23

There appears to be somewhat of an excess in conductive and contractile dysfunction from what might reasonably be expected in this coronary disease prone population. This is reinforced by the increase in EKG abnormalities noted. Keep in mind that a majority of the events were classified as conductive and that 51/96 (53%) of these were either moderate or severe. The contractile disturbances may be a function of the drug's mechanism of action whereby it both inhibits fatty acid oxidation and decreases the shuttling of reducing equivalents from the cytoplasm to the mitochondria. Certainly the tendency of sulonylureas alone to decrease the coronary vasodilatory response to ischemia has been well documented.

The function of the heart depends critically on an adequate oxygen supply through the coronary arteries. Coronary arteries dilate when the intravascular oxygen tension decreases. Hypoxic vasodilation in isolated, perfused guinea pig hearts can be prevented by glibenclamide, a blocker of adenosine triphosphate (ATP)-sensitive potassium channels, and can be mimicked by cromakalim, which opens ATP-sensitive potassium channels. Opening of potassium channels in coronary smooth muscle cells and the subsequent drop in intracellular calcium is probably the major cause of hypoxic and ischemic vasodilation in the mammalian heart.[36,37]

Nevertheless, the potential synergic effects of metformin and sulfonylureas have never been studied under this paradigm.

36Daut J ; Maier-Rudolph W ; von Beckerath N ; Mehrke G ; Gunther K ; Goedel-Meinen L. Hypoxic dilation of coronary arteries is mediated by ATP-sensitive potassium channels. [Physiologisches Institut der Technischen Universitat Munchen, Biedersteiner, Federal Republic of Germany] *Science* 247(4948):1341-4, 1990

37Grover GJ ; McCullough JR ; Henry DE ; Conder ML ; Sleph PG Anti-ischemic effects of the potassium channel activators pinacidil and cromakalim and the reversal of these effects with the potassium channel blocker glyburide. Department of Pharmacology, Squibb Institute for Medical Research, Princeton, New Jersey. *J Pharmacol Exp Ther* Oct;251(1):98-104, 1989

7.12.3 PANCREATITIS:

Since cases of pancreatitis have been associated with metformin in the lactic acidosis database, it is not unreasonable to ascribe some possible link which might be related to acidosis.[38]

AE/IME	total	mild	moderate	severe
pancreatitis	**3**	**0**	**0**	**3**

7.12.4 HYPOGLYCEMIA:

As seen previously, there was a highly significant increase in hypoglycemia manifested by patients taking combined metformin-sulfonylurea therapy in all controlled trials submitted in this NDA. Combined therapy had an 14.5% excess in hypoglycemia compared with controls for which the 99% CI was 7 to 22%. Though none of these in the short-duration double blind phase appeared to be severe, there were 5 severe and 94 moderate hypoglycemic episodes seen in the US open enrollment 1C trial.

AE/IME	total	mild	moderate	severe
diaphoresis	**15**	**6**	**8**	**1**
glucose_blood_decreased	**6**	**4**	**2**	**0**
hunger_abnormal	**1**	**0**	**0**	**1**
hypoglycemia	**124**	**80**	**42**	**2**
hypoglycemic_reaction	**24**	**14**	**0**	**0**
irritability	**1**	**0**	**1**	**0**
jitteriness	**1**	**0**	**1**	**0**
night sweat	**4**	**3**	**1**	**0**
shakiness	**10**	**8**	**2**	**0**
sweating increased	**17**	**10**	**7**	**0**
tension nervous	**14**	**3**	**10**	**1**
tingling	**7**	**6**	**1**	**0**
tremor	**25**	**17**	**8**	**0**
tremulousness	**3**	**2**	**1**	**0**
TOTAL	**252**	**153**	**94**	**5**

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38 Kahler SG; Sherwood WG; Woolf D; Lawless ST; Zaritsky A; Bonham J; Taylor CJ; Clarke JTR; Durie P; Leonard JV. Pancreatitis in patients with organic acidemias. *J Ped* 124(2):240-243, 1994

As discussed previously, the (1) selective self-removal of better controlled [glibenclamide] patients from open enrollment (see **Section 7.2.9.1**) and the (2) absent incidence of death in that arm contrasted with the highly significant increase in the other two arms (see **Section 7.2.9.1**) taken with the (3) highly significant increase in hypoglycemia seen with combination therapy (see **Sections 7.4.1-2**) suggests that hypoglycemia might very well be a meaningful factor contributing to the deaths seen in those ther two arms (see **Section 7.17.4**).

7.12.5 DEPRESSION:
Although depression in the open enrollment was only noted 26 times with 12 events classified as mild, 13 as moderate, and 1 severe. Suicidal attempts comprise 11/255 or 4.3% of the lactic acidosis cases on record here [as of 18 Mar 1994]. Therefore, depression could possibly be drug-related.

7.12.6 WEAKNESS/LETHARGY/ASTHENIA:
This lack of energy complex was seen frequently enough in all trials to suggest some possible association. Most of the events were mild to moderate.

AE/IME	total	mild	moderate	severe
asthenia	15	5	10	0
fatigue	69	37	30	2
lethargy	18	14	4	0
malaise	8	5	3	0
myasthenia	5	3	2	0
tiredness	8	6	2	0
weakness-generalized	24	12	8	4
weakness-muscle	1	1	0	0
TOTAL	148	83	59	6

7.13 SERIOUS ADVERSE EVENTS UNLIKELY TO BE DRUG-RELATED:

The following serious AE's/IME's seen in clinical trials were not felt to have enough discriminatory power within the content of the relatively few events seen in this NDA to be causally asssociated with metformin therapy at this time:

BODY AS A WHOLE
accidental injury
ascites
back pain
cellulitis
flank pain

flu (syndrome)
gangrene
infections
lumbo-sacral pain
neck pain
neoplasm (nos)
pain
pain foot
pain leg

CARDIOVASCULAR
aortic stenosis

ENDOCRINE
hypercholesterolemia

MUSCULOSKELETAL
arthritis
bursitis
carpal tunnel syndrome
leg cramps
joint disorder
strain
trigger finger

NERVOUS SYSTEM
insomnia
muscle spasm

RESPIRATORY SYSTEM
bronchitis
carcinoma of the lung
cough
pneumonia
rhinitis
sinusitis
sore throat
upper respiratory tract infection

SKIN
basal cell carcinoma
genital herpes
hives
nail disorder

psoriasis aggravated
rash
skin scaly
ulcer skin

SPECIAL SENSES
cataract
ear disorder (nos)
eye inflamed
macula degeneration
otitis media
retinal hemorrhage
uveitis
vision loss

UROGENITAL SYSTEM
breast carcinoma
calculus ureteral
carcinoma prostatic
cystitis
impotence
kidney pain
kidney stone
menorrhagia
nocturia
polyuria
pyelonephritis
urethral disorder
urinary tract infection

7.14 DRUG-DEMOGRAPHIC INTERACTIONS:

7.14.1 AGE:
Patients over age 65 (n=69) vs those under age 65 (n=495) reported more:

- AE's/IME's (52% vs 43%)
- asthenia (22% vs 11%)
- hypoglycemia (12% vs 7%)
- musculoskeletal symptoms (29% vs 22%)
- nervous system symptoms (25% vs 16%)
- GI symptoms and malabsorption (74% vs 66%)

7.14.2 RACE:

Blacks (84) vs whites (405) experienced *less*:

AE's/IME's (74% vs 89%)
GI symptoms (56% vs 69%)
abdominal discomfort (7% vs 14%)
indigestion (4% vs 11%)
diarrhea (37% vs 50%)
musculoskeletal symptoms (13% vs 25%)
nervous system symptoms (8% vs 18%)
respiratory symptoms (27% vs 37%)

Blacks vs whites experienced *more*:
back pain (9% vs 1%)
lowering of HbA1c (? <-significantly higher baseline , see Section 6.2.14)

Accounting for 119/566 (21%) of the US population exposed to metformin, blacks and hispanics had 2/7 (28.6%) of the deaths seen in that population.

The sponsor states on page 02 000464 of Volume 1.1 of this NDA, **"No clear racial differences in occurrence of AE/IMEs were noted excepted** (sic!) **for a greater incidence of Digestive System symptoms in whites compared to blacks."** The author of another MOR of this NDA mimes on page 55, **"No clear racial differences in occurrence of AE/IMEs were noted excepted** (sic!) **for a greater incidence of Digestive System symptoms in whites compared to blacks."**

Nevertheless, this reviewer's analysis of patients reporting "hypertension" as an AE reveals the following significant finding(where treatment-emergent hypertension had to be present on at least two-visits in order to be "sustained"):

TREATMENT EMERGENT SUSTAINED HYPERTENSION

drug \study	87-1D		87-2D	
	whites	blacks	whites	blacks
metformin	3/100	0/26	5/151	4/28
placebo	5/101	2/29	--	--
glibenclamide	--	--	12/160#	1/30
combination	--	--	3/149	3/30

#p<0.05 vs metformin pool MTD +4.83% 95%CI from +1.07% to +8.6% (whites 2D)

The overall changes either pooled (metformin vs control) or in the 2D study (metformin vs glibenclamide) showed no significant differences. However, there was a significant decrease (4.83%) in reports of sustained treatment-emergent hypertension in white patients with sulfonylurea-failure, and a trend in the opposite direction (8.74% increase)

among blacks in this very same population. These opposing effects, if confirmed, could partially explain the seemingly greater acceptance of biguanides in European countries.

7.14.3 SEX:
Women (309) vs men (255) experienced *more*:
GI symptoms (72% vs 62%)
diarrhea (53% vs 43%)
nausea/vomiting (34% vs 19%)
musculoskeletal symptoms (28% vs 18%)
urogenital events (22% vs 10%)

The 7 deaths in the US trials were evenly distributed among 4 males and 3 females.

7.15 DRUG-DISEASE INTERACTIONS

7.15.1 SEVERITY OF DIABETES AT BASELINE:
Patients with FBS <200 (n=120) vs >=200 (n=381) had *more*:
respiratory symptoms (40% vs 4%)

Patients with FBS <200 vs >=200 had *less*:
reduction in HbA1c at EOT from baseline (-0.76±1.42 vs -1.27±1.83)
difference -0.51% with 99% CI 0.0388 to 0.981%
reduction in MTD from control HbA1c at EOT (-1.26±1.60 vs -1.45±1.78) (NS)

7.15.2 DIABETES WITH SULFONYLUREA FAILURE:
The highly significant major toxicity, morbidity, and mortality seen in this NDA from therapy with metformin were all seen in patients with sulfonylurea-failure ($p < 0.01$).

7.15.3 RENAL IMPAIRMENT (DECREASED GFR)
Sirtori[39] showed a significant inverse correlation between creatinine clearance and plasma half life for metformin. Study 90-13-6023 showed a significant inverse correlation between age and plasma renal clearance of metformin resulting in a positive correlation between age and plasma levels in the elderly.

Renal impairment appears to correlate significantly with lactic acidosis (see **Section 7.17.1.6**)

39Sirtori CR; Franceschini G; Galli-Kienle M; Cighetti G; Galli G; Bondioli A; Conti F; Disposition of metformin (N,N,-dimethylbiguanide) in man *Clin Pharm Ther* **24**:683-93, 1978

7.15.4 INTERSTITIAL NEPHRITIS/PYELONEPHRITIS/TUBULAR DYSFUNCTION:-

Since metformin is extensively secreted in the renal tubule (over fourfold the filtered load), disorders which impair this function place the individual patient at increased risk of lactic acidosis. Several patients with lactic acidosis and normal creatinine levels who were non-alcoholics had evidence of interstitial types of nephritis (see **Section 7.17.1.6**).

7.15.5 ALCOHOLISM/LIVER DISEASE:-

A significant percentage of patients with metformin associated lactic acidosis (MALA) and low plasma levels of metformin had a history of ethanolism or significant hepatic disease (see **Section 7.17.1.6**). This may also associate with a hepatorenal syndrome. This interaction has been well documented in the fasted guinea pig model.

Although lactic acidosis has been recognized as a potential hazard in biguanide therapy, this complication has been claimed to be extremely rare with dimethylbiguanide (DMBG) (metformin). In the present studies, using the fasted guinea pig, DMBG (125-500 mg/kg i.p.) caused marked dose-related changes in both plasma glucose (43-88% reduction) and blood lactate (3.5-13 fold increase). Lactate/pyruvate ratios were substantially increased. While i.p. doses of 100 mg/kg of DMBG or of 1 g/kg of ethanol produced no changes in plasma glucose, lactate or pyruvate, the two drugs administered conjointly at the indicated doses produced a 53% decrease in plasma glucose and 2 and 10-fold increases in pyruvate and lactate levels respectively, and correspondingly, an increase in the lactate/pyruvate ratio. Ethanol decay curves indicated that DMBG did not significantly influence the disappearance of ethanol from the blood. These results indicate that: (1) doses of DMBG which produce hypoglycemia are associated with lactic acidosis, and (2) this effect of DMBG can be markedly potentiated by ethanol.[40]

7.16 DRUG-DRUG INTERACTIONS:

7.16.1 SULFONYLUREAS:

The highly significant major toxicity, morbidity, and mortality seen in this NDA from therapy with metformin were all seen in patients with sulfonylurea-failure ($p < 0.01$).

As mentioned previously, glibenclamide appeared to significantly increase plasma metformin levels in clinical trials despite the lack of effect in a single dose interaction study. [There were significantly higher drug levels of metformin ($p < 0.05$) in patients also on glibenclamide at both the 1000 (MTD 195 µg/ml with 95% CI of 3.69 to 386 µg/ml) and 2500mg (MTD 112 µg/ml with 95% CI of 6.2 to 218 µg/ml) metformin dose levels when compared to patients at the same doses on metformin monotherapy (in the 87-2D study).]

The major mortality was seen in this population among patients who were not randomized to treatment with glibenclamide alone ($p < 0.01$), but who were treated in open-enrollment with combination metformin-sulfonylurea therapy.

40Dubas TC ; Johnson W. Metformin-induced lactic acidosis: potentiation by ethanol. *Res Commun Chem Pathol Pharmacol* 33(1):21-31, 1981.

That death was not seen in patients randomized to glibenclamide alone but who took combination therapy in open-enrollment may relate to a major morbidity seen in this NDA, i.e. hypoglycemia. (The (1) selective self-removal of better controlled [glibenclamide] patients from open enrollment and the (2) decreased incidence of death in that arm followed in open enrollment taken with the (3) highly significant increase in hypoglycemia seen with combination therapy suggests that hypoglycemia may be a significant contributing factor to the deaths seen in the other two arms. If this is the case than it renders somewhat less credible the sponsor's argument that the hypoglycemia seen in the double-blind phase of the trials was an ersatz function of the design which kept maximum sulfonylurea therapy fixed while only allowing titration of metformin.)

Metformin appeared to decrease glibenclamide absorption by roughly 25%.

N.B. No other sulfonylureas - all of which have increased renal handling as compared to glibenclamide - had interactions studied.

7.16.2 DRUGS (CATIONIC) SECRETED BY TUBULAR SECRETION:
Studied: cimetidine
Result: "significant increase in plasma and whole blood metformin levels"

7.16.3 DRUGS (ANIONIC) SECRETED BY TUBULAR SECRETION:
Studied: furosemide
Result: increased plasma and whole blood levels (15-22%) despite unchanged urinary excretion and unchanged plasma half-life implying increased filtration secondary to increased Km for secretion, i.e., competitive inhibition of secretion. There was a concomitant decrease (13-31%) in the plasma levels of furosemide.

There were 27/139 or 19.42% patients with lactic acidosis [who had any concomitant therapy listed] taking furosemide at the time of the event.

7.16.4 OTHER DRUGS:
Studied: nifedipine
Result: increased plasma and whole blood levels despite increased urinary excretion and unchanged plasma half-life implying increased absorption from the GI tract

Studied: propranolol
Result: no interactions

Studied: ibuprofen
Result: nc interactions

7.17 OTHER HUMAN SAFETY DATA

Two major sources of safety information with respect to metformin relate to (1) surveillance and journal reports of lactic acidosis and (2) the UK Prospective Study of Diabetes (UKPDS). The UGDP data will be discussed as it relative to phenformin; hypoglycemia will also be discussed relative to sulfonylureas.

7.17.1 Metformin-Associated Lactic Acidosis (MALA)

7.17.1.1 The most recent data available from the Läkesmedelswerket - the Swedish regulatory authority[41] - records 24 cases of acidosis and 19 deaths with metformin therapy. This translates to 0.12045 cases per thousand per year and 0.09 deaths per thousand per year. The comparable incidence rate for phenformin-associated acidosis was 5.3 fold higher at 0.63838 cases per thousand per year and the mortality rate was 4.6 fold higher at 0.41825 deaths per thousand per year.

7.17.1.2 Joseph Lowenstein, a member of the DMEDP Advisory Committee in 1981, summarized the available ratio data at the time[26] for MALA and PALA (phenformin associated lactic acidosis) world-wide which ranged from 1:13 to 2:1 and believed that a ratio of 1:8 appeared to be the most conservative estimate. At the time phenformin was withdrawn and based on prospective studies where spontaneous reports were tabulated retrospectively, FDA had calculated a very high but presumably likely "true incidence" for PALA in the United States of 5 cases per thousand per year ibid. **Based on this figure, a ratio of MALA to PALA of 1:8 suggested a reasonably likely "true incidence" of MALA in the US would be about 0.6 cases per thousand per year**. Lowenstein calculated a mortality rate of 50% from the 18 deaths in 37 cumulative reports over the 24 years from 1968 to 1981 - amply confirmed in this review of 129 fatalities in 255 cases (50.6% [99%CI 42.5 to 58.7]) of MALA reported to date (2/94). Over that ensuing 13 years the reporting rate increased almost sixfold (5.89x) by some 218 cases. (At any rate, 385(,000) x 0.3(deaths per thousand per year) would amount to 115 projected deaths per year from MALA.)

41Benson L, Data from SWEDIS, Läkesmedelswerket, Uppsala, 17 Nov 1993

7.17.1.3 MALA reports have been steadily increasing since the drug was marketed in 1959.

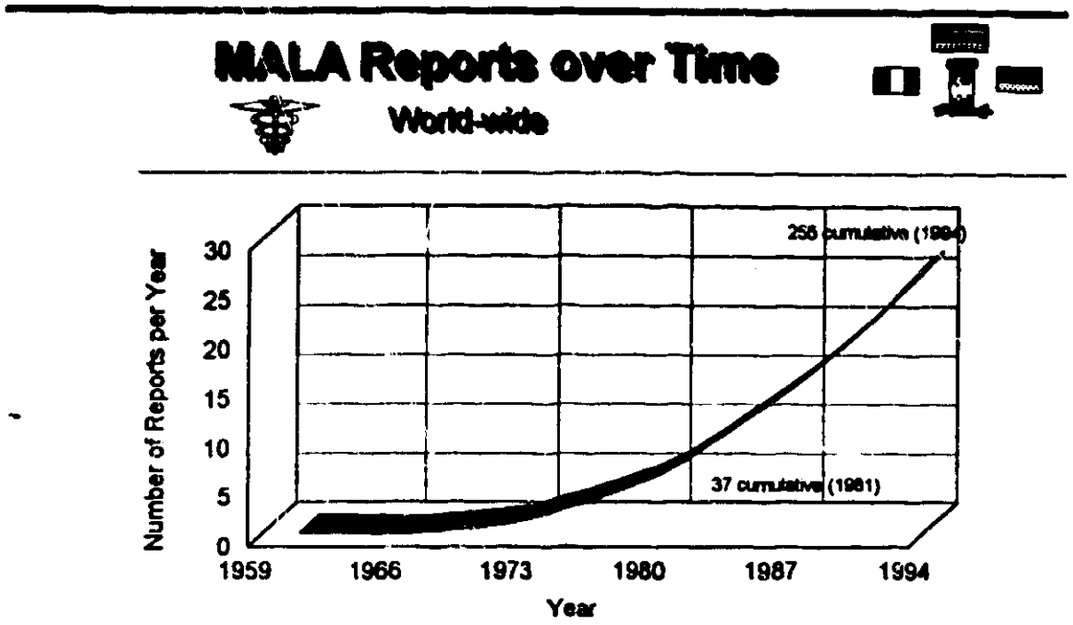

Figure 9

7.17.1.4 There does not appear to be dose-reponsiveness in MALA , but rather a "U-shaped" curve with increased frequency at both the lower and higher doses.

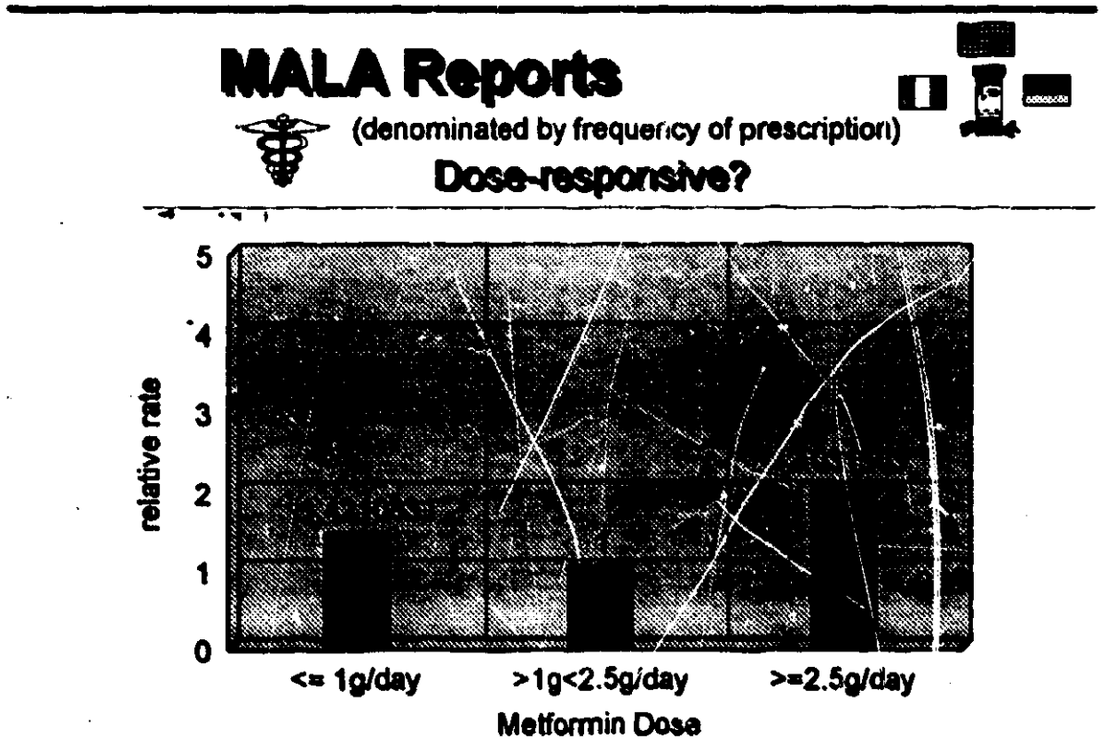

Figure10

	n(age)	Age	metformin level	dose	glucose
Total	250	65.39±12.3	22.07±27.0	2.604±3.8	267±225
Men	107	63.90±12.1	24.74±30.4	2.7098±3.3	260±213
Women	143	66.51±12.3	19.80±23.6	2.547±4.2	273±236
Deceased	127	67.63±11.0	19.02±28.4	2.303±4.0	294±233
Men	50	65.90±10.9	26.53±34.7	2.427±3.4	260±188
Women	77	68.75±11.0	13.00±20.2	2.223±4.4	327±265
Survived	123	63.11±13.1	24.58±25.6	2.912±3.5	244±215
Men	57	62.14±12.9	23.35±26.4	2.961±3.2	261±232
Women	66	63.89±13.4	25.68±25.8	2.925±3.8	229±198

7.17.1.5 **The 255 cases in the database current as of the advisory committee does not include the open label death, nor does it include 17 more cases from the UK and 2 more cases from Canada** reported by Robert Turner at the DMEDP Advisory Committee meeting of 18 Mar 1994. That database (of 255 cases) provides the basis for the ensuing discussion.

7.17.1.6 As can be seen from some of these statistics, the "average" patient with MALA
was 65.390 ±12.3 years old (99% CI 63.4 to 67.4)
taking 2.604 ±3.8 grams (99% CI 1.98 to 3.23) of metformin per day
for a 1275.880 ±1870.36 day (99% CI 844 to 1708) duration
with a 22.070 ± 27 µg/ml (99% CI 17.6 to 26.5) metformin blood level
and a 267.000 ± 225 mg/dl (99% CI 230 to 304) glucose level
and a 4.625 ±6.29 mg/dl (99% CI 3.19 to 6.06) creatinine level
and a 7.053 ± 0.254 (99% CI 7.00 to 7.10) pH
and a 24.24 ±10.29 mmHg (99% CI 21.9 to 26.6) pCO2
and a 8.65 ±5.3964 mEq/L (99% CI 7.50 to 9.81) bicarbonate level
and a 16.499 ±32.093 mM/L (99% CI 10.7 to 22.3) lactic acid level
and a 50.800 ±3.16% death rate (99%CI 42.6 to 59).

Women with lactic acidosis tended be highly significantly overrepresented (by 14.4 ± 4.43% [99%CI 2.98 to 25.8]), 2.6 ± 1.56 years older taking 161 ± 491 mg/day less metformin with blood levels 4.94 ± 3.42 µg/ml lower, glucose 13 ± 28.9 mg/dl higher and a death rate 7.12 ± 6.38% higher than men with lactic acidosis.

Men and women combined who died were significantly older (4.52 ± 1.53 years

[99%CI 0.553 to 8.49]) than those who survived. Women who died were significantly older (4.86 ± 2.04 years [95%CI 0.826 to 8.89]) than women who survived, with highly significantly lower metformin blood levels (-12.7 ± 3.85 µg/ml [99%CI -2.63 to -22.7]), significantly higher glucose levels (+98 ± 39.7 [95%CI +19.6 to +176]), significantly lower partial pressures of pCO2 (-4.36 ± 2.07 [95%CI -0.231 to -8.49]), and somewhat lower doses of metformin (-702 ± 693 mg/day) being taken.

Of 140 patients for whom concomitant medication information was provided, 91 (65 ± 4.03% [99% CI 54.6 to 75.4%]) were taking concomitant sulfonylureas, 27 (19.3 ± 3.33% [99% CI 10.7 to 27.9%]) taking digoxin, 66 (47.1 ± 4.22% [99% CI 36.3 to 58.0%]) were taking diuretics (including amiloride, triamterene, spironolactone, furosemide, and others), 12 (8.57 ± 2.37% [99% CI 2.47 to 14.7%]) were taking cimetidine or ranitidine, 14 (10 ± 2.54% [99% CI 3.46 to 16.5%]) were taking calcium channel blockers, 7 (5 ± 1.84% (99%CI 1.47 to 11.8%) had urinary tract infections, and 4 (2.86 ± qns% 99% CI (0.482 to 8.72%) were taking NSAID's.

If this data is representative, it can be estimated with reasonable certainty that 35% (at least 24.6% to at most 45.4%) of patients with MALA (100 - limits of 99% CI for concomitant SFU therapy) come from a population of diabetic *monotherapy* with metformin.

["GP-normal" creatinines are <2 mg/dl]
(Elevated creatinines are >=2mg/dl)

	[Metformin] >=5	[Metformin] <5	Totals
Ethanolics	11	11	22
Creatinine data	9	8	17
GP-normal	2	6	8
Elevated	7	2	9
Non-ethanolics	60	41	101
Creatinine data	43	17	60
GP-normal	11	5	16
Elevated	32	12	44
TOTALS	71	52	123
Creatinine data	52	25	77
GP-normal	13	11	24
Elevated	39	14	53

For some reason there is greater deficiciency of metformin drug level data and creatinine data available together in the same patient for those non-ethanolic

patients with normal metformin levels.

For those MALA patients who have metformin blood level information available (123/255), it was above normal (>=5 µg/ml) in 71 (57.7 ± 4.45%) and normal (<5 µg/ml) in 52 (42.3 ± 4.45% [99% CI 30.8 to 53.8%]). Of these 123 patients, 22 (17.9 ± 3.46% [99% CI 8.97 to 26.8%) patients had a history of ethanolism and 101 (82.1 ± 3.46%) patients had no such history.

Of those 22 patients with ethanol history, 11 (50 ± 10.7% [99% CI 22.5 to 77.5%]) had normal metformin levels and the other 11 (same statistics) had elevated levels. The patients with ethanolism and elevated metformin levels had worse acidosis and significantly less [CNS] respiratory compensation than the other groups with a mean pH of 6.87 ± 0.31, a mean pCO2 of 27.99 ± 11.16 mmHg, and a mean bicarbonate of 6.14 ± 4.96 mEq/L. Of those patients, the 6 who died had the very worst acidosis ($p < 0.01$) and the most ($p < .05$) CNS respiratory depression with a mean pH of 6.75 ± 0.31, a mean pCO2 of 31.51 ± 10.07 mmHg, and a mean bicarbonate of 4.80 ± 2.66 mEq/L. The 5 alcoholics who survived had better ABG's with a mean pH of 7.01 ± 0.23, a mean pCO2 of 23.76 ± 10.94 mmHG, and a mean bicarbonate level of 7.74 ± 6.40 mEq/L.

Of the 22 ethanolic patients, 8 had creatinine levels < 2mg/dl (here defined as "GP-normal"): 6 of those had normal metformin levels and 2 had elevated metformin levels - a difference of 50 ± 21.7% [95% CI 7.56 to 92.4%]).

Of the 101 non-ethanolic patients, 16 had GP-normal creatinine levels:
5 of those had normal metformin levels and 11 had elevated metformin levels - a difference of -37.5 ± 16.4% [95% CI -5.38 to -69.6%]).

Of those patients with normal metformin and GP-normal creatinine levels, there were significantly more ethanolics (6/8) than non-ethanolics (5/16) by 43.8 ± 19.2% [95% CI 6.12 to 81.4%] and vice-versa for those patients with elevated metformin levels.

Of those 13 patients with elevated metformin levels and GP-normal creatinines, there were sigificantly more non-ethanolics (11) than ethanolics (2) by a difference of 69.2 ± 14.2% [95% CI 41.5 to 97%].

Of the eleven patients with normal metformin levels and GP-normal creatinines, 6 were ethanolics. These were significantly more than the 2 ethanolics from the 13 patients with elevated metformin levels and GP-normal creatinines and by a difference of 39.2 ± 18% [95% CI 3.8 to 74.5%]. This situation is vice-versa for the non-ethanolics.

How is it that metformin levels were increased in 11/16 non-ethanolics with GP-normal creatinines? Was tubular secretion impacted in these patients?

Only 2/8 ethanolic patients had elevated metformin levels and GP-normal creatinines - a difference as seen above (*) of 43.8 ± 19.2% [95% CI 6.12 to 81.4%]. A review of the 11/16 non-ethanolics reveals only the following:

A) nifedipine, nicardipine in 2 patients
cimetidine, spironolactone in 1 patient
loop diuretics in 5 patients
digitoxin in 1 patient with dig toxicity (also on loop diuretic)

B) UTI, pyelonephritis in 2 patients

C) overdose in 2 patients

Of the 17 non-ethanolic patients with normal metformin levels, 12/14 had elevated creatinines versus 5/11 who had GP-normal creatinines - a difference of 40.3 ± 17.7% [95% CI 5.59 to 74.9%]. How is it the metformin levels were not elevated in these patients most of whom had abnormal creatinine clearance? Does this imply some synergic effect of renal failure on lactic acidosis (as seen with alcohol) before metformin concentrations elevate?

Most of the events occured in the population (53/77) with elevated creatinines - 68.8 ± 5.28% [99% CI 53.7 to 81.5%]. This excess was enriched in the 39/52 patients with elevated metformin levels - 75 ± 6% [99% CI 56.8 to 88.5%].

There were 19/604 patients who developed elevated creatinines in open-enrollment and who had to be removed from the study for that very reason. This is an event rate of 3.15% with a 99%CI of 1.61 to 5.46%.

==> Elevations of previously normal creatinines into the abnormal range do occur while patients are on metformin.

Lowenstein presented further data that metformin inhibits the excretion of an acid load[16] and that many patients with elevated creatinines at the time of MALA normalized after treatment. The Pharmacology Officer Reviewer has documented dose-related amyloid-cystic nephropathy with associated mortality in mice (see also Section 3.2).

Women appear to be at increased risk for development of and death from MALA.

Considering two events of lactic acidosis and one death in the clinical trials yields an event rate of 1.76/1000 PYE and a death rate of 0.88/1000 PYE. This death rate is about threefold our point estimate of 0.3/1000 PYE[26] In addition, both of these events have occurred in females. Moreover, there were no episodes of lactic acidosis ascribable to patients taking placebo or glibenclamide monotherapy in the US clinical trials.

7.17.2 The UK Prospective Diabetes Study(UKPDS)[35]:
The UK Prospective Diabetes Study is a 15-center, prospective, randomized, intervention trial of 2,520 NIDDM patients aged 25 to 65. The UKPDS began in 1977 to determine whether *improved* glycemic control could prevent diabetic complications together with their associated morbidity and mortality. If diet therapy could not lower the fasting glucose to 108 mg/dl or below then patients were randomized to either placebo chlorpropamide, glibenclamide, basal ultralente insulin, or, if obese, to all of the preceding plus metformin.

This study noted an annual hospital admissions rate of 4.4% of 262 obese patients exposed to metformin versus 1.75% of 994 patients unexposed (291 on diet alone, 187 on chlorpropamide, 212 on glibenclamide, and 304 on insulin) - an excess yearly morbidity of 2.83% with 95% CI of this point estimate at 0.195% to 5.46%.

7.17.3 The UGDP Data[27]
7.17.3.1 In the phenformin arm of the UGDP, there were 33 non-lactic acidosis deaths out of 204 patients enrolled into that arm. Over the eight years of the study, this amounted to 161.76 deaths per thousand or 20.22 deaths per thousand per year. There were 27 cardiovascular deaths or 132.35 deaths per thousand or 16.544 cardiovascular deaths per thousand per year.

7.17.3.2 In the tolbutamide arm of the UGDP, there were 30 non-lactic acidosis deaths out of 204 patients enrolled into that arm. Over the eight years of the study, this amounted to 147.06 deaths per thousand or 18.38 deaths per thousand per year. There were 26 cardiovascular deaths or 127.45 deaths per thousand or 15.93 cardiovascular deaths per thousand per year.

7.17.3.3 In the insulin arm of the UGDP, there were 10 non-lactic acidosis deaths out of 133 patients enrolled into that arm. Over the eight years of the study, this amounted to 75.19 deaths per thousand or 9.40 deaths per thousand per year. There were 9 cardiovascular deaths or 67.67 deaths per thousand or 8.46 cardiovascular deaths per thousand per year.

7.17.3.4 In the placebo arm of the UGDP, there were 7 non-lactic acidosis deaths out of 64 patients enrolled into that arm. Over the eight years of the study, this amounted to 109.37 deaths per thousand or 13.68 deaths per thousand per year. There were 3 cardiovascular deaths or 46.88 deaths per thousand or 5.86 cardiovascular deaths per thousand per year.

7.17.3.5 The excess total mortality of phenformin over placebo was 6.55 deaths per thousand per year. Assuming that metformin has 1/8th the excess mortality of phenformin, and that 385,000 patients will be taking phenformin of whom ¼ would come from diet-alone, the excess total mortality over diet-alone attributable to metformin would be 6.55 x 385 x 0.125 x ¼ or 79 patients per year. [The excess cardiovascular mortality of phenformin over placebo was 10.68 deaths per thousand per year.]

7.17.3.6 The excess total mortality of phenformin over tolbutamide was 1.84 deaths per thousand per year. Assuming that metformin has 1/8th the excess mortality of phenformin, and that 385,000 patients will be taking phenformin of whom ½ would come from sulfonylureas, the excess total mortality over sulfonylureas attributable to metformin would be 1.84 x 385 x 0.125 x ½ or 44 patients per year. [The excess cardiovascular mortality of phenformin over tolbutamide was 0.613 deaths per thousand per year.]

7.17.3.7 The excess total mortality of phenformin over insulin was 10.83 deaths per thousand per year. Assuming that metformin has 1/8th the excess mortality of phenformin, and that 385,000 patients will be taking phenformin of whom ¼ would come from insulin, the excess total mortality over insulin attributable to metformin would be 10.83 x 385 x 0.125 x ¼ or 130 patients per year. [The excess cardiovascular mortality of phenformin over insulin was 8.083 deaths per thousand per year.]

7.17.4 Comparative Risks of Hypoglycemia

7.17.4.1 Campbell[42] has calculated that according to SADRAC (Swedish Adverse Drug Reactions Advisory Committee) data, the difference between the attributable risk for mortality from MALA (Metformin-Associated Lactic Acidosis) of 0.0240 deaths per thousand per year and that from glibenclamide-associated hypoglycemia of 0.0332 deaths per thousand per year was negligeable, i.e., 0.0092 deaths per thousand patients per year. This was based on 7 cases of MALA and 2 deaths from 1972-1981.

7.17.4.2 The most recent data available from the Swedish regulatory authorities[41] records 24 cases of MALA and 19 deaths. This translates to 0.12045 cases per thousand per year and 0.09 deaths per thousand per year. This suggests an excess mortality of MALA over that of glibenclamide-hypoglycemia (0.062 deaths per thousand per year.)

7.17.4.3 For the sake of argument, grant that for all practical purposes the rates are equivalent. Data from the NDA[43] show that 7 glibenclamide patients out of 209 (3.35%) in study 87-2D reported hypoglycemic episodes as opposed to 38 combination metformin + glibenclamide patients out of 213 (17.85%). The net difference of 14.5% attributable to adding metformin was highly statistically significant - 99% CI's (7 to 22%).

7.17.4.4 Lowenstein[26] estimated US MALA mortality at 0.3 deaths per thousand per year. Assume that ½ the 385,000 patients taking metformin will be switched from

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42Campbell IW. Metformin and the sulfonylureas: the comparative risk. *Horm Metab Res* Suppl 15:105-11, 1985

43*NDA 20-357*, Volume 1.1, p.02 000426, (Table 56)

sulfonylureas (SFU's), of which half again (¼ x 385,000) will be on monotherapy with the other (¼ x 385,000) on combination therapy. This implies a mortality savings of ¼ x 385 x 0.3 or 29 lives. **The projected excess risk attributable to sulfonylurea hypoglycemia would then be** 0.3 x ¼ or **0.075 deaths /1000 PYE**. However, since the incidence of hypoglycemia in the combination therapy patients is higher by 14.5%, it is reasonable to expect some comparable increase in mortality. Campbell, himself[42], suggested a mortality of 9% of the reported cases of sulfonylurea-induced hypoglycemia. The incidence of hypoglycemia in SFU-monotherapy should then be 3.333 cases per thousand per year. Using the lower bounds of the 99% CI of 7% for the attributable difference the projected incidence attributable to combination therapy should be 70 per thousand plus 3.333 per thousand or 73.333 cases per thousand per year. Again using Campbell's figure of 9% for mortality yields an estimate of 6.6 deaths per thousand per year. [This may be confirmed by using Campbell's figure, and using the lower bounds of the 99% CI of 7% for the attributable difference the projected excess mortality attributable to combination therapy should be (0.07 x .09) or 6.3 cases per thousand per year which, when added to the 0.3 deaths per thousand per year yields 6.6 deaths per thousand per year.] This amounts to 385 x 6.6 x ¼ or 635 deaths per year. Assuming Campbell has exaggerated the hypoglycemic mortality fivefold still yields 127 excess hypoglycemic deaths per year from combination. **The projected excess risk attributable to metformin+sulfonylurea combination induced hypoglycemia would then be** 6.6 x ¼ x 0.2 or **0.33 deaths /1000 PYE**.

8. DOSAGE AND INDICATIONS:

The use of metformin, if approved in NIDDM as monotherapy, should be placed in the context of targetable lowering and/or maintenance of HbA1c to below 7% within two-years of initiation of therapy.

[See MOR of John Gueriguian valuable mainly for some dose-ranging considerations. Nevertheless, lactic acidosis appears even at the lowest metformin doses, particularly in alcoholics, cirrhotics, or others with synergistic inhibition of NADH[H+] oxidation or its mitochondrial shuttling.]

If approved, metformin should only be indicated in diabetics who are obese (BMI males >=27, females>=25).

If approved, metformin should be absolutely contraindicated in patients with sulfonylurea failure or in those who are taking concomitant sulfonylurea therapy.

If approved, metformin should be absolutely contraindicated in patients with existing CHD or who are at any increased risk therefrom.

If approved, hemoglobin A1c, creatinine, and electrolytes, blood pressure, and EKG's

should be performed every 8 weeks. A line on a date chart (plotted against A1c) should be drawn connecting the before-therapy A1c to a value of 7% exactly 730 days (2 years) later. That line should never lie below the line A1c=7 (parallel to the X-axis) or have any slope >0. Then:

If any two successive values lie above the line, therapy with metformin should be discontinued.

If creatinine values increase above 1.5 therapy with metformin should be ceased.

If any EKG changes develop, therapy with metformin should be ceased.

If blood pressure elevates, therapy with metformin should be discontinued.

If any intercurrent illnesses develop, therapy with metformin should cease until the illness is completely resolved.

If approved, metformin should be contraindicated in patients over age 53 (1 standard deviation below the mean age of patients with lactic acidosis).

If approved, metformin should be contraindicated in patients whose alcoholic intake may exceed 1 oz. on any given day.

If approved, metformin should be contraindicated in patients with clinically significant depression.

If approved, large black box warnings should appear for lactic acidosis, UGDP data, [as well as the findings within this NDA of significantly increased] death, EKG changes, angina, hypoglycemia, and hospitalizations.

9. LABELING REVIEW:

Not applicable *pro-tempore*

10. SPECIAL CONSIDERATIONS:

1) The sponsor has submitted an exceedingly poor application which has required extensive effort to integrate data in order to discover problems which should have been readily apparent. The most revealing data is to be found in the US open-enrollment study (89-1C-6023) for which a complete study report has yet to be finalized or submitted (see Section 7.3.3).

2) It would have been better, perhaps, if proper dose-ranging studies and more meaningful drug-interaction studies had been required before NDA submission.

11.1 CONCLUSIONS

1) The UGDP Study[27] suggested increased mortality, predominantly cardiovascular in nature, associated with phenformin monotherapy. The excess (non-lactic acidosis) mortality was 6.55/1000 over placebo, 1.84/1000 over tolbutamide, and 10.83/1000 over insulin. This was over 1632 patient-years of long- (8 years-)duration, continuous exposure (PYE).

2) This NDA has in its US trials 1136 PYE with more patients exposed but over relatively shorter-duration, and yet therein associated with metformin therapy can be found:

a) **Highly significant excess mortality** (***+6.16 deaths/1000 PYE***, $p<0.01$) in the patients randomized to metformin, and only in those patients randomized to metformin, particularly among the patients with sulfonylurea-failure. At the end of the observation period the death rate exceeded 29/1000 PYE (see **Section 7.2**).

b) **Significant excess in clinically meaningful EKG changes** (***+78/1000 PYE***, $p<0.05$, see **Section 7.7**). There appeared to be somewhat of an excess in moderate to severe conductive and contractile dysfunction than the expected ischemic events in this coronary disease-prone population (see also **Section 7.12.2**).

c) **Highly significantly excess hypoglycemia** (***+290 cases/1000 PYE***, $p<0.01$) in patients taking concomitant sulfonylureas compared with sulfonylurea alone (**see Sections 7.4, 7.12.4**)

d) **Lactic acidosis deaths** occurring at a rate (**0.88/1000 PYE**) which approximates some of the estimates (based on *reports*) for phenformin-associated lactic acidosis deaths in the US (0.90 to 1.05/1000 PYE)[44].

3) The European NDA (**Category ii**) controlled trials with less than 124 PYE has manifested:

Significant excess angina pectoris in pooled patients randomized to therapy with metformin (***+32 cases/1000 PYE***, $p<0.05$, see **Sections 7.4.2, 7.12.2**)

4) The **UKPDS** with 786 PYE has noted:

Significant excess annual hospitalization rates in patients randomized to *mono*therapy with metformin compared to pooled controls (***+28 hospitalizations/1000 PYE***, $p<0.05$, see **Section 7.17.2**)

5) The patients at most risk of metformin-induced mortality in the US clinical trials appear to be those with sulfonylurea-failure (see **Sections 7.2.12, 7.15.2, 7.16.1**). It is difficult to sort out the precise mechanisms which may underlie this association. The

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44Lowenstein, *Loc.Cit*, p.128 (reports estimates of 1.8 to 2.1 cases/1000 PYE) and 50% death rate is estimated on page 145

University Group Diabetes Program[27] (UGDP) showed significant excess mortality independently in both the sulfonylurea and biguanide arms - but no study was made of the potential additive effects of the two classes of medication taken simultaneously. The significant excess mortality displayed by the combination therapy among patients with sulfonylurea-failure in the comparatively well-underpowered US trials may, indeed, be a function of this additive phenomenon. Any benefits obtained in patients with sulfonylurea failure - increased compliance (? <= delay of insulin therapy), improved control, decreased treatment emergent sustained hypertension in whites - are far outweighed by the above risks. **Therefore this population of sulfonylurea-failures and/or sulfonylurea concomitants certainly ought to be absolutely excluded from any indication.**

6) *Should this drug be approved for only obese diabetics with dietary-failure who are not taking concurrent therapy with sulfonylureas*?

1) **Pro**:

a) The savings rate for deaths due to ESRD would be 0.08/1000 PYE. (see **Section 6.2.8**)

b) The savings rate for blacks due to ESRD would be 0.33/1000 PYE. (see **Section 6.2.10**)

c) None of the deaths or hypoglycemia occurred in this population. (see **Section 7.2.9**)

d) A registry is likely to be in place to improve the detection of any adverse mortality

2) **Con**:

a) EKG changes were significant only by pooling across *both* populations (see **Section 7.7**)

b) The significant increase in hospitalizations in the UKPDS was demonstrated by just this *mono*therapy population (see **Section 7.17.2**)

c) It can be estimated with reasonable certainty that 35% (at least 24.6% to at most 45.4%) of patients with MALA come from this population of diabetic *mono*therapy with metformin (see **Section 7.17.1.6**)

d) The savings in blacks may only reflect a sampling error with a population manifesting poorer glycemic control at baseline (see **Section 6.2.14**)

e) The UGDP Study showed increased total and cardiovascular mortality in a similar population treated with phenformin *mono*therapy (see **Section 7.17.3**)

f) The projected mortality of metformin in this *mono*therapy population (estimated at 20.2 deaths/1000 PYE) amongst a background estimated at 16 deaths/1000 PYE (see **Section 7.17.3**) is such that not only would 10,000 metformin patients have to be registered, but so also would 10,000 of their matched controls in order to detect a difference in mortality of 42 patients per year with 95% CI of 5 to 80 excess deaths/year. The logistics of accomplishing this might be a bit cumbersome.

g) **The excess mortality seen in the US trials is still highly significant** (12.4 excess deaths/1000 with 99% CI of 0.4 to 24.4 excess deaths/1000) **when all**

metformin-randomized patients from both populations are pooled against all patients randomized to a control.

7) This morbidity and mortality information was *not* available to the advisory committee when it recommended approval of metformin on March 18, 1994.

8) The burden of proof in ***removing*** phenformin from the market for "imminent hazard", according to the Administrative Law Judge at the time, was that FDA

> **..need only raise significant doubts as to the prior showing of safety. Once this threshold burden is met, the manufacturers are required to prove the safety of phenformin.**[45]

This threshold has been far exceeded already, and we are only considering approval. The burden is now upon the sponsor to "prove the safety" of metformin in any given population.

12. RECOMMENDATIONS:

The simplest, safest, and most expedient solution is for non-approval.

Ronald Jay Innerfield, M.D.
Medical Officer
Apr 18, 1994

20-357
HFD-510/20-357/Fleming/Gueriguian/Innerfield
HFD-510/Chiu/Ysern
HFD-510/Jordan/Hertig
HFD-510/Short
HFD-426/Hunt
20-357.rvw

45Federal Register, 6 April 1979

The extensive, concientious efforts reflected in this review are much appreciated. However, I have come to a different conclusion regarding the approvability of this NDA. My interpretation of the data will be interpreted in a separat review.

D Fleming
5/16/94

Leche Acidosis - Cases
(n = 255)

Sorted by Death by Country

BES #/ NPR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/BA-35 77	N	0.7000			4	24.030	F	850		75	acidosis, lactic; apoplexy; coagulopathy (DIC); hemodialysis; hepato-renal syndrome; pleural effusions	glibenclamide;		AUS
/BA-2 052.27		2.2200	6.890	8.9125093	1.7000000	15.900		3000	30.00	48	acidosis, lactic; arrhythmia; atrial fibrillation; ethanolism; hypothermia; peritoneal dialysis; renal failure, moderate		Phillips PJ et al, Aust N Z J Med 8:281-284,1978	AUS
/BA-35 79					1700	18.00	23	acidosis, lactic; gastroenteritis				furfluramide; insulin (actrapid/ultra lente)	scanty data	BEL
/BA-36 76		1.4095	7.100	25.0000000	7.5491838	11.200		2550		79	abdominal pain; acidosis, lactic; anemia normochromic, normocytic; DIC; febrile; hepatic necrosis; hepatorenal syndrome; pulmonary edema; renal failure; shock	glibenclamide; clobazam	Hepatitis A was positive. Eight years before Rx and because of mild renal insufficiency "it was urgently recommended at that time that her diabetes therapy be switched to insulin. But since the attending	BEL

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
													family physician felt that insulin therapy was impossible because of the patient's miserable compliance, her oral antidiabetic therapy was continued at his express wish. In spite of the renal failure, the dosage of this therapy was later apparently even increased."	
/8A-01 826		1.4000	6.720			20.000	M	3400		71	acidosis, lactic; anuria; bradycardia; dialysis, peritoneal; dysarthria; dyspnea; headache; nausea; vomiting		Recovery p dechallenge p prolonged hospitalization	BEL
/8A-36 95							F	2000	12.00	44	abdominal pain; acidosis, lactic; nausea; vomiting		Switch to glibenclamide restored bicarbonate to normal	CAN
/819		1.0323	7.400	33.0000000	19.8836279	7.300	M	2550		81	abdominal pain; acidosis, lactic; hematochezia;		Switch to insulin restored bicarbonate to normal	CAN
/08A-2 832.31		1.1000	6.910			16.500		500		41	abdominal pain; acidosis, lactic; ethanolism, acute and	glibenclamide	Korhonen T et al, Duodecim 94:1504-1508, 1978	FIN

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											chronic; coronary artery disease			
/533			6.000		4.0000000	18.000	F			48	acidosis, lactic; chronic renal insufficiency; chronic hemodialysis;		Rx breast Ca and renal failure p mitomycin Rx -> hemodialysis 3x/week. Suspected overdose.	FR
/08A-2 052.54			7.210	20.5636601	8.0000000	12.000				56	acidosis, lactic; ; coma; psychoneuroses; renal failure, moderate		Larcan A; Lambert H et al, Ann Med Nancy Est 20:989-996, 1981//Perrot D et al, Med Urg 2(2):85-91, 1986	Fr
/603		3.8000	7.170	46.0000000	18.0000000	15.470				58	acidosis, lactic; acute pulmonary edema; cyanosis; dyspnea	gliclazide; furosemide; nicardipine	CHF c pulmonary edema (?pulmonary embolism vs venous gases). ? chronic renal status	FR
/446										65	acidosis, keto; myocardial infarction;	???	MI -> cardiogenic shock -> pulmonary edema -> oligoanuria	FR
/323		2.2000	7.170	30.0000000	11.0000000	9.500				67	acidosis, lactic; anemia; atrial fibrillation; circulatory failure; ethanolism; hepatomegaly; hypertension; mitral stenosis; pulmonary		[Responded to cardiotonic Rx and changeover to insulin]	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											edema; rheumatic heart disease;			
/586										68	acidosis, lactic; duodenal ulcer - perforation; shock		metabolic acidosis p perforation. Several surgical interventions and d/c metformin -> good outcome	FR
/192		11.6400	7.140			33.000		850		61	abdominal pain; acidosis, lactic; antibiotics, aminoglycoside; coma; fever; hemodialysis; prothrombin time elevation; sepsis; vomiting;	acenocoumarol; amiloride; cefotaxime; chlorothiazide ; cimetidine; cotrimazole; digoxin; gentamycin; thyroxine	PT = 10% favorable response p hemodialysis	FR
/08A-2 032.61		11.1666	6.630	13.4896287	1.4000000	28.600		1000		74	acidosis, lactic; hemodialysis; hyperparathyroidism; renal failure		Perrot D et al, In Reunion del la Societe de Reanimation de la Langue Francaise. Paris 24 Nov 83, Paris, Expension Scientifique Francaise 1983	Fr
/08A-2 032.5			6.900	41.9855642	8.0000000	6.500			7300.00		acidosis, lactic; angiography; cardiovascular disease; dialysis,peritoneal;		Mayat, Diabetologia 10:485,1974	Fr

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											renal failure (moderate); tachypnea; vomiting			
/08A-2 032.56						5.600				75	acidosis, lactic; diarrhea; renal failure, moderate; retrosternal pain; tachycardia, paroxysmal; vomiting		Lefort C et al, Est-Med 3:266-271, 1983 // Perrot B et al, Med Urg 2(2):85-91, 1986	Fr
/08A-2 032.6			7.200	26.3026796	10.0000000	17.000		1500	3650.00	56	acidosis, lactic; angiography; cirrhosis; coma; dialysis,peritoneal; ethanolism; headache; renal failure (moderate); waiting		Royat, Diabetologia 10:485,1974	Fr
/08A-2 032.10			7.200			15.000		1600	1825.00	65	acidosis, lactic; peritoneal dialysis; renal failure;		Mirouze et al, Nouv. Presse Medic. 5:1004,1976	Fr
/08A-2 032.16		2.1000	6.770	32.5162156	4.7000000	18.000			5475.00		acidosis, lactic; anuria; coma; dehydration; gastroenteritis; hypothermia		Assan R et al, Diabetologia 13:211-217,1977	Fr
/08A-2 032.15		1.1000	7.170	14.0928878	5.0000000	13.200			300.00	66	acidosis, lactic; aminoglycosides; anuria; coma;	gentamycin;	Assan R et al, Diabetologia 13:211-217,1977	Fr

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											dehydration; gastroenteritis; urinary tract infection;			
/08A-2 032.14		2.0000	7.030	32.5911732	8.5000000	13.000			5475.00	67	acidosis, lactic; angiography; anuria; coma; coronary artery disease; hemodialysis; hypoglycemia;	glibenclamide	Assan R et al, Diabetologia 13:211-217,1977	Fr
/08A-2 032.68						6.640		1700	1460.00	38	acidosis, lactic;		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/1167		0.9324	7.140	22.4000000	7.6278123	2.580				49	abdominal pain; acidosis, lactic; asthenia; hemodialysis; renal failure, acute; somnolence; tachycardia; urinary tract infection		UTI (+ metformin) -> acute renal failure	FR
/806		3.5000	7.170	26.0000000	9.2257142					52	abdominal pain; acidosis, ?lactic; coma; polydipsia; polyuria	ciprofibrate; gliclazide	E. coli septicemia of ?urogenital origin	FR
/549		2.2000	7.380			5.700			1825.00	60	acidosis, lactic;	glibenclamide	Hx "serious psychiatric	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											dehydration		problems."	
/485		7.8000	7.010	21.7500000	5.2143478	28.000				61	acidosis, lactic; acute renal insufficiency; hemodialysis; surgery, orthopedic;	diflazide; a-methyldopa	"slow regression of red cell metformin content after hemodialysis for 5 consecutive days; recurrence of plasma metformin elevation following dialysis sessions."	FR
/08A-2 052.43			6.800	9.5000000	1.4099379	25.300			150.00		abdominal pain (LUQ?); acidosis, lactic; anorexia; asthenia; dialysate, peritoneal; diarrhea; dyspnea; vomiting		Reboul A, Thesis Med Univ Nantes, 1979	Fr
/08A-2 052.36		10.5000	7.200	19.0000000	7.2077547	12.000				62	acidosis, lactic; bradycardia; hypotension; obtundation; polypnea; shock		Charpentier D, Diagnostics 209:31, 1978	FR
/205		9.0300	7.300			16.000				64	abdominal pain; acidosis, lactic; angiography; CVA; hemodialysis; oliguranuria; renal failure; vomiting;	allopurinol; clonidine; furosemide; a-methyl dopa	favorable response p hemodialysis	FR
/08A-2 052.89		3.3300	6.700	22.0000000	2.6448436	13.200			6.00		acidosis, lactic; hemodialysis; renal		Chalopin JM et al, Arch Int Med 144:203-5, 1984	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Durin in Days	Age	CoStart	Conc Rx	Review	Loc
											failure, chronic, mild; shock			
/47[illegible]		11.4000									acidosis, lactic; cardiovascular collapse; renal failure; sepsis	gliclazide	metformin discontinued	FR
/722		2.7639	6.990	31.0000000	7.2677503	20.800				66	acidosis, lactic; dehydration; hemodialysis; hyperosmolar;	amiloride; digoxin; gliclazide; hydrochlorthiazide; mannitol	During hospitalization in 1990 for hemorrhagic CVA.	FR
/08A-2 032.47		9.0000	6.780	20.7539132	3.0000000	14.400			730.00		abdominal pain; acidosis, lactic; angiography; coma; obtundation; peritoneal dialysis; polypnea;		Barbare JC et al, Sem Hop Paris 57:11-12, 1981	Fr
/607		1.1100	6.800	17.5792360	2.6607251	13.000				67	abdominal pain; acidosis, lactic; hypocalcemia; hypomagnesemia; pulmonary edema; renal insufficiency, acute		Ureteral tumor. Creatinine 2.5 on admission but was 1.1 after left neprectomy.	FR
/795		7.4370	6.950	18.7111291	4.0000000	13.100			1460.00		acidosis, lactic; coma; hemodialysis; ketonuria; shock	altizide; bisoprolol; captopril; glibenclamide; hydrochlorthiaz	Hx breast Ca c surgery on 11/25/91 -> ICU admission c anuria and shock on 12/3/91	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
												ide;		
/08A-2 052.57		2.4420	6.640	15.8489318	1.7000000	23.800			9125.00	68	acidosis, lactic; coma; death; delirium; hepatic failure; hyperthyroidism; shock;	glybutamide	Oksenhendler G et al, Ann Fr Anesth Reanim 2.3:249,1983	Fr
/608		2.2089	7.240	26.9153477	11.2201844	7.600				69	acidosis, lactic; angiography; dyspnea; renal insufficiency, acute	acetyldigitoxin ; buflomedil; diltiazem; furosemide; propacetamol	Neuropathic ulcer, aortic stenosis, MI, pulmonary hypertension	FR
/08A-2 052.62		3.1191	6.630	17.1790837	1.8000000	18.420			7.00	70	acidosis, lactic; coma; diarrhea; hemetemesis; hemodialysis; polypnea; renal failure; ulcer, duodenal; urinary tract infection; vomiting		Daumal M et al, Forum des clubs et associations francaise d'anesthesie et reanimation chirurgicale, Paris, 13-16 Sep 1984 // Lalau JD et al, La Presse Medicale 13: 2581, 1984. Ref #1 pH->7.15 @ T0 whereas Ref #2 ph->6.88 @T0	FR
/347			6.750	24.0000000	3.4000000					71	acidosis, lactic; coma; dyspnea; hypothermia; shock;	aluminum phosphate; dihydralazine; furosemide; α-methyldopa	hypertension; obesity	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/333	N	1.1800	7.350		18.9000000	5.300	F	1700		80	acidosis, lactic; depression; circulatory failure; ethanolism; hypertension;	diltizide; captopril; digoxin; gliclazide; meprobamate; spironolactone	[Responded to changeover to insulin]	FR
/902		8.0586	7.200			17.000					acidosis, lactic; angiography; arrhythmia, supraventricular; melena		S/P Venography	FR
/522						4.500			120.00	83	acidosis, lactic;	digitoxin; enalapril; furosemide; gliclazide	no clinical symptoms	FR
/445										85	acidosis, keto; diarrhea; vomiting	gliclazide; meprobamate; paraflutazide; pentoxyphylline	sick after NSAID's for arthritis	FR
/553		7.8000	7.240		10.0000000	6.700		2500	1500.00	82	acidosis, lactic; anorexia; bowel obstruction; dehydration; diarrhea; hemodialysis	digoxin; glibenclamide	Diarrhea x 2 weeks duration -> "partial bowel obstruction," dehydration, and anuria -> severe hypoglycemia -> hemodialysis > favorable outcome,	FR
/389		1.2900	7.360	27.0000000	14.8388415	5.800		2550	8395.00	42	acidosis, lactic;	insulin;	depressed IDDM (?)	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											suicide attempt;		patient on insulin + metformin for 23 years who took 40 tablets of metformin	
/08A-2 032.65						12.000			1095.00	56	acidosis, lactic; hemodialysis;		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/344			7.280	33.4500000	15.0834260	8.000			4380.00	68	abdominal pains; acidosis, lactic; anemia; diarrhea, chronic; falling; coma; dyspnea; hypoglycemia; hypothermia; ketonuria; myocardial infarction; nausea; pulmonary infection; weight loss (23kg); vomiting	chlorpropamide	Hx diabetic retinopathy, HI, COPD, peripheral neuropathy. Responded to bicarbonates and switch to insulin	FR
/351			7.400		20.0000000	2.800				72	acidosis, lactic;	glibenclamide; a-methyldopa	favorable response to switching Rx to benfluorex and d/c metformin	FR
/08A-2 032.26 .a		3.0000	7.320	31.9227278	16.0000000	2.500			8.00	76	acidosis, lactic; angiography; anuria; hemodialysis; renal failure, moderate		Prinseau J et al, Ann Med Interne:128:173-177,1978	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/258	N	4.6600	7.050	13.3000000	3.5800000	4.200	F	2550		76	acidosis, lactic; hemodialysis; shock;	glibenclamide	creatinine 106 mM/L = 1.18 since 1982 (favorable outcome p hemodialysis)	FR
/08A-2 032.87		1.1100	7.240	25.0000000	10.4207745	14.000			+++	80	acidosis, lactic; angiography; hemodialysis; normal renal function	furosemide; gliclazide	Lalau et al, Intensive Care Med 13:383-387, 1986	FR
/336			7.240	25.0000000	10.4200000	5.900			1825.00		acidosis, lactic ; angina; angiography; arteritis; hemiparesis, focal; hemodialysis; shock;	gliclazide; digoxin		FR
/761		1.2987	7.470	27.7000000	19.3374852	4.300				81	acidosis, lactic; asthenia; dehydration; hypokalemia; hyponatremia	bufomadil; clonidine; glibenclamide; indapamide; naftidrofuryl; nicardipine	Hx retinopathy, HT, ASPVD	FR
/348		1.8600	7.400		18.0000000	3.200	3000			71	acidosis, lactic; arrhythmia; prothrombin time increased	acenocoumarol; colistin; digoxin; fenofibrate; gliclazide; α-methyldopa	hypertension; hyperlipidemia; heart failure	FR
/335		7.6000			13.0000000	6.300	3400	1095.00		58	acidosis, lactic ; anuria; paralysis,	captopril; cyclothiazide;	(Responded to peritoneal dialysis)	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											focal; peritoneal dialysis; shock;	gliclazide; triamterene		
/08A-2 032.86		4.2846	7.140	42.8000000	13.9059286	12.700			+++	62	acidosis, lactic; hemodialysis; sepsis; shock		Lalau et al, Intensive Care Med 13:383-387, 1986	FR
/228			7.240	26.3876062	11.2000000	12.700			7300.00		acidosis, lactic; angiography(?); collapse; hemodialysis; oligoanuria; renal failure; shock; ulcer, leg;	buflomedil; clonidine; fenofibrate; glenclamide; lorazepam	favorable response p hemodialysis	FR
/349					12.5000000					65	acidosis, lactic; diarrhea	clonidine; furosemide; haloperidol; phenobarbital; prazosin	hypertension, hemiplegia => responded to w/d, but apparently replaced on 1 tablet/day (850 mg)	FR
/821		6.6045	7.270	31.3400723	14.0000000	9.000				67	abdominal pain; acidosis, lactic; coma; diarrhea; duodenal ulcer; hematemesis; renal failure; ureteral calculus	gliclazide; lorazepam; loperamide; trimetazedine	Recovered p dialysis, d/c metformin, and discovery/removal of ureteral calculus.	FR
/08A-2 032.4						15.000		4500	730.00	58	acidosis, lactic; cardiovascular disease; renal		Robert et al	Fr

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											failure (moderate)			
/612		1.0101	7.490	23.9883289	17.7827939	380.000		7650	1.00	16	acidosis, lactic; ingestion; suicidal gesture	altizide; spironolactone; cimetidine	Given bicarbonate and lavage on admission.	FR
/799			7.360	36.3915031	20.0000000	3.130		12750		44	acidosis, mild; suicidal ingestion	benfluorex; dexfenfluramine; doxycycline; endotelon; erythromycin; floctafenine; minaprine; niflumic acid; phloroglucinol; rimantadine; tritoqualine	4th suicidal ingestion	FR
/08A-2 032.83			6.980			25.000		15000	0.25	83	acidosis, lactic; ingestion, suidcidal	cimetidine; glibenclamide; isoniazide; rifampicin;	Ryder REJ Br J Clin Prac 58:229-230, 1984	FR
/1174			7.340	36.0000000	18.8929596	1.400		25500		41	acidosis, lactic; suicidal attempt;		Overdose.	FR
/742		0.9990	6.630	17.1790837	1.8000000	14.250	M			54	acidosis, lactic; ethanolism; hypothermia; ketoacidosis; shock	altizide; benfluorex; glibenclamide; enalapril; loprazolam;	During hospitalization in 1990 for hemorrhagic CVA.	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
												spironolactone		
/167			6.660			25.000			90.00	60	acidosis, lactic; dehydration; diarrhea; hemodialysis; malnutrition; parotid tumour	nifuroxazide	(metformin -> 28.9 <- hemodialysis -> favorable response)	FR
/820		3.8739	7.090	19.5000000	5.6597858	16.300			1095.00	61	acidosis, lactic; ethanolism; febrile; hepatocellular insufficiency; hepatorenal syndrome; ventricular tachycardia		Recovered	FR
/443						2.000				64	acidosis		metabolic acidosis presumably documented without elevation of lactate (no data given)	FR
/460		6.5000	7.340	25.0000000	13.1200000	7.000				79	abdominal pain; acidosis, lactic; circulatory failure; dehydration; fever;	allopurinol; α-methyldopa	Rx hypertension, prostatic adenoma, gout, and renal insufficiency.. Favorable response to hydration and switch to insulin Rx.	FR
/334									850	30.00	67 abdominal pain; acidosis, lactic (?);	carbutamide	(Responded to changeover to glibornuride)	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											diarrhea; flushing; sweating; vomiting;			
/08A-2 032.26		4.0000	6.900	20.9942521	4.0000000	6.500		1000		74	acidosis, lactic; angiography; anuria; CVA; hypertension; peritoneal dialysis ; renal failure, moderate		Prinseau J et al, Ann Med Interne:128:173-177,1978	FR
/550		0.3000	7.400	34.0000000	22.0000000	2.000		1500	3650.00	65	?acidosis; dehydration; glomerulonephritis, proliferative; hypothermia; neurotrophic ulcer; obtundation; skin infection - ?streptococcal;	allopurinol; captopril; cephaloeporin; gliclazide	Hx nl acetoacetate 4.5 µg/ml (2.5-6.5). Nl. ß- hydoxybutyrate 24 µg/ml (20-30)	FR
/08A-2 032.9			6.940			14.000		1600	2555.00	78	acidosis, lactic; cardiovascular disease; renal failure; sepsis		Mirouze et al, Nouv. Presse Medic.5:1004,1976	Fr
/08A-2 032.75						5.800		1700	730.00	48	acidosis, lactic;		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/585		0.9000	7.370		21.0000000	4.900			270.00	52	acidosis, lactic; asthenia; myalgias	clorazepate; doxepin;	Ketosis at onset. Metformin, doxepin, and	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
												gliclazide; valproate	clorazepate discontinued -> normalization of lactate levels	
/08A-2 032.43 b		2.8000	7.170	15.0000000	5.3223079	5.500			5.00	54	acidosis, lactic; angiography; coma vigil; dialysis, peritoneal; hypotension; renal failure		Reboul A, Thesis Med Univ Nantes, 1979	Fr
/393		0.9000	7.310		15.2000000	5.000				59	acidosis, lactic; agitation	acetylsalicylate of lysine; pentoxyphylline	? alcohol -> agitation	FR
/502		22.0000	6.840			7.850				61	abdominal pain; acidosis, lactic; aerophagia; anorexia; coma vigil; ; diarrhea; dyspnea; hypertension; kidney, atrophic; nausea; pulmonary edema; renal calculi; renal insufficiency;		[favourable course p hemodialysis]	FR
/1175			7.320	38.4000000	18.8929596	58.300				62	acidosis, lactic; coma; ethanolism	difeberbamate; feberbamate; furosemide; glibenclamide; nitrazepam;	Blood alcohol was 3.22 g/L. ABG's ? after Rx.	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
												phenobarbital; urapadil		
/583		4.7000	7.200	19.0000000	8.0000000	6.940			5475.00	64	acidosis, lactic; dehydration; ketosis	gliclazide	acute pulmonary infection -> dehydration -> rehydration -> switch to insulin	FR
/08A-2 032.88		1.2210	6.840	17.2000000	2.8209799	7.850			+++	68	acidosis, lactic; coma vigil; hemodialysis; renal failure, acute; nephrolithiasis; pyelonephritis, acute and chronic	furosemide; gliclazide	Lalau et al, Intensive Care Med 13:383-387, 1986	FR
/777		2.2755	7.300	29.0000000	13.8803365	5.790			1825.00	69	acidosis, lactic; anemia; ethanolism; ?hepatorenal syndrome; pleural effusions; shock	aluminum magnesium hydroxide; clonidine; chlormezanone; digoxin; furosemide; gliclazide; naftidrofuryl; pyridoxine; thiamine; tiemonium; ticlopidine;	Hx cirrhosis and renal insufficiency	FR
/08A-2						8.700			2190.00	71	acidosis, lactic;		Lambert H et al, Ann Fr	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
032.67											hemodialysis;		Anesth Reanim 6:88-94, 1987	
/482					15.0000000	8.800				72	acidosis, lactic; chest pain; peritoneal dialysis; pulmonary edema; tachycardia;	amiodarone; carbutamide; cardizem; digoxin; fluindione; indapamide; isorbide; nifedipine; naftidrofuryl	Favorable outcome following peritoneal dialysis. Normal renal function before episode.	FR
/580		3.7000	7.110	17.0000000	6.0000000	17.000				75	acidosis, lactic; anorexia; bowel obstruction; dehydration; diarrhea; hematochezia; rehydration	flurbiprofen; nifedipine; piribedil; trimetazidine	Diarrhea x 2 weeks duration -> "partial bowel obstruction," dehydration, and anuria -> rehydration -> favorable outcome,	FR
/651		3.9294	7.340	22.9086763	12.0226442	11.490			2920.00	76	acidosis, lactic; common duct stone; jaundice; somnolence;		Hx depression	FR
/08A-2 032.80						10.400			3650.00	80	acidosis, lactic; hemodialysis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 032.12		2.0000	7.250	23.4422879	10.0000000	7.200		2400	7.00	49	acidosis, lactic; angiography; anuria;	dihydralazine; furosemide;	Assan R et al, Diabetologia	Fr

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											hemodialysis; hypoglycemia; hypothermia	spironolactone	13:211-217,1977	
/08A-2 032.13		3.6000	7.1[illegible]	16.1510215	6.0000000	13.200			168.00	52	acidosis, lactic; angiography; anuria; hypothermia; peritoneal dialysis;	clofibrate; clonidine; furosemide; propranolol	Assan R et al, Diabetologia 13:211-217,1977	Fr
/08A-2 032.48		2.7000	7.290	21.3796206	10.0000000	8.890		2500	1095.00	80	abdominal pain; acidosis, lactic; obtundation; peritoneal dialysis; polypnea;		Barbare JC et al, Sem Hop Paris 57:11-12, 1981	Fr
/396		1.6700	6.940	26.2500000	5.4325033	15.900		2550		45	acidosis, lactic; diarrhea; dyspnea; hemodialysis; muscle cramps	furosemide; glibenclamide; α-methyldopa; nifedipine	normal creatinine levels increased at the time of presentation to "11mg/dl. Responded to hemodialysis.	FR
/523		7.8000								47	?acidosis, lactic; acute renal insufficiency; coma; dry mouth; hypoglycemia;	acebutolol; clomipramine; furosemide; gliclazide; lorazepam; α-methyldopa	dry mouth -> somnolence -> hypoglycemia -> semi-comatose state -> acute renal insufficiency. Improved p metformin and gliclazide discontinued. Carbutamide added.	FR
/678						8.800				57	acidosis, lactic;		immediately after	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											cardiovascular surgery; cardiovasular collapse;		coronary surgery	
/245		6.5500	7.230	18.5000000	7.5300000	20.000					acidosis, lactic; antibiotics, aminoglycoside; arterial insufficiency; asthma; carcinoma of the lung; dyspnea; hemodialysis; hemoptysis; pulmonary infection; renal insufficiency; thoracotomy;	amikacin; gentamycin	favorable response p hemodialysis	FR
/526		4.5000	6.870	13.2000000	2.3115325	35.500				59	acidosis, lactic; ethanolism, chronic; acute renal insufficiency; cirrhosis; dyspnea; shock	cimetidine; glibenclamide; lactulose; spironolactone	Hospitalized for decompensated cirrhosis with ascites and edema. Progressive renal insufficency followed by state of shock c lactic acidosis	FR
/536		9.5000	6.770	15.0000000	2.0000000	15.000			4745.00		acidosis, lactic; chills; diarrhea; fever; hemodialysis; nausea; vomiting	glibenclamide	Suspected malaria p trip to Vietnam -> 2 weeks later c lactic acidosis.	FR
/605		2.3310	7.290	24.2000000	11.2253527	8.110				62	acidosis, lactic; angiography;	acebutolol; furosemide;	angiography "to evaluate his hypertension" [sic]	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											hemodialysis; hypertension;	gliclazide; ramipril		
/08A-2 032.69						6.260			730.00	67	acidosis, lactic; ARDS		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 032.72						5.600			3650.00	80	acidosis, lactic;		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 032.28 //08A-8291// 08A-91 10		1.0000	6.720	11.7489754	1.5000000	13.500		3400		44	abdominal pain; acidosis, lactic; air-fluid levels; bradycardia; coma vigil; ethanolism, acute and chronic; guarding; hypothermia; intestinal obstruction; nausea; sepsis; shock; vomiting		Charbonnel et al, Nouv Presse Medic 7:2573-4, 1978	FR
/653		9.0354	6.720	29.6551411	3.8000000	14.500				68	acidosis, lactic; ethanolism, chronic; hypertension	digoxin; dihydralazine; enalapril; glibenclamide; hydrochlorthiazide	Catarract surgery -> anuria	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/433	N	1.3900	6.650	13.5000000	1.4252794	21.000	M	3400		72	abdominal pain; acidosis, lactic; anemia, megaloblastic (pernicious); back pain; consciousness disturbed; dyspnea;	pentoxyphylline;	switched to diet therapy alone	FR
/08A-2 032.63		2.0335	7.060	6.3826348	2.7000000	20.200		5100		48	abscess, inguino-scrotal; acidosis, lactic; angiography; hemodialysis; polypnea;	glibonuride; colimycin	Daumal M et al, Forum des clubs et associations francaise d'anesthesie et reanimation chirurgicale, Paris, 13-16 Sep 1984 // Lalau JD et al, La Presse Medicale 13: 2581, 1984. Ref #1 pH->7.15 @ T0 whereas Ref #2 ph->6.88 @T0	FR
/08A-2 032.45			7.270	38.0539720	17.0000000	9.100		5850	75.00	55	abdominal pain; acidosis, lactic; anorexia; diarrhea; dysuria; edema, peripheral; ethanolism,chronic; polypnea; somnolence	Pancreozymin	Beaudot C et al, ADiabete Metab 6.3:199-203, 1980. Moderate renal insufficiency induced by prostatic adenoma.	Fr
/08A-2 032.85		2.3310	7.060	38.2500000	10.9597336	12.600		12750	0.33	38	acidosis, lactic; ingestion, suicidal; hemodialysis; hypoglycemia; stupor	librax	Huguet et al, Revue de Med de Tours 20:521-524, 1986	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/08A-2 032.53	N		7.240	28.7872377	12.0000000	12.200	M	15000		53	acidosis, lactic; ; coma; ingestion, suicidal?;	phenobarbital	Larcan A; Lambert H et al, Ann Med Nancy Est 20:989-996, 1981//Perrot D et al, Med Urg 2(2):85-91, 1986	Fr
/431								17000		21	acidosis, lactic; suicide attempt;		took diabetic brother's pills	FR
/8A-01 820.1							F			62	acidosis, lactic; ?death		NOIA	FRG
/8A-01 820.2										72	acidosis, lactic; nausea; vomiting	glibenclamide	Hx multiple problems including heart failure and rectal carcinoma. Switch to insulin resolved problems. NOIA	FRG
/8A-01 819.2						4.800		1500			abdominal pain; acidosis, lactic; diarrhea; weight loss	glibenclamide	Metformin discontinued <- elevated lactate	FRG
/08A-2 032.94		1.9980	7.200	21.2862910	8.3000000	5.400	M	1000	2555.00	73	acidosis, lactic; dyspepsia; dyspnea; edema, pulmonary ; hip fracture;		Lebech M; Olesen LL; Ugeskrift Laeger 152: 2511-12, 1990	FRG
/08A-3 564;08 A-1822 .2						5.700		1700		67	acidosis, lactic; benzodiazepine abuse;	glibenclamide; metoprolol	Ca of the cecal pole.	FRG

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/08A-2 032.29	N	2.1000	6.690			8.700		850		63	acidosis, lactic;		Berger W; Amrein R. Schweiz Rundsachau Med: 67:661,1978	SW
/08A-2 032.30			7.000					1700		67	acidosis, lactic;		Berger W; Amrein R. Schweiz Rundsachau Med: 67:661,1978	SW
/08A-2 032.17			6.900				M	3000	240.00	84	acidosis, lactic; cardiovascular disease; renal failure, moderate; sepsis		The National Board of Health and Welfare, Sweden 1977	SW
080088 /8.12. 2.249. 16			7.170			8.900	F	1000	1825.00	62	acidosis, lactic; anuria; cardiomyopathy; coronary heart disease		Wilholm BE; Myrhed M; Eur J Clin Pharm 44:589-591, 1993	SWE
791306 /8.12. 2.249. 6			7.300			9.400	M	1000		59	acidosis, lactic; congestive heart failure; myocardial infarction	?digoxin	Wilholm BE; Myrhed M; Eur J Clin Pharmacom 44:589-591, 1993	SWE
780408 /8.12. 2.249. 2			7.300			2.000			11.00	71	acidosis, lactic; cirrhosis; coronary heart disease		Wilholm BE; Myrhed M; Eur J Clin Pharmacom 44:589-591, 1993	SWE
770602			6.300					3000	180.00	83	acidosis, lactic;		Wilholm BE; Myrhed M; Eur	SWE

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/8.12. 2.249. 1											congestive heart failure		J Clin Pharmacom 44:589-591, 1993	
/UI923 73223									1095.00	59	abdominal pain; acidosis, lactic; coma; dyspnea; hemodialysis; hypotension; nausea; vomiting		Lim PS et al, J Formos Med Assos 91:374-6, 1992	TAI
/08A-2 032.82			6.690	51.0740143	6.0000000			1000	270.00	35	acidosis, lactic; coma; convulsions; ethanolism (acute and chronic); hepatic disease; hypoglycemia; hypothermia	cimetidine; glibenclamide; isoniazide; rifampicin;	Ryder REJ Br J Clin Prac 58:229-230, 1984	UK
/8A-01 817.1									730.00	65	acidosis, lactic; hypotension	bumetanide; cimetidine; fenbufen; glipizide; nifedipine; pancrex; triazolam; trimeprazine	NOIA	UK
/08A-2 032.84			7.020	20.6250000	5.0815944	9.600		4000	450.00	65	acidosis, lactic; angina pectoris; hemodialysis;	bumetamide; cimetidine; cotrimoxazole;	Hutchison SMJ and Catterall JR, Br J Clin Prac 41:673-4, 1987	UK

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											dyspnea; ethanolism, acute and chronic; pancreatitis, chronic; pulmonary disease, chronic obstructive;	fenbufen; glipizide; glyceryl trinitrate; nifedipine; pancreozymin; triazolam; trimeprazine;		
/UI930 74242		6.760	11.3501081	1.6000000	10.900					62	abdominal pain; acidosis, lactic; hemodialysis, long-term; nausea; nephrolithiasic; renal failure, chronic; vomiting	allopurinol; isorbide dinitrate; nicardipine; pancreozymin;	Gan SC et al, Arch Int Med 152:2333-6, 1992	USA
/BA-35 Y 68		6.3000	6.780	10.0000000	1.4454398	22.600	F	250		71	acidosis, lactic; coma; death; dehydration; diarrhea; dyspnea; hemodialysis; hypothermia; lipase elevation; shock; renal failure			BEL
/08A-2 032.1		4.9062	7.170			9.200		2000	4.00	79	acidosis, lactic; death; renal failure (moderate)		Lebacq, Tirzmalis	Bel
/08A-2			6.800			13.100	M	1500	120.00	56	acidosis, lactic;		Beaujean MA et al, Brux	BEL

DES #/ NPR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	Co/Start	Conc Rx	Review	Loc
032.34											death		Med 58:191-8, 1978	
/08A-2 032.32		3.4000	6.800			14.000			21.00	58	acidosis, lactic; death		Beaujean MA et al, Brux Med 58:191-8, 1978	BEL
/08A-2 032.33			6.850			13.000		3000	21.00	71	acidosis, lactic; death		Beaujean MA et al, Brux Med 58:191-8, 1978	BEL
/8A-35 88 (GM737 88)			6.900	20.9942321	4.0000000	10.000	F			67	acidosis, lactic; death; hemodialysis; shock		Hx "known renal insufficiency"	CAN
/8A-35 86 (73122)								1500	8.00	67	acidosis, lactic; death; shock	calcium carbonate; diazepam; dimenhydrinate; furosemide; glyburide; procardia	Hx chronic renal failure on intermittent peritoneal dialysis	CAN
/8A-35 89						28.000	M			47	acidosis, lactic; death; dyspnea; ethanolism; hemodialysis; nausea; shock; vomiting		Hx ethanol binge. Ethanol level 35 mM/L	CAN
/711			6.960			36.000	F			28	acidosis, lactic; anuria; coma death; dehydration	azathioprine; sulfamethoxazole; trimethoprim		FR

BMDP # / NPR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/770	Y	3.7962	6.730	12.0000000	1.5459662	35.000	F			52	acidosis, lactic; death; dehydration; hemodialysis; hyponatremia; suicidal ingestion; shock	alginic acid; domperidone; ranitidine	Hx cirrhosis, esophageal varices	FR
/OBA-2 852.49			7.300	20.8929611	10.0000000	7.900				65	acidosis, lactic; death; UTI		Larcan A; Lambert H et al, Ann Med Nancy Est 20:989-996, 1981//Perrot D et al, Med Urg 2(2):85-91, 1986	Fr
/254		11.5000								72	acidosis, lactic (???); coma; death; hypertension; renal insufficiency;		rapidly fatal course	FR
/255		0.8000	7.130		10.0000000	12.000				80	acidosis, lactic; death; ketoacidosis; hemodialysis shock, cardiogenic	glibenclamide; isorbide; nifedipine		FR
/351											acidosis, lactic; death; splenic infarct; shock		No further Hx available.	FR
/OBA-2 852.35			6.750	16.0000000	2.0611044	25.000					acidosis, lactic; bradycardia; death; obtundation; polypnea; shock		Viet N. Thesis Med (Fac. Med Paris Ouest) 1978, 1-55 (BCA-490)	FR
/447						2.000				89	acidosis; coma,	???	MI -> cardiogenic shock	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											hyperosmolar; death; dehydration		-> pulmonary edema -> oligoanuria	
/780		3.1857	7.250	28.0000000	11.9453807	14.500		500		60	abdominal pain; acidosis, lactic; coma; hypothermia; nausea; shock; vomiting	captopril; hydrochlorthiazide	"septic shock". Data available was apparently missing (BA-3663) but faxed in after request as BA-3663A	FR
/08A-2 032.76						10.000		850	2.00	69	acidosis, lactic; death		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 032.79						10.400			1825.00	72	acidosis, lactic; death; hemodialysis; sepsis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/394		1.5000	6.930	44.0000000	10.1000000	10.800					acidosis, lactic; agitation; cardiorespiratory arrest; death; dyspnea;	betamethasone; enalapril; gliclazide; quinidine;	dwarfism; obesity	FR
/08A-2 032.56 C		14.0000				2.200			1095.00	73	acidosis, lactic; coma; death; delirium; hepatic failure; hyperthyroidism; shock;		Lefort C et al, Est-Med 3:266-271, 1983	Fr
/08A-2 032.24		1.6650	7.250	18.7542627	8.0000000	16.500		1000	10.00	59	acidosis, lactic; angiography; anuria;		Primeau J et al, Ann Med Interne:128:173-177,1978	FR

DES #/ NFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											death; hypertension; microangiopathy; peritoneal dialysis			
/08A-2 052.55						10.100				77	acidosis, lactic; anuria; colon carcinoma [+ metastases]; death; hemodialysis; renal failure, moderate		Lefort C et al, Eat-Med 3:266-271, 1983 // Perrot D et al, Med Urg 2(2):85-91, 1986	Fr
/08A-2 052.39		7.200	22.0000000	10.5293120	8.000			1500	+++	65	acidosis, lactic; coma; death; liver disease;		Larcan,A; Lambert H. Journ.Ann.Diabetol.Hotel-Dieu,Flammarion. Paris p 99-133;/Larcan,A; Lambert H. et al Diabete Metab 5.2:103-112, 1979	Fr
/525		6.780						1700			acidosis, lactic; ethanolism, acute and chronic; acute renal insufficiency; death; septic shock	glibenclamide	Hospitalized in a state of acute alcoholism with blood alcohol level of 2.56 mg/ml. Cardiac arrest and death in 2 days.	FR
/08A-2 052.51		7.040	24.0000000	6.3124797	12.400			1825.00		47	acidosis, lactic; cirrhosis; death;		Larcan A; Lambert H et al, Ann Med Nancy Est 20:989-996, 1981//Perrot D et al, Med Urg 2(2):85-91, 1986	Fr

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
/08A-2 032.75 b	Y					12.900	F	1700	1825.00	48	acidosis, lactic;		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/08A-2 032.38			6.680	23.0000000	2.6405841	13.000			+++	54	acidosis, lactic; coma; death; liver disease;renal failure		Larcan,A; Lambert H. Journ.Ann.Diabetol.Hotel-Dieu,Flammarion. Paris p 99-133;/Larcan,A; Lambert H. et al Diabete Metab 5.2:103-112, 1979	Fr
/483		5.6000	6.940	11.0000000	3.0000000	268.000				56	acidosis, lactic; convulsions; death; hemiplegia; leukocytosis	aspirin; dipyridamole; gliclazide; heparin; a-methyldopa	2 months p CVA unexpected convulsive disorder c hyperglycemia and lactic acidosis and acute renal insufficiency.	FR
/08A-2 032.78						21.000			730.00	60	acidosis, lactic; death; hemodialysis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/716		2.3000	7.370	35.3000000	19.6833944	2.700				61	?acidosis; anemia, multifactorial; cephalgia; coma; death; dehydration; ?hypothyroidism; melena; nausea; shock	clonidine; digoxin; enalapril; hydrochlorthiazide; L-thyroxine		FR
/717		3.0000				11.955				65	acidosis, lactic; aortic valve replacement; CVA;	acenocoumarol; digoxin; furosemide;	Staphylococcal septicemia	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											coma; death; dehydration; shock	glibenclamide; spironolactone		
/06A-2 052.60		8.9577	6.770	14.1579577	2.0000000	28.600				67	acidosis, lactic; death; hemodialysis; septicemia		Perrot D et al, In Reunion del la Societe de Reanimation de la Langue Francaise. Paris 24 Nov 83, Paris, Expansion Scientifique Francaise 1983	Fr
/06A-2 052.74						13.800			365.00	68	acidosis, lactic; death; hemodialysis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR
/60A		0.9000	7.180	17.3000000	6.9000000	26.900				69	acidosis, lactic; acute pulmonary edema; cardiomyopathy; death	acenocoumarol; benfluorex; dextropropoxyphene; digoxin; furosemide; nicardipine; paracetamol; potassium canrenoate; tamoxifen	CHF Rxed c diuretics including Na/K ATPase inhibitors -> renal failure and lactic acidosis and death. ***NORMAL RENAL FUNCTION*** "This seems to be an interaction between metformin and diuretics, with the diuretics having brought about an acute renal insufficiency, resulting in accumulation of metformin, which in turn caused fatal lactic	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
													acidosis." (p. 08A-03503)	
/623									3650.00		abdominal pain; acidosis, lactic; death; ketoacidosis; dehydration; dyspnea; shock; vomiting;		Hx gallstones	FR
/661			7.290	38.6857535	18.4000000	20.000				73	acidosis, lactic; coma, hyperosmolar; death; diarrhea, chronic	mesalazine; metronidazole;	"chronic diarrhea" OR "Crohn's Disease"????	FR
/343		13.3200	7.100						60.00		abdominal pains; acidosis; death; dyspnea; hemodialysis; hypothermia; pancreatitis	a-methyl dopa		FR
/479			7.240	17.0250000	7.0859812	9.800				76	acidosis, lactic; angiography; cardiovascular collapse; death; hemodialysis; renal failure;	allopurinol; clomipramine; clomipramine; clorazepate; dipotassium; gliclazide; lomiphylline; norethandrolone; propranolol	plethoric diabetic; chronic renal insufficiency; cirrhosis	FR
/475		2.8000	7.400	20.9250000	12.3310482	8.000					abdominal pain; acidosis, lactic; arrhythmia; cardiovascular	indapamide	Hx hypertension	FR

DES #/ MFR #	Death	Cr	pH	pCO2	HCO3-	Lactate	Sex	Dose	Rx Dur'n in Days	Age	CoStart	Conc Rx	Review	Loc
											collapse; death; gastroenteritis; hypokalemia; hypoxia; vomiting			
/430		3.9300	7.370		14.5000000					77	acidosis, lactic; acute abdominal pain; death	glibenclamide; guanfacine;	Hx ethanolism; cirrhosis; pancreatitis;	FR
/650		2.1867	7.210	20.8929611	8.1283051	9.000				79	abdominal pain; acidosis, lactic; bronchospasm; death; dehydration; diarrhea; dyspnea; hematochezia; mesenteric infarction; shock; vomiting;	acefylline heptaminol; acetylsalicylic acid; ciprofibrate; declofenac; flavinoids; glibenclamide; hydroxycarbamide; tedelparine		FR
/514		5.5000	7.210	17.0000000	6.6130224	7.900				80	acidosis, lactic; acute renal insufficiency; death; dyspnea; pulmonary embolism; hematemesis; hemodialysis; melena;	amiloride; hydrochlorthiazide; netilmicine	2 year rx of bronchial infection c sulfamide.	FR
/88A-2 852.71						11.500			2555.00		acidosis, lactic; death; hemodialysis		Lambert H et al, Ann Fr Anesth Reanim 6:88-94, 1987	FR

Sodium Changes from Baseline (4)
in Patients with >20% Drops in GFR

udy_ID	Group	Visit_No	SAF12_CFB
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	-5.000
		Average:	-5.000
		Count:	1
		Standard Deviation:	0.000
		6.5	
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-49.000
		Average:	-1.361
		Count:	36
		Standard Deviation:	3.473
		7.1	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-66.000
		Average:	-1.535
		Count:	43
		Standard Deviation:	3.364
		8.1	
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-44.000
		Average:	-1.128
		Count:	39
		Standard Deviation:	2.398
		10.0	
		Total:	-22.000
		Average:	-0.688

Sodium Changes from Baseline in Patients with >20% Drops in GFR (5)

udy_ID	Group	Visit_No	SAF12_CFB
		Count:	32
		Standard Deviation:	3.147
		10.1	
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	-54.000
		Average:	-1.227
		Count:	44
		Standard Deviation:	3.096
		11.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
	Total:		-301.000
	Average:		-1.229
	Count:		245
	Standard Deviation:		3.236
	C	2.1	
		Total:	6.000
		Average:	6.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-29.000
		Average:	-1.074
		Count:	27
		Standard Deviation:	3.066
		6.1	
		Total:	6.000
		Average:	3.000
		Count:	2
		Standard Deviation:	0.000
		7.0	
		Total:	-45.000
		Average:	-1.667
		Count:	27
		Standard Deviation:	3.232

Sodium Changes from Baseline (6)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF12_CFB
	C	8.0	
		Total:	-32.000
		Average:	-1.455
		Count:	22
		Standard Deviation:	2.426
		8.1	
		Total:	-5.000
		Average:	-5.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-16.000
		Average:	-0.593
		Count:	27
		Standard Deviation:	3.280
		10.0	
		Total:	-47.000
		Average:	-1.679
		Count:	28
		Standard Deviation:	2.965
		10.2	
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	-36.000
		Average:	-1.440
		Count:	25
		Standard Deviation:	2.994
	Total:		-200.000
	Average:		-1.242
	Count:		161
	Standard Deviation:		3.106
	D	1.0	
		Total:	2.000
		Average:	2.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-1.000

Sodium Changes from Baseline
in Patients with >20% Drops in GFR

(7)

Study_ID	Group	Visit_No	SAF12_CFB
		Average:	-1.000
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	3.000
		Average:	3.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	5.000
		Average:	0.172
		Count:	29
		Standard Deviation:	5.966
		6.1	
		Total:	2.000
		Average:	2.000
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	8.000
		Average:	0.333
		Count:	24
		Standard Deviation:	2.285
		8.0	
		Total:	12.000
		Average:	0.364
		Count:	33
		Standard Deviation:	2.615
		8.1	
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	-30.000
		Average:	-1.071
		Count:	28

Sodium Changes from Baseline (8)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF12_CFB
		Standard Deviation:	3.251
		9.1	
		Total:	0.000
		Average:	0.000
		Count:	4
		Standard Deviation:	1.225
		10.0	
		Total:	-10.000
		Average:	-0.385
		Count:	26
		Standard Deviation:	2.040
		11.0	
		Total:	-19.000
		Average:	-0.442
		Count:	43
		Standard Deviation:	2.688
		11.2	
		Total:	3.000
		Average:	3.000
		Count:	1
		Standard Deviation:	0.000
	Total:		-26.000
	Average:		-0.134
	Count:		194
	Standard Deviation:		3.356
Total:			-527.000
Average:			-0.878
Count:			600
Standard Deviation:			3.282
Total:			-700.000
Average:			-0.799
Count:			876
Standard Deviation:			3.114

Phosphate Changes from Baseline (1)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF10_CFB
	A	3.1	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	4.000
		Average:	0.211
		Count:	19
		Standard Deviation:	0.388
		5.0	
		Total:	3.200
		Average:	0.188
		Count:	17
		Standard Deviation:	0.318
		5.1	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		5.2	
		Total:	-0.300
		Average:	-0.300
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	5.200
		Average:	0.193
		Count:	27
		Standard Deviation:	0.378
		6.1	
		Total:	-0.200
		Average:	-0.100
		Count:	2
		Standard Deviation:	0.600
		7.0	
		Total:	3.300
		Average:	0.110
		Count:	30
		Standard Deviation:	0.355
		7.1	

Phosphate Changes from Baseline (2)
in Patients with >20% Drops in GFR

'udy_ID	Group	Visit_No	SAF10_CFB
		Total:	0.300
		Average:	0.300
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	3.800
		Average:	0.211
		Count:	18
		Standard Deviation:	0.513
		8.1	
		Total:	-0.100
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	6.200
		Average:	0.214
		Count:	29
		Standard Deviation:	0.414
	Total:		25.700
	Average:		0.175
	Count:		147
	Standard Deviation:		0.399
	B	3.1	
		Total:	-0.100
		Average:	-0.033
		Count:	3
		Standard Deviation:	0.236
		4.0	
		Total:	-3.200
		Average:	-0.200
		Count:	16
		Standard Deviation:	0.465
		5.0	
		Total:	1.300
		Average:	0.059
		Count:	22
		Standard Deviation:	0.419
		6.0	
		Total:	4.100
		Average:	0.164
		Count:	25

Phosphate Changes from Baseline (3)
in Patients with >20% Drops in GFR

'tudy_ID	Group	Visit_No	SAF10_CFB
		Standard Deviation:	0.415
		7.0	
		Total:	4.400
		Average:	0.200
		Count:	22
		Standard Deviation:	0.451
		8.0	
		Total:	4.000
		Average:	0.211
		Count:	19
		Standard Deviation:	0.477
		9.0	
		Total:	3.900
		Average:	0.170
		Count:	23
		Standard Deviation:	0.426
	Total:		14.400
	Average:		0.111
	Count:		130
	Standard Deviation:		0.455
Total:			40.100
Average:			0.145
Count:			277
Standard Deviation:			0.427
87-2D	A	1.0	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	-0.600
		Average:	-0.600
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-0.100
		Average:	-0.100
		Count:	1
		Standard Deviation:	0.000
		6.0	

Phosphate Changes from Baseline (4)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF10_CFB
		Total:	3.100
		Average:	0.074
		Count:	42
		Standard Deviation:	0.432
		6.1	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	-0.300
		Average:	-0.300
		Count:	1
		Standard Deviation:	0.000
		6.5	
		Total:	0.500
		Average:	0.500
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-3.600
		Average:	-0.100
		Count:	36
		Standard Deviation:	0.616
		7.1	
		Total:	-0.800
		Average:	-0.800
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	5.200
		Average:	0.121
		Count:	43
		Standard Deviation:	0.434
		8.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	7.300
		Average:	0.187

Phosphate Changes from Baseline (5)
in Patients with >20% Drops in GFR

tudy_ID	Group	Visit_No	SAF10_CFB
		Count:	39
		Standard Deviation:	0.368
		10.0	
		Total:	4.500
		Average:	0.141
		Count:	32
		Standard Deviation:	0.464
		10.1	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	5.400
		Average:	0.123
		Count:	44
		Standard Deviation:	0.507
		11.1	
		Total:	-1.100
		Average:	-1.100
		Count:	1
		Standard Deviation:	0.000
	Total:		19.600
	Average:		0.080
	Count:		246
	Standard Deviation:		0.486
	C	2.1	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-0.500
		Average:	-0.019
		Count:	27
		Standard Deviation:	0.361

Phosphate Changes from Baseline (6)
in Patients with >20% Drops in GFR

udy_ID	Group	Visit_No	SAF10_CFB
8	C	6.1	
		Total:	0.600
		Average:	0.300
		Count:	2
		Standard Deviation:	0.600
		7.0	
		Total:	-1.300
		Average:	-0.048
		Count:	27
		Standard Deviation:	0.377
		8.0	
		Total:	-1.700
		Average:	-0.077
		Count:	22
		Standard Deviation:	0.585
		8.1	
		Total:	0.800
		Average:	0.800
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	1.200
		Average:	0.044
		Count:	27
		Standard Deviation:	0.358
		10.0	
		Total:	0.200
		Average:	0.007
		Count:	28
		Standard Deviation:	0.503
		10.2	
		Total:	-0.200
		Average:	-0.200
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	2.900
		Average:	0.116
		Count:	25
		Standard Deviation:	0.401
Total:			2.000

Phosphate Changes from Baseline (7)
in Patients with >20% Drops in GFR

udy_ID	Group	Visit_No	SAF10_CFB
	Average:		0.012
	Count:		162
	Standard Deviation:		0.442
	D	1.0	
		Total:	-0.700
		Average:	-0.700
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	0.300
		Average:	0.300
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	4.000
		Average:	0.138
		Count:	29
		Standard Deviation:	0.461
		6.1	
		Total:	0.400
		Average:	0.400
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-3.000
		Average:	-0.125
		Count:	24
		Standard Deviation:	0.550
		8.0	
		Total:	1.500
		Average:	0.044
		Count:	34
		Standard Deviation:	0.589
		8.1	
		Total:	-1.300
		Average:	-0.650
		Count:	2
		Standard Deviation:	0.450
		9.0	
		Total:	-0.900
		Average:	-0.032
		Count:	28

Phosphate Changes from Baseline (8)
in Patients with >20% Drops in GFR

Study_ID	Group	Visit_No	SAF10_CFB
		Standard Deviation:	0.539
		9.1	
		Total:	0.400
		Average:	0.100
		Count:	4
		Standard Deviation:	0.495
		10.0	
		Total:	3.500
		Average:	0.135
		Count:	26
		Standard Deviation:	0.444
		11.0	
		Total:	7.000
		Average:	0.163
		Count:	43
		Standard Deviation:	0.534
		11.1	
		Total:	0.200
		Average:	0.200
		Count:	1
		Standard Deviation:	0.000
		11.2	
		Total:	-0.700
		Average:	-0.700
		Count:	1
		Standard Deviation:	0.000
		Total:	10.700
		Average:	0.055
		Count:	195
		Standard Deviation:	0.538
Total:			32.300
Average:			0.054
Count:			603
Standard Deviation:			0.493
T			72.400
A e:			0.082
Count:			880
Standard Deviation:			0.475

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(1)

Study_ID	Group	Visit_No	SAF06_CFB
D	A	3.1	
		Total:	-2.500
		Average:	-2.500
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-2.100
		Average:	-0.111
		Count:	19
		Standard Deviation:	4.095
		5.0	
		Total:	3.400
		Average:	0.200
		Count:	17
		Standard Deviation:	4.497
		5.1	
		Total:	-5.200
		Average:	-5.200
		Count:	1
		Standard Deviation:	0.000
		5.2	
		Total:	3.400
		Average:	3.400
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	16.500
		Average:	0.611
		Count:	27
		Standard Deviation:	4.012
		6.1	
		Total:	-5.900
		Average:	-2.950
		Count:	2
		Standard Deviation:	1.950
		7.0	
		Total:	4.100
		Average:	0.137
		Count:	30
		Standard Deviation:	4.841
		7.1	

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(2)

udy_ID	Group	Visit_No	SAF06_CFB
		Total:	-3.200
		Average:	-3.200
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-3.500
		Average:	-0.194
		Count:	18
		Standard Deviation:	4.482
		8.1	
		Total:	12.100
		Average:	12.100
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	16.100
		Average:	0.555
		Count:	29
		Standard Deviation:	5.228
	Total:		33.200
	Average:		0.226
	Count:		147
	Standard Deviation:		4.662
	B	3.1	
		Total:	-1.600
		Average:	-0.800
		Count:	2
		Standard Deviation:	1.100
		4.0	
		Total:	21.300
		Average:	1.331
		Count:	16
		Standard Deviation:	3.517
		5.0	
		Total:	33.900
		Average:	1.541
		Count:	22
		Standard Deviation:	3.723
		6.0	
		Total:	14.400
		Average:	0.576
		Count:	25

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(3) dy_ID	Group	Visit_No	SAF06_CFB
		Standard Deviation:	4.161
		7.0	
		Total:	48.300
		Average:	2.195
		Count:	22
		Standard Deviation:	3.778
		8.0	
		Total:	49.600
		Average:	2.611
		Count:	19
		Standard Deviation:	3.688
		9.0	
		Total:	38.000
		Average:	1.652
		Count:	23
		Standard Deviation:	3.379
	Total:		203.900
	Average:		1.581
	Count:		129
	Standard Deviation:		3.776
Total:			237.100
Average:			0.859
Count:			276
Standard Deviation:			4.324
87-2D	A	1.0	
		Total:	-4.200
		Average:	-4.200
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	-5.800
		Average:	-5.800
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	1.400
		Average:	0.033
		Count:	42
		Standard Deviation:	2.864
		6.1	

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(4) tudy_ID	Group	Visit_No	SAF06_CFB
		Total:	0.300
		Average:	0.300
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	-4.400
		Average:	-4.400
		Count:	1
		Standard Deviation:	0.000
		6.5	
		Total:	1.200
		Average:	1.200
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-29.400
		Average:	-0.817
		Count:	36
		Standard Deviation:	3.747
		7.1	
		Total:	-2.000
		Average:	-2.000
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-17.400
		Average:	-0.405
		Count:	43
		Standard Deviation:	3.400
		8.1	
		Total:	1.600
		Average:	1.600
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	9.500
		Average:	0.244
		Count:	39
		Standard Deviation:	3.123
		10.0	
		Total:	4.900
		Average:	0.153

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(5) tudy_ID	Group	Visit_No	SAF06_CFB
		Count:	32
		Standard Deviation:	4.125
		10.1	
		Total:	7.700
		Average:	7.700
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	17.900
		Average:	0.407
		Count:	44
		Standard Deviation:	4.470
		11.1	
		Total:	-8.400
		Average:	-8.400
		Count:	1
		Standard Deviation:	0.000
	Total:		-27.100
	Average:		-0.111
	Count:		245
	Standard Deviation:		3.724
	C	6.0	
		Total:	-6.900
		Average:	-0.256
		Count:	27
		Standard Deviation:	4.073
		6.1	
		Total:	-14.200
		Average:	-7.100
		Count:	2
		Standard Deviation:	0.700
		7.0	
		Total:	-13.600
		Average:	-0.504
		Count:	27
		Standard Deviation:	3.951
		8.0	
		Total:	-17.100
		Average:	-0.777
		Count:	22
		Standard Deviation:	5.240

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(6)

Study_	Group	Visit_No	SAF06_CFB
	C	8.1	
		Total:	-1.100
		Average:	-1.100
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	0.500
		Average:	0.019
		Count:	26
		Standard Deviation:	4.153
		10.0	
		Total:	15.700
		Average:	0.561
		Count:	28
		Standard Deviation:	3.908
		10.2	
		Total:	-2.600
		Average:	-2.600
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	2.100
		Average:	0.084
		Count:	25
		Standard Deviation:	3.844
	Total:		-37.200
	Average:		-0.234
	Count:		159
	Standard Deviation:		4.234
	D	1.0	
		Total:	-1.400
		Average:	-1.400
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	3.300
		Average:	3.300
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	-3.200

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(7)

Study_ID	Group	Visit_No	SAF06_CFB
		Average:	-3.200
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	50.100
		Average:	1.728
		Count:	29
		Standard Deviation:	3.994
		6.1	
		Total:	-9.300
		Average:	-9.300
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	5.100
		Average:	5.100
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	23.900
		Average:	1.039
		Count:	23
		Standard Deviation:	2.867
		8.0	
		Total:	26.400
		Average:	0.800
		Count:	33
		Standard Deviation:	4.251
		8.1	
		Total:	4.900
		Average:	4.900
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	6.800
		Average:	0.243
		Count:	28
		Standard Deviation:	4.352
		9.1	
		Total:	-0.800
		Average:	-0.200
		Count:	4

Anion Gap Changes from Baseline
in Patients with >20% Drops in GFR

(8) udy_ID	Group	Visit_No	SAF06_CFB
		Standard Deviation:	3.064
		10.0	
		Total:	12.600
		Average:	0.485
		Count:	26
		Standard Deviation:	3.711
		11.0	
		Total:	22.100
		Average:	0.514
		Count:	43
		Standard Deviation:	4.273
		11.2	
		Total:	0.800
		Average:	0.800
		Count:	1
		Standard Deviation:	0.000
	Total:		141.300
	Average:		0.732
	Count:		193
	Standard Deviation:		4.051
Total:			77.000
Average:			0.129
Count:			597
Standard Deviation:			3.994
Total:			314.100
Average:			0.360
Count:			873
Standard Deviation:			4.115

Hematocrit vs Lactates

Hematocrit Changes from Baseline in Metformin Patients
Sorted by Levels of Increasing Lactic Acid
(1)

SAF19	Hct_CFB
0.4	
Total:	-2.000
Average:	-2.000
Count:	1
Maximum:	-2.000
Minimum:	-2.000
Standard Deviation:	0.000
0.6	
Total:	0.000
Average:	0.000
Count:	2
Maximum:	1.000
Minimum:	-1.000
Standard Deviation:	1.000
0.7	
Total:	-19.000
Average:	-0.950
Count:	20
Maximum:	5.000
Minimum:	-7.000
S rd Deviation:	3.090
0.8	
Total:	-72.000
Average:	-1.946
Count:	37
Maximum:	3.000
Minimum:	-24.000
Standard Deviation:	4.562
0.9	
Total:	-88.000
Average:	-1.517
Count:	58
Maximum:	4.000
Minimum:	-11.000
Standard Deviation:	2.890
1.0	
Total:	-60.000
Average:	-0.870
Count:	69
M num:	6.000
M um:	-8.000
S d Deviation:	2.775
1.1	
Total:	-99.000
Average:	-1.010

Hematocrit Changes from Baseline in Metformin Patients
Sorted by Levels of Increasing Lactic Acid
(2)

SAF19	Hct_CFB
:	98
Maximum:	6.000
Minimum:	-8.000
Standard Deviation:	3.115
1.2	
Total:	-95.000
Average:	-1.105
Count:	86
Maximum:	6.000
Minimum:	-20.000
Standard Deviation:	3.407
1.3	
Total:	-64.000
Average:	-0.719
Count:	89
Maximum:	14.000
Minimum:	-7.000
Standard Deviation:	3.369
1.4	
T	-109.000
A e:	-1.397
Count:	78
Maximum:	6.000
Minimum:	-12.000
Standard Deviation:	3.224
1.6	
Total:	-37.000
Average:	-0.685
Count:	54
Maximum:	7.000
Minimum:	-9.000
Standard Deviation:	2.987
1.7	
Total:	-94.000
Average:	-1.270
Count:	74
Maximum:	10.000
Minimum:	-14.000
Standard Deviation:	3.864
1.8	
T	-144.000
Average:	-2.057
Count:	70
Maximum:	3.000
Minimum:	-9.000
Standard Deviation:	2.501

Hematocrit Changes from Baseline in Metformin Patients
Sorted by Levels of Increasing Lactic Acid
(3)

S.	Hct_CFB
.9	
Total:	-72.000
Average:	-1.309
Count:	55
Maximum:	5.000
Minimum:	-10.000
Standard Deviation:	3.044
2.0	
Total:	-47.000
Average:	-0.810
Count:	58
Maximum:	8.000
Minimum:	-9.000
Standard Deviation:	3.416
2.1	
Total:	-10.000
Average:	-0.294
Count:	34
Maximum:	7.000
Minimum:	-6.000
S rd Deviation:	3.321
2.2	
Total:	-38.000
Average:	-1.652
Count:	23
Maximum:	3.000
Minimum:	-6.000
Standard Deviation:	3.129
2.3	
Total:	-41.000
Average:	-1.952
Count:	21
Maximum:	4.000
Minimum:	-5.000
Standard Deviation:	2.278
2.4	
Total:	-43.000
Average:	-1.792
Count:	24
M um:	3.000
M im:	-9.000
S d Deviation:	3.027
2.6	
Total:	-5.000
Average:	-0.385

Hematocrit Changes from Baseline in Metformin Patients
Sorted by Levels of Increasing Lactic Acid
(4)

SAF19	Hct_CFB
[illegible]	13
Maximum:	8.000
Minimum:	-8.000
Standard Deviation:	5.167
2.7	
Total:	-27.000
Average:	-2.077
Count:	13
Maximum:	5.000
Minimum:	-7.000
Standard Deviation:	3.751
2.8	
Total:	-3.000
Average:	-0.750
Count:	4
Maximum:	5.000
Minimum:	-6.000
Standard Deviation:	4.815
2.9	
[illegible]	6.000
[illegible]ge:	0.750
Count:	8
Maximum:	11.000
Minimum:	-6.000
Standard Deviation:	5.739
3.0	
Total:	5.000
Average:	0.833
Count:	6
Maximum:	5.000
Minimum:	-2.000
Standard Deviation:	2.267
3.1	
Total:	-8.000
Average:	-2.667
Count:	3
Maximum:	-1.000
Minimum:	-5.000
Standard Deviation:	1.700
3.2	
[illegible]	-4.000
Average:	-1.000
Count:	4
Maximum:	3.000
Minimum:	-3.000
Standard Deviation:	2.345

Hematocrit Changes from Baseline in Metformin Patients
Sorted by Levels of Increasing Lactic Acid
(5)

SAF19	Hct_CFB
3.3	
Total:	4.000
Average:	1.000
Count:	4
Maximum:	4.000
Minimum:	-5.000
Standard Deviation:	3.674
3.4	
Total:	-6.000
Average:	-3.000
Count:	2
Maximum:	-2.000
Minimum:	-4.000
Standard Deviation:	1.000
3.6	
Total:	1.000
Average:	0.200
Count:	5
Maximum:	5.000
Minimum:	-5.000
Standard Deviation:	3.429
4.6	
Total:	-4.000
Average:	-4.000
Count:	1
Maximum:	-4.000
Minimum:	-4.000
Standard Deviation:	0.000
==========	=======
Total:	-1175.000
Average:	-1.159
Count:	1014
Maximum:	14.000
Minimum:	-24.000
Standard Deviation:	3.334

Lactate

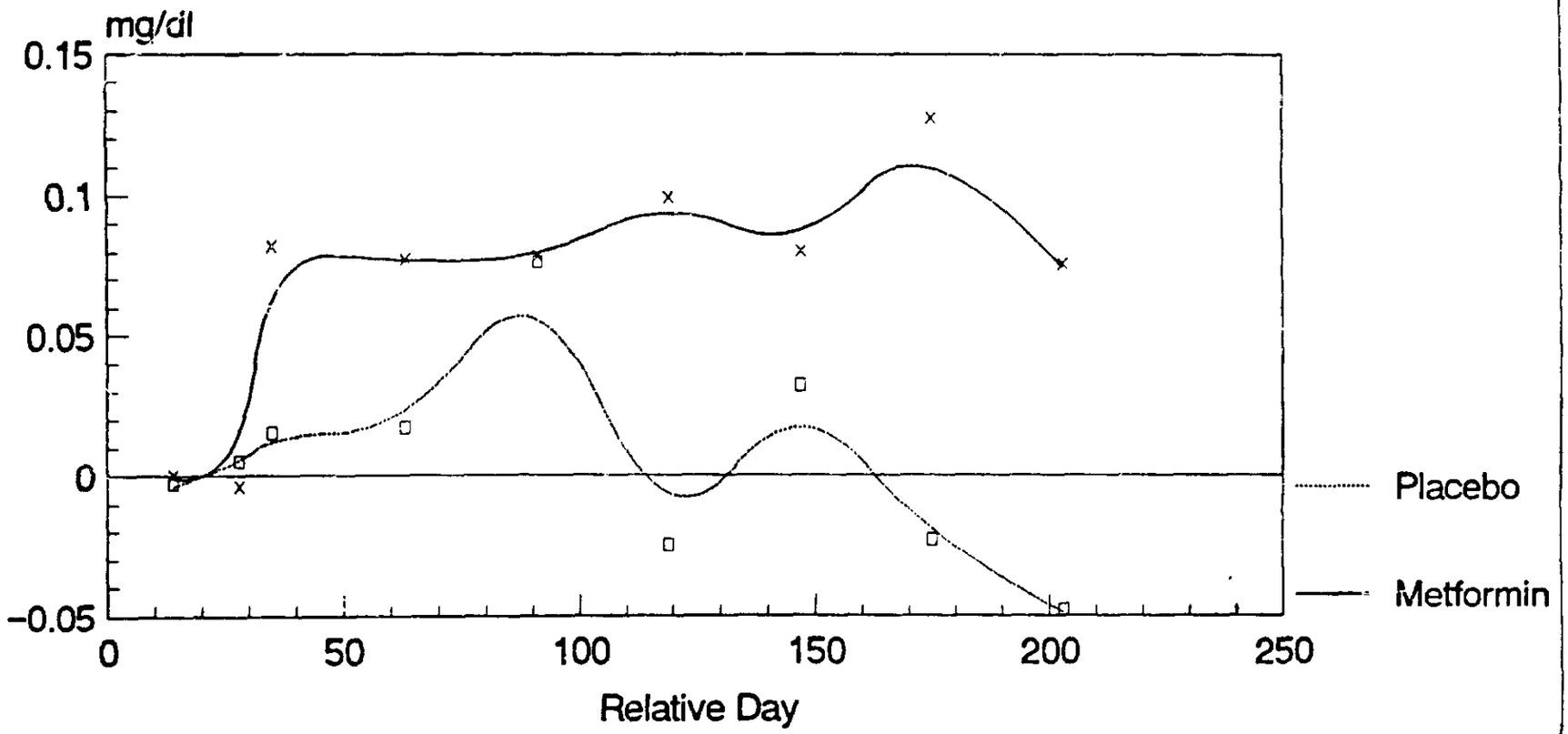
+

Lactate

vs

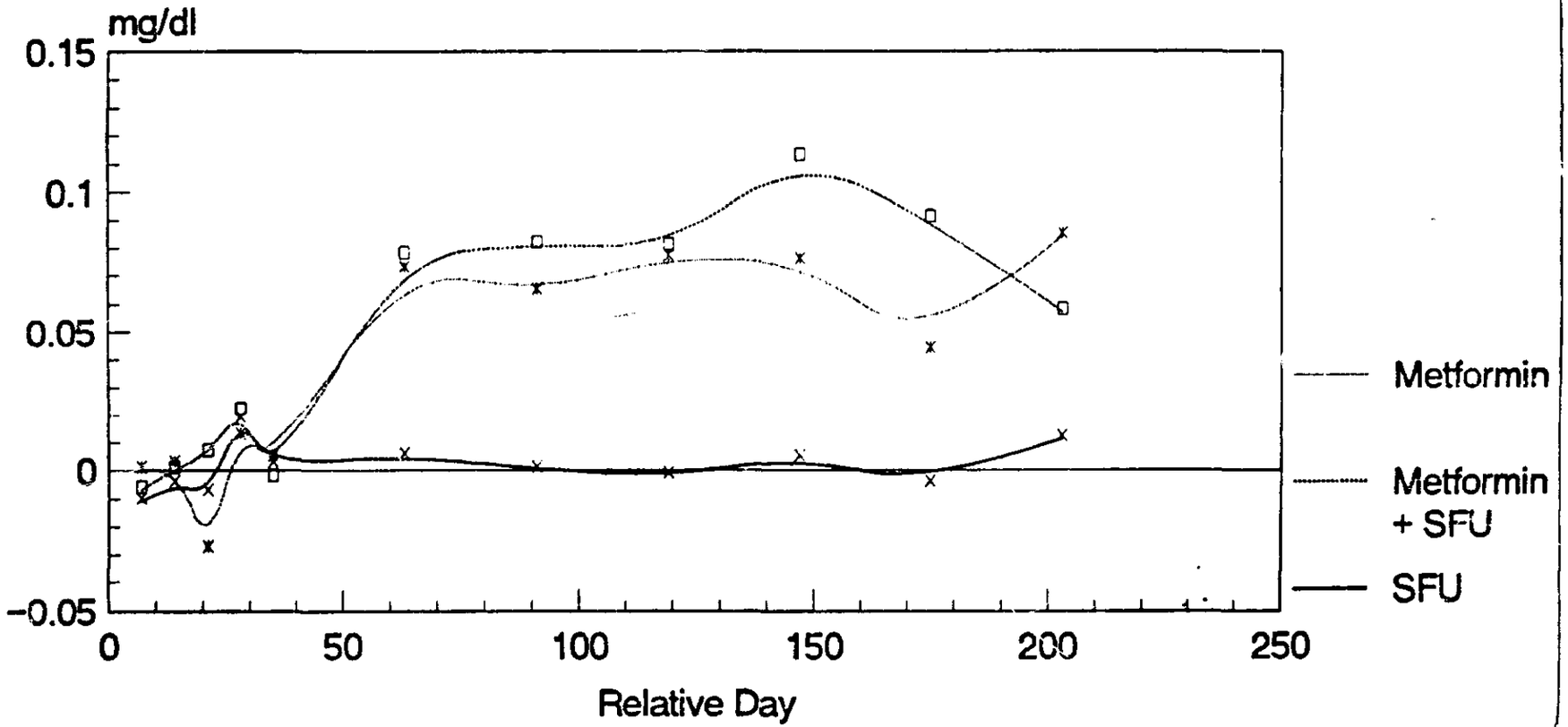
Creatinine

Mean Lactic Acid
Change from Baseline
Study 87-1D



graphs by gnome

Mean Lactic Acid
Change from Baseline
Study 87-2D



graphs by gnome

Creatinine Levels in Patients with 1 mEq/L increases in Lactate to >3 mEq/L by Changes in Creatinine

Cr_CFB	Cr
-0.300	
Total:	6.00
Average:	0.86
Count:	7
Maximum:	1.10
Minimum:	0.70
Standard Deviation:	0.16
-0.200	
Total:	2.40
Average:	0.80
Count:	3
Maximum:	1.00
Minimum:	0.70
Standard Deviation:	0.14
-0.100	
Total:	8.00
Average:	0.89
Count:	9
Maximum:	1.10
Minimum:	0.60
Standard Deviation:	0.17
0.000	
Total:	8.70
Average:	0.97
Count:	9
Maximum:	1.30
Minimum:	0.70
Standard Deviation:	0.16
0.100	
Total:	11.20
Average:	1.02
Count:	11
Maximum:	1.20
Minimum:	0.70
Standard Deviation:	0.17
0.200	
Total:	4.70
Average:	0.94
Count:	5
Maximum:	1.00
Minimum:	0.80
Standard Deviation:	0.08
0.300	
Total:	3.70
Average:	1.23

Creatinine Levels in Patients with
1 mEq/L increases in Lactate to >3 mEq/L
by Changes in Creatinine

r_CFB	Cr
C .:	3
Maximum:	1.30
Minimum:	1.20
Standard Deviation:	0.05
==========	====
Total:	44.70
Average:	0.95
Count:	47
Maximum:	1.30
Minimum:	0.60
Standard Deviation:	0.18

Lactic Acid Changes from Baseline in Metformin Patients
Sorted by levels of Increasing Creatinine
(1)

Cr	SAF19_CFB
0.4	
Total:	1.000
Average:	1.000
Count:	1
Maximum:	1.000
Minimum:	1.000
Standard Deviation:	0.000
0.5	
Total:	-0.700
Average:	-0.058
Count:	12
Maximum:	1.300
Minimum:	-1.500
Standard Deviation:	0.748
0.6	
Total:	11.400
Average:	0.106
Count:	108
Maximum:	1.800
Minimum:	-0.900
Standard Deviation:	0.476
0.7	
Total:	44.100
Average:	0.120
Count:	368
Maximum:	2.500
Minimum:	-1.600
Standard Deviation:	0.564
0.8	
Total:	56.100
Average:	0.092
Count:	612
Maximum:	3.100
Minimum:	-2.100
Standard Deviation:	0.548
0.9	
Total:	70.200
Average:	0.113
Count:	620
Maximum:	3.090
Minimum:	-2.700
Standard Deviation:	0.610
1.0	
Total:	29.300
Average:	0.050

Lactic Acid Changes from Baseline in Metformin Patients
Sorted by levels of Increasing Creatinine
(2)

Cr	SAF19_CFB
C	581
Maximum:	2.000
Minimum:	-2.300
Standard Deviation:	0.554
1.1	
Total:	40.400
Average:	0.110
Count:	366
Maximum:	2.500
Minimum:	-1.500
Standard Deviation:	0.532
1.2	
Total:	15.100
Average:	0.078
Count:	193
Maximum:	2.300
Minimum:	-2.100
Standard Deviation:	0.571
1.3	
T	5.500
A e:	0.056
Count:	98
Maximum:	1.400
Minimum:	-0.900
Standard Deviation:	0.414
1.4	
Total:	3.300
Average:	0.062
Count:	53
Maximum:	0.900
Minimum:	-0.800
Standard Deviation:	0.395
1.5	
Total:	2.700
Average:	0.245
Count:	11
Maximum:	0.800
Minimum:	-0.100
Standard Deviation:	0.274
1.6	
Tc	0.100
Average:	0.025
Count:	4
Maximum:	0.200
Minimum:	-0.100
Standard Deviation:	0.130

Lactic Acid Changes from Baseline in Metformin Patients
Sorted by levels of Increasing Creatinine
(3)

Cr	SAF19_CFB
1.8	
Total:	-0.100
Average:	-0.050
Count:	2
Maximum:	0.000
Minimum:	-0.100
Standard Deviation:	0.050
1.9	
Total:	0.200
Average:	0.200
Count:	1
Maximum:	0.200
Minimum:	0.200
Standard Deviation:	0.000
==========	======
Total:	278.600
Average:	0.092
Count:	3030
Maximum:	3.100
Minimum:	-2.700
Standard Deviation:	0.556

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

Study_ID (1)	Group	Visit_No	SAF19_CFB
)	A	3.1	
		Total:	-0.900
		Average:	-0.900
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-0.100
		Average:	-0.006
		Count:	18
		Standard Deviation:	0.504
		5.0	
		Total:	5.700
		Average:	0.335
		Count:	17
		Standard Deviation:	0.745
		5.1	
		Total:	0.300
		Average:	0.300
		Count:	1
		Standard Deviation:	0.000
		5.2	
		Total:	0.300
		Average:	0.300
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	3.400
		Average:	0.126
		Count:	27
		Standard Deviation:	0.493
		6.1	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-2.300
		Average:	-0.079
		Count:	29
		Standard Deviation:	0.697
		8.0	

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

(2) udy_ID	Group	Visit_No	SAF19_CFB
		Total:	1.300
		Average:	0.072
		Count:	18
		Standard Deviation:	0.603
		8.1	
		Total:	0.700
		Average:	0.700
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	3.300
		Average:	0.114
		Count:	29
		Standard Deviation:	0.630
	Total:		11.800
	Average:		0.083
	Count:		143
	Standard Deviation:		0.627
	B	3.1	
		Total:	0.300
		Average:	0.100
		Count:	3
		Standard Deviation:	0.283
		4.0	
		Total:	-1.300
		Average:	-0.081
		Count:	16
		Standard Deviation:	0.350
		5.0	
		Total:	1.400
		Average:	0.064
		Count:	22
		Standard Deviation:	0.346
		6.0	
		Total:	1.500
		Average:	0.065
		Count:	23
		Standard Deviation:	0.485
		7.0	
		Total:	1.000
		Average:	0.045
		Count:	22

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

(3) 'tudy_ID	Group	Visit_No	SAF19_CFB
		Standard Deviation:	0.327
		8.0	
		Total:	-0.400
		Average:	-0.021
		Count:	19
		Standard Deviation:	0.337
		9.0	
		Total:	1.000
		Average:	0.043
		Count:	23
		Standard Deviation:	0.683
	Total:		3.500
	Average:		0.027
	Count:		128
	Standard Deviation:		0.449
Total:			15.300
A...ge:			0.056
C			271
S ard Deviation:			0.551
87-2D	A	1.0	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
		3.0	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	0.600
		Average:	0.600
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	2.600
		Average:	0.062
		Count:	42
		Standard Deviation:	0.541
		6.1	

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

(4) udy_ID	Group	Visit_No	SAF19_CFB
		Total:	0.500
		Average:	0.500
		Count:	1
		Standard Deviation:	0.000
		6.2	
		Total:	0.600
		Average:	0.600
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	0.600
		Average:	0.017
		Count:	36
		Standard Deviation:	0.620
		8.0	
		Total:	3.600
		Average:	0.084
		Count:	43
		Standard Deviation:	0.479
		8.1	
		Total:	-0.500
		Average:	-0.250
		Count:	2
		Standard Deviation:	0.150
		9.0	
		Total:	2.900
		Average:	0.076
		Count:	38
		Standard Deviation:	0.466
		10.0	
		Total:	0.700
		Average:	0.022
		Count:	32
		Standard Deviation:	0.569
		11.0	
		Total:	2.600
		Average:	0.060
		Count:	43
		Standard Deviation:	0.523
Total:			15.300
Average:			0.063
Count:			241

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

(5) udy_ID	Group	Visit_No	SAF19_CFB
	Standard Deviation:		0.533
	C	3.0	
		Total:	-0.400
		Average:	-0.400
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	1.500
		Average:	0.056
		Count:	27
		Standard Deviation:	0.447
		6.1	
		Total:	-0.500
		Average:	-0.500
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-1.700
		Average:	-0.063
		Count:	27
		Standard Deviation:	0.420
		8.0	
		Total:	1.700
		Average:	0.077
		Count:	22
		Standard Deviation:	0.478
		9.0	
		Total:	-0.400
		Average:	-0.015
		Count:	27
		Standard Deviation:	0.349
		10.0	
		Total:	3.000
		Average:	0.111
		Count:	27
		Standard Deviation:	0.663
		11.0	
		Total:	4.200
		Average:	0.168
		Count:	25
		Standard Deviation:	0.370

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

(6)

Study_ID	Group	Visit_No	SAF19_CFB
	Total:		7.400
	Average:		0.047
	Count:		157
	Standard Deviation:		0.473
	D	4.0	
		Total:	-0.300
		Average:	-0.300
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	-0.600
		Average:	-0.600
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	1.500
		Average:	0.054
		Count:	28
		Standard Deviation:	0.382
		7.0	
		Total:	8.400
		Average:	0.365
		Count:	23
		Standard Deviation:	0.562
		8.0	
		Total:	4.700
		Average:	0.138
		Count:	34
		Standard Deviation:	0.470
		8.1	
		Total:	0.100
		Average:	0.050
		Count:	2
		Standard Deviation:	0.450
		9.0	
		Total:	7.200
		Average:	0.257
		Count:	28
		Standard Deviation:	0.801
		9.1	
		Total:	0.400

Lactic Acid Changes from Baseline
in Patients with >20% Drops in GFR

(7)

Study_ID	Group	Visit_No	SAF19_CFB
		Average:	0.200
		Count:	2
		Standard Deviation:	0.100
		10.0	
		Total:	2.900
		Average:	0.112
		Count:	26
		Standard Deviation:	0.553
		11.0	
		Total:	3.100
		Average:	0.072
		Count:	43
		Standard Deviation:	0.447
		11.2	
		Total:	0.100
		Average:	0.100
		Count:	1
		Standard Deviation:	0.000
	Total:		27.500
	Average:		0.146
	Count:		189
	Standard Deviation:		0.547
Total:			50.200
Average:			0.086
Count:			587
Standard Deviation:			0.524
Total:			65.500
Average:			0.076
Count:			858
Standard Deviation:			0.533

Creatinine Levels in Metformin Patients with
at least 1 mEq/L increases in Lactate
by Lactate Levels

SAF19	Cr_CFB
1.9	
Total:	-0.700
Average:	-0.140
Count:	5
Maximum:	0.100
Minimum:	-0.400
Standard Deviation:	0.162
2.0	
Total:	-0.300
Average:	-0.030
Count:	10
Maximum:	0.100
Minimum:	-0.300
Standard Deviation:	0.149
2.1	
Total:	0.000
Average:	0.000
Count:	8
Maximum:	0.100
Minimum:	-0.100
Standard Deviation:	0.071
2.2	
Total:	-0.500
Average:	-0.071
Count:	7
Maximum:	0.300
Minimum:	-0.500
Standard Deviation:	0.231
2.3	
Total:	0.200
Average:	0.067
Count:	3
Maximum:	0.100
Minimum:	0.000
Standard Deviation:	0.047
2.4	
Total:	-0.300
Average:	-0.027
Count:	11
Maximum:	0.200
Minimum:	-0.200
Standard Deviation:	0.114
2.6	
Total:	-0.600
Average:	-0.060

Creatinine Levels in Metformin Patients with
at least 1 mEq/L increases in Lactate
by Lactate Levels

SAF19	Cr_CFB
C	10
Maximum:	0.100
Minimum:	-0.200
Standard Deviation:	0.080
2.7	
Total:	-0.500
Average:	-0.045
Count:	11
Maximum:	0.100
Minimum:	-0.300
Standard Deviation:	0.123
2.8	
Total:	-0.400
Average:	-0.044
Count:	9
Maximum:	0.300
Minimum:	-0.200
Standard Deviation:	0.142
2.9	
Tr	-0.200
A :	-0.040
Coun:	5
Maximum:	0.100
Minimum:	-0.200
Standard Deviation:	0.102
3.0	
Total:	-0.700
Average:	-0.070
Count:	10
Maximum:	-0.100
Minimum:	-0.200
Standard Deviation:	0.078
3.1	
Total:	-0.500
Average:	-0.100
Count:	5
Maximum:	0.100
Minimum:	-0.300
Standard Deviation:	0.126
3.2	
To	0.300
Average:	0.050
Count:	6
Maximum:	0.200
Minimum:	-0.100
Standard Deviation:	0.096

Creatinine Levels in Metformin Patients with
at least 1 mEq/L increases in Lactate
by Lactate Levels

SAF19	Cr_CFB
3.3	
Total:	0.600
Average:	0.120
Count:	5
Maximum:	0.200
Minimum:	0.000
Standard Deviation:	0.075
3.4	
Total:	-0.500
Average:	-0.250
Count:	2
Maximum:	-0.200
Minimum:	-0.300
Standard Deviation:	0.050
3.6	
Total:	0.100
Average:	0.025
Count:	4
Maximum:	0.200
Minimum:	-0.300
S d Deviation:	0.192
3.7	
Total:	0.100
Average:	0.050
Count:	2
Maximum:	0.100
Minimum:	0.000
Standard Deviation:	0.050
3.8	
Total:	-0.100
Average:	-0.100
Count:	1
Maximum:	-0.100
Minimum:	-0.100
Standard Deviation:	0.000
3.9	
Total:	0.100
Average:	0.050
Count:	2
M um:	0.300
M im:	-0.200
St d Deviation:	0.250
4.0	
Total:	-0.300
Average:	-0.300

Creatinine Levels in Metformin Patients with
at least 1 mEq/L increases in Lactate
by Lactate Levels

SAF19	Cr_CFB
t:	1
Maximum:	-0.300
Minimum:	-0.300
Standard Deviation:	0.000
4.1	
Total:	-0.100
Average:	-0.100
Count:	1
Maximum:	-0.100
Minimum:	-0.100
Standard Deviation:	0.000
4.3	
Total:	-0.400
Average:	-0.133
Count:	3
Maximum:	0.000
Minimum:	-0.300
Standard Deviation:	0.125
4.4	
	-0.300
ge:	-0.300
Count:	1
Maximum:	-0.300
Minimum:	-0.300
Standard Deviation:	0.000
4.6	
Total:	0.000
Average:	0.000
Count:	1
Maximum:	0.000
Minimum:	0.000
Standard Deviation:	0.000
4.8	
Total:	0.100
Average:	0.100
Count:	1
Maximum:	0.100
Minimum:	0.100
Standard Deviation:	0.000
=======	====
	-4.900
ge:	-0.040
Count:	124
Maximum:	0.300
Minimum:	-0.500
Standard Deviation:	0.144

Creatinine Levels in Metformin Patients by Levels of Increasing Lactic Acid
(1)

SAF19	Cr_CFB
0.4	
Total:	-0.200
Average:	-0.200
Count:	1
Maximum:	-0.200
Minimum:	-0.200
Standard Deviation:	0.000
0.6	
Total:	-0.200
Average:	-0.017
Count:	12
Maximum:	0.200
Minimum:	-0.300
Standard Deviation:	0.140
0.7	
Total:	0.200
Average:	0.005
Count:	44
Maximum:	0.300
Minimum:	-0.400
Standard Deviation:	0.148
0.8	
Total:	-0.500
Average:	-0.004
Count:	114
Maximum:	0.700
Minimum:	-0.400
Standard Deviation:	0.175
0.9	
Total:	-4.700
Average:	-0.025
Count:	185
Maximum:	0.600
Minimum:	-0.600
Standard Deviation:	0.171
1.0	
Total:	-6.500
Average:	-0.030
Count:	220
Maximum:	0.800
Minimum:	-0.400
Standard Deviation:	0.154
1.1	
Total:	-6.100
Average:	-0.023

Creatinine Levels in Metformin Patients
by Levels of Increasing Lactic Acid
(2)

SAF19	Cr_CFB
C	263
Maximum:	0.900
Minimum:	-0.400
Standard Deviation:	0.152
1.2	
Total:	-12.200
Average:	-0.046
Count:	266
Maximum:	0.500
Minimum:	-0.500
Standard Deviation:	0.160
1.3	
Total:	-9.100
Average:	-0.032
Count:	281
Maximum:	0.500
Minimum:	-0.400
Standard Deviation:	0.152
1.4	
T	-7.200
A e:	-0.028
Count:	258
Maximum:	0.700
Minimum:	-0.400
Standard Deviation:	0.144
1.6	
Total:	-5.500
Average:	-0.028
Count:	199
Maximum:	0.500
Minimum:	-0.600
Standard Deviation:	0.149
1.7	
Total:	-8.300
Average:	-0.041
Count:	202
Maximum:	0.500
Minimum:	-0.600
Standard Deviation:	0.150
1.8	
Tc	-6.600
Average:	-0.036
Count:	183
Maximum:	0.500
Minimum:	-0.500
Standard Deviation:	0.155

Creatinine Levels in Metformin Patients
by Levels of Increasing Lactic Acid
(3)

SAF19	Cr_CFB
1.9	
Total:	-5.400
Average:	-0.038
Count:	141
Maximum:	0.700
Minimum	-0.400
Standard Deviation:	0.179
2.0	
Total:	-3.300
Average:	-0.023
Count:	143
Maximum:	0.600
Minimum:	-0.400
Standard Deviation:	0.163
2.1	
Total:	-3.200
Average:	-0.025
Count:	127
Maximum:	0.700
Minimum:	-0.500
S rd Deviation:	0.160
2.2	
Total:	-2.200
Average:	-0.028
Count:	78
Maximum:	0.300
Minimum:	-0.500
Standard Deviation:	0.140
2.3	
Total:	-0.200
Average:	-0.004
Count:	51
Maximum:	0.200
Minimum:	-0.300
Standard Deviation:	0.117
2.4	
Total:	-1.500
Average:	-0.025
Count:	61
M um:	0.500
M im:	-0.400
St .d Deviation:	0.161
2.6	
Total:	-1.600
Average:	-0.041

Creatinine Levels in Metformin Patients
by Levels of Increasing Lactic Acid
(4)

SAF19	Cr_CFB
(:	39
Maximum:	0.200
Minimum:	-0.400
Standard Deviation:	0.137
2.7	
Total:	-2.000
Average:	-0.057
Count:	35
Maximum:	0.200
Minimum:	-0.400
Standard Deviation:	0.152
2.8	
Total:	-1.700
Average:	-0.061
Count:	28
Maximum:	0.300
Minimum:	-0.400
Standard Deviation:	0.132
2.9	
T	-0.600
A e:	-0.032
Count:	19
Maximum:	0.200
Minimum:	-0.300
Standard Deviation:	0.130
3.0	
Total:	-1.200
Average:	-0.067
Count:	18
Maximum:	0.100
Minimum:	-0.300
Standard Deviation:	0.125
3.1	
Total:	-0.400
Average:	-0.033
Count:	12
Maximum:	0.200
Minimum:	-0.300
Standard Deviation:	0.137
3.2	
T	0.600
Average:	0.038
Count:	16
Maximum:	0.200
Minimum:	-0.100
Standard Deviation:	0.105

Creatinine Levels in Metformin Patients
by Levels of Increasing Lactic Acid
(5)

SAF19	Cr_CFB
3.3	
Total:	0.300
Average:	0.030
Count:	10
Maximum:	0.200
Minimum:	-0.200
Standard Deviation:	0.119
3.4	
Total:	-0.400
Average:	-0.067
Count:	6
Maximum:	0.100
Minimum:	-0.300
Standard Deviation:	0.149
3.6	
Total:	0.100
Average:	0.017
Count:	6
Maximum:	0.200
Minimum:	-0.300
ard Deviation:	0.167
3.7	
Total:	0.100
Average:	0.050
Count:	2
Maximum:	0.100
Minimum:	0.000
Standard Deviation:	0.050
3.8	
Total:	-0.100
Average:	-0.050
Count:	2
Maximum:	0.000
Minimum:	-0.100
Standard Deviation:	0.050
3.9	
Total:	0.100
Average:	0.033
Count:	3
num:	0.300
ıum:	-0.200
ard Deviation:	0.205
4.0	
Total:	-0.200
Average:	-0.100

Creatinine Levels in Metformin Patients
by Levels of Increasing Lactic Acid
(6)

SAF19	Cr_CFB
ıt:	2
Maximum:	0.100
Minimum:	-0.300
Standard Deviation:	0.200
4.1	
Total:	-0.100
Average:	-0.100
Count:	1
Maximum:	-0.100
Minimum:	-0.100
Standard Deviation:	0.000
4.3	
Total:	-0.400
Average:	-0.133
Count:	3
Maximum:	0.000
Minimum:	-0.300
Standard Deviation:	0.125
4.4	
	-0.300
ıge:	-0.300
Count:	1
Maximum:	-0.300
Minimum:	-0.300
Standard Deviation:	0.000
4.6	
Total:	0.000
Average:	0.000
Count:	1
Maximum:	0.000
Minimum:	0.000
Standard Deviation:	0.000
4.8	
Total:	0.100
Average:	0.100
Count:	1
Maximum:	0.100
Minimum:	0.100
Standard Deviation:	0.000
=======	=====
	-90.400
ge:	-0.030
Count:	3034
Maximum:	0.900
Minimum:	-0.600
Standard Deviation:	0.155

Lactate vs
Urinary pH

Urinary pH Change from Baseline in Patients with >2x Increases in Lactate (1)

ıdy_ID	Group	Visit_No	SAF14_CFB
87-1D	A	3.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	1.000
		Average:	0.125
		Count:	8
		Standard Deviation:	1.269
		5.0	
		Total:	2.000
		Average:	0.222
		Count:	9
		Standard Deviation:	0.916
		6.0	
		Total:	-2.000
		Average:	-0.400
		Count:	5
		Standard Deviation:	0.800
		7.0	
		Total:	-1.000
		Average:	-0.125
		Count:	8
		Standard Deviation:	0.599
		8.0	
		Total:	1.000
		Average:	0.125
		Count:	8
		Standard Deviation:	0.927
		9.0	
		Total:	0.000
		Average:	0.000
		Count:	6
		Standard Deviation:	0.816
	Total:		1.000
	Average:		0.022
	Count:		45
	Standard Deviation:		0.931
	B	4.0	
		Total:	0.000

Urinary pH Change from Baseline in Patients with >2x Increases in Lactate (2)

udy_ID	Group	Visit_No	SAF14_CFB
		Average:	0.000
		Count:	3
		Standard Deviation:	0.000
		5.0	
		Total:	1.000
		Average:	0.200
		Count:	5
		Standard Deviation:	0.980
		6.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	1.000
		Average:	1.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	0.000
		Average:	0.000
		Count:	2
		Standard Deviation:	1.000
	Total:		2.000
	Average:		0.167
	Count:		12
	Standard Deviation:		0.799
Total:			3.000
Average:			0.053
Count:			57
Standard Deviation:			0.907
87-2D	A	3.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	1.000
		Average:	0.125
		Count:	8
		Standard Deviation:	0.927

Urinary pH Change from Baseline in Patients with >2x Increases in Lactate (3)

Study_ID	Group	Visit_No	SAF14_CFB
	A	7.0	
		Total:	3.000
		Average:	0.429
		Count:	7
		Standard Deviation:	0.904
		8.0	
		Total:	-1.000
		Average:	-0.125
		Count:	8
		Standard Deviation:	0.781
		9.0	
		Total:	1.000
		Average:	0.250
		Count:	4
		Standard Deviation:	0.829
		10.0	
		Total:	-2.000
		Average:	-0.286
		Count:	7
		Standard Deviation:	0.881
		11.0	
		Total:	0.000
		Average:	0.000
		Count:	4
		Standard Deviation:	0.000
	Total:		2.000
	Average:		0.051
	Count:		39
	Standard Deviation:		0.846
	C	6.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	-1.000
		Average:	-0.333
		Count:	3
		Standard Deviation:	0.471
		8.0	
		Total:	-1.000

Urinary pH Change from Baseline (4)
in Patients with >2x Increases in Lactate

Study_ID	Group	Visit_No	SAF14_CFB
		Average:	-0.200
		Count:	5
		Standard Deviation:	0.400
		9.0	
		Total.	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		10.0	
		Total:	1.000
		Average:	0.143
		Count:	7
		Standard Deviation:	0.990
		11.0	
		Total:	-1.000
		Average:	-0.333
		Count:	3
		Standard Deviation:	0.471
	Total:		-2.000
	Average:		-0.100
	Count:		20
	Standard Deviation:		0.700
	D	6.0	
		Total:	1.000
		Average:	0.143
		Count:	7
		Standard Deviation:	0.639
		7.0	
		Total:	4.000
		Average:	1.000
		Count:	4
		Standard Deviation:	0.000
		8.0	
		Total:	0.000
		Average:	0.000
		Count:	8
		Standard Deviation:	0.707
		9.0	
		Total:	0.000
		Average:	0.000
		Count:	6
		Standard Deviation:	0.000

Urinary pH Change from Baseline (5)
in Patients with >2x Increases in Lactate

Study_ID	Group	Visit_No	SAF14_CFB
[illegible]	D	10.0	
		Total:	2.000
		Average:	0.286
		Count:	7
		Standard Deviation:	0.700
		11.0	
		Total:	0.000
		Average:	0.000
		Count:	6
		Standard Deviation:	0.000
	Total:		7.000
	Average:		0.184
	Count:		38
	Standard Deviation:		0.601
Total:			7.000
Average:			0.072
Count:			97
Standard Deviation:			0.736
======	=========	=========	=====
Total:			10.000
Average:			0.065
Count:			154
Standard Deviation:			0.803

Urinary pH Change from Baseline (1)
in Patients with Lactate Increases of >=1mEq/L

udy_ID	Group	Visit_No	SAF14_CFB
87-1D	A	3.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	-1.000
		Average:	-0.167
		Count:	6
		Standard Deviation:	0.373
		5.0	
		Total:	3.000
		Average:	0.500
		Count:	6
		Standard Deviation:	0.957
		5.4	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-1.000
		Average:	-0.250
		Count:	4
		Standard Deviation:	0.433
		7.0	
		Total:	-1.000
		Average:	-0.125
		Count:	8
		Standard Deviation:	0.599
		8.0	
		Total:	2.000
		Average:	0.222
		Count:	9
		Standard Deviation:	0.786
		9.0	
		Total:	2.000
		Average:	0.333
		Count:	6
		Standard Deviation:	1.106
	Total:		4.000

Urinary pH Change from Baseline (2)
in Patients with Lactate Increases of >=1mEq/L

Study_ID	Group	Visit_No	SAF14_CFB
	Average:		0.098
	Count:		41
	Standard Deviation:		0.790
	B	3.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	0.000
		Average:	0.000
		Count:	5
		Standard Deviation:	0.000
		5.0	
		Total:	2.000
		Average:	0.286
		Count:	7
		Standard Deviation:	0.881
		5.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	0.000
		Average:	0.000
		Count:	2
		Standard Deviation:	0.000
		7.0	
		Total:	1.000
		Average:	0.250
		Count:	4
		Standard Deviation:	1.479
		7.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	1.000
		Average:	0.167
		Count:	6

Urinary pH Change from Baseline (3)
in Patients with Lactate Increases of > = 1mEq/L

Study_ID	Group	Visit_No	SAF14_CFB
		Standard Deviation:	0.898
	Total:		4.000
	Average:		0.148
	Count:		27
	Standard Deviation:		0.848
Total:			8.000
Average:			0.118
Count:			68
Standard Deviation:			0.814
87-2D	A	3.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	1.000
		Average:	0.071
		Count:	14
		Standard Deviation:	0.703
		7.0	
		Total:	4.000
		Average:	0.444
		Count:	9
		Standard Deviation:	0.831
		8.0	
		Total:	1.000
		Average:	0.125
		Count:	8
		Standard Deviation:	0.781
		9.0	
		Total:	1.000
		Average:	0.167
		Count:	6
		Standard Deviation:	0.898
		10.0	

Urinary pH Change from Baseline (4)
in Patients with Lactate Increases of >=1mEq/L

Study_ID	Group	Visit_No	SAF14_CFB
		Total:	-1.000
		Average:	-0.143
		Count:	7
		Standard Deviation:	1.125
		11.0	
		Total:	0.000
		Average:	0.000
		Count:	9
		Standard Deviation:	0.471
	Total:		6.000
	Average:		0.109
	Count:		55
	Standard Deviation:		0.802
	C	6.0	
		Total:	-1.000
		Average:	-0.200
		Count:	5
		Standard Deviation:	0.400
		7.0	
		Total:	-1.000
		Average:	-0.333
		Count:	3
		Standard Deviation:	0.471
		7.1	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-1.000
		Average:	-0.200
		Count:	5
		Standard Deviation:	0.400
		9.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		10.0	
		Total:	-2.000
		Average:	-0.250
		Count:	8

Urinary pH Change from Baseline (5)
in Patients with Lactate Increases of > =1mEq/L

Study_ID	Group	Visit_No	SAF14_CFB
		Standard Deviation:	0.661
		11.0	
		Total:	-1.000
		Average:	-0.250
		Count:	4
		Standard Deviation:	0.433
	Total:		-6.000
	Average:		-0.222
	Count:		27
	Standard Deviation:		0.497
	D	6.0	
		Total:	-1.000
		Average:	-0.091
		Count:	11
		Standard Deviation:	0.514
		7.0	
		Total:	3.000
		Average:	0.375
		Count:	8
		Standard Deviation:	0.696
		8.0	
		Total:	-2.000
		Average:	-0.182
		Count:	11
		Standard Deviation:	0.575
		9.0	
		Total:	1.000
		Average:	0.125
		Count:	8
		Standard Deviation:	0.331
		10.0	
		Total:	4.000
		Average:	0.286
		Count:	14
		Standard Deviation:	0.700
		11.0	
		Total:	0.000
		Average:	0.000
		Count:	7
		Standard Deviation:	0.000

Urinary pH Change from Baseline (6)
in Patients with Lactate Increases of >=1mEq/L

Study_ID	Group	Visit_No	SAF14_CFB
	Total:		5.000
	Average:		0.085
	Count:		59
	Standard Deviation:		0.591
Total:			5.000
Average:			0.035
Count:			141
Standard Deviation:			0.678
Total:			13.000
Average:			0.062
Count:			209
Standard Deviation:			0.726

Anion Gaps
vs
Lactate

Anion gap Changes from Baseline (1)

Study_ID	Group	Visit_No	SAF06_CFB
)	A	0.0	
		Total:	0.000
		Average:	0.000
		Count:	140
		Standard Deviation:	0.000
		0.1	
		Total:	0.000
		Average:	0.000
		Count:	5
		Standard Deviation:	0.000
		0.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		1.0	
		Total:	3.000
		Average:	0.750
		Count:	4
		Standard Deviation:	2.225
		1.1	
		Total:	4.400
		Average:	2.200
		Count:	2
		Standard Deviation:	0.100
		2.0	
		Total:	-3.800
		Average:	-1.267
		Count:	3
		Standard Deviation:	4.928
		3.0	
		Total:	-0.900
		Average:	-0.900
		Count:	1
		Standard Deviation:	0.000
		3.1	
		Total:	-1.100
		Average:	-0.367
		Count:	3
		Standard Deviation:	1.613
		4.0	

Anion gap Changes from Baseline (2)

Study_ID	Group	Visit_No	SAF06_CFB
		Total:	14.300
		Average:	0.109
		Count:	131
		Standard Deviation:	3.778
		4.1	
		Total:	-7.500
		Average:	-1.500
		Count:	5
		Standard Deviation:	3.667
		4.2	
		Total:	-2.500
		Average:	-1.250
		Count:	2
		Standard Deviation:	2.550
		5.0	
		Total:	51.700
		Average:	0.417
		Count:	124
		Standard Deviation:	3.858
		5.1	
		Total:	-8.300
		Average:	-1.660
		Count:	5
		Standard Deviation:	3.544
		5.2	
		Total:	8.400
		Average:	4.200
		Count:	2
		Standard Deviation:	0.800
		5.3	
		Total:	0.600
		Average:	0.600
		Count:	1
		Standard Deviation:	0.000
		5.4	
		Total:	1.200
		Average:	1.200
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	9.600
		Average:	0.080

Anion gap Changes from Baseline (3)

Study_ID	Group	Visit_No	SAF06_CFB
		Count:	120
		Standard Deviation:	4.061
		6.1	
		Total:	-7.900
		Average:	-1.317
		Count:	6
		Standard Deviation:	4.645
		6.3	
		Total:	-5.000
		Average:	-5.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	43.900
		Average:	0.385
		Count:	114
		Standard Deviation:	4.593
		7.1	
		Total:	-14.400
		Average:	-4.800
		Count:	3
		Standard Deviation:	2.772
		7.2	
		Total:	-1.800
		Average:	-1.800
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	49.500
		Average:	0.442
		Count:	112
		Standard Deviation:	4.001
		8.1	
		Total:	15.000
		Average:	1.875
		Count:	8
		Standard Deviation:	6.755
		8.2	
		Total:	1.300
		Average:	1.300
		Count:	1
		Standard Deviation:	0.000

Anion gap Changes from Baseline (4)

Study_ID	Group	Visit_No	SAF06_CFB
	A	9.0	
		Total:	62.900
		Average:	0.567
		Count:	111
		Standard Deviation:	4.258
		9.1	
		Total:	-12.100
		Average:	-6.050
		Count:	2
		Standard Deviation:	2.250
		9.2	
		Total:	-12.100
		Average:	-12.100
		Count:	1
		Standard Deviation:	0.000
	Total:		188.400
	Average:		0.207
	Count:		910
	Standard Deviation:		3.805
	B	-3.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		-1.9	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		-0.9	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		0.0	
		Total:	0.000
		Average:	0.000
		Count:	142
		Standard Deviation:	0.000
		0.1	
		Total:	0.000

Anion gap Changes from Baseline (5)

Study_ID	Group	Visit_No	SAF06_CFB
		Average:	0.000
		Count:	5
		Standard Deviation:	0.000
		0.2	
		Total:	0.000
		Average:	0.000
		Count:	2
		Standard Deviation:	0.000
		1.0	
		Total:	4.600
		Average:	1.533
		Count:	3
		Standard Deviation:	0.189
		2.0	
		Total:	0.300
		Average:	0.075
		Count:	4
		Standard Deviation:	1.365
		3.0	
		Total:	0.900
		Average:	0.300
		Count:	3
		Standard Deviation:	1.551
		3.1	
		Total:	-1.500
		Average:	-0.500
		Count:	3
		Standard Deviation:	0.993
		4.0	
		Total:	8.400
		Average:	0.063
		Count:	133
		Standard Deviation:	4.245
		4.1	
		Total:	2.600
		Average:	1.300
		Count:	2
		Standard Deviation:	2.000
		4.2	
		Total:	0.900
		Average:	0.900
		Count:	1

Anion gap Changes from Baseline (6)

Study_ID	Group	Visit_No	SAF06_CFB
		Standard Deviation:	0.000
		5.0	
		Total:	36.200
		Average:	0.299
		Count:	121
		Standard Deviation:	4.256
		5.1	
		Total:	-8.400
		Average:	-1.400
		Count:	6
		Standard Deviation:	2.157
		6.0	
		Total:	-27.600
		Average:	-0.242
		Count:	114
		Standard Deviation:	4.121
		6.1	
		Total:	1.800
		Average:	1.800
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	41.500
		Average:	0.377
		Count:	110
		Standard Deviation:	4.137
		7.1	
		Total:	1.800
		Average:	0.900
		Count:	2
		Standard Deviation:	0.900
		7.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	61.100
		Average:	0.582
		Count:	105
		Standard Deviation:	3.991

Anion gap Changes from Baseline (7)

Study_ID	Group	Visit_No	SAF06_CFB
D	B	8.1	
		Total:	-3.500
		Average:	-1.167
		Count:	3
		Standard Deviation:	4.451
		9.0	
		Total:	-23.200
		Average:	-0.223
		Count:	104
		Standard Deviation:	4.222
		9.1	
		Total:	-1.900
		Average:	-0.950
		Count:	2
		Standard Deviation:	3.150
	Total:		94.000
	Average:		0.108
	Count:		870
	Standard Deviation:		3.740
Total:			282.400
Average:			0.159
Count:			1780
Standard Deviation:			3.774
87-2D	A	-2.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		-1.7	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		0.0	
		Total:	0.000
		Average:	0.000
		Count:	206
		Standard Deviation:	0.000
		0.1	
		Total:	0.000
		Average:	0.000

Anion gap Changes from Baseline (8)

Study_ID	Group	Visit_No	SAF06_CFB
		Count:	11
		Standard Deviation:	0.000
		0.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		1.0	
		Total:	1.900
		Average:	0.380
		Count:	5
		Standard Deviation:	2.825
		1.1	
		Total:	-4.500
		Average:	-4.500
		Count:	1
		Standard Deviation:	0.000
		2.0	
		Total:	-10.600
		Average:	-2.120
		Count:	5
		Standard Deviation:	2.856
		3.0	
		Total:	-9.400
		Average:	-2.350
		Count:	4
		Standard Deviation:	2.148
		3.1	
		Total:	1.000
		Average:	0.500
		Count:	2
		Standard Deviation:	2.200
		4.0	
		Total:	-10.100
		Average:	-2.020
		Count:	5
		Standard Deviation:	3.762
		4.1	
		Total:	-3.600
		Average:	-3.600
		Count:	1
		Standard Deviation:	0.000

Anion gap Changes from Baseline (9)

Study_ID	Group	Visit_No	SAF06_CFB
[illegible]J	A	5 0	
		Total:	-1.700
		Average:	-0.850
		Count:	2
		Standard Deviation:	1.250
		5.1	
		Total:	-15.100
		Average:	-3.775
		Count:	4
		Standard Deviation:	0.991
		5.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		5.3	
		Total:	2.300
		Average:	2.300
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	115.900
		Average:	0.588
		Count:	197
		Standard Deviation:	4.100
		6.1	
		Total:	11.800
		Average:	1.311
		Count:	9
		Standard Deviation:	4.054
		6.2	
		Total:	-6.200
		Average:	-3.100
		Count:	2
		Standard Deviation:	1.300
		6.5	
		Total:	1.200
		Average:	1.200
		Count:	1
		Standard Deviation:	0.000
		7.0	

Anion gap Changes from Baseline (10)

Study_ID	Group	Visit_No	SAF06_CFB
		Total:	88.600
		Average:	0.464
		Count:	191
		Standard Deviation:	5.003
		7.1	
		Total:	-4.300
		Average:	-0.860
		Count:	5
		Standard Deviation:	1.622
		8.0	
		Total:	13.800
		Average:	0.081
		Count:	171
		Standard Deviation:	4.337
		8.1	
		Total:	-5.300
		Average:	-2.650
		Count:	2
		Standard Deviation:	4.250
		9.0	
		Total:	128.300
		Average:	0.792
		Count:	162
		Standard Deviation:	3.970
		9.1	
		Total:	-9.500
		Average:	-4.750
		Count:	2
		Standard Deviation:	1.650
		10.0	
		Total:	98.000
		Average:	0.613
		Count:	160
		Standard Deviation:	4.358
		10.1	
		Total:	0.800
		Average:	0.400
		Count:	2
		Standard Deviation:	7.300
		11.0	
		Total:	119.000
		Average:	0.758

Anion gap Changes from Baseline (11)

Study_ID	Group	Visit_No	SAF06_CFB
		Count:	157
		Standard Deviation:	4.465
		11.1	
		Total:	-11.800
		Average:	-5.900
		Count:	2
		Standard Deviation:	2.500
	Total:		490.500
	Average:		0.373
	Count:		1314
	Standard Deviation:		4.003
	C	-5.0	
		Total:	0.000
		Average:	0.000
		Count:	4
		Standard Deviation:	0.000
		0.0	
		Total:	0.000
		Average:	0.000
		Count:	206
		Standard Deviation:	0.000
		0.1	
		Total:	0.000
		Average:	0.000
		Count:	3
		Standard Deviation:	0.000
		0.6	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		1.0	
		Total:	-4.200
		Average:	-4.200
		Count:	1
		Standard Deviation:	0.000
		2.0	
		Total:	-0.900
		Average:	-0.900
		Count:	1
		Standard Deviation:	0.000

Anion gap Changes from Baseline (12)

Study_ID	Group	Visit_No	SAF06_CFB
)	C	4.0	
		Total:	2.400
		Average:	0.600
		Count:	4
		Standard Deviation:	5.475
		5.0	
		Total:	-2.900
		Average:	-1.450
		Count:	2
		Standard Deviation:	3.450
		5.1	
		Total:	5.000
		Average:	1.667
		Count:	3
		Standard Deviation:	2.043
		5.2	
		Total:	3.100
		Average:	3.100
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-123.100
		Average:	-0.631
		Count:	195
		Standard Deviation:	4.016
		6.1	
		Total:	-22.500
		Average:	-2.813
		Count:	8
		Standard Deviation:	4.517
		7.0	
		Total:	-74.700
		Average:	-0.389
		Count:	192
		Standard Deviation:	3.932
		7.1	
		Total:	-10.600
		Average:	-3.533
		Count:	3
		Standard Deviation:	1.987
		7.2	

Anion gap Changes from Baseline (13)

Study_ID	Group	Visit_No	SAF06_CFB
		Total:	0.500
		Average:	0.500
		Count:	1
		Standard Deviation:	0.000
		7.4	
		Total:	-1.200
		Average:	-1.200
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	-31.700
		Average:	-0.172
		Count:	184
		Standard Deviation:	3.980
		8.1	
		Total:	5.400
		Average:	1.800
		Count:	3
		Standard Deviation:	4.031
		9.0	
		Total:	10.800
		Average:	0.061
		Count:	176
		Standard Deviation:	4.308
		9.1	
		Total:	-0.400
		Average:	-0.133
		Count:	3
		Standard Deviation:	3.694
		9.2	
		Total:	3.300
		Average:	3.300
		Count:	1
		Standard Deviation:	0.000
		9.4	
		Total:	-0.600
		Average:	-0.600
		Count:	1
		Standard Deviation:	0.000
		10.0	
		Total:	16.900
		Average:	0.097

Anion gap Changes from Baseline (14)

Study_ID	Group	Visit_No	SAF06_CFB
		Count:	175
		Standard Deviation:	4.162
		10.1	
		Total:	2.300
		Average:	1.150
		Count:	2
		Standard Deviation:	0.750
		10.2	
		Total:	-2.600
		Average:	-2.600
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	-27.800
		Average:	-0.160
		Count:	174
		Standard Deviation:	4.117
	Total:		-253.500
	Average:		-0.188
	Count:		1346
	Standard Deviation:		3.751
	D	-5.0	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		0.0	
		Total:	0.000
		Average:	0.000
		Count:	212
		Standard Deviation:	0.000
		0.1	
		Total:	0.000
		Average:	0.000
		Count:	9
		Standard Deviation:	0.000
		0.3	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000

Anion gap Changes from Baseline (15)

Study_ID	Group	Visit_No	SAF06_CFB
)	D	0.5	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		0.6	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		1.0	
		Total:	-2.700
		Average:	-0.900
		Count:	3
		Standard Deviation:	2.192
		2.0	
		Total:	-5.600
		Average:	-2.800
		Count:	2
		Standard Deviation:	0.000
		3.0	
		Total:	-4.200
		Average:	-4.200
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	12.400
		Average:	2.480
		Count:	5
		Standard Deviation:	2.616
		5.0	
		Total:	5.000
		Average:	0.833
		Count:	6
		Standard Deviation:	1.930
		5.1	
		Total:	0.000
		Average:	0.000
		Count:	2
		Standard Deviation:	1.300
		6.0	

Anion gap Changes from Baseline (16)

Study_ID	Group	Visit_No	SAF06_CFB
		Total:	33.100
		Average:	0.159
		Count:	208
		Standard Deviation:	3.834
		6.1	
		Total:	-6.300
		Average:	-1.050
		Count:	6
		Standard Deviation:	6.579
		6.2	
		Total:	5.100
		Average:	5.100
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	129.900
		Average:	0.650
		Count:	200
		Standard Deviation:	3.910
		7.1	
		Total:	5.600
		Average:	0.800
		Count:	7
		Standard Deviation:	4.299
		7.3	
		Total:	-0.400
		Average:	-0.400
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	44.300
		Average:	0.220
		Count:	201
		Standard Deviation:	4.220
		8.1	
		Total:	1.400
		Average:	0.700
		Count:	2
		Standard Deviation:	4.200
		8.2	
		Total:	2.800
		Average:	2.800

Anion gap Changes from Baseline (17)

Study_ID	Group	Visit_No	SAF06_CFB
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	61.800
		Average:	0.314
		Count:	197
		Standard Deviation:	3.871
		9.1	
		Total:	11.700
		Average:	1.950
		Count:	6
		Standard Deviation:	3.946
		10.0	
		Total:	49.100
		Average:	0.252
		Count:	195
		Standard Deviation:	3.822
		10.1	
		Total:	15.200
		Average:	3.800
		Count:	4
		Standard Deviation:	2.582
		10.2	
		Total:	-6.400
		Average:	-6.400
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	120.700
		Average:	0.629
		Count:	192
		Standard Deviation:	4.109
		11.1	
		Total:	-6.100
		Average:	-3.050
		Count:	2
		Standard Deviation:	0.350
		11.2	
		Total:	0.800
		Average:	0.800
		Count:	1
		Standard Deviation:	0.000

Anion gap Changes from Baseline (18)

Study_ID	Group	Visit_No	SAF06_CFB
	Total:		467.200
	Average:		0.318
	Count:		1469
	Standard Deviation:		3.659
Total:			704.200
Average:			0.171
Count:			4129
Standard Deviation:			3.810
Total:			986.600
Average:			0.167
Count:			5909
Standard Deviation:			3.799

Anion Gap Change from Baseline by Rx Group

Study_ID	Group	Visit_No	SAF06_CFB
3	A	1.0	
		Total:	3.000
		Average:	0.750
		Count:	4
		Standard Deviation:	2.225
		1.1	
		Total:	4.400
		Average:	2.200
		Count:	2
		Standard Deviation:	0.100
		2.0	
		Total:	-3.800
		Average:	-1.267
		Count:	3
		Standard Deviation:	4.928
		3.0	
		Total:	-0.900
		Average:	-0.900
		Count:	1
		Standard Deviation:	0.000
		3.1	
		Total:	-1.100
		Average:	-0.367
		Count:	3
		Standard Deviation:	1.613
		4.0	
		Total:	14.300
		Average:	0.109
		Count:	131
		Standard Deviation:	3.778
		4.1	
		Total:	-7.500
		Average:	-1.500
		Count:	5
		Standard Deviation:	3.667
		4.2	
		Total:	-2.500
		Average:	-1.250
		Count:	2
		Standard Deviation:	2.550
		5.0	

Anion Gap Change from Baseline by Rx Group

udy_ID	Group	Visit_No	SAF06_CFB
		Total:	51.700
		Average:	0.417
		Count:	124
		Standard Deviation:	3.858
		5.1	
		Total:	-8.300
		Average:	-1.660
		Count:	5
		Standard Deviation:	3.544
		5.2	
		Total:	8.400
		Average:	4.200
		Count:	2
		Standard Deviation:	0.800
		5.3	
		Total:	0.600
		Average:	0.600
		Count:	1
		Standard Deviation:	0.000
		5.4	
		Total:	1.200
		Average:	1.200
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	9.600
		Average:	0.080
		Count:	120
		Standard Deviation:	4.061
		6.1	
		Total:	-7.900
		Average:	-1.317
		Count:	6
		Standard Deviation:	4.645
		6.3	
		Total:	-5.000
		Average:	5.000
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	43.900
		Average:	0.385

Anion Gap Change from Baseline by Rx Group

tudy_ID	Group	Visit_No	SAF06_CFB
		Count:	114
		Standard Deviation:	4.593
		7.1	
		Total:	-14.400
		Average:	-4.800
		Count:	3
		Standard Deviation:	2.772
		7.2	
		Total:	-1.800
		Average:	-1.800
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	49.500
		Average:	0.442
		Count:	112
		Standard Deviation:	4.001
		8.1	
		Total:	15.000
		Average:	1.875
		Count:	8
		Standard Deviation:	6.755
		8.2	
		Total:	1.300
		Average:	1.300
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	62.900
		Average:	0.567
		Count:	111
		Standard Deviation:	4.258
		9.1	
		Total:	-12.100
		Average:	-6.050
		Count:	2
		Standard Deviation:	2.250
		9.2	
		Total:	-12.100
		Average:	-12.100
		Count:	1
		Standard Deviation:	0.000

Anion Gap Change from Baseline by Rx Group

idy_ID	Group	Visit_No	SAF06_CFB
	Total:		188.400
	Average:		0.247
	Count:		764
	Standard Deviation:		4.152
	B	1.0	
		Total:	4.600
		Average:	1.533
		Count:	3
		Standard Deviation:	0.189
		2.0	
		Total:	0.300
		Average:	0.075
		Count:	4
		Standard Deviation:	1.365
		3.0	
		Total:	0.900
		Average:	0.300
		Count:	3
		Standard Deviation:	1.551
		3.1	
		Total:	-1.500
		Average:	-0.500
		Count:	3
		Standard Deviation:	0.993
		4.0	
		Total:	8.400
		Average:	0.063
		Count:	133
		Standard Deviation:	4.245
		4.1	
		Total:	2.600
		Average:	1.300
		Count:	2
		Standard Deviation:	2.000
		4.2	
		Total:	0.900
		Average:	0.900
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	36.200

Anion Gap Change from Baseline by Rx Group

udy_ID	Group	Visit_No	SAF06_CFB
		Average:	0.299
		Count:	121
		Standard Deviation:	4.256
		5.1	
		Total:	-8.400
		Average:	-1.400
		Count:	6
		Standard Deviation:	2.157
		6.0	
		Total:	-27.600
		Average:	-0.242
		Count:	114
		Standard Deviation:	4.121
		6.1	
		Total:	1.800
		Average:	1.800
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	41.500
		Average:	0.377
		Count:	110
		Standard Deviation:	4.137
		7.1	
		Total:	1.800
		Average:	0.900
		Count:	2
		Standard Deviation:	0.900
		7.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	61.100
		Average:	0.582
		Count:	105
		Standard Deviation:	3.991
		8.1	
		Total:	-3.500
		Average:	-1.167
		Count:	3

Anion Gap Change from Baseline by Rx Group

Study_ID	Group	Visit_No	SAF06_CFB
		Standard Deviation:	4.451
		9.0	
		Total:	-23.200
		Average:	-0.223
		Count:	104
		Standard Deviation:	4.222
		9.1	
		Total:	-1.900
		Average:	-0.950
		Count:	2
		Standard Deviation:	3.150
	Total:		94.000
	Average:		0.131
	Count:		718
	Standard Deviation:		4.116
Total:			282.400
Average:			0.191
			1482
ard Deviation:			4.135
87-2D	A	1.0	
		Total:	1.900
		Average:	0.380
		Count:	5
		Standard Deviation:	2.825
		1.1	
		Total:	-4.500
		Average:	-4.500
		Count:	1
		Standard Deviation:	0.000
		2.0	
		Total:	-10.600
		Average:	-2.120
		Count:	5
		Standard Deviation:	2.856
		3.0	
		Total:	-9.400
		Average:	-2.350
		Count:	4
		Standard Deviation:	2.148
		3.1	

Anion Gap Change from Baseline by Rx Group

Study_ID	Group	Visit_No	SAF06_CFB
		Total:	1.000
		Average:	0.500
		Count:	2
		Standard Deviation:	2.200
		4.0	
		Total:	-10.100
		Average:	-2.020
		Count:	5
		Standard Deviation:	3.762
		4.1	
		Total:	-3.600
		Average:	-3.600
		Count:	1
		Standard Deviation:	0.000
		5.0	
		Total:	-1.700
		Average:	-0.850
		Count:	2
		Standard Deviation:	1.250
		5.1	
		Total:	-15.100
		Average:	-3.775
		Count:	4
		Standard Deviation:	0.991
		5.2	
		Total:	0.000
		Average:	0.000
		Count:	1
		Standard Deviation:	0.000
		5.3	
		Total:	2.300
		Average:	2.300
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	115.900
		Average:	0.588
		Count:	197
		Standard Deviation:	4.100
		6.1	
		Total:	11.800
		Average:	1.311

Anion Gap Change from Baseline by Rx Group

Study_ID	Group	Visit_No	SAF06_CFB
		Count:	9
		Standard Deviation:	4.054
		6.2	
		Total:	-6.200
		Average:	-3.100
		Count:	2
		Standard Deviation:	1.300
		6.5	
		Total:	1.200
		Average:	1.200
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	88.600
		Average:	0.464
		Count:	191
		Standard Deviation:	5.003
		7.1	
		Total:	-4.300
		Average:	-0.860
		Count:	5
		Standard Deviation:	1.622
		8.0	
		Total:	13.800
		Average:	0.081
		Count:	171
		Standard Deviation:	4.337
		8.1	
		Total:	-5.300
		Average:	-2.650
		Count:	2
		Standard Deviation:	4.250
		9.0	
		Total:	128.300
		Average:	0.792
		Count:	162
		Standard Deviation:	3.970
		9.1	
		Total:	-9.500
		Average:	-4.750
		Count:	2
		Standard Deviation:	1.650

Anion Gap Change from Baseline by Rx Group

udy_ID	Group	Visit_No	SAF06_CFB
	A	10.0	
		Total:	98.000
		Average:	0.613
		Count:	160
		Standard Deviation:	4.358
		10.1	
		Total:	0.800
		Average:	0.400
		Count:	2
		Standard Deviation:	7.300
		11.0	
		Total:	119.000
		Average:	0.758
		Count:	157
		Standard Deviation:	4.465
		11.1	
		Total:	-11.800
		Average:	-5.900
		Count:	2
		Standard Deviation:	2.500
	Total:		490.500
	Average:		0.448
	Count:		1094
	Standard Deviation:		4.383
	C	1.0	
		Total:	-4.200
		Average:	-4.200
		Count:	1
		Standard Deviation:	0.000
		2.0	
		Total:	-0.900
		Average:	-0.900
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	2.400
		Average:	0.600
		Count:	4
		Standard Deviation:	5.475
		5.0	
		Total:	-2.900

Anion Gap Change from Baseline by Rx Group

udy_ID	Group	Visit_No	SAF06_CFB
		Average:	-1.450
		Count:	2
		Standard Deviation:	3.450
		5.1	
		Total:	5.000
		Average:	1.667
		Count:	3
		Standard Deviation:	2.043
		5.2	
		Total:	3.100
		Average:	3.100
		Count:	1
		Standard Deviation:	0.000
		6.0	
		Total:	-123.100
		Average:	-0.631
		Count:	195
		Standard Deviation:	4.016
		6.1	
		Total:	-22.500
		Average:	-2.813
		Count:	8
		Standard Deviation:	4.517
		7.0	
		Total:	-74.700
		Average:	-0.389
		Count:	192
		Standard Deviation:	3.932
		7.1	
		Total:	-10.600
		Average:	-3.533
		Count:	3
		Standard Deviation:	1.987
		7.2	
		Total:	0.500
		Average:	0.500
		Count:	1
		Standard Deviation:	0.000
		7.4	
		Total:	-1.200
		Average:	-1.200
		Count:	1

Anion Gap Change from Baseline by Rx Group

Study_ID	Group	Visit_No	SAF06_CFB
		Standard Deviation:	0.000
		8.0	
		Total:	-31.700
		Average:	-0.172
		Count:	184
		Standard Deviation:	3.980
		8.1	
		Total:	5.400
		Average:	1.800
		Count:	3
		Standard Deviation:	4.031
		9.0	
		Total:	10.800
		Average:	0.061
		Count:	176
		Standard Deviation:	4.308
		9.1	
		Total:	-0.400
		Average:	-0.133
		Count:	3
		Standard Deviation:	3.694
		9.2	
		Total:	3.300
		Average:	3.300
		Count:	1
		Standard Deviation:	0.000
		9.4	
		Total:	-0.600
		Average:	-0.600
		Count:	1
		Standard Deviation:	0.000
		10.0	
		Total:	16.900
		Average:	0.097
		Count:	175
		Standard Deviation:	4.162
		10.1	
		Total:	2.300
		Average:	1.150
		Count:	2
		Standard Deviation:	0.750

Anion Gap Change from Baseline by Rx Group

Study_ID	Group	Visit_No	SAF06_CFB
.D	C	10.2	
		Total:	-2.600
		Average:	-2.600
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	-27.800
		Average:	-0.160
		Count:	174
		Standard Deviation:	4.117
	Total:		-253.500
	Average:		-0.224
	Count:		1132
	Standard Deviation:		4.090
	D	1.0	
		Total:	-2.700
		Average:	-0.900
		Count:	3
		Standard Deviation:	2.192
		2.0	
		Total:	-5.600
		Average:	-2.800
		Count:	2
		Standard Deviation:	0.000
		3.0	
		Total:	-4.200
		Average:	-4.200
		Count:	1
		Standard Deviation:	0.000
		4.0	
		Total:	12.400
		Average:	2.480
		Count:	5
		Standard Deviation:	2.616
		5.0	
		Total:	5.000
		Average:	0.833
		Count:	6
		Standard Deviation:	1.930
		5.1	
		Total:	0.000

Anion Gap Change from Baseline by Rx Group

tudy_ID	Group	Visit_No	SAF06_CFB
		Average:	0.000
		Count:	2
		Standard Deviation:	1.300
		6.0	
		Total:	33.100
		Average:	0.159
		Count:	208
		Standard Deviation:	3.834
		6.1	
		Total:	-6.300
		Average:	-1.050
		Count:	6
		Standard Deviation:	6.579
		6.2	
		Total:	5.100
		Average:	5.100
		Count:	1
		Standard Deviation:	0.000
		7.0	
		Total:	129.900
		Average:	0.650
		Count:	200
		Standard Deviation:	3.910
		7.1	
		Total:	5.600
		Average:	0.800
		Count:	7
		Standard Deviation:	4.299
		7.3	
		Total:	-0.400
		Average:	-0.400
		Count:	1
		Standard Deviation:	0.000
		8.0	
		Total:	44.300
		Average:	0.220
		Count:	201
		Standard Deviation:	4.220
		8.1	
		Total:	1.400
		Average:	0.700
		Count:	2

Anion Gap Change from Baseline by Rx Group

udy_ID	Group	Visit_No	SAF06_CFB
		Standard Deviation:	4.200
		8.2	
		Total:	2.800
		Average:	2.800
		Count:	1
		Standard Deviation:	0.000
		9.0	
		Total:	61.800
		Average:	0.314
		Count:	197
		Standard Deviation:	3.871
		9.1	
		Total:	11.700
		Average:	1.950
		Count:	6
		Standard Deviation:	3.946
		10.0	
		Total:	49.100
		Average:	0.252
		Count:	195
		Standard Deviation:	3.822
		10.1	
		Total:	15.200
		Average:	3.800
		Count:	4
		Standard Deviation:	2.582
		10.2	
		Total:	-6.400
		Average:	-6.400
		Count:	1
		Standard Deviation:	0.000
		11.0	
		Total:	120.700
		Average:	0.629
		Count:	192
		Standard Deviation:	4.109
		11.1	
		Total:	-6.100
		Average:	-3.050
		Count:	2
		Standard Deviation:	0.350

Anion Gap Change from Baseline by Rx Group

udy_ID	Group	Visit_No	SAF06_CFB
8	D	11.2	
		Total:	0.800
		Average:	0.800
		Count:	1
		Standard Deviation:	0.000
	Total:		467.200
	Average:		0.376
	Count:		1244
	Standard Deviation:		3.974
Total:			704.200
Average:			0.203
Count:			3470
Standard Deviation:			4.155
Total:			986.600
Average:			0.199
Count:			4952
Standard Deviation:			4.149

Categorical Printout of Patients with Anion Gap Changes from Baseline > 10

Study_ID	Group	Visit_No	Patient	SAF06_CFB
87-1D	A	5.0	87-1DG010400025	12.000
		Count:	1	
		6.0	87-1DP011100002	11.900
			87-1DK041000010	10.100
		Count:	2	
		7.0	~~87-1DP011100002~~	10.200
			87-1DK030900019	13.500
			87-1DK030900014	10.300
			~~87-1DK041000010~~	10.900
			87-1DG020500016	10.300
			~~87-1DG010400025~~	10.400
		Count:	6	
		8.0	~~87-1DP011100002~~	12.400
		Count:	1	
		8.1	~~87-1DP011100002~~	12.100
		Count:	1	
		9.0	~~87-1DP011100002~~	12.100
			87-1DC020300004	10.300
		Count:	2	
	Count:		~~13~~ 7	
	B	4.0	87-1DG020500011	12.300
			87-1DG040700007	10.300
			87-1DG020500004	10.800
		Count:	3	
		5.0	87-1DP011100005	11.600
		Count:	1	
		6.0	87-1DG030600014	10.100
			87-1DA011200012	10.600
		Count:	2	
		9.0	~~87-1DG030600014~~	10.100
		Count:	1	
	Count:		7 6	
Count:			20	

Categorical Printout of Patients with Anion Gap Changes from Baseline > 10

Study_ID	Group	Visit_No	Patient	SAF06_CFB
87-2D	A	6.0	87-2DB0202012	10.400
			87-2DF0108018	11.500
			87-2DK0309027	10.800
		Count:	3	
		7.0	87-2DK0309023	11.200
			87-2DF0311014	20.300
			87-2DR0117025	30.200
		Count:	3	
		8.0	87-2DG0407013	16.500
		Count:	1	
		9.0	~~87-2DB0202012~~	10.300
		Count:	1	
		10.0	87-2DD0204017	14.200
		Count:	1	
		11.0	87-2DK0114007	12.200
		Count:	1	
	Count:		~~10~~ 9	
	C	6.0	87-2DF0108012	11.300
		Count:	1	
		8.0	87-2DG0407005	12.100
		Count:	1	
		9.0	87-2DF0311022	18.800
		Count:	1	
		10.0	~~87-2DF0311022~~	12.900
			87-2DR0117020	11.600
			87-2DG0407018	10.200
			87-2DT0106020	11.500
		Count:	4	
		11.0	~~87-2DF0311022~~	12.400
		Count:	1	
	Count:		~~8~~ 6	
	D	6.0	87-2DF0421014	10.800

Categorical Printout of Patients with Anion Gap Changes from Baseline > 10

Study_ID	Group	Visit_No	Patient	SAF06_CFB
		Count:	1	
		6.1	87-2DG0512011	11.100
		Count:	1	
		7.0	87-2DT0106014	12.200
		Count:	1	
		8.0	87-2DV0120013	12.900
			87-2DF0311013	11.400
			87-2DR0117030	11.900
			87-2DK0114003	10.300
		Count:	4	
		11.0	87-2DD0103029	10.100
			~~87-2DV0120613~~	10.600
		Count:	2	
	Count:		9 8	
Count:			27	
Count:			47	

Anion Gap Changes from Baseline (1)
in Patients with >2x Increases in Lactate

Study_ID	Group	Visit_No	SAF06
)	A	3.1	
		Total:	9.40
		Average:	9.40
		Count:	1
		Standard Deviation:	0.00
		4.0	
		Total:	45.90
		Average:	11.48
		Count:	4
		Standard Deviation:	3.22
		4.1	
		Total:	9.20
		Average:	9.20
		Count:	1
		Standard Deviation:	0.00
		5.0	
		Total:	41.60
		Average:	10.40
		Count:	4
		Standard Deviation:	3.39
		6.0	
		Total:	28.10
		Average:	9.37
		Count:	3
		Standard Deviation:	0.48
		7.0	
		Total:	104.80
		Average:	11.64
		Count:	9
		Standard Deviation:	4.56
		8.0	
		Total:	66.40
		Average:	11.07
		Count:	6
		Standard Deviation:	1.78
		9.0	
		Total:	44.40
		Average:	8.88
		Count:	5
		Standard Deviation:	4.41
		9.1	

		Total:	7.80
		Average:	7.80
		Count:	1
		Standard Deviation:	0.00
	Total:		357.60
	Average:		10.52
	Count:		34
	Standard Deviation:		3.58
	B	4.0	
		Total:	46.80
		Average:	15.60
		Count:	3
		Standard Deviation:	1.61
		5.0	
		Total:	64.60
		Average:	12.92
		Count:	5
		Standard Deviation:	2.17
		7.0	
		Total:	14.80
		Average:	14.80
		Count:	1
		Standard Deviation:	0.00
		9.0	
		Total:	6.20
		Average:	6.20
		Count:	1
		Standard Deviation:	0.00
	Total:		132.40
	Average:		13.24
	Count:		10
	Standard Deviation:		3.17
Total:			490.00
Average:			11.14
Count:			44
Standard Deviation:			3.67
8	A	6.0	
		Total:	71.10
		Average:	11.85
		Count:	6
		Standard Deviation:	2.67

Anion Gap Changes from Baseline (3)
in Patients with >2x Increases in Lactate

Study_ID	Group	Visit_No	SAF06
	A	7.0	
		Total:	48.10
		Average:	9.62
		Count:	5
		Standard Deviation:	3.40
		8.0	
		Total:	56.30
		Average:	11.26
		Count:	5
		Standard Deviation:	1.85
		9.0	
		Total:	25.80
		Average:	12.90
		Count:	2
		Standard Deviation:	3.50
		10.0	
		Total:	39.70
		Average:	13.23
		Count:	3
		Standard Deviation:	2.50
		11.0	
		Total:	37.70
		Average:	12.57
		Count:	3
		Standard Deviation:	1.51
	Total:		278.70
	Average:		11.61
	Count:		24
	Standard Deviation:		2.90
	C	7.0	
		Total:	27.80
		Average:	13.90
		Count:	2
		Standard Deviation:	1.50
		8.0	
		Total:	37.40
		Average:	12.47
		Count:	3
		Standard Deviation:	2.88
		9.0	
		Total:	9.20

Anion Gap Changes from Baseline (4)
in Patients with >2x Increases in Lactate

Study_ID	Group	Visit_No	SAF06
		Average:	9.20
		Count:	1
		Standard Deviation:	0.00
		10.0	
		Total:	55.10
		Average:	13.78
		Count:	4
		Standard Deviation:	1.47
		11.0	
		Total:	8.40
		Average:	8.40
		Count:	1
		Standard Deviation:	0.00
	Total:		137.90
	Average:		12.54
	Count:		11
	Standard Deviation:		2.63
	D	6.0	
		Total:	58.50
		Average:	11.70
		Count:	5
		Standard Deviation:	2.72
		7.0	
		Total:	34.10
		Average:	11.37
		Count:	3
		Standard Deviation:	1.62
		7.1	
		Total:	8.70
		Average:	8.70
		Count:	1
		Standard Deviation:	0.00
		8.0	
		Total:	65.90
		Average:	10.98
		Count:	6
		Standard Deviation:	3.28
		9.0	
		Total:	61.60
		Average:	12.32
		Count:	5
		Standard Deviation:	2.74

Anion Gap Changes from Baseline (5)
in Patients with >2x Increases in Lactate

Study_ID	Group	Visit_No	SAF06
)	D	10.0	
		Total:	62.40
		Average:	12.48
		Count:	5
		Standard Deviation:	2.90
		11.0	
		Total:	68.60
		Average:	11.43
		Count:	6
		Standard Deviation:	2.65
	Total:		359.80
	Average:		11.61
	Count:		31
	Standard Deviation:		2.83
Total:			776.40
Average:			11.76
Count:			66
Standard Deviation:			2.85
Total:			1266.40
Average:			11.51
Count:			110
Standard Deviation:			3.22

Diarrhea and Hb Drops

Diarrhea and Hb 1 Point Drops

		Study_ID		
Group		87-1D	87-2D	Hb_CFB
A	Avg	-1.340	-1.275	-1.311
	Tot	-20.1	-15.3	-35.4
	Cnt	15	12	27
	Min	-2.4	-2.1	-2.4
	Max	-1	-1	-1
	Var	0.165	0.087	0.131
	StD	0.406	0.295	0.362
B	Avg	-1.300		-1.300
	Tot	-1.3	0	-1.3
	Cnt	1	0	1
	Min	-1.3		-1.3
	Max	-1.3		-1.3
	Var	0.000	0.000	0.000
	StD	0.000	0.000	0.000
C	Avg		-1.100	-1.100
	Tot	0	-1.1	-1.1
	Cnt	0	1	1
	Min		-1.1	-1.1
	Max		-1.1	-1.1
	Var	0.000	0.000	0.000
	StD	0.000	0.000	0.000
D	Avg		-1.585	-1.585
	Tot	0	-20.6	-20.6
	Cnt	0	13	13
	Min		-2.9	-2.9
	Max		-1	-1
	Var	0.000	0.281	0.281
	StD	0.000	0.530	0.530
Hb_CFB	Avg	-1.338	-1.423	-1.390
	Tot	-21.4	-37	-58.4
	Cnt	16	26	42
	Min	-2.4	-2.9	-2.9
	Max	-1	-1	-1
	Var	0.155	0.208	0.189
	StD	0.394	0.456	0.435

Diarrhea and 1 Point Hb Drop [in those with B12 values]

Group	Study_ID	Ca++_CFB	B12_CFB	Hb_CFB
A	87-1D			
	Total:	-3.300	-1059.000	-9.300
	Average:	-0.471	-151.286	-1.329
	Count:	7	7	7
	Maximum:	0.200	92.000	-1.000
	Minimum:	-1.300	-651.000	-2.400
	Variance:	0.305	56139.918	0.222
	Standard Deviation:	0.552	236.939	0.471
	87-2D			
	Total:	0.200	-875.000	-3.900
	Average:	0.067	-291.667	-1.300
	Count:	3	3	3
	Maximum:	0.500	-235.000	-1.000
	Minimum:	-0.300	-382.000	-1.500
	Variance:	0.109	4168.222	0.047
	Standard Deviation:	0.330	64.562	0.216
Total:		-3.100	-1934.000	-13.200
Average:		-0.310	-193.400	-1.320
Count:		10	10	10
Maximum:		0.500	92.000	-1.000
Minimum:		-1.300	-651.000	-2.400
Variance:		0.307	44686.840	0.170
Standard Deviation:		0.554	211.393	0.412
C	87-2D			
	Total:	-0.100	-54.000	-1.100
	Average:	-0.100	-54.000	-1.100
	Count:	1	1	1
	Maximum:	-0.100	-54.000	-1.100
	Minimum:	-0.100	-54.000	-1.100
	Variance:	0.000	0.000	0.000
	Standard Deviation:	0.000	0.000	0.000
Total:		-0.100	-54.000	-1.100
Average:		-0.100	-54.000	-1.100
Count:		1	1	1
Maximum:		-0.100	-54.000	-1.100
Minimum:		-0.100	-54.000	-1.100
Variance:		0.000	0.000	0.000
Standard Deviation:		0.000	0.000	0.000

Diarrhea and 1 Point Hb Drop [in those with B12 values]

Group	Study_ID	Ca++_CFB	B12_CFB	Hb_CFB
D	87-2D			
	Total:	2.100	-395.000	-12.500
	Average:	0.300	-56.429	-1.786
	Count:	7	7	7
	Maximum:	1.200	441.000	-1.200
	Minimum:	-0.500	-335.000	-2.900
	Variance:	0.377	54251.388	0.330
	Standard Deviation:	0.614	232.919	0.574
Total:		2.100	-395.000	-12.500
Average:		0.300	-56.429	-1.786
Count:		7	7	7
Maximum:		1.200	441.000	-1.200
Minimum:		-0.500	-335.000	-2.900
Variance:		0.377	54251.388	0.330
Standard Deviation:		0.614	232.919	0.574
Total:		-1.100	-2383.000	-26.800
Average:		-0.061	-132.389	-1.489
Count:		18	18	18
Maximum:		1.200	441.000	-1.000
Minimum:		-1.300	-651.000	-2.900
Variance:		0.402	50577.015	0.281
Standard Deviation:		0.634	224.893	0.530

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-357 Trade (generic) names Glucophage (metformin HCl) Tab

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&MC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

5. Usage in children is specifically prohibited in the package insert.

Signature of Preparer

11/16/94
Date

cc: Orig NDA
HFD-5[illegible] Div File
NDA Action Package

Part A. Draft Proposal for a Phase IV Safety Study

Lipha Pharmaceuticals, Inc./Bristol-Myers Squibb August 31, 1994
NDA 20-357
Amendment #29-94: Part A: Phase IV Safety Study Proposal

DRAFT PROPOSAL

A Phase IV Safety Study

for Glucophage (Metformin Hydrochloride)

I. INTRODUCTION AND BACKGROUND

This draft proposal for a postmarketing study of Glucophage® brand of metformin hydrochloride is in response to the request to provide further safety assurance as discussed at the FDA's Endocrinologic and Metabolism Drugs Advisory Committee meeting of March 18, 1994 and as stated in the letter of June 29, 1994 from Dr. Sobel, Director of the Division of Metabolism and Endocrine Drug Products to Lipha Pharmaceuticals, Inc.

Clinical trials worldwide, and extensive postmarketing experience in Europe have shown metformin to be safe and effective. However, in part due to the association of the biguanide phenformin and lactic acidosis, it is requested by the Division that further safety data on the risk of lactic acidosis in U.S. patients on metformin be obtained. The June 29, 1994 letter indicates that "...It is important that a Phase 4 study be conducted to define better the safety of metformin therapy in the treatment of Type II Diabetes Mellitus under the conditions of medical care that are generally prevalent in the United States..." The letter further stated that it was not the Division's intent to specify the study design, but indicated that the protocol should address issues of 1) representativeness, 2) confounding, 3) power, 4) validation and 5) timeliness.

Lipha Pharmaceuticals, Inc./Bristol-Myers Squibb **August 31, 1994**
NDA 20-357
Amendment #29-94: Part A: Phase IV Safety Study Proposal

Metformin has been in clinical use for more than 30 years and is currently commercially available in more than 80 countries worldwide, including all major western European and Scandinavian countries and Canada. Glucophage® brand of metformin hydrochloride has never been withdrawn from any commercial market for either safety or efficacy reasons. In fact, use of metformin is increasing in many countries and its pharmacologic properties continue to be of considerable interest, from both a clinical and basic science perspective.

As is the case for all biguanides, metformin use has been associated with the occurrence of lactic acidosis. However, as has been extensively discussed in NDA 20-357, the incidence of such occurrence is vastly different among the biguanides, with metformin having the lowest incidence of any biguanide which is or has been commercially available. Biguanides, although members of the same family of compounds, are distinguished from each other on the basis of significant structural, pharmacokinetic and metabolic differences and significant differences in their actions and reactivity on a molecular level. Such differences between metformin and, particularly, phenformin have been presented in detail in NDA 20-357 and are thought to account for the reported differences in clinical safety experience with the two compounds.

Metformin use in France since 1984 (when adverse event reporting was mandated), accounts for approximately 2.5 million patient-years of exposure to metformin. In France (where the use of metformin is the greatest and where detailed pharmacovigilance and sales information is available from 1984 to the

present), cases of lactic acidosis in patients taking metformin, have shown a remarkable pattern of constancy over this time period. Per 1,000 patient-years of exposure, there has been an average of 0.03 reported cases of lactic acidosis, with 0.015 fatal cases per 1,000 patient-years. In Sweden, where very careful adverse event reporting and metformin usage information is available, a very similar incidence rate has been reported (0.024 cases per 1,000 patient-years) over the five year period 1987-1991, with 0.012 fatalities directly attributable to the acidosis per 1,000 patient-years[1]. Compared to an earlier five year period (1977 to 1981), this represents a more than threefold decrease in incidence of reported cases of lactic acidosis, despite concomitant steady increase in metformin usage in Sweden[1]. *(For purposes of comparison, it should be noted that at the time of phenformin's withdrawal from most world markets, FDA estimates of phenformin-associated lactic acidosis in the U.S. varied from 0.25 to 4.0 cases per 1,000 patient-years, with a mortality rate of from 0.125 to 2.0 per 1,000 patient years).*

Furthermore, many of the cases of lactic acidosis temporally associated with metformin use lack supportive evidence (i.e., elevated blood metformin levels consistent with metformin accumulation) to unequivocally establish causality and, thus, the incidence may be even less than these figures indicate.

---

[1] - WIHOLM B.E., MYRHED M. Metformin-associated lactic acidosis in Sweden 1977-1991. *Eur. J. Clin. Pharmacol.* 1993, 44: 589-591.

All cases of lactic acidosis reported in patients taking metformin have occurred in the setting of at least one or more acute or chronic illnesses, known to be either direct risk factors for the development of lactic acidosis in such patients (e.g., acute or chronic renal impairment with resultant metformin accumulation) or independent risk factors for lactic acidosis (acute or chronic cardiovascular disease, pulmonary disease with hypoxia, sepsis or acute or chronic hepatic disease with or without associated alcoholism). Thus, the risk of occurrence of lactic acidosis in patients taking metformin can be minimized by heeding the recognized contraindications to its use.

Finally, comparative risk estimates for fatal adverse reactions for products which continue to be widely used include a death rate from anaphylaxis with penicillin use of 0.02 patients per 1,000 patients treated and a death rate from thromboembolism amongst oral contraceptive users of 0.01 to 0.03 per 1,000 patient-years. Estimates of fatal hypoglycemic reactions due to use of oral sulfonylureas average 0.020 per 1,000 patient-years.

It is widely accepted that assessment of adverse event incidence based on spontaneous adverse event reporting is affected by underreporting (perhaps by a factor of 10). The current proposal, therefore, seeks to obtain additional relevant safety information on metformin in a prospective fashion in a representative U.S. patient population, through the conduct of a large scale simplified clinical trial.

Lipha Pharmaceuticals, Inc./Bristol-Myers Squibb **August 31, 1994**
NDA 20-357
Amendment #29-94: Part A: Phase IV Safety Study Proposal

II. DRAFT PROPOSAL

Overview

It is proposed that a 10,000 patient, prospective, simplified clinical trial of metformin be conducted. This trial will be open-label and controlled *(see Page 6, D.)* and will reflect actual practice (i.e., will not be overly restrictive in terms of investigator and patient enrollment and will have inclusion/exclusion criteria consistent with that given by the label of metformin). It will collect crucial safety outcome data in a standardized and efficient manner which will minimize loss to follow-up. This trial will particularly focus on detection, confirmation, and evaluation of the incidence of lactic acidosis.

A. Purpose

The primary purpose of the study is to monitor the safety of metformin vs usual care in a large number of "usual practice" patients with Type II diabetes mellitus (NIDDM) with particular emphasis on lactic acidosis.

B. Design

Multicenter, prospective, randomized, controlled, open-label study of Type II diabetic patients, followed for a period of 6 months.

C. Patient Population

Patients with newly diagnosed NIDDM or patients with established NIDDM, either non-drug treated or drug treated, will participate after providing informed consent. Patients will be eligible if their diabetes is not adequately controlled by diet alone or by diet and their present oral antidiabetic medication. In all cases, eligibility will be in accord with metformin labeling.

D. Comparison Groups

Randomization will be 4:1 to metformin or usual care, respectively, with open label treatment. At each participating site, 5 to 20 sequential NIDDM patients who have provided informed consent and who meet the inclusion/exclusion criteria will be entered into the study.

E. Drug Supplies and Administration

Metformin will be prescribed and administered in accordance with the label, with dose adjustments made as clinically indicated.

Usual care will also be prescribed. "Usual care" here is defined as the use of diet, sulfonylureas and other treatments as is the customary treatment of NIDDM by the individual investigator.

F. Outcomes

The key outcome will be hospitalizations and deaths due to lactic acidosis. All serious adverse events will be evaluated. All cause mortality and hospitalization rates will also be examined.

G. Outline of Procedures

1. Investigator recruitment

Potential investigators will be identified from listings and will be recruited from among physicians in a variety of practice situations in order to reflect the usual practice distribution (i.e., specialists and family practitioners/general practitioners). They will be initially contacted by letter and/or telephone.

To identify issues which may impact on enrollment and to better estimate the time necessary to enroll investigators and patients, 50 investigators will be recruited and potentially eligible patients will be identified, in an initial feasibility-pilot study.

2. Patient selection

Patients will be those having the labeled indication for metformin

with the inclusion/exclusion criteria dictated by the label.

Enrollment will include patients with newly diagnosed NIDDM or patients with established NIDDM, either non-drug treated or drug treated, as described above. Both types of patients are included so that the study populations will reflect actual use populations and facilitiate patient recruitment.

3. Comparison groups

The 4:1 metformin to usual care ratio was chosen to increase the ability to detect metformin-associated events while still providing enough power to compare relatively frequent events (eg. hospitalizations, deaths).

Usual care here is defined as the use of diet, sulfonylureas and other treatments, as is the customary treatment of NIDDM by the individual investigator.

Sequential qualifying consenting patients will be enrolled to lessen selection bias. After exposure assignment, observations will be made with knowledge of that exposure. The potential for observation and diagnostic bias are lessened because only "hard" endpoints will be in the critical analyses (see *Pages 17 and 19*).

4. Baseline and 3 Month Follow-up

Data will be collected at baseline and after 3 months of treatment using a short case report form restricted to demographic and disease variables which may be important for stratification and multivariate analysis. These include age, gender, race, known duration of diabetes, severity of hyperglycemia at enrollment, weight status, concomitant medications, concomitant illnesses, and hospitalizations in the prior year.

Key 3 month data will be collected at a second visit and will include treatment status and hospitalizations. Reasons for cessation of assigned therapy will be assessed and appropriate follow-up done.

5. Six Month Follow-up

Treatment status and history of hospitalizations will be obtained by telephone calls to the patient or next of kin. In this way, loss to follow-up should be minimized.

6. Hospitalization and Death Follow-up

Death and hospitalization possibly related to lactic acidosis will be identified by using an algorithm. Hospital records and death certificates will be sought and abstracted when appropriate (see following paragraph).

In order to ensure that all cases of lactic acidosis are identified, investigators will be provided with a suggested procedure for the diagnosis and treatment of lactic acidosis. To ensure that lactic acidosis cases and deaths are identified, each hospitalization, death and drug cessation will be carefully characterized. Information will be obtained from the investigator, other physicians and hospital and death records. For hospitalizations, if initial data review indicates an elective admission for non-metabolic reasons (eg. trauma, elective surgery), not associated with in-hospital death or acidosis, no further information will be obtained. In all other cases, the discharge summary, electrolyte and blood gas data, when available, will be obtained. These hospitalizations will then be characterized as ketoacidotic, possible lactic acidosis (anion gap present), and acidosis NOS and other. For outpatient deaths, an algorithm allowing for classification by cause (eg. metabolic/lactic acidosis - possible, remote), will be developed.

A safety-review committee will periodically review and evaluate all reported events. A mechanism will also be established for the timely reporting of all serious events in compliance with Federal regulations.

7. Data analysis

The primary analysis will be the comparison of incidence rates in the metformin exposed patients to those not exposed to metformin (the internal comparison group receiving usual care), for the following: 1) hospitalization for lactic acidosis; 2) hospitalization for metabolic cause; 3) all cause hospitalizations; and 4) death. With 8,000 and 2,000 patients, respectively, in each of these arms there will be 80% power to rule out 2 fold-risk differences for background rates of 5/1000 (see *Page 16, Power Analysis for Sample Size Justification*). In addition, the metformin arm will be sufficiently large to be able to detect events occurring at a rate of 0.5 per 1,000.

In addition, a confidence interval approach will be used to demonstrate that the incidence of lactic acidosis is lower than a small number, e.g., 3 per 10,000[2]. For example, if we do not observe any incidence during the study, the selected sample size

[2] . See O'NEILL, R.T. (1988). Assessment of Safety in Biopharmaceutical Statistics for Drug Development. Ed. by K. Peace, Marcel Dekker, Inc., New York, New York.

would provide 95% assurance that the incidence rate is lower than 3 per 10,000.

In addition, estimates of the expected rates of hospitalizations, hospitalizations for metabolic cause, and deaths in NIDDM may be made **(external comparators)**. These will be refined in accordance with the actual age, gender and disease profile found after enrollment is complete. A **supplementary** outcome analysis may then consist of observed vs expected ratios for these critical events.

H. Summary

A large simplified clinical trial of metformin vs usual care is proposed to provide further safety assurance. The trial is a randomized, controlled, open label study in NIDDM, which will commence immediately after approval and which will be completed within a 3 year period.

III. DISCUSSION OF DRAFT PROPOSAL

The following provides the rationale for the proposed study design as well as discussion of the specific issues raised in the Division's letter of June 29, 1994 relative to this DRAFT proposal.

A. Rationale for the Use of a Large Scale Simplified Clinical Trial (SCT)

The described study is for a SCT. It is simple in that, relative to usual randomized phase III trials, it uses a relatively short case report form, concentrates only on collection of critical data, has broad inclusion criteria and includes a simple visit schedule. These characteristics are required in order to replicate "usual practice" as closely as possible and also if large numbers of investigators and patients are to be enrolled. Similarly, innovative means for patient follow-up (eg. telephone interviews) are mandatory if such an undertaking is to be feasible. Data collection and intensive follow-up must be tightly defined.

It might be helpful to note that one model for SCTs is given by the original International Study of Infarction Survival (ISIS). This used 250 centers and 16,000 patients to evaluate the effect of beta blockage on survival following myocardial infarction. ISIS demonstrated that SCTs can study pharmaceutical efficacy and safety, particularly in large non-selected populations, in ways not amenable to usual randomized trials.

Because of their size, especially if longitudinal patient follow-up is involved, SCTs have characteristics similar to prospective epidemiologic cohort studies. These include simplified data collection, anticipation of intercurrent events and definition of the critical outcomes of interest. However, in contrast to cohort studies, SCTs are based on assignment of exposure and hence are experimental (vs observational) and can be actively designed to lessen selection bias, speed enrollment and provide a comparison group as is the case in the present study.

B. FDA Study Design Issues and Endpoints

1. Representativeness

As indicated, the study will be designed and conducted in a manner intended to reflect actual use patterns of metformin in NIDDM patients. Geographic representativeness will also be achieved through site selection across the United States.

2. Confounding

Outcomes will clearly be influenced by severity of diabetes and other patient risk factors (e.g., age, gender, renal status, other diseases and concomitant medications). Given the size of the study and randomization, it is highly likely that the distribution of risk factors

will be comparable in the two arms of the study.

In addition, appropriate statistical methods will be used to investigate the relationship between patient characteristics at study entry and outcome. Subgroup analyses will be performed to evaluate the potential confounding effects of these various risk factors on outcome(s).

3. Power

Preliminary power estimates are shown below. It should be noted that for Phase IV studies intending to examine relatively uncommon safety effects, confidence interval considerations usually have been recommended (*see Footnote 2, Page 11*). These are presented below.

# of Cases Observed in 8000 Metformin Patients	Rate in Metformin Patients	Approximate 95% Confidence Intervals
0	0	(0 - 0.00024)
2	0.00025	(0 - 0.00060)
5	0.000625	(0.00007 - 0.00118)
10	0.00125	(0.00046 - 0.00204)
20	0.0025	(0.00138 - 0.00361)
50	0.00625	(0.00449 - 0.00801)

Power Analysis for Sample Size Justification[3]

a. Internal Comparison Group

Incidence Rate in Control Group	Incidence Rate in Metformin Group	Relative Risk
0.0005	0.00405	8.10
0.001	0.0051	5.10
0.005	0.0116	2.32
0.01	0.01855	1.86

b. External Comparison Group

Estimated Incidence Rate in Control Group	Incidence Rate in Metformin Group	Relative Risk
0.0005	0.00134	2.68
0.001	0.00212	2.12
0.005	0.00735	1.47
0.01	0.01325	1.33

[3] - Power analysis was performed to justify the selected sample size (Metformin = 8,000 and Control = 2,000). The selected sample size will have a 80% power for detection of a desired relative risk.

4. Validation

A sample of sites (10%) will be visited to verify source data and protocol adherence. A sample of 6 month interviews will be recorded, re-entered and cross correlated. Similarly, a sample of hospital and death certificates can be re-abstracted and cross correlated.

5. Timeliness

It is estimated that the study could begin within three months of launch; patient enrollment will take 12-18 months and individual patient follow-up will be carried out for a period of six months. Allowing four months for analysis, the study should be completed approximately three years after its initiation.

6. Endpoints in Relation to Study Design

The required size and complexity of a randomized long-term study with a mortality endpoint would make such a study exceedingly difficult if not impossible to conduct. A non-randomized study would be plagued by immeasurable selection bias which would be extremely difficult to assess and control.

For these reasons, the proposed study focuses on lactic acidotic and all cause hospitalizations and deaths in a controlled, randomized manner. Lactic acidosis has been the primary safety issue for metformin, even though considerable evidence indicates the occurrence to be rare.

Part B. Overview of Proposed Education Program

Lipha Pharmaceuticals, Inc./Bristol-Myers Squibb **August 31, 1994**
NDA 20-357
Amendment #29-94: Part B: Overview of Proposed Education Program

GLUCOPHAGE EDUCATION ACTIVITIES

We fully recognize the need for expedient dissemination of balanced product information to the medical community. As such, the market introduction of Glucophage will be accompanied by an extensive array of communications directed toward physicians, pharmacists, diabetes educators, and other allied health professionals. Our intent will be to create an immediate broad awareness of the product labeling, as well as to provide continuing education to support appropriate use.

Immediately following approval, Bristol-Myers Squibb (BMS) will initiate priority mailings with detailed and balanced information on Glucophage including contraindications, drug interactions, and appropriate discussion of lactic acidosis, to:

- General/Family Practitioners
- Endocrinologists
- Internists
- Physician Assistants
- Diabetes Educators
- Emergency Room Physicians
- Radiologists
- Drug Information Officers
- Hospital Pharmacists
- Retail Pharmacists

A major medical education campaign will be implemented, each element of which will include an emphasis on the importance of appropriate patient selection to minimize the risk of lactic acidosis. Key elements of the targeted physician education program will include support of CME and CPE programs, symposia at

major medical meetings, and speaker programs. In addition, BMS sales force training and activities will strictly adhere to fair balance requirements, and appropriate patient selection will be emphasized.

To further facilitate broad dissemination of appropriate information on Glucophage, BMS will work closely with the American Diabetes Association (ADA), the American Association of Diabetes Educators (AADE), and other professional organizations (such as the American Academy of Family Physicians [AAFP] and the American College of Physicians [ACP]) in developing additional communications for Healthcare professionals and information for diabetes patients.

Lipha

LIPHA PHARMACEUTICALS, INC. — TELECOMMUNICATION

To:	From:
Capt. John Short Division of Metabolism and Endocrine Drug Products HFD-510 Food and Drug Administration Rockville, MD	Anita M. Goodman, M.D. Lipha Pharmaceuticals, Inc. 9 West 57th Street, Suite 3825 New York, NY 10019-2701
Fax Number: (301)-443-9282	Fax Number: 212-223-1398

Number of pages including this one: 25 Transmitted by: AG Date: Sept. 20, 1994

FAX MODEL: XEROX 7033. IF YOU HAVE ANY PROBLEMS WITH THIS TRANSMISSION, PLEASE ADVISE BY FAX OR CALL OUR MAIN TELEPHONE NUMBER: 212-223-1280.

May 24, 1994

Dear John:

As per your request, here is a copy of Amendment #29, submitted Aug. 31, 1994, concerning the proposal for a Phase IV Safety Study as well as an overview of the proposed education program. The cover letter, but not the transmittal form, has been included.

With best regards,

Sincerely,

Anita M. Goodman, M.D.

cc: GLD

I N T E R O F F I C E M E M O R A N D U M

DATE: 9 September 1994

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

SUBJECT: Deaths in metformin studies
NDA 20-357/Glucophage (Metformin)/Lipha Pharmaceuticals

TO: Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products

This replies to your request that I review Dr. Innerfield's memo of 18 July 1994 (attachment 1), which discusses my 18 May 1994 memo on deaths reported in NDA 20-357 (attachment 2), and which presents his own analyses of the deaths.

Dr. Innerfield's analyses pertain to the two pivotal metformin studies (U.S. Study 87-1D-6023 & U.S. Study 87-2D-60230), each of which was 29 weeks long, and to the open-enrollment extension of the pivotal studies (U.S. Study 89-1C-6023), which was 116 weeks long (4 x 29 weeks). I will call these as the 1D, 2D, and 1C studies. Tables 1 and 2 provide descriptive information about the three studies.

In my opinion, Dr. Innerfield's analyses lead toward inaccurate conclusions, because of inappropriate pooling of the 1D & 2D studies, and insufficient consideration of basic differences in design between the 2D and 1C studies.

Pooling of 1D & 2D studies

Page 1 of Dr. Innerfield's memo presents an analysis of pooled data from the 1D, 2D, and 1C studies. It is stated that "there were 7 deaths in 564* patients randomized to any metformin and 0 deaths in 354* patients randomized to control medication," and it is shown that the difference between 7/564* and 0/354* is statistically significant.

However, all of the seven deaths occurred in the 423 patients who were randomized in the 2D study to either metformin alone or metformin and glyburide -- there were no in the 143 patients who were randomized to metformin in the 1D study. Data pooling is not appropriate in this situation, because it suggests that patients in both the 1D and 2D studies were at risk of death, when only patients in the 2D study were in fact at risk.

---

*I believe there were actually 566 patients randomized to "any metformin" and 355 to "control medication."

The preceding discussion of the 1D and 2D studies supports the statement in my 18 May 1994 memo that:

> "The 2D study was designed to enroll patients with more severe NIDDM than was the 1D study, i.e., patients were eligible for the 1D study if they met the general criterion of not having improved on a weight-loss diet, whereas patients were eligible for the 2D study only if they met the restrictive criterion of not having improved with at least one month of maximum-dose glyburide. Thus, it is not surprising that deaths occurred only in patients enrolled in the 2D study."

Analysis of 2D & 1C studies

The remainder of Dr. Innerfield's memo, pages 2-7, is focused on the 2D and 1C studies, which is appropriate, although there is no apparent recognition that the page 1 analysis conveys an inaccurate impression. I will first review the analyses on pages 2, 3, and 6, which are all based upon a statistical test for the difference between two proportions, and then review the analysis on pages 4-5, which is described as using life-table methodology.

Analyses based upon testing two proportions

Page 2 shows that, if the 2D and 1C studies are combined, the seven deaths that occurred in the 426* patients randomized to "any metformin" in the 2D study are statistically significant, when compared to no deaths in the 209 patients randomized to glyburide alone. However, six of the seven deaths occurred in the 1C study, which:

- enrolled only 300 (70.1%) of the 423* patients randomized to "any metformin" in the 2D study and 142 (67.9%) of the 209 patients randomized to glyburide alone;
- involved the treatment of all enrolled patients with metformin -- by initial titration with metformin alone, with the later addition of glyburide, if needed;
- was neither randomized nor blinded, and was four times longer than the 2D study.

In light of these basic differences in design between the 1C study and the randomized, double-blind, parallel-group 2D study, I believe it is unwise to rely upon the 2D study randomization as a basis for analyzing the 1C study deaths.

---

*I believe the correct number is 423.

Page 3 shows that the six deaths in the 300 patients randomized to "any metformin" in the 2D study and later enrolled in the 1C study are statistically significant, when compared to no deaths in the 142 patients randomized to glyburide alone in the 2D study and enrolled in the 1C study. This analysis is an improvement over the one on page 2, but only a minor improvement, since the 2D study randomization is still being used as the basis for analyzing the 1C study deaths.

Page 6 presents another analysis based upon combining the 2D and 1C studies. Here, it is shown that the three deaths in the 210 patients randomized in the 2D study to metformin alone are almost statistically significant, when compared to no deaths in the 209 patients randomized in the 2D study to glyburide alone. However, two of the three deaths occurred in the 1C study -- and one of these patients was taking both metformin and glyburide at the time of death -- not metformin alone. This shows the importance of analyzing the 1C study according to drug exposure in the 1C study itself, rather than on the basis of randomization in the 2D study.

Lifetable analysis

Pages 4-5 present an analysis of the seven deaths in patients treated with "any metformin," in the 2D and 1C studies combined, based upon total person-years of exposure (PYE). This is labeled as a "Life Table Analysis," but does not use standard lifetable methodology. Instead, the label "Death Rate/1000 PYE" has been applied to a series of seven rates which have been calculated by dividing the cumulative number of deaths, at the time of each death, by the person-years of metformin exposure, at time of that death, for persons who remained in the database at the time of that death. This is incorrect because it progressively inflates the true cumulative death rate -- which is the sum, over the time intervals in a study, of interval-specific death rates, in which the number of deaths in each time interval is divided by the number of persons exposed in that interval.

A standard lifetable analysis of the 2D and 1C studies combined, for patients randomized in the 2d study to "any metformin," is given in Table 3. This shows that, after 2.8 years of exposure to metformin, the cumulative death rate was 4.1%. The seven deaths, by total weeks of exposure to "any metformin," age, sex, and reported cause, are as follows:

15 wks - 52 y/o man - myocardial infarction
36 wks - 68 y/o woman - coronary occlusion
49 wks - 62 y/o man - cardiovascular disease
66 wks - 53 y/o man - suicide
73 wks - 61 y/o man - lung cancer
108 wks - 66 y/o woman - cardiovascular disease
118 wks - 68 y/o woman - myocardial infarction

Table 4 give a standard lifetable analysis of the 1C study for patients randomized in the 2D study to glyburide alone.

Tables 3 and 4 were prepared with statistical consultation by Mr. Marticello. In these tables, time intervals 1-4 represent approximately comparable data on exposure to "any metformin" for patients randomized in the 2D study to "any metformin" versus patients randomized to glyburide alone. Comparing Tables 3 and 4, for time intervals 1-4, Mr. Marticello has calculated that the difference in cumulative death rates is not statistically significant (p = 0.13).

Finally, the 4.1% death rate after at 2.8 years of exposure to "any metformin," in the 2D and 1C studies combined (Table 3) is similar to the 3-year death rates that were reported by the University Group Diabetes Program (UGDP) for placebo ((4.4%) and tolbutamide (4.9%)*, and is lower that the rate reported for phenformin (7.4%)**. Although there are a number of differences between the UGDP and the combined 2D and 1C studies which limit the methodological rigor of this comparison. I believe that it does provide at least some measure of historical perspective, when considering the safety of metformin compared to tolbutamide, which is on the U.S. market, and to phenformin, which is not.

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* UGDP. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes. 1970;19 (suppl 2):789-830.

** UGDP. A study of the effects of hypoglycemic agents on vascular complication in patient with adult-onset diabetes. V. Evaluation of phenformin therapy. Diabetes. 1975;24 (suppl 1):65-104.

cc:
NDA 20-357
HFD 510/GueriguianJ/FlemingA/StadelB
HFD 730/MarticelloD

TABLE 1

Numbers of patients and deaths in the 1D, 2D, and 1C studies by drug exposure

	1D study To--29 weeks--T1			1C study T2--116 weeks--T3		
	N	D1,2	N	N	D1	D2
Met	143	0	112	85	0	0
Pla	146	0	105	75	0	0
	289	0	217	160	0	0

	2D study To--29 weeks--T1			1C study T2--116 weeks--T3		
	N	D1,2	N	N	D1	D2
Met	210	1	157	132	2	1
Met-Gly	213	0	192	168	4	5
Gly	209	0	174	142	0	0
	632	1	523	442	6	6

Met = metformin alone
Met-Gly = metformin & glyburide
Gly = glyburide alone
Pla = placebo

To = start of 2D study
T1 = end of 2D study
T2 = start of 1C study--all patients are titrated with metformin, after which glyburide is added if needed.
T3 = end of 1C study

N = number of patients at time "T"
D1 = number of deaths by drug(s) at start of 2D study
D2 = number of deaths by drug(s) at the time of death

TABLE 2

Completion rates for 1D and 2D studies
and enrollment rates in the 1C study

1D Study

Completed 1D study

Total = 217/289 = 75.1%
Met = 112/132 = 84.8%
Pla = 105/146 = 71.9%

Enrolled in 1C study

Of 1D beginners

Total = 160/289 = 55.4%
Met = 85/146 = 58.2%
Pla = 75/146 = 51.4%

Of 1D completers

Total = 160/217 = 73.7%
Met = 85/112 = 75.9%
Pla = 75/105 = 71.4%

2D study

Completed 2D study

Total = 523/632 = 82.8%
Met = 157/210 = 74.8%
Met-Gly = 192/213 = 90.1%
Gly = 174/209 = 83.3%

Enrolled in 1C study

Of 2D beginners

Total = 442/632 = 69.9%
Met = 132/210 = 62.9%
Met-Gly = 168/213 = 78.9%
Gly = 142/209 = 67.9%

Of 2D completers

Total = 442/523 = 84.5%
Met = 132/157 = 84.1%
Met-Gly = 168/192 = 87.5%
Gly = 142/174 = 81.6%

TABLE 3

Lifetable analysis for "any metformin" use
in the 2D and 1C studies combined
based upon patients randomized to "any metformin"
in the 2D study

1	2	3	4	5	6	7	8
0	0	0	423	-	-	1	0
1	1	124	361	0.00277	0.99723	0.99723	0.00277
2	2	28	284	0.00704	0.99296	0.99021	0.00979
3	2	65	235.5	0.00849	0.99151	0.98180	0.01820
4	1	85	158.5	0.00631	0.99369	0.97561	0.02439
5	1	114	58.0	0.01724	0.98276	0.95879	0.04121
	7	416					

CUMULATIVE DEATH RATE AT 29 WEEKS (0.6 YEARS) = 0.3%
58 WEEKS (1.1 YEARS) = 1.0%
87 WEEKS (1.7 YEARS) = 1.8%
116 WEEKS (2.2 YEARS) = 2.4%
145 WEEKS (2.8 YEARS) = 4.1%

1 = time interval (each interval = 29 weeks)
2 = number of deaths in interval
3 = number of live withdrawals in interval
4 = effective sample size
5 = conditional probability of death
6 = conditional probability of survival
7 = cumulative probability of survival
8 = cumulative probability of death

TABLE 1

Lifetable analysis for "any metformin" use
in the UP study
based upon patients randomized to glyburide alone
in the UD study

1	2	3	4	5	6	7	8
0	0	0	142	-	-	0	1
1	0	16	134	0	1	0	1
2	0	28	126	0	1	0	1
3	0	40	92	0	1	0	1
4	0	58	42	0	1	0	1
	0	142					

CUMULATIVE DEATH RATE AT 29 WEEKS (0.6 YEARS) = 0
58 WEEKS (1.1 YEARS) = 0
87 WEEKS (1.7 YEARS) = 0
116 WEEKS (2.2 YEARS) = 0

1 = time interval (each interval = 29 weeks)
2 = number of deaths in interval
3 = number of live withdrawals in interval
4 = effective sample size
5 = conditional probability of death
6 = conditional probability of survival
7 = cumulative probability of survival
8 = cumulative probability of death

DF
NDA 20-357

I N T E R O F F I C E M E M O R A N D U M

DATE: 18 August 1994

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

SUBJECT: Deaths in metformin studies
NDA 20-357/Glucophage (Metformin)/Lipha Pharmaceuticals

TO: Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products

10/5/94

This replies to your request that I review Dr. Innerfield's memo of 18 July 1994 (attachment 1), which discusses my 18 May 1994 memo on deaths reported in NDA 20-357 (attachment 2), and which presents his own analyses of the deaths.

Dr. Innerfield's analyses pertain to the two pivotal metformin studies (U.S. Study 87-1D-6023 & U.S. Study 87-2D-60230), each of which was 29 weeks long, and to the open-enrollment extension of the pivotal studies (U.S. Study 89-1C-6023), which was 116 weeks long (4 x 29 weeks). I will call these as the 1D, 2D, and 1C studies. Tables 1 and 2 provide descriptive information about the three studies.

In my opinion, Dr. Innerfield's analyses lead toward inaccurate conclusions, because of inappropriate pooling of the 1D & 2D studies, and insufficient consideration of basic differences in design between the 2D and 1C studies.

Pooling of 1D & 2D studies

Page 1 of Dr. Innerfield's memo presents an analysis of pooled data from the 1D, 2D, and 1C studies. It is stated that "there were 7 deaths in 564* patients randomized to any metformin and 0 deaths in 354* patients randomized to control medication," and it is shown that the difference between 7/564* and 0/354* is statistically significant.

However, all of the seven deaths occurred in the 423 patients who were randomized in the 2D study to either metformin alone or metformin and glyburide -- there were no in the 143 patients who were randomized to metformin in the 1D study. Data pooling is not appropriate in this situation, because it suggests that patients in both the 1D and 2D studies were at risk of death, when only patients in the 2D study were in fact at risk.

---

*I believe there were actually 566 patients randomized to "any metformin" and 355 to "control medication."

The preceding discussion of the 1D and 2D studies supports the statement in my 18 May 1994 memo that:

> "The 2D study was designed to enroll patients with more severe NIDDM than was the 1D study, i.e., patients were eligible for the 1D study if they met the general criterion of not having improved on a weight-loss diet, whereas patients were eligible for the 2D study only if they met the restrictive criterion of not having improved with at least one month of maximum-dose glyburide. Thus, it is not surprising that deaths occurred only in patients enrolled in the 2D study."

Analysis of 2D & 1C studies

The remainder of Dr. Innerfield's memo, pages 2-7, is focused on the 2D and 1C studies, which is appropriate, although there is no apparent recognition that the page 1 analysis conveys an inaccurate impression. I will first review the analyses on pages 2, 3, and 6, which are all based upon a statistical test for the difference between two proportions, and then review the analysis on pages 4-5, which is described as using life-table methodology.

Analyses based upon testing two proportions

Page 2 shows that, if the 2D and 1C studies are combined, the seven deaths that occurred in the 426* patients randomized to "any metformin" in the 2D study are statistically significant, when compared to no deaths in the 209 patients randomized to glyburide alone. However, six of the seven deaths occurred in the 1C study, which:

- enrolled only 300 (70.1%) of the 423* patients randomized to "any metformin" in the 2D study and 142 (67.9%) of the 209 patients randomized to glyburide alone;
- involved the treatment of <u>all</u> enrolled patients with metformin -- by initial titration with metformin alone, with the later addition of glyburide, if needed;
- was neither randomized nor blinded, and was four times longer than the 2D study.

In spite of these basic differences in design between the [illegible] and the randomized, double-blind, parallel-group 2D study, I believe it is unwise to rely upon the 2D study randomization as a basis for analyzing the 1C study deaths.

---

*I believe the correct number is 423.

Page 3 shows that the six deaths in the 300 patients randomized to "any metformin" in the 2D study and later enrolled in the 1C study are statistically significant, when compared to no deaths in the 142 patients randomized to glyburide alone in the 2D study and enrolled in the 1C study. This analysis is an improvement over the one on page 2, but only a minor improvement, since the 2D study randomization is still being used as the basis for analyzing the 1C study deaths.

Page 6 presents another analysis based upon combining the 2D and 1C studies. Here, it is shown that the three deaths in the 210 patients randomized in the 2D study to metformin alone are almost statistically significant, when compared to no deaths in the 209 patients randomized in the 2D study to glyburide alone. However, two of the three deaths occurred in the 1C study -- and one of these patients was taking both metformin and glyburide at the time of death -- not metformin alone. This shows the importance of analyzing the 1C study according to drug exposure in the 1C study itself, rather than on the basis of randomization in the 2D study.

Lifetable analysis

Pages 4-5 present an analysis of the seven deaths in patients treated with "any metformin," in the 2D and 1C studies combined, based upon total person-years of exposure (PYE). This is labeled as a "Life Table Analysis," but does not use standard lifetable methodology. Instead, the label "Death Rate/1000 PYE" has been applied to a series of seven rates which have been calculated by dividing the cumulative number of deaths, at the time of each death, by the person-years of metformin exposure, at time of that death, for persons who remained in the database at the time of that death. This is incorrect because it progressively inflates the true cumulative death rate -- which is the sum, over the time intervals in a study, of interval-specific death rates, in which the number of deaths in each time interval is divided by the number of persons exposed in that interval.

A standard lifetable analysis of the 2D and 1C studies combined, for patients randomized in the 2d study to "any metformin," is given in Table 3. This shows that, after 2.8 years of exposure to metformin, the cumulative death rate was 4.1%. The seven deaths, by total weeks of exposure to "any metformin," age, sex, and reported cause, are as follows:

15 wks - 52 y/o man - myocardial infarction
36 wks - 68 y/o woman - coronary occlusion
49 wks - 62 y/o man - cardiovascular disease
66 wks - 53 y/o man - suicide
73 wks - 61 y/o man - lung cancer
108 wks - 66 y/o woman - cardiovascular disease
118 wks - 68 y/o woman - myocardial infarction

Table 4 give a standard lifetable analysis of the 1C study for patients randomized in the 2D study to glyburide alone.

Tables 3 and 4 were prepared with statistical consultation by Mr. Marticello. In these tables, time intervals 1-4 represent approximately comparable data on exposure to "any metformin" for patients randomized in the 2D study to "any metformin" versus patients randomized to glyburide alone. Comparing Tables 3 and 4, for time intervals 1-4, Mr. Marticello has calculated that the difference in cumulative death rates is not statistically significant ($p = 0.13$).

Finally, the 4.1% death rate after at 2.8 years of exposure to "any metformin," in the 2D and 1C studies combined (Table 3) is similar to the 3-year death rates that were reported by the University Group Diabetes Program (UGDP) for placebo ((4.4%) and tolbutamide (4.9%)*, and is lower that the rate reported for phenformin (7.4%)**. Although there are a number of differences between the UGDP and the combined 2D and 1C studies which limit the methodological rigor of this comparison, I believe that it does provide at least some measure of historical perspective, when considering the safety of metformin compared to tolbutamide, which is on the U.S. market, and to phenformin, which is not.

---

* UGDP. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes. 1970;19 (suppl 2):789-830.

** UGDP. A study of the effects of hypoglycemic agents on vascular complication in patient with adult-onset diabetes. V. Evaluation of phenformin therapy. Diabetes. 1975;24 (suppl,1):65-184.

cc:
NDA 20-357
HFD 510/InnerfieldR/GueriguianJ/FlemingA/StadelB/JShortT
HFD 730/MarticelloD

TABLE 1

Numbers of patients and deaths in the 1D, 2D, and 1C studies by drug exposure

	1D study To--29 weeks--T_1			1C study T_2--116 weeks--T_3		
	N	$D_{1,2}$	N	N	D_1	D_2
Met	143	0	112	85	0	0
Pla	146	0	105	75	0	0
	289	0	217	160	0	0

	2D study To--29 weeks--T_1			1C study T_2--116 weeks--T_3		
	N	$D_{1,2}$	N	N	D_1	D_2
Met	210	1	157	132	2	1
Met-Gly	213	0	192	168	4	5
Gly	209	0	174	142	0	0
	632	1	523	442	6	6

Met = metformin alone
Met-Gly = metformin & glyburide
Gly = glyburide alone
Pla = placebo

To = start of 2D study
T_1 = end of 2D study
T_2 = start of 1C study--all patients are titrated with metformin, after which glyburide is added if needed.
T_3 = end of 1C study

N = number of patients at time "T"
D_1 = number of deaths by drug(s) at start of 2D study
D_2 = number of deaths by drug(s) at the time of death

TABLE 2

Completion rates for 1D and 2D studies
and enrollment rates in the 1C study

1D Study

Completed 1D study

Total = 217/289 = 75.1%
Met = 112/132 = 84.8%
Pla = 105/146 = 71.9%

Enrolled in 1C study

Of 1D beginners

Total = 160/289 = 55.4%
Met = 85/146 = 58.2%
Pla = 75/146 = 51.4%

Of 1D completers

Total = 160/217 = 73.7%
Met = 85/112 = 75.9%
Pla = 75/105 = 71.4%

2D study

Completed 2D study

Total = 523/632 = 82.8%
Met = 157/210 = 74.8%
Met-Gly = 192/213 = 90.1%
Gly = 174/209 = 83.3%

Enrolled in 1C study

Of 2D beginners

Total = 442/632 = 69.9%
Met = 132/210 = 62.9%
Met-Gly = 168/213 = 78.9%
Gly = 142/209 = 67.9%

Of 2D completers

Total = 442/523 = 84.5%
Met = 132/157 = 84.1%
Met-Gly = 168/192 = 87.5%
Gly = 142/174 = 81.6%

TABLE 3

Lifetable analysis for "any metformin" use
in the 2D and 1C studies combined
based upon patients randomized to "any metformin"
in the 2D study

1	2	3	4	5	6	7	8
0	0	0	423	-	-	1	0
1	1	124	361	0.00277	0.99723	0.99723	0.00277
2	2	28	284	0.00704	0.99296	0.99021	0.00979
3	2	65	235.5	0.00849	0.99151	0.98180	0.01820
4	1	85	158.5	0.00631	0.99369	0.97561	0.02439
5	1	114	58.0	0.01724	0.98276	0.95879	0.04121
	7	416					

CUMULATIVE DEATH RATE AT 29 WEEKS (0.6 YEARS) = 0.3%
58 WEEKS (1.1 YEARS) = 1.0%
87 WEEKS (1.7 YEARS) = 1.8%
116 WEEKS (2.2 YEARS) = 2.4%
145 WEEKS (2.8 YEARS) = 4.1%

1 = time interval (each interval = 29 weeks)
2 = number of deaths in interval
3 = number of live withdrawals in interval
4 = effective sample size
5 = conditional probability of death
6 = conditional probability of survival
7 = cumulative probability of survival
8 = cumulative probability of death

TABLE 4

Lifetable analysis for "any metformin" use
in the 1C study
based upon patients randomized to glyburide alone
in the 2D study

1	2	3	4	5	6	7	8
0	0	0	142	-	-	0	1
1	0	16	134	0	1	0	1
2	0	28	126	0	1	0	1
3	0	40	92	0	1	0	1
4	0	58	43	0	1	0	1
	0	142					

CUMULATIVE DEATH RATE AT 29 WEEKS (0.6 YEARS) = 0
58 WEEKS (1.1 YEARS) = 0
87 WEEKS (1.7 YEARS) = 0
116 WEEKS (2.2 YEARS) = 0

1 = time interval (each interval = 29 weeks)
2 = number of deaths in interval
3 = number of live withdrawals in interval
4 = effective sample size
5 = conditional probability of death
6 = conditional probability of survival
7 = cumulative probability of survival
8 = cumulative probability of death

JUL 18 1994

Memo to File

The Division Director asked Dr. Bruce Stadel, to "review the 20 deaths reported in NDA 20-357." Dr. Stadel's conclusions included:

> **...the 1C study does raise the possibility of a somewhat higher death rate for patients randomized in the 2D study to metformin/glyburide than patients randomized to glyburide alone, but the evidence is not strong.**

What is the evidence? In the US trials with 1136 patient years of exposure (PYE) to metformin there were 7 deaths in 564 patients randomized to any metformin and 0 deaths in 354 patients randomized to control medication.

FIRST SAMPLE :
SAMPLE SIZE : 564
NUMBER WITH FEATURE : 7

SECOND SAMPLE :
SAMPLE SIZE : 354
NUMBER WITH FEATURE : 0

FIRST SAMPLE PROPORTION = .0124
SECOND SAMPLE PROPORTION = 0
OBSERVED DIFFERENCE BETWEEN PROPORTIONS = .0124

% CONFIDENCE REQUIRED : 99

Standard Error of Difference = .00466 NORMAL Value = 2.58

99% CONFIDENCE INTERVAL FOR THE DIFFERENCE BETWEEN PROPORTIONS IS:
.000384 TO .0244

All of the deaths occurred in patients randomized to any metformin arms in the 87-2D trial.

FIRST SAMPLE :
SAMPLE SIZE : **426**
NUMBER WITH FEATURE : **7**

SECOND SAMPLE :
SAMPLE SIZE : **209**
NUMBER WITH FEATURE : **0**

FIRST SAMPLE PROPORTION = **.0164**
SECOND SAMPLE PROPORTION = **0**
OBSERVED DIFFERENCE BETWEEN PROPORTIONS = **.0164**

% CONFIDENCE REQUIRED : 99

Standard Error of Difference = .00616 NORMAL Value = 2.58

99% CONFIDENCE INTERVAL FOR THE DIFFERENCE BETWEEN PROPORTIONS IS:
.000541 TO .0323

Dr. Stadel argues that this highly significant difference may be due to "selection bias." [It is true that 3% (ns) more metformin-randomized patients elected open-enrollment than glybenclamide patients. Yet this is both mathematically and statistically insufficient to account for the highly significant excess mortality.] Nevertheless, more of this later.

Dr. Stadel also found:

a) 1 death in the 87-2D trial [randomized to metformin]
b) 2 deaths in the 89-1C trial [randomized to metformin]
c) 4 deaths in the 89-1C trial [randomized to combination]
d) **0 deaths in ANY US trial [not randomized to any metformin]**

Of these 7 deaths, he then proceded to analyze:

=> the 6 deaths in the 1C trial
=> patients denominated strictly by group enrollment into that trial
=> comparisons between:
i) metformin vs glyburide
ii) combination vs metformin
iii) combination vs glyburide

Nevertheless, what he found was "**a statistically significant excess of deaths in the 1C study for patients who were randomized in the 2D study to metformin/glyburide versus patients randomized to glyburide alone (96% CI not including 0).**" The point estimate for this excess difference was 2.38% with 95%-CI of 0.0756 to 4.69%.

However, if one **pools** metformin versus controls in the 1C trial using his denominators there an even more significant 2% difference between groups:

FIRST SAMPLE :
SAMPLE SIZE : **300**
NUMBER WITH FEATURE : **6**

SECOND SAMPLE :
SAMPLE SIZE : **142**
NUMBER WITH FEATURE : **0**

FIRST SAMPLE PROPORTION = **.0200**
SECOND SAMPLE PROPORTION = **0**
OBSERVED DIFFERENCE BETWEEN PROPORTIONS = **.0200**

% CONFIDENCE REQUIRED : 95

Standard Error of Difference = .00808 NORMAL Value = 1.96

95% CONFIDENCE INTERVAL FOR THE DIFFERENCE BETWEEN PROPORTIONS IS:
.00416 TO .0358

Now what about the selection bias?

> **However, of the 213 patients randomized to metformin/glyburide in the 2D study, 168 (78.9%) enrolled in the 1C study, compared to only 142 (67.9%) of the 209 patients randomized to glyburide alone and 132 (62.9%) of the 210 patients randomized to metformin alone. These differences are statistically significant....Thus, selection bias could be a factor in the excess deaths for patients randomized in the 2D study to metformin/glyburide.**

Dr. Stadel found that 10.9% more patients randomized to combination entered open-enrollment than did patients randomized to glyburide ($p<0.05$) - and presumably accounted for the statistically significant 2.38% excess mortality. Nevertheless, 16.0% more patients randomized to combination entered open-enrollment than did patients randomized to metformin (also $p<0.05$) - accounting for a statistically **insignificant** 0.87% excess. If the excess attributable mortality were due to "selection bias", then why was a significant excess mortality only seen versus glyburide and not against the metformin group with at least the same degree of selection bias (+5.1%-ns)?

Perhaps realizing that his denominators may be flawed in that [1] they do not consider all randomized patients equally and [2] frozen in time at the beginning of open-enrollment, they can not be applied to time-to-event analyses either, Dr. Stadel goes on to argue that death rates should be based upon life table analyses of the 87-1C trial ["**instead of the approximation used above**"] but again only between groups and without any pooling:

> **However, no data are currently available about the amount of person-time in the 2D study that came from the 168 patients randomized in the 2D study to metformin/glyburide compared to the amount from the 142 patients randomized to glyburide alone and the amount from the 132 patients randomized to metformin alone.**

Nevertheless, a time-to-event analysis **does exist** for patients pooled on the basis of randomization to any metformin (**Figure 8, page 26 of my MOSR**).

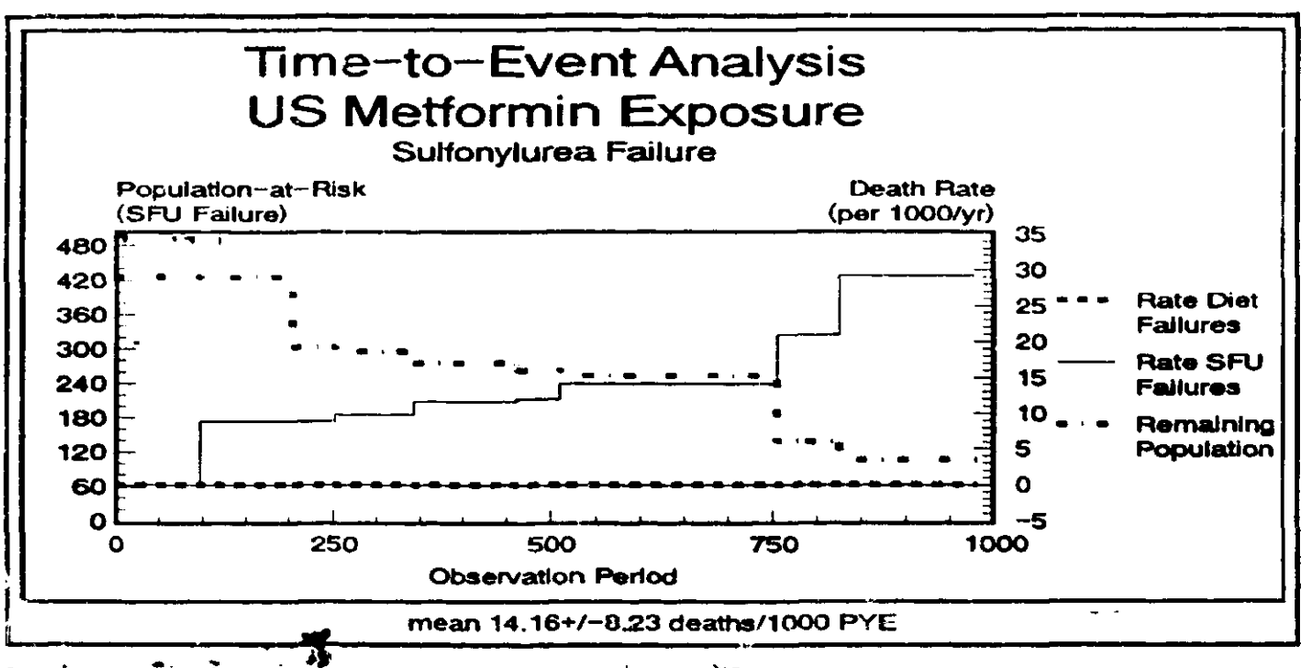


Figure 1
Life Table Analysis

This analysis, based on the 426 [87-2D] metformin-randomized sulfonylurea-failure patients reveals an average of 14.16 ± 8.23 deaths/1000 PYE during the observation period. (The estimate based on just total mortality divided by total patient years of exposure for all of the 781 patients exposed during any trial was 6.16/1000 PYE.) Looking at the time-to-event curve in Figure 1, the rate appeared fairly constant from approximately 100 to 750 days (0.27 to 2.05 years) at roughly 9 to 14 deaths/1000 PYE. After about two years, however, the rate increased to its maximum of 29 deaths/1000 PYE apparently due to enrichment of the remaining population by patients at risk of increased metformin mortality. The association of drop-outs with lack of efficacy in this population (see **MOSR, Section 7.3**), suggests that these later deaths are occurring in patients in whom the drug is efficacious, i.e., that the cause of these deaths is directly related somehow to its mechanism of action.

Duration Exposure (days)	Metformin Deaths	Remaining Population	Death Rate (/1000 PYE)	Control Rate
0	0	426	0	0
97	0	426	0	0
97	1	425	8.85385082	0
252	1	303	8.85385082	0
252	1	302	8.85385082	0
252	2	295	9.81974465	0
343	2	294	9.81974465	0
343	3	275	11.6087885	0
461	3	274	11.6087885	0
461	4	263	12.0419267	0
510	4	262	12.0419267	0
510	5	253	14.1440018	0
754	5	252	14.1440018	0
754	6	139	20.8957354	0
783	6	138	20.8957354	0
783	6	138	20.8957354	0
825	6	138	20.8957354	0
825	7	106	29.2166878	0

Life Table Data

The smallest duration of exposure to metformin in the glyburide monotherapy control group was 14 days. The longest was 783 days. The mean was 498.28 ± 209.70 days. These compare quite favorably to the statistics manifested by those patients from the other two groups in the 2D study who died. The earliest duration of exposure to metformin resulting in a death was 97 days. The latest was 825 days. The mean was 463.14 ± 242.26 days.

Getting back to Dr. Stadel's analysis, there was more statistical difference in mortality between glyburide patients and metformin patients (1.52% with 95%CI of -0.569 to +3.60%) than between metformin patients and combination patients (0.87% with 95%CI of -2.24 to +3.97%.) Indeed, based on the original randomization and considering *all* deaths the excess mortality from metformin alone compared to glyburide alone is significant at the $p<0.1$ level:

FIRST SAMPLE :
SAMPLE SIZE : **210**
NUMBER WITH FEATURE : **3**

SECOND SAMPLE :
SAMPLE SIZE : **209**
NUMBER WITH FEATURE : **0**

FIRST SAMPLE PROPORTION = **.0143**
SECOND SAMPLE PROPORTION = **0**
OBSERVED DIFFERENCE BETWEEN PROPORTIONS = **.0143**

% CONFIDENCE REQUIRED : 90

Standard Error of Difference = .00819 NORMAL Value = 1.65

90% CONFIDENCE INTERVAL FOR THE DIFFERENCE BETWEEN PROPORTIONS IS:
.000774 TO .0278

Since the metformin monotherapy versus metformin combination therapy difference remains insignificant no matter what the denominator, then why does Dr. Stadel seem to restrict his analysis to only the metformin combination versus glyburide monotherapy comparison? Does not the intention-to-treat look obviate most of the difficulties encumbent in Dr. Stadel's analyses? Again why look only between groups when all of the mortality was seen in patients originally prescribed metformin? Is that not, after all is said and done, the fundamental comparison of interest?

In the US trials with 1136 PYE to metformin there were 7 deaths in 564 patients randomized to any metformin and 0 deaths in 354 patients randomized to controls. This difference is highly statistically significant at a $p<0.01$.

This excess mortality is occurring not in isolation, but in the context of significantly increased EKG changes, significantly increased coronary events, increased arrhythmias, highly significantly excess hypoglycemia, significantly increased cardiovascular events, and increased hospitalizations.

Reasonable men may disagree, nevertheless, I find the evidence appears quite strong, indeed.

Ronald Jay Innerfield, M.D.,
Medical Officer
20 May 1994

NDA 20-357
HFD-510/Sobel/Stadel/Fleming/Gueriguian/Innerfield/Short
HFD-713/Nevius/Marticello

This analysis is helpful and should be pursued. The critical Kaplan-Meier comparisons to be made is of patient exposure to non-metformin treatment and metformin treatments. This should resolve ~~whether~~ the issue of whether the groups are comparable in terms of risks attributable to drug exposure. The issue of pooling is also very important here. We should ask Dan Marticello to advise us on this.

7/18/94

JUN 16 1994

NDA 20357
Sponsor: Lipha
Drug: Metformin

Received: 6/11/94
Reviewed: 6/16/94
Doct: I42775B/G105

REVIEW OF A PROPOSED PHASE IV PROTOCOL

The Sponsor has sent, on May 27, 1994, a protocol proposal to study the minimal effective dose of metformin with greater precision than heretofore.

In essence, the study -- multicenter, prospective, double-blind, randomized, placebo-controlled -- will involve six parallel arms: Five dose levels of metformin (from 500 mg to 2500 mg/day) and one placebo (control) group.

To achieve the higher doses, initially lower doses are going to be administered, then a forced titration will be instituted to achieve the final desired dose while minimizing the initial gastro-intestinal effects seen with such high doses of metformin.

At all doses, fasting plasma glucose values will be measured serially, till, at any given dose, a steady state is achieved in this measurement. At the end of the study, it will be possible to establish a dose-response relationship which, in turn, will help us determine with greater precision and confidence, a minimal effective dose for the drug.

RECOMMENDED REGULATORY ACTION

The study may proceed, since it proposes to fulfill one of our requirements for a conditional approval of the drug.

John L. Gueriguian
Medical Officer
6/16/94

cc.
The File
Dr. Fleming

DRAFT 1

5/18/94

INTE MORANDUM

ORIGINAL

DATE: 18 May 1993

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology Bruce V Stadel

SUBJECT: Death Review
NDA 20-357/Glucophage (Metformin)/Lipha Pharmaceuticals

TO: Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products

This replies to your request that I review the 20 deaths reported in NDA 20-357. I will review these deaths according to the NDA priority of the studies in which they occurred: 1) the pivotal studies and its open-enrollment extension, 2) other controlled studies, 3) uncontrolled studies.

Pivotal studies & open-enrollment extension: seven deaths

The pivotal studies are U.S. Studies 87-1D-6023 and 87-2D-6023; both were 29 weeks long. The open-enrollment extension of the pivotal studies is U.S. Study 89-1C-6023; it was 116 weeks long. I will refer to these as the 1D, 2D, & 1C studies, respectively. The experimental design and demographics for the pivotal studies are summarized in sections 7.1 & 7.2 of the 10 March 1994 draft of Dr. Gueriguian's review (attachment 1). Copies of the death reports are attached(attachment 2).

1D Study
Metformin vs. Placebo

Metformin: 143 patients were randomized to metformin and 112 (78.3%) of these completed the 29 weeks. Of the 112, 85 (75.9%) enrolled in the 1C study.

There were no deaths in either the 1D or 1C studies.

Placebo: 146 patients were randomized to placebo and 105 (71.9%) of these completed the 29 weeks. Of the 105, 75 (71.4%) enrolled in the 1C study.

There were nc deaths in either the 1D or 1C studies.

2D Study

Metformin vs. Glyburide vs. Metformin/Glyburide Combination

Metformin: 210 patients were randomized to metformin and 157 (74.8%) of these completed the 29 weeks. Of the 157, 132 (84.1%) enrolled in the 1C study.

There was one death in the 2D study (a 52 year old man treated for 15 weeks) and two in the 1C study. These two were:

- a 65 year old woman enrolled for 17 months, on metformin/glyburide at time of death;
- a 60 year old man enrolled for 15 months, on metformin at time of death.

Glyburide: 209 patients were randomized to glyburide and 174 (83.3%) of these completed the 29 weeks. Of the 174, 142 (81.6%) enrolled in the 1C study.

There were no deaths.

Metformin/ Glyburide: 213 patients were randomized to metformin/glyburide and 192 (90.1%) of these completed the 29 weeks. Of the 192, 168 (87.5%) enrolled in the 1C study.

There were no deaths in the 2D study and four in the 1C study. These four were:

- a 67 year old woman enrolled for 10 months, on metformin/glyburide at time of death;
- a 68 year old woman enrolled for one month, on metformin/glyburide at time of death;
- a 61 year old man enrolled for five months, on metformin/glyburide at time of death;
- a 53 year old man enrolled for nine months, on metformin /glyburide at time of death.

Discussion

The 2D study was designed to enroll patients with more severe NIDDM than was the 1D study, i.e., patients were eligible for the 1D study if they met the general criterion of not having improved on a weight-loss diet, whereas patients were eligible for the 2D study only if they met the restrictive criterion of not having improved with at least one month of maximum-dose glyburide. Thus, it is not surprising that deaths occurred only in patients enrolled in the 2D study.

The death rate in the 1C study according to drug group in the 2D study was 2/132 for metformin (M), 0/142 for glyburide (G), and 4/168 for metformin/glyburide (MG). The death rate difference and 95% confidence interval (CI) for each drug comparison is as follows:

M vs. G = 2/132 - 0/142 = 0.0152 (-0.00569 - 0.0360)
MG vs. M = 4/168 - 2/132 = 0.00866 (-0.0224 - 0.0397)
MG vs. G = 4/168 - 0/142 = 0.0238 (0.000756 - 0.0469)

Thus, there was a statistically significant excess of deaths in the 1C study for patients who were randomized in the 2D study to metformin/glyburide versus patients randomized to glyburide alone (96% CI not including 0).

However, of the 213 patients randomized to metformin/glyburide in the 2D study, 168 (78.9%) enrolled in the 1C study, compared to only 142 (67.9%) of the 209 patients randomized to glyburide alone and 132 (62.9%) of the 210 patients randomized to metformin alone. These difference are statistically significant:

MG vs. G: 168/213 - 142/209 = 0.109 (95% CI 0.0256 - 0.183)
MG vs. M: 168/213 - 132/210 = 0.160 (95% CI 0.0749 - 0.245)

Thus, selection bias could be a factor in the excess deaths for patients randomized in the 2D study to metformin/glyburide. Also, death rates in the 1C study, according to drug group treatment group in the 2D study, should be based upon person-time in the 1C study itself, instead of the approximation used above. However, no data are currently available about the amount of person-time in the 1C study that came from the 168 patients randomized in the 2D study to metformin/glyburide compared to the amount from the 142 patients randomized to glyburide alone and the amount from the 132 patients randomized to metformin alone.

In conclusion, the 1C study does raise the possibility of a somewhat higher death rate for patients randomized in the 2D study to metformin/glyburide than patients randomized to glyburide alone, but the evidence is not strong.

OTHER CONTROLLED STUDIES

One patient died while taking glipizide in a one-year randomized trial of metformin (N=25) and glipizide (N=25) which was conducted in the U.K. (Study # MET/GB/86/CAMP1)

One patient died while taking metformin/glibenclamide in a randomized trial of metformin (N=38), glibenclamide (N=34), and metformin/glibenclamide (N=72) which was conducted in Sweden. The study began with a variable length titration phase followed by a six-month maintainance phase. (Study # MET/S/86/HERMA)

There are no other deaths reported from controlled studies.

UNCONTROLLED STUDIES

There were 11 deaths in a six-month Phase IV study of 4,374 private-practice patients in France who had failed diet therapy or were not adequately controlled with their current treatment. The study drugs were metformin or metformin/sulfonylurea. It does not appear that death rates were computed according to the amount of person-time on metformin alone or metformin/sulfonylurea, and the study is therefore not informative.
(Study # MET/AM/87/PHASE)

cc:
NDA 20-357
HFD 510/InnerfieldR/GueriguianJ/FlemingA/StadelB

6.2.2 Foreign Post-Marketing Experience

During at least ten years of adverse event reporting to the parent company Lipha S.A., Lyon, France, from within France and from its subsidiaries and licensees of Glucophage® brand of metformin hydrochloride, including subsidiaries in the United Kingdom, Germany, Belgium, Italy, Switzerland and Portugal and licensees in Australia, Austria, Canada, Denmark, Holland, Japan, New Zealand, South Africa and Sweden, there have been 279 adverse events reported, consistent with the reporting requirements of the respective countries. Needless to say, each country has its own reporting requirements which are, forsome countries at least, laxer than the United States requirements. The number of these adverse events, therefore, do not reflect the totality of the toxic experience. In order to obtain a better picture of the toxic potential of the medication, we need to carefully scrutinize the studies performed in the United States, together with an analysis of scientifically rigorous and valid studies published in this country as well as abroad, for studies performed here as well as outside our borders.

7. PIVOTAL CLINICAL STUDIES

7.1. First Pivotal Study: Study No. 87-1D-6023

7.1.1 Description of Study

7.1.1.1 Title, Objective and Rationale

U.S. Study No. 87-1D-6023: "A Double-Blind, Placebo-Controlled, Randomized, Parallel Group, Multi-Center Study to Determine the Safety and Effectiveness of Metformin in the Control of Obese, Type II, Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Patients who are not Adequately Controlled with Diet Alone" was conducted to evaluate the safety and efficacy of metformin in the patient population described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

7.1. 1.2 Experimental Design

U.S. Study No. 87-1D-6023, conducted from March, 1988 through May, 1991, was a randomized, parallel-group (two), double-blind, multi-center (13 centers) study comparing the safety and efficacy of 29 weeks treatment with either metformin (up to 2,550 mg/day) or placebo in 289 obese (120-170% of ideal body weight) NIDDM outpatients who had either never received pharmacologic antidiabetic therapy or had not received such treatment for the two months preceding randomization. Potentially eligible patients were randomized (143 to metformin; 146 to placebo) if body weight remained within ± 3% of entry body weight and FPG remained >140 mg/dL, despite two months on a weight-reduction diet. The 850 mg dosage strength of metformin was used in this study.

Subsequent to the two month dietary run-in phase, eligible patients were randomized and began a five week metformin dose titration phase (biweekly increases of metformin [or placebo] by 850 mg increments [based on FPG levels and tolerance], starting with 850 mg/day and increasing to a maximum of 850 mg t.i.d., with meals), followed by a 24 week treatment phase, while on the maintenance dose of metformin (or placebo).

7.1.1.3 Demographics

A total of 289 patients were randomized to treatment with 143 receiving metformin and 146 receiving placebo. The patients ranged in age from 31 to 70 with a mean age of 53. There were 43% males and 57% females.

7.1. 1.4 Safety Considerations

This reviewer wants also to express slightly discordants opinions from those of the Sponsor, as far as this trial is concerned: (1) The gastrointestinal effects of the drug are at least incommodating, and are also relatively frequent (see Josephkutty & Potter, 1990); and (2) The reduction of plasma vitamin B12 need to be followed in the individual patient eventually treated with this medication, inasmuch as at least a single case of megaloblastic anemia has been reported recently in the literature (See Levesque et al., 1991).

It's more important, however, to emphasize the following: In my opinion, the Company has failed to determine the lowest dose effective in most patients. This is due to the protocolar choice of titrating upward based on FPG values alone during relatively short intervals. As a result, a hodge-podge of doses were used and not a single one was tested for true efficacy. Under the circumstances, it is very difficult to recommend approval of the drug, though its efficacy seems to be real and significant.

7.2. Second Pivotal Study: Study No. 87-2D-6023

7.2.1. Description of Study

7.2.1.1 Title, Objective and Rationale

U.S. Study No. 87-2D-6023: "A Double-Blind, Placebo Controlled, Randomized, Parallel Group, Multi-Center Study to Compare the Safety and Effectiveness of Metformin Alone to Metformin in Combination with a Second Generation Sulfonylurea (Glyburide) to Glyburide Alone in the Control of Obese, Type II, Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Patients who are not Well Controlled at the Maximum Dose of a First or Second Generation Sulfonylurea" was conducted to evaluate the safety and efficacy of metformin as described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug in this patient population.

7.2.1.2 Experimental Design

U.S. Study No. 87-2D-6023, conducted from Sept., 1988 through July, 1991, was a double-blind, placebo-controlled (placebos for metformin and glyburide), randomized, parallel group (three), multi-center (20 centers) study comparing the efficacy and safety of 29 weeks of treatment with either metformin (M) alone (with placebo for glyburide) vs. metformin in combination with maximum dose glyburide (M + G) vs. maximum dose glyburide (G) alone (with placebo for metformin), in 632 obese (120-170% of ideal body weight) NIDDM outpatients, not achieving acceptable glycemic control despite maximum doses of a sulfonylurea for at least one month, including one month of maximum dose glyburide (20 mg/day), immediately prior to randomization. Potentially eligible patients were randomized if FPG remained >140 mg/dL, despite maximum dose glyburide for at least one month. (All baseline evaluations occurred while patients were on maximum dose glyburide). In this study, the 500 mg dosage strength of metformin was used.

Subsequent to the one month pre-enrollment run-in phase, in which all potential candidates received maximum dose glyburide, eligible patients were randomized and began a five week metformin dose titration phase (weekly increases of metformin [or placebo M] by 500 mg increments [based on FPG and tolerance], starting with 500 mg/day and increasing to a maximum of 2500 mg/day [1000-500-1000, with meals]), followed by a 24 week treatment phase. Glyburide (or placebo G) treatment was continued throughout the study at a daily dose of 20 mg/day (i.e., identical to pre-randomization dose).

7.2.1.3 Demographics

A total of 632 patients were randomized to treatment with 210 receiving metformin alone, 209 receiving glyburide alone and 213 receiving metformin/glyburide combination. The patients ranged in

age from 40 to 70 with a mean age of 55. There were 47% males and 53% females.

7.2.1.4 Safety Considerations

Adverse experiences and intercurrent events (AE/MEs) were recorded at each visit.

7.2.1.5 Efficacy Endpoints

The primary efficacy parameter was the integrated value of glycemic control, i.e., HbA1c values.

Supportive efficacy parameters comprised other measurements of glycemic control, i.e., FPG, and plasma glucose response during a 3-hour oral glucose tolerance test [OGTT]).

Secondary efficacy parameters included: (a) lipid parameters: total cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL) cholesterol, HDL subfractions and apolipoproteins;(b) body weight change; and, (c) Others: blood pressure and insulin and C-peptide effects (measured as part of the 3-hour OGTT).

7.2.1.6 Statistical Approaches

The population of interest was the intent-to-treat population. For the efficacy analysis this was defined as any patient who took study medication and completed at least one post-baseline visit. For the safety analysis this was defined as any patient who took study medication and was assessed for safety. Observed values and change from baseline values were compared for all efficacy and safety laboratory measures to determine if significant differences existed among the three treatment groups, based on a visit-wise analysis and a last observation carried forward analysis. The primary analyses were the within- and between-treatment comparisons of change from baseline values. The incidence of AE/IMEs were tabulated and compared between treatment groups using the Fisher's Exact test.

7.2.2 Results and Conclusions

7.2.2.1 Patient Comparability

Patient groups were well-matched for all demographic features, as well as for baseline values of efficacy parameters.

7.2.2.2 Patient Disposition

A total of 157 (75%) metformin-treated patients, 174 (83%) glyburide-treated and 192 (90%) metformin/glyburide combination treated patients completed the study.

Eleven patients (four patients in the metformin group [1.9%] vs. three patients in the glyburide group [1.4%] vs. four patients in the metformin/glyburide group [1.9%]) withdrew due to an adverse experience.

7.2.2.3 Efficacy Data

The group of greatest interest in this study was the metformin/glyburide group. This treatment combination resulted in very significant improvement in all parameters of glycemic control (i.e., FPG, HbA_{1c} and 2-hour post-glucose load plasma glucose), with addition of metformin to continued glyburide therapy. For FPG the combination therapy group had a 63.5 mg/dL decrease from baseline whereas the metformin alone group decrease 0.9 mg/dL and the glyburide alone group increased 13.7 mg/dL.

Subgroup analysis of FPG and HbA_{1c} changes at final visit, according to baseline FPG subgroup, indicated that the magnitude of the response for these parameters in the metformin/glyburide group

Attachment 2

U.S. Controlled Clinical Trials:

In the U.S. controlled clinical trials, there was only one death among randomized patients. This patients: Patient #20/06, enrolled in U.S. Study No. 87-2D-6023, had been randomized to treatment with metformin and Placebo G. This 52 year old obese male smoker, with a 12 year history of NIDDM, died of an apparent myocardial infarction, after approximately 15 weeks on study. At the time of his death, he was taking 2.5 g/day of metformin and 4 tabs/day of Placebo G. His complete case report form, including available ECGs, has been previously submitted with the NDA (*see Vol. 1.394, Pages 12/009864 through 12/010016*) and a narrative summary of his case has also been submitted (*see Vol. 1.80, Pages 08A-02293 and 02294*). These ECGs are now resubmitted as Item 2, Part B.

ADVERSE EXPERIENCE/INTERCURRENT MEDICAL EVENT			
Protocol No.: 89-1C-6023			Death/Cardiac
Patient Identification Number: 06021-2			
Patient Initials:	Date of Birth:	Male [ ]	Female [X]
Study Drug: METFORMIN/GLYBURIDE			

Narrative Summary

Study History
This 65 year old female was pre-enrolled into the 87-2D-6023 study on 1/3/90, was begun on therapy with METFORMIN and PLACEBO G on 1/25/90, and completed the study on 8/28/90. Her course during the study was essentially uneventful. She entered the 89-1C-6023 study on 8/28/90, at which time her FPG was 167 mg/dL on 5 tabs/day of METFORMIN.

Patient Medical History/Diabetes History/Concomitant Medications
Her medical history includes hypertension (1982-on) and arthritis (1989-on).

She was diagnosed as having NIDDM in 1982. She had no known complications of diabetes. Management had been with tolazamide 250 mg QD (1982-12/88), glipizide 20 mg BID (12/88-12/89) and glyburide 10 mg BID (12/20/89-on).

Her concomitant medications were verapamil SR 240 mg QD and Vitamin C 1000 mg QD.

Adverse Experience/Intercurrent Medical Event
Other than persistent fatigue/lethargy throughout the study, no major medical events occurred.

She was last seen at Visit 18 on 2/19/92. Other than lethargy she was feeling fine. Her labs were: FPG=169 mg/dL, lactate=1.0 mmol/L, Na=138 mEq/L, K=4.5 mEq/L, HCO_3=23.3 mEq/L, Cl=107 mEq/L, BUN=26 mg/dL, creat=1.2 mg/dL, chemistries were all normal. She was on 3 tabs/day of metformin and 1 tab/day of glyburide.

On 2/28/92 the site had been trying to contact the patient to repeat some labs and a UA. the patient's daughter answered the phone and informed the site that she had just discovered her mother deceased in her apartment. The police/paramedics deemed this "death due to natural causes." The death certificate listed "arteriosclerotic cardiovascular disease, diabetes mellitus and hypertension" as the cause of death. No autopsy was done.

ADVERSE EXPERIENCE/INTERCURRENT MEDICAL EVENT

Protocol No.: 89-1C-6023		Termination/Death/Lung Cancer	
Patient Identification Number: 07026-2			
Patient Initials:	Date of Birth:	Male [X]	Female [ ]
Study Drug: METFORMIN/GLYBURIDE			

Narrative Summary

Study History

This 60 year old male was pre-enrolled into the 87-2D-6023 study on 8/9/90, was begun on therapy with METFORMIN and PLACEBO G on 9/21/90, and completed the study on 4/4/91. During the study he experienced problems with balanitis (prior to Visit 0), tooth pain/extraction, cough and bronchitis (Visit 8), and bronchospasm (Visit 10). He entered the 89-1C-6023 study on 4/4/91, at which time his FPG was 285 mg/dL on 5 tabs/day of METFORMIN.

Patient Medical History/Diabetes History/Concomitant Medications

His medical history includes tonsillectomy (1942), left wrist fracture (1946), fracture-nose (1950), and cholecystectomy (1960).

He was diagnosed as having NIDDM in 1990. He had no known complications of diabetes. Management had been with glipizide 5 mg QD (3/90-4/90), 5 mg BID (4/90-7/90), and 10 mg BID (7/90-on).

His only concomitant medication was acetylsalicylic acid 325 mg BID.

Adverse Experience/Intercurrent Medical Event

At Visit 6 (6/4/91), he complained of an upper respiratory infection, beginning on 5/31/91. This reportedly ended on 7/1/91 and had required no treatment.

At Visit 9 (8/27/91) he reported that he had been diagnosed as having diffuse interstitial pneumonitis/fibrosis and had been started on prednisone 60 mg QD on 8/20/91. This had recently been diagnosed by gallium scan and a transbronchial lung biopsy.

Initially his prednisone therapy was to be short-term with a rapid-taper schedule. The taper schedule was less than rapid, being reduced on a monthly basis. While on the higher doses of prednisone his WBCs remained high and his FPGs were less than optimally controlled, but with the taper his FPGs became much better controlled while his WBCs remained quite high.

He was last seen at Visit 18 on 7/16/92. At this time he had been off prednisone for one month and he had had a repeat lung biopsy. His recovery post-biopsy was poor. He expired at home in his sleep on 8/16/92, presumably of a cerebrovascular or cardiovascular event. No autopsy was performed.

Note: Subsequently, the site was informed that this patient had been diagnosed as having non-small cell lung cancer which was considered inoperable. He had been on oxygen therapy at home for dyspnea.

ADVERSE EXPERIENCE/INTERCURRENT MEDICAL EVENT			
Protocol No.: 89-1C-6023		Death/Termination/Cardiogenic Shock post MI	
Patient Identification Number: 10023-2			
Patient Initials:	Date of Birth:	Male [ ]	Female [X]
Study Drug: METFORMIN			

Narrative Summary

Study History

This 67 year old female was pre-enrolled into the 87-2D-6023 study on 7/19/89, was begun on therapy with METFORMIN and GLYBURIDE on 8/11/89, and completed the study on 2/28/90. During the study, she experienced heel pain, left deltoid shoulder pain, diarrhea, and had laser surgery-left eye (2/5/90). She entered the 89-1C-6023 study on 2/28/90, at which time her FPG was 148 mg/dL on full dosages of METFORMIN and GLYBURIDE.

Patient Medical History/Diabetes History/Concomitant Medications

Her medical history includes head tremor (1988-on), right cataract surgery (6/88), umbilical herniorrhaphy (1958), left heel spur (1987-on), leg varicosities (1979-on), appendectomy (1935), endometrial cancer (1984), hysterectomy (1984), peripheral edema (1989-on).

She was diagnosed as having NIDDM in 1973, complicated with retinopathy (1988-on). Management had been with chlorpropamide (1973-1987) and glyburide 10 mg BID (1987-on).

She was taking no other medication.

Adverse Experience/Intercurrent Medical Event

During the study, she developed a dental infection (V2) treated with Tylenol #2, erythromycin and penicillin VK, cystitis (V4) treated with norfloxacin, muscle strain, ankle edema (V8), upper respiratory infection (V10.1) treated with acetaminophen and Tussar SF, burn on hand, hypoglycemia (V12), urinary tract infection (V15.1) treated with Septra DS, dry cough treated with Tussar SF, myalgias and fatigue, head tremor (V16), mid-back pain (V16.1), pedal edema (V17) treated with furosemide 20 mg QD, blurring of vision (V18) treated with laser surgery on 7/26/91, 7/29/91 and 7/31/91, and herpes lesions-right leg (V19.1) treated with Acyclovir PO. Prior to Visit 20 (11/8/91) she had been started on isosorbide dinitrate 40 mg BID for "cardiac prophylaxis."

At Visit 20.2 (12/17/91) she was seen in the office with chest pain, nausea, vomiting and weakness evolving over the previous 24 hours. She was found to be in extreme distress and to have a profound wide-QRS arrhythmia. With this evidence of an acute myocardial infarction and cardiogenic shock, she was emergently admitted to the hospital. Attempts were made to catheterize her and dilate her occlusion, but post angioplasty she developed an acute closure followed by continued deterioration. She was placed on an intra-aortic balloon pump which stabilized her somewhat. A transient lactic acidosis existed during her first 24 hours in the hospital, presumed 2° to her cardiogenic shock and hypoperfusion. Her condition deteriorated over the next few days and, and she expired on 12/20/91.

Unbeknownst to us, this patient had been seen by a cardiologist since April 1991. She had developed ST-T wave changes on her routine EKG and was sent for further work-up. An echo cardiogram was done which suggested severe coronary artery disease. She had refused further cardiac evaluation on a number of occasions. Likewise, the day she developed chest pain (12/16/91) she refused to go to the Emergency Room despite family and physician urging.

ADVERSE EXPERIENCE/INTERCURRENT MEDICAL EVENT

Protocol No.: 89-1C-6023 Termination/Death

Patient Identification Number: 11024-2

Patient Initials:	Date of Birth:	Male [ ]	Female [X]

Study Drug: METFORMIN

Narrative Summary

Study History

This 68 year old female was pre-enrolled into the 87-2D-6023 study on 3/1/90, was begun on therapy with METFORMIN and GLYBURIDE on 4/9/90, and completed the study on 11/20/90. Her course during the study was quite benign and she entered the 89-1C-6023 study on 11/20/90. Her FPG at that time was 255 mg/dL on maximal dosages of METFORMIN and GLYBURIDE.

Patient Medical History/Diabetes History/Concomitant Medications

Her medical history includes renal tuberculosis/left nephrectomy (1951), malignant melanoma/right radical neck dissection (1982), right hip replacements (1974, 1985, 1987), left breast carcinoma/mastectomy (1976), right breast carcinoma/mastectomy (1979), hypertension, osteoarthritis, and retinopathy/laser surgery - right eye (dates unknown).

She was diagnosed as having NIDDM in 1969, complicated with hospitalization for hyperglycemia (10/89). Management had been with tolbutamide (1969-1973), NPH Insulin (1973-1988), glipizide 20 mg BID (1988-10/89), and glyburide 10 mg BID (10/89-on).

Her concomitant medications were ibuprofen 800 mg BID and enalapril maleate 5 mg QD.

Adverse Experience/Intercurrent Medical Event

At Visit 2 (12/14/90), a creatinine clearance was 42.7 ml/min/1.73M^2 which was done because the site wished to rapidly titrate her on metformin. Once these results were obtained, it was decided to terminate her from the study. When the site called the patient, the caretaker of her home informed the site that he had just discovered the patient deceased. This was not believed to be study drug-related. Her Visit 3 (12/18/90) FPG was 266 mg/dL and lactate was 0.8 mmol/L.

The cause of death was listed as cardiac arrest/coronary occlusion.

ADVERSE EXPERIENCE/INTERCURRENT MEDICAL EVENT			
Protocol No.: 89-1C-6023		Termination/Death/Cardiac Disease	
Patient Identification Number: 13002-2			
Patient Initials:	Date of Birth:	Male [X]	Female [ ]
Study Drug: METFORMIN/GLYBURIDE			

Narrative Summary

Study History

This 61 year old male was pre-enrolled into the 87-2D-6023 study on 10/20/88, was begun on therapy with METFORMIN and GLYBURIDE on 11/16/88, and completed the study on 6/6/89. His course during the study was uneventful. He entered the 89-1C-6023 study on 3/13/90, at which time his FPG was 200 mg/dL on glyburide 10 mg BID.

Patient Medical History/Diabetes History/Concomitant Medications

His medical history includes hypertension (7/83-on), right eye aneurysm (2/85-on), redwood allergy (1984-on), arthritis (1968-on), and left pulmonary nodule-stable (1984-on).

He was diagnosed as having NIDDM in 1983, complicated with peripheral neuropathy (1986-on) and retinopathy (1985-on). Management had been with glyburide 10 mg BID (4/7/88-on).

His concomitant medications were lisinopril 10 mg QD, and aspirin 2 gm QD.

Adverse Experience/Intercurrent Medical Event

He expired on 8/14/90 - cause of death was listed as arteriosclerotic cardiovascular disease. He had last been seen at Visit 8 on 8/2/90, at which time his FPG had been 139 mg/dL on maximal dosages of metformin and glyburide. His most recent ECG had shown "nonspecific ST-T wave abnormalities, consistent with ischemia, drugs, etc.; the tracing has returned toward normal since the record of 6/6/89". This event was not believed to be study drug-related.

ADVERSE EXPERIENCE/INTERCURRENT MEDICAL EVENT			
Protocol No.: 89-1C-6023	Termination/Death/Suicide		
Patient Identification Number: 18018-2			
Patient Initials:	Date of Birth:	Male [X]	Female [ ]
Study Drug: METFORMIN/GLYBURIDE			

Narrative Summary

Diabetes History

This 53 year old male was pre-enrolled into the 87-2D-6023 study on 11/8/89, was begun on therapy with METFORMIN and GLYBURIDE on 12/21/89, and completed the study on 7/5/90. His course during the study was uneventful. He entered the 89-1C-6023 study on 7/5/90, at which time his FPG was 180 mg/dL on maximal dosages of METFORMIN and GLYBURIDE.

Patient Medical History and Concomitant Medications

He had no medical history other than NIDDM diagnosed in 1988. Management had been with diet alone. He was on no medication.

Adverse Experience/Intercurrent Medical Event

This patient was last seen at Visit 12 (3/28/91).

When he failed to keep his Visit 13 appointment, the site attempted to contact him. They were informed by his employer that he had committed suicide on 4/19/91, by ingestion of chemicals (he had worked in a chemical plant).

SEE VOLUME 2 FOR

DR. RONALD INNERFIELD'S

REVIEWS DATED

MAY 17, 1994

&

MAY 20, 1994

MAR 2 2 1994

DA 20-357
Lipha Pharmaceuticals
Metformin

Received:11/20/93
Reviewed:03/22/94
N20357A/G105

MEDICAL OFFICER'S PRIMARY REVIEW OF ORIGINAL NDA

TABLE OF CONTENTS

REVIEW PROPER

1. GENERAL INFORMATION

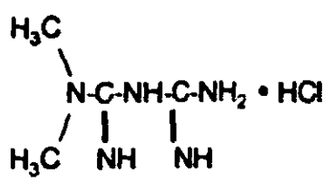
1.1 Drug Name and Structure

1.1.1 Generic Name: Metformin Hydrochloride

1.1.2 Proposed Trade Name: Glucophage, Diabefagos, Haurymellin, Meguan, Metiguanide

1.1.3 Chemical Names: (1) N,N-dimethylimidodicarbonimidic diamide; (2) N,N-dimethylbiguanide; (3) 1,1-dimethylbiguanide; (4) N'-dimethylguanylguanidine

1.1.4 Chemical structure



1.2 Scientific Information

1.2.1 Pharmacological Category: Metformin is a biguanide classified pharmacologically as an oral anti-hyperglycemic agent.

1.2.2 Proposed Indication(s): For use in treatment of non-insulin dependent diabetes mellitus in patients uncontrolled by diet as a monotherapy or as a concomitant therapy with a second-generation sulfonylurea.

1.2.3 Dosage Forms(s): Tablet

1.2.4 Route(s) of Administration: Oral

1.3 Regulatory Information

1.3.1 Review Priority Rating: To be determined by Group Leader and Division Director. At present, this is the file that the Medical Officer has been instructed to review before any other new drug application submission.

1.3.2 Related Drug: Phenformin was the only biguanide approved in the United States for the treatment of non-insulin dependent diabetes mellitus (NIDDM). It was removed from the market in 1979 as an imminent hazard following reports of deaths from lactic acidosis.

1.3.3 Related Reviews From Other Discipline: None available to the knowledge of the present reviewer.

2. LISTING OF VOLUMES REVIEWED

Volume 1.1 was reviewed entirely. In addition, pertinent sections of other volumes were also consulted, and the listing, below, provides the main volumes (underlined numbers) that were reviewed and (within each volume) the beginning page of each reviewed section:
1.1, pp 1, 3, 36, , 75, 77, , 80, 83, 106, 131, 154, 177, 189, 289, 375, 416; 1.2, p. 3 5; 1.6, pp. 5 16, 24, 46, 62, 72, 210; 1.7, p. 371; 1.9, pp. 5 1109, 1151; 1.10, pp. 5 1213, 1282, 1348, 1424; 1.11, p. 5 1523; 1.14, p. 5 2633; 1.20, pp. 5 4371, 4510; 1.21, p. 5 4730; 1.24, p. 5 5659; 1.26, p. 5 6218; 1.34, p. 5 8854, 9060; 1.35, p. 5 9237; 1.36, p. 5 9502; 1.38, p. 5 9688, 10378; 1.37, p. 5 9929; 1.39, pp. 5 1079, 210, 10769, 10782, 10824, 11061; 1.40, pp. 5 10926, 10992 ; 1.41, p. 6 23, 31; 1.42, p. 6 157; 1.44, p. 6 719; 1.49, pp. 6 2703; 1.61, p. 6 53210; 1.62, p. 6 5481; , p9. 6 5905, 5913; 1.67, p. 92 ; 1.68, pp. 8A210, 305, 323, 366; 1.69, pp. 8A 453, 461, 477, 479, 633; 1.70, p. 08A 00708; 1.101, p. 8A 8335; 1.104, p. 8B 1; 1.120, p. 8B 5357; 1.157, p. 8B 18605; 1.158, p. 18921; 1.159, p. 8B 19194; 1.160, p. 8B 19555; 1.164, p. 6 5913; 1.165, p. 8B 21366; 1.167, p. 8B 21839 ; 1.169, p. 8B 22391; 1.170, p. 8B 22672; 1.180, p. 8B 26196; 1.190, p. 8B 29829, 31975.

The Sponsor has also supplied a volume 2.1, which consists of a revised index of the entire submission. This volume has been extremely helpful in identifying specific sections pertaining to given

issues that the reviewer wanted to focus on. As such, it has been intensively used by the reviewing medical officer.

3. CHEMISTRY AND MANUFACTURING CONTROLS

The application provides that the bulk drug substance metformin hydrochloride will be produced by Lipha S.A., Lyon, France, at their manufacturing plant, Lipha Calais, in Calais, France. The drug product, metformin hydrochloride tablets, will be manufactured, packaged and labeled by Lipha Pharmaceuticals Limited, United Kingdom, at their facilities in Hitchin, Hertfordshire and Letchworth, Hertfordshire, respectively, in England. Supplies for clinical trials have been imported into the United States by Lipha Pharmaceuticals, Inc., New York, New York. The clinical studies have been conducted under IND #27,966.

Both the 500-mg and 850-mg tablets are to be packaged in approved containers known as "Securitainers", child-resistant "TraCer PACKS" (Jaycare Ltd.) and "SNAP SECURE" (McKechnie PBC Ltd.), comprising a polypropylene body and polyethylene cap. All materials used in the production of these containers are warranted Food Grade by the manufacturers and have FDA approval for use with either foods or drugs.

Prior to initial opening, there is a tamper-evident tearband. After that, the wadless cap has a thumb tab for opening, and snaps shut to provide a seal which has adequate moisture resistant properties for this product. The product is reported to be very stable in such a configuration.

The majority of clinical studies conducted in the U.S., including the pivotal studies (87-1D-6023 and 87-2D-6023), used formulations intended for the US market. Several early U.S. clinical pharmacology studies were conducted with an earlier formulation, which differed only slightly from the proposed for market.

4 PHARMACOTOXICOLOGY

4.1 Pharmacodynamics

4.1.1 Primary Pharmacologic Classification and Mechanisms of Action: An anti-hyperglycemic agent which appears to facilitate post-receptor sensitivity to insulin. Metformin reduces plasma glucose levels in several animal models of NIDDM but does not reduce basal glucose concentrations below the normal physiological range. It also improves glucose tolerance in diabetic animals and humans. At therapeutic doses, metformin does not lower plasma glucose levels in non-diabetic animals or humans.

4.1.2 Secondary Pharmacologic Activity: Metformin has hypolipidemic effects and significantly decreases the progression and promotes the regression of atherosclerotic lesions in animals fed a cholesterol-rich diet. It inhibits the transfer of dietary triglyceride from the gastrointestinal tract into plasma and reduces the uptake of the absorbed lipid by adipose tissue. Metformin has a broad range of actions on the vasculature including beneficial effects on microcirculation and microvascular leakage, and an inhibition of angiogenesis. Chronic treatment with metformin was shown to reduce the incidence

of glomerulosclerosis in genetically diabetic mice.

4.1.3 Other Actions Metformin reduces food intake in lean and genetically obese mice after IP, but not PO, administration.

4.2 Pharmacokinetics

4.2.1 Blood Level Data amd Absorption: Single tablet doses of 500 and 800 mg in healthy human subjects produced peak plasma drug levels in approximately two to three hours; food decreased the extent and slightly delayed absorption. There is an apparent plasma half-life of 1.5 to 4.5 hours (See, among other literature, Kartunnen et al., 1979; Sirtori et al., 1978; Karttunen et al., 1983). It should be noted that phenformin elicits a plasma half-life of 7-15 hrs (See Sirtori CR et al., 1978). Also, metformin shows a terminal elimination half-life in plasma of 12.6 hours, but this seems to implicated a quantitative minor component(See Pentikainen et al., 1986). Metformin is not bound to plasma proteins. Healthy subjects and diabetic patients treated with multiple doses of metformin (850 mg t.i.d for a total of 19 doses) achieved steady state levels in 24 to 48 hours. Multiple dosing with metformin did not significantly alter pharmacokinetics compared to those following single doses. The pharmacokinetic disposition of orally administered metformin is the same in NIDDM and non-diabetic subjects, both for single and multiple doses. Renal function greatly influences metformin pharmacokinetics and subjects with impaired renal function showed a significant prolongation of the metformin plasma elimination half-life. Elderly subjects administered a single 850 mg oral dose of metformin had higher metformin plasma concentrations than young subjects due to the decrease in renal clearance with age.

Absorption in animals was rapid, with peak plasma levels obtained within 30 minutes in mice, 1 to 2 hours in rats, 1.5 hours in dogs, and 0.75 to 2 hours in monkeys. In man, serum levels peaked in 2 to 3 hours and bioavailability was calculated to be 50%.

4.2.2 Excretion

Mouse: 48% in urine and 34% in feces after 120 hours.

Rat: 58% in urine and 38% in feces after 120 hours; partial placental barrier; radiolabelled components derived from [^{14}C]-metformin excreted in milk.

Rabbit: 57% in urine and 35% in feces after 120 hours; partial placental barrier.

Dog: 87% in urine and 18% in feces after 120 hours.

Monkey: 45% in urine and 42% in feces after 120 hours.

Man: 56% in feces after 72 hours. This requires an explanation: Only about half of the orally administered dose is absorbed (perhaps, in part, to the the diarrhea which is one of the more common side-effects of the drug), and, of the absorbed, only a small fraction is perhaps excreted in the feces. Overall, therefore, the fecal excretion rate noteed above is easily explained.

4.2.3 Distribution

Distribution of metformin was studied in mice, rats, and rabbits with the highest levels of radioactivity observed in highly perfused organs (liver and kidney) as well as the gastrointestinal tract. It would also seem that significant circulating levels are bound to red blood cells (perhaps to hemoglobin since metformin has two electron doublet donor nitrogens), this reservoir explaining, no doubt, the long termination plasma half-life.

4.2.4 Metabolism

No metabolites of metformin found on chromatography of urine, fecal, and/or plasma samples from mice, rats, dogs, monkeys, or humans; one metabolite (N-desmethyl metformin) was found in rabbit.

4.3 Toxicology

4.3.1 Acute toxicity: Oral LD_{50} : Mouse = 2.4 g/kg; rat = 1.77 g/kg; rabbit = 0.552 g/kg; and dog = 0.375 g/kg. Signs of toxicity included decreased activity, ataxia, and diarrhea in all species; in addition, in rabbits and dogs, convulsions were observed prior to death.

4.3.2 Multidose Toxicity

Mouse: (1) 90-day oral (dietary); 0, 500, 1000, 2000 mg/kg/day: increased plasma glucose in high-dose males and all treated females. (2) 52-week oral (dietary); 0, 150, 450, 1500 mg/kg/day: no adverse effects up to and including 450 mg/kg/day; compound-related kidney lesions consisting of increased tubular dilatation in both sexes and increased tubular vacuolization in males at 1500 mg/kg/day.

Rat: (1) 90-day oral (dietary); 0, 150, 450, 1500 mg/kg/day: increased mortality in MD and HD males; compound-related lesions in kidney consisting of increased incidence and severity of cystic tubular dilatation in all male treatment groups and in MD and HD females; increased tubular vacuolization in treated males; increased incidence of urogenital lesions in MD and HD males. (2) 90-day oral (dietary): 0, 300, 600, 900 mg/kg/day: increased relative kidney weight in MD males and HD males and females; no histopathology data. (3) 6-month oral (dietary); 0, 120, 300, 600, 900 mg/kg/day: increased degree of vacuolation of epithelial cells in kidney tubules in HD females.(4) 52-week oral (dietary); 0, 150, 300, 600, 900 mg/kg/day: decreased mean body weight in MD and HD group, no treatment-related lesions on gross or histopathological examination. (5) 78-week oral (dietary); 0, 120, 300, 600, 900 mg/kg/day: increased incidence of uterine polyps at 300, 600, and 900 mg/kg/day; increased incidence of squamous metaplasia of endometrial glands at 600 and 900 mg/kg/day.

Dog: (1) 6-month oral; 0, 50, 100, 150 mg/kg/day: alterations in histopathology of brain, heart, kidney, liver, stomach, and intestinal tract of MD and HD animals including: necrotic neurons, myocardial atrophy, thickened mesangium of the glomerular tufts, increased incidence of pericholangitis, general infiltration of the liver with neutrophils, stomach ulcer, mild enteritis. (2) 78-week oral; 0, 50, 100 mg/kg/day: no specific consistent macroscopic or microscopic changes observed except for one HD female with vascular alterations in the brain, kidney, and skeletal muscle and degenerative changes in

brain and skeletal muscle.

Monkey: (1) 2-year oral; 0, 60, 180, 360 mg/kg/day: increased mortality in HD group, cause of death could not be determined; surviving HD monkeys showed decrease in cytoplasmic vacuolation in cells of the adrenal glands, marked lymphoid and reticuloendothelial tissue depletion.

4.3.3 Mutagenicity: Negative

4.3.4 Reproduction Studies: No adverse effects in terms of fertility, reproductive performance, or perinatal/postnatal development. No teratogenic effects were observed in rats or rabbits.

4.3.5 Carcinogenicity

Mouse: In a 91-week oral carcinogenicity study, increased tubular dilatation was observed in males at the lowest dose studied (150 mg/kg/day), females were affected at 450 and 1500 mg/kg/day; mortality was increased in males at 450 and 1500 mg/kg/day, primarily due to an increase in urogenital lesions resulting from the renal toxicity. There was no evidence of any direct carcinogenic effect.

Rat: In a 104-week carcinogenicity study, there was an increased incidence of uterine stromal polyps in female rats at a dose of 900 mg/kg/day (high dose).

5. CLINICAL BACKGROUND

5.1 Direct Information

5.1.1 Human Pharmacodynamics

5.1.1.1 Glucose-Lowering Effect of Metformin (Primary Pharmacodynamic Property

From animal data and U.S. human data, as well as from Category III clinical pharmacology studies, it may be tentatively concluded that metformin's plasma glucose-action in diabetes is multifactorial. It is clear that metformin does not act through stimulation of pancreatic insulin secretion, since insulin levels are not raised and plasma glucose lowering does not occur under usual conditions in the presence of normoglycemia. There is evidence supporting improved peripheral glucose uptake with metformin, possibly both glucose-mediated as well as insulin-mediated. Effects on basal plasma glucose levels suggest that, in the presence of insulin, metformin decreases hepatic glucose production possibly by reduction in available substrates (such as free fatty acids) for hepatic gluconeogenesis. Metformin also may have an important action at the intestinal level, which may involve transmural processing of glucose rather than interference with glucose absorption. Metformin also appears to have an effect on insulin receptors and related factors which, most likely, is at a post-receptor level. However, which of metformin's effects are predominant as well as the possibility of additional actions of metformin, remain open to study. In summary, two statements may be made: (1) It is established that metformin does not affect insulin secretion by pancreas (therefore not contributing, through that mechanism) to increased insulinemia); and, (2) the relevant mechanisms of action, and their relative contribution to the

pharmacodynamics of the medication, may be suspected but are not conclusively known.

5.1.1.2 Lipid Effects of Metformin

The clinical pharmacology studies described herein, as well as data from U.S. Category I controlled trials and non-U.S. Category II controlled and uncontrolled clinical trials and non-U.S. Category III clinical pharmacology studies, may be compared with animal studies which also provide evidence that somewhat improves the blood lipid profile (triglycerides, total cholesterol and LDL-cholesterol but, apparently, not HDL cholesterol) in hyperlipidemic states and may thus exert an anti-atherogenic influence. However, this effect can be deemed as marginal. Indeed, as stated above and in the majority of studies cited in this NDA, metformin can reduce fasting levels of total triglycerides and cholesterol, particularly in hyperlipemic states. This effect appears to be independent of an effect on glycemia and on body weight, since it occur in non-diabetic subjects in whose glycemia is not affected by the drug and also in subjects whose weight has remained stable while on metformin. The lowering of triglycerides appears to be quantitatively greater than of cholesterol, attributable primarily to decreased VLDL-triglycerides, but the effects of such changes in triglyceridemia are not proven. Minor alterations have been reported in the distribution of cholesterol among the major lipoprotein fractions, but a consistent pattern has not emerged. There is the suggestion from some studies, that metformin's lipid-lowering effect might be dose dependent, although metformin does not lower lipid concentrations below the normal range and, as noted, is more effective when lipid levels are moderately elevated. The Sponsor states that "perhaps even more important than the effects of metformin on fasting lipid levels, are the observations of Reaven and colleagues that metformin has a dramatic postprandial lipid-lowering effect (triglyceride and intestinally-derived lipoprotein levels), either when given as monotherapy or when added to continued sulfonylurea therapy. It is possible that postprandial lipemia, which appears to differ in NIDDM and non-diabetics, may be related to increased risk of cardiovascular disease. Metformin may have a beneficial effect on postprandial lipemia patterns in diabetic subjects." Dr. Reaven is a prolific author highly appreciated by the pharmaceutical industry. He has come up with a number of hypotheses that should be taken earnestly only after they have been conclusively or suggestively proved. Such is not the case, at present, with any of the hypotheses advanced by Dr. Reaven.

5.1.1.3 Effects of Metformin on Rheology and Related Parameters

Metformin has been shown to exert several potentially beneficial effects on rheology. A number of studies suggest that metformin can reduce platelet aggregation (without causing palpable hypocoagulation), particularly if platelets are abnormally reactive. Metformin may also have an effect on reducing platelet (and plasma) β-thromboglobulin and thromboxane B_2. A number of published accounts of open-label studies have shown a decrease in plasma fibrinogen levels in both diabetic and non-diabetic subjects with metformin treatment as well as an increase in fibrinolytic activity (See, for example, Grant PJ, 1991). The latter may be related to increased tPA activity or, more likely, decreased PAI-1 activity and the effect of metformin may vary with the population (e.g., obese vs. non-obese; diabetic, vs. non-diabetic) and may be more marked in obese hyperinsulinemic patients without established diabetes. These changes may also have an impact on improving blood flow both in vitro and in vivo, with a possible influence of metformin-related changes in red cell deformability. Overall, there are some suggestive studies that metformin may improve rheology but no systematic study has

been performed to date to allow, if one will, an official recognition of this putative effect. Besides, the important consideration, here, is that only surrogate parameters seem to go in the right direction but we have not seen yet any study showing or strongly suggesting a clinically significant effect.

5.1.1.4 Effects of Metformin on Insulin and C-Peptide

It is reasonable to state that metformin achieves its therapeutic effects without enhancing plasma insulin concentrations and, may, in fact, actually reduce day-long insulin concentrations, particularly in hyperinsulinemic states. This may be contrasted with the insulin-stimulating/releasing effect of sulfonylureas. Whether the simultaneous reduction in parameters reflecting glycemic control and lack of plasma insulin increases with metformin administration to diabetic subjects reflects increased insulin sensitivity in peripheral tissues or perhaps in hepatic tissue remains a subject of investigation and debate. The data also seem to suggest that metformin may have an insulin-sparing effect in insulin-dependent or insulin-requiring diabetics. Finally, the fact that metformin can reduce insulin levels in non-diabetics without significantly lowering blood glucose levels suggests other potential applications for metformin in the future, should theories concerning the relationship between insulin resistance and various cardiovascular risk factors prove valid. Such applications may not be fully sanctionned by the FDA unless convincing studies are submitted to it in the form of supplements.

5.1.1.5 Effects of Metformin on Lactate

The Sponsor states that "It can be concluded that metformin has minimal effect on fasting plasma lactate levels. Metformin does appear to increase postprandial lactate levels relative to placebo or sulfonylurea but, although statistically significant this is probably not clinically relevant. The effect of metformin on lactate levels is significantly and relevantly less than that of the biguanide phenformin, both in the fasting state and postprandially." The first part of the statement is, as noted by the Sponsor, hypothetical. I recommend that no emphasis be put on such statements, either in the labelling, or in any upcoming promotional material, since such statements may increase a false sense of security. The second part of the Sponsor's statement, that pertainiNGg to the comparative effects of phenformin and metformin with regard to lactic acidosis is supported by some authors (see Cavallo-Perin et al., 1989; Westerholm, 1984) which state that epidemiological and other studies in human seem to support the following conclusion: that phenformin, at clinically equivalent dose, presents a higher risk of lactic acidosis than metformin; this, despite the fact that 20-25 times (in moles) metformin than phenformin to achieve a comparable clinical effect.

5.1.1.6 Effects of Metformin on Vitamin B_{12} and Folic Acid

The Sponsor states: "Controlled clinical studies, conducted in the U.S., confirm that metformin influences serum vitamin B_{12} levels, presumably through decreased absorption of vitamin B_{12}, resulting in subnormal serum vitamin B_{12} levels in approximately 7% of patients treated for six months with metformin, either alone or in combination with sulfonylurea. The mechanism of this decreased absorption is currently under investigation (**U.S. Study No. 92-05-6023**) and may be related to interaction of metformin with ionic calcium, thereby interfering the vitamin B_{12}/intrinsic factor complex interaction at its ileal receptor. Hematologic manifestations are very rare and neurologic manifestations

of such deficiency have not been reported. During the course of U.S. controlled clinical trials, neither hematologic nor neurologic consequences of vitamin B_{12} deficiency were seen." However, these statements are better placed under the safety issues, since the reduction of serum vitamin B12 level may lead to megaloblastic anemia, have been proven to exist (see Berger, 1985), and at least one case of megaloblastic anemia has been cited in the literature as having occurered during metformin treatment (See Levesque et al., 1991).

5. 1. 1. 7 Metformin Dose-Response

The Sponsor states: "The results, derived, in part, from recently conducted, U.S. double-blind, controlled clinical trials in well-defined, relatively homogeneous diabetic populations suggest both a stepwise dose-response of blood glucose to metformin (with multiple dosing and under steady state conditions), but also confirm the empirically derived and now well-established concept that the effective therapeutic range for metformin lies between 1 - 3 g/day (albeit that this dose must be individually tailored, according to glycemic response, tolerance, and concomitant use of other glucose-lowering drugs). " We have requested the company (on November 30, 1993)to provide us with an independent set of data clearly relating dose (in mg/d, for comparable periods of time, in relatively homogenous populations) to HbA1c values, after the proper equilibration period. When received, this essential set of data will be analyzed to try to determine the lowest dose effective in a majority of treated subjects.

5.1.2 Human Pharmacokinetics

On this issue, the following lengthy opinions and conclusions have been submitted by the sponsor:

(1) Metformin is not significantly metabolized and is not significantly bound to plasma proteins. This information is consistent with most animal species studies (the exception is the rabbit, in which a single urinary metabolite [N-desmethyl metformin] has been identified);

(2) Metformin is eliminated unchanged via the urinary tract, through combined glomerular filtration and tubular secretion, with a similar renal clearance rate in both normal and NIDDM subjects with normal renal function. Peak urinary excretion occurs at approximately 3 hours following oral dosing;

(3) Following intravenous administration, metformin disappears rapidly from plasma with a multi-exponential concentration-time curve, best represented by a three-compartment open mode;

(4) .The red blood cell mass may represent a second compartment of distribution for metformin;

(5) Metformin bioavailability is approximately 50% and similar quantities of metformin in aqueous solution or in tablet formulation are bioequivalent. Bioavailability decreases with increasing doses, with absorption a rate-limiting step;

(6) Food decreases the extent and slightly delays the absorption of metformin;

(7) The pharmacokinetic disposition of orally administered metformin is the same in NIDDM and

non-diabetic subjects, both for single and multiple doses;

(8) Steady state plasma concentrations are achieved within 24 to 48 hours;

(9) Renal function greatly influences metformin pharmacokinetics. In subjects with impaired renal function, there is a significant prolongation of the metformin plasma elimination half-life, related to a significant decrease in metformin plasma total clearance and renal clearance;

(10) Metformin renal clearance decreases with age, resulting in higher metformin concentrations in plasma and whole blood of older subjects;

(11) Glyburide does not affect metformin pharmacokinetics; metformin decreases glyburide plasma C_{max} and AUCX, however, these effects do not appear to be clinically relevant;

(12) Cimetidine significantly increases the metformin C_{max} and AUCUN; metformin has no effect on cimetidine pharmacokinetics. The mechanism of the interaction may be competition for renal tubular secretion;

(13) Nifedipine causes a significant increase in metformin plasma C_{max} and AUC, but also greatly increases the amount of urinary metformin excretion; metformin had no significant effect on nifedipine pharmacokinetics;

(14) Propranolol produces a statistically significant, but clinically irrelevant, decrease in plasma concentrations of metformin; metformin had no effect on propranolol pharmacokinetics;

(15) Furosemide and metformin interact such that an increase in metformin concentration and a decrease in furosemide concentration is observed when the two drugs are given simultaneously;

(16) The t_{max} of metformin and ibuprofen are both decreased when these two drugs are administered in combination.

5.1.3. Human Clinical Experience

In addition to the controlled U.S. Category I and non-U.S. Category II studies and the non-U.S. Category II Phase IV studies, 100 non-U.S. Category III studies, are included in this NDA and integrated, as possible and appropriate in the clinical pharmacology and clinical sections. Also, all the studies were reviewed for safety-related information. Fifty-one of the 100 non-U.S. Category III studies were

clinical pharmacology studies (35 completed, 11 ongoing, 3 incomplete, 2 never initiated). Forty-nine of the 100 non-U.S. Category III studies were clinical trials. There were 24 controlled studies, related to claims of effectiveness sought in this NDA. Five were placebo-controlled (2 completed, 1 ongoing, 2 incomplete) and 18 were with an active-treatment comparator (9 completed, 2 ongoing, 7 incomplete) and one was a completed dose-comparison study. There were seven uncontrolled studies, related to claims of effectiveness sought in this NDA (4 completed, 3 incomplete). For the above studies, the sponsor provided tabular summaries and synopses for each and the results generally supported the conclusions of effectiveness and safety of metformin. There were 18 studies (15 controlled and 3 uncontrolled) related to uses of metformin other than those related to claims of effectiveness.

5.2 Indirect Information

5.2.1 Information From Foreign Sources

5.2.2 Related INDs and NDAs

5.3 Other Information

5.3.1 Regulatory Background

Phenformin, the only other biguanide approved for marketing in the United States, was the only product ever removed from the market under the 'imminent hazard' provisions of the FD&C Act. Numerous cases of lactic acidosis, some leading to death, were associated with its use. Phenformin was also removed from the market in virtually every other country worldwide. Cases of lactic acidosis have also been reported for metformin, but unlike phenformin, these are quite rare and have not prompted removal of the product from any of over 70 markets worldwide. No reports of lactic acidosis were encountered in U.S. clinical trials.

5.3.2 Directions For Use

6. CLINICAL DATA SOURCES

6.1 IND and NDA Studies

6.1.1 Type of Studies

6.1.1.1 Clinical Pharmacology

Phase I U.S. studies were conducted to define the mechanism of metformin's blood glucose-lowering effect, through open-labelled, before/after type studies, with additional emphasis on clinical research techniques for assessment of metformin's effects on parameters of carbohydrate and lipid metabolism.

Other studies addressed dose-response assessment, with comparison of pharmacokinetics and pharmacodynamic effects of various clinically relevant single doses of metformin, in a single-blind,

placebo-controlled, four-way crossover study of the 850 mg dosage strength (U.S. Study No. 89-12-6023) and a double-blind, placebo-controlled, four-way crossover study of the 500 mg dosage strength (non-U.S. Study No. MET/GB/89/HOCKA).

Additional special situations and parameters were also explored as follows:

(1) a metformin pharmacokinetics in diabetics vs. non-diabetics (U.S. Study No. 89-12-6023);

(2) a metformin pharmacokinetics following single doses of metformin vs. the final dose of a multiple dose phase (U.S. Study No. 89-12-6023);

(3) the relative bioavailability of various formulations and dosage strengths of metformin (U.S. Study No. 89-11-6023 and non-U.S. Study Nos. Simbec 1 and 2);

(4) the effects of food vs. fasting on metformin pharmacokinetics (U.S. Study No. 89-11-6023);

(5) the effects of aging on metformin pharmacokinetics (U.S. Study No. 90-13-6023);

(6) and various drug interactions, (selected on the basis of drugs most likely to be co-prescribed in diabetic subjects) including a sulfonylurea (glyburide), an H_2-receptor antagonist (cimetidine), a calcium-channel blocking agent (nifedipine), a b-adrenergic blocking agent (propranolol), a non-steroidal anti-inflammatory agent (ibuprofen) and a loop diuretic (furosemide).

6.1.1.2 Controlled and Uncontrolled Clinical Studies

Two major controlled clinical trials were conducted in the U.S. (Study Nos. 87-1D-6023 and 87-2D-6023), each of 29 weeks treatment duration. These studies were intended to fulfill the statutory requirements as adequate and well-controlled trials and were defined as Category I studies by the sponsor. Both studies were prospective, randomized, double-blind, multi-center, parallel arm studies, comparing the effects of metformin vs. placebo in a population of NIDDM patients unresponsive to dietary management alone (Study No. 87-1D-6023) or of metformin monotherapy vs. glyburide monotherapy vs. metformin plus glyburide in a population of NIDDM patients unresponsive or no longer responsive to maximum dose sulfonylurea (Study No. 87-2D-6023). In Study No. 87-1D-6023, the 850 mg dosage strength of metformin was used, while in Study No. 87-2D-6023, the 500 mg dosage strength was used. Both studies had a dose titration period, followed by a maintenance phase, with a total treatment duration of 29 weeks. Together they involved 921 randomized NIDDM subjects. The primary analysis of these two Phase III studies involved the intent-to-treat population. An open-label, uncontrolled safety extension (Study No. 89-1C-6023) of these two studies, was recently completed.

With respect to the additional 110 non-U.S. studies known to the sponsor "were reviewed from the perspective of study design, objectives, availability of case report forms, completion status and ability to audit the data base. Ten of these studies were judged by the sponsor to satisfy quality assessments and criteria consonant with objectives sought for metformin and were integrated into the data base as

Category II studies."

Seven of the ten non-U.S. Category II studies were prospective, randomized, parallel arm controlled studies, comparing the effects of metformin to either placebo (three studies), active treatment (three studies: vs. the sulfonylureas glipizide, gliclazide or glibenclamide and glibenclamide plus metformin), or diet alone (one study). Six of the seven studies involved patients with NIDDM whereas the seventh study involved patients with impaired glucose tolerance but with fasting normoglycemia. The studies varied in duration from 60 days to one year.

Two open-label, uncontrolled Phase IV foreign post-marketing studies (of 4 months and 6 months treatment duration, respectively) were also included because they involved approximately 8,000 diabetic subjects taking either metformin alone or metformin plus a sulfonylurea.

The final study was a controlled pharmacokinetic and pharmacodynamic study involving NIDDM subjects, mentioned above (MET/GB/89/HOCKA). Data from these studies were reanalyzed, applying the same statistical approach to these non-U.S. studies as to the U.S. Category I studies.

The remaining 100 non-U.S. studies were classified as Category III. Approximately half of them are clinical pharmacology studies. In addition, all Category III studies were reviewed by the sponsor for safety-related information and for serious adverse drug experiences.

6.1.2 Patient Population

The clinical pharmacology studies enrolled healthy volunteers and, when appropriate, NIDDM patients. The controlled and uncontrolled clinical studies enrolled NIDDM patients, except for MET/AM/86/DORF2 which evaluated carbohydrate intolerant patients.

The integrated summary of safety (ISS) results were based on patients compiled from three clinical studies data bases: the U.S. Phase III Category I studies, the seven non-U.S. randomized, controlled Category II studies, and the two non-U.S. Phase IV studies. This ISS dataset was used to make all safety tabulations.

For the randomized studies, the safety analysis was carried out for the intent-to-treat (ITT) population, i.e., all patients who received study medication and were assessed for safety. In the case of a patient randomized to a treatment group but with no (or insufficient) medication records, it was assumed that the patient actually received study medication. For the non-U.S. Phase IV studies, all patients who were enrolled were included in the ISS dataset. The numbers of patients reported in the ISS dataset are listed in Table 1.

6.1.3 Human Exposure to Date

Metformin drug exposure data was compiled from the eleven studies listed below:

(1) ***U.S. Randomized, Controlled Studies (Category I):***

Study No. 87-1D-6023 and Study No. 87-2D-6023)

(2) Non-U.S. Randomized, Controlled Studies (Category II):
Study No. MET/AM/84/DORF1, Study No. MET/AM/86/DORF2,
Study No. MET/GB/85/DORNA, Study No. MET/D/86/BERGI,
Study No. MET/GB/86/CAMP1,
Study No. MET/AM/88/DUCHI ; and,
Study No. MET/S/86/HERMA

(3) Non-U.S. Uncontrolled Studies - Phase IV:
Study No. MET/D/86/HAUPT;
Study No. MET/AM/87/PHASE

Table 2 shows the extent of drug exposure in terms of the number of patients in each study and the length of time subjects were exposed to metformin (i.e., duration of the treatment period for each study). Dosage exposure is discussed in terms of number (percent) of each study population, treated within a specific dose range of metformin (i.e., 500-1000 mg/day; >1000-2000 mg/day; >2000-3000 mg/day).

For the U.S. studies, mean total daily dosages of metformin are also available. The mean total daily dose of metformin for U.S. Study No. 87-1D-6023 (placebo-controlled) was 1980 mg/day and the mean duration of treatment was 27 weeks (out of a possible 29 weeks). The mean total daily dose of metformin for U.S. Study No. 87-2D-6023 (active treatment-controlled) was 2050 mg/day for the monotherapy treatment group with a mean duration of treatment of 25 weeks. For the metformin/glyburide combination therapy treatment group, the mean total daily dose of metformin was 1894 mg/day and the mean duration of treatment was 28 weeks (out of a possible 29 weeks).

Precise drug compliance data was unavailable for most of the non-US studies and, therefore, calculations of mean daily doses were not possible. Thus, information relative to the dosage of medication *prescribed* rather than actually *taken* is presented for individual patients.

6.2 Additional Sources

Fifty-one of the 100 non-U.S. Category III studies were clinical pharmacology studies (35 completed, 11 ongoing, 3 incomplete, 2 never initiated). Forty-nine of the Category III studies were clinical trials. There were 24 controlled studies, related to claims of effectiveness sought in this NDA. Five of these were placebo-controlled (2 completed, 1 ongoing, 2 incomplete) and 18 were with an active-treatment comparator (9 completed, 2 ongoing, 7 incomplete) and one was a completed dose-comparison study. Eighteen 18 studies (15 controlled and 3 uncontrolled) studied to uses of metformin other than those related to claims of effectiveness. Summaries, synopses and publications for all these studies were included in the NDA.

6.2.1 Literature

A listing of more than 2,000 citations involving metformin (primarily published but also including unpublished reports, theses, etc.) were provided in the NDA.

6.2.2 Foreign Post-Marketing Experience

During at least ten years of adverse event reporting to the parent company Lipha S.A., Lyon, France, from within France and from its subsidiaries and licensees of Glucophage® brand of metformin hydrochloride, including subsidiaries in the United Kingdom, Germany, Belgium, Italy, Switzerland and Portugal and licensees in Australia, Austria, Canada, Denmark, Holland, Japan, New Zealand, South Africa and Sweden, there have been 279 adverse events reported, consistent with the reporting requirements of the respective countries. Needless to say, each country has its own reporting requirements which are, for some countries at least, less rigorous than the United States' requirements. The number of these adverse events, therefore, do not reflect the totality of the toxic experience. In order to obtain a better picture of the toxic potential of the medication, we need to carefully scrutinize the studies performed in the United States, together with an analysis of scientifically rigorous and valid studies published in this country as well as abroad, for studies performed here as well as outside our borders.

7. PIVOTAL CLINICAL STUDIES

7.1. First Pivotal Study: Study No. 87-1D-6023

7.1.1 Description of Study

7.1.1.1 Title, Objective and Rationale

U.S. Study No. 87-1D-6023: "A Double-Blind, Placebo-Controlled, Randomized, Parallel Group, Multi-Center Study to Determine the Safety and Effectiveness of Metformin in the Control of Obese, Type II, Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Patients who are not Adequately Controlled with Diet Alone" was conducted to evaluate the safety and efficacy of metformin in the patient population described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug.

7.1. 1.2 Experimental Design

U.S. Study No. 87-1D-6023, conducted from March, 1988 through May, 1991, was a randomized, parallel-group (two), double-blind, multi-center (13 centers) study comparing the safety and efficacy of 29 weeks treatment with either metformin (up to 2,550 mg/day) or placebo in 289 obese (120-170% of ideal body weight) NIDDM outpatients who had either never received pharmacologic antidiabetic therapy or had not received such treatment for the two months preceding randomization. Potentially eligible patients were randomized (143 to metformin; 146 to placebo) if body weight remained within ± 3% of entry body weight and FPG remained >140 mg/dL, despite two months on a weight-reduction diet. The 850 mg dosage strength of metformin was used in this study.

Subsequent to the two month dietary run-in phase, eligible patients were randomized and began a five week metformin dose titration phase (biweekly increases of metformin [or placebo] by 850 mg increments [based on FPG levels and tolerance], starting with 850 mg/day and increasing to a maximum of 850 mg t.i.d., with meals), followed by a 24 week treatment phase, while on the maintenance dose of metformin (or placebo).

7.1.1.3 Demographics

A total of 289 patients were randomized to treatment with 143 receiving metformin and 146 receiving placebo. The patients ranged in age from 31 to 70 with a mean age of 53. There were 43% males and 57% females.

7.1. 1.4 Safety Considerations

Adverse experiences and intercurrent medical events (AE/IMEs) were recorded at each visit.

7.1.1.5 Efficacy Endpoints

The primary efficacy parameter was the integrated value of glycemic control. i.e., HbA1c values.

Supportive efficacy parameters comprised other measurements of glycemic control, i.e., FPG, and plasma glucose response during a 3-hour oral glucose tolerance test [OGTT]).

Secondary efficacy parameters included: (a) lipid parameters: total cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL) cholesterol, HDL subfractions and apolipoproteins;(b) body weight change; and, (c) Others: blood pressure and insulin and C-peptide effects (measured as part of the 3-hour OGTT).

7.1.1.6 Statistical Approaches

The population of interest was the intent-to-treat population. For the efficacy analysis this was defined as any patient who took study medication and completed at least one post-baseline visit. For the safety analysis this was defined as any patient who took study medication and was assessed for safety. Observed values and change from baseline values were compared for all efficacy and safety laboratory measures to determine if significant differences existed among the metformin and placebo treatment groups, based on a visit-wise analysis and a last observation carried forward analysis. The primary analyses were the within- and between-treatment comparisons of change from baseline values. The incidence of AE/IMEs were tabulated and compared between treatment groups using the Fisher's Exact test.

7.1.2 Results and Conclusions

7.1. 2.1 Patient Comparability

Patient groups were well-matched for all demographic features, as well as for baseline values of efficacy parameters.

7.1.2.2 Patient Disposition

A total of 112 (78%) metformin-treated patients and 105 (72%) placebo-treated patients completed the study. Nineteen patients in the metformin group and six patients in the placebo group withdrew due to adverse experiences/intercurrent medical events or an abnormal lab result.

7.1. 2.3 Efficacy Data

At the final visit, metformin had produced statistically significantly superior metabolic control compared to placebo ($p=0.001$) as evidenced by reductions in HbA1c, fasting plasma glucose, post-glucose load plasma glucose (FPG) and glucosuria. For HbA1c, the metformin group improved, against placebo, by 1.8 % units. For FPG, the metformin group had a 53 mg/dL decrease from baseline whereas the placebo group an increase of 6.3 mg/dL. When patient responses at final visit were further analyzed according to FPG subgroups at baseline, it was evident that metformin had its greatest effect, both on FPG and HbA_{1c}, in those patients with the most severe hyperglycemia at baseline. Both treatment groups had modest decreases in mean body weight at study conclusion. In addition, the metformin group showed mean reductions in total cholesterol which were significantly different from placebo and due largely due to significant reductions in LDL. The metformin group experienced a mean reduction in the triglycerides vs. a slight increase in the placebo group ($p=0.085$).

7.1. 2.4 Safety Data

AE/IMEs were reported by 89% of the patients in the metformin group compared to 79% in the placebo group (p=0.013). Although the overall incidence of AE/IMEs was higher in the metformin group, this was accounted for by significantly more AE/IMEs in only one body system---the digestive system. This was primarily due to more patients in the metformin group experiencing diarrhea (79 vs. 21, p=0.001) and nausea/vomiting (42 vs. 14, p=0.001). In general, these symptoms tended to be mild to moderate, intermittent in occurrence, with the majority of episodes occurring during the metformin Titration Phase (during first introduction of metformin).

There were no deaths in either patient group. Twenty-five patients (19 in the metformin group [13%] and six in the placebo group [4%]) withdrew due to a medical event (AE/IME) or abnormal lab result. Eleven (8%) of the 19 withdrawals due to medical events in the metformin group were gastrointestinal in nature and nine of these 11 included "diarrhea" as a reason.

The mean serum vitamin B_{12} level in the metformin group went from 489.9 pg/mL at baseline to 384.2 pg/mL at final visit (NR: 200-900 pg/mL), with a mean change from baseline of -105.2 pg/mL (p=0.001). There was no significant change in the placebo group. Thirteen patients (11%) in the metformin group, with normal serum vitamin B_{12} values at baseline, had subnormal values at final visit, compared to no such shifts in the placebo group. None of these patients had any associated hematologic abnormalities.

Overall, except for the differences in effect on serum vitamin B_{12} levels and the rather frequent bothersome but not forbidding gastrointestinal effects, few meaningful or consistent differences among the treatment groups were noted for laboratory safety parameters at any visit, including liver function tests, renal function tests or hematology profiles, and, where noted, differences were relatively small. Fasting plasma lactate levels were similar between the two treatment groups at final visit. There were no instances of lactic acidosis.

7.1. 2.5 Sponsor's Conclusions

The sponsor concluded: "In this randomized, placebo-controlled, double-blind multi-center study, *metformin had a definite strong antihyperglycemic effect as shown* by a significant difference from placebo in FPG, 2-hour post-glucose load plasma glucose, HbA_{1c} and glucosuria. Metformin had a moderate effect on lipids, with lowering of total cholesterol, LDL-cholesterol and triglycerides. In general, the effects on lipids seemed to be more accentuated in patients with higher cholesterol or triglycerides at baseline. There was no significant increase in fasting plasma insulin levels among the metformin group and there were no differences between the groups in degree of weight loss. Persistent glucosuria may have contributed to the weight loss seen in the placebo group. The magnitude of effect on both parameters of glycemic control and lipid parameters seemed directly related to the degree of baseline abnormality. The metformin side effect profile identified in this study confirmed what is already well-established in the literature and was characterized by an increase in gastrointestinal system symptoms of which diarrhea and nausea/vomiting were the most frequent, with, however, a low percentage of patient withdrawal from the study because of diarrhea and/or nausea/vomiting. Asymptomatic decreases in serum vitamin B_{12} levels occurred in 11% of subjects receiving metformin."

7.1. 2.6 Reviewer's Conclusions

This reviewer concurs with the following conclusions: (1) Metformin is a relatively potent glycemic normalizer (in this study, HbA1c values were 1.8% units better than in the placebo group); (2) Metformin improves dyslipimic profiles moderately, and this is a small but added advantage of the therapy, considering that most cardiovascular accidents in the diabetic are probably related to macrovasculopathies apparently unrelated to the microvasculopathies due probably to hyperglycemia and hyperinsulinemia.

This reviewer wants also to express slightly discordants opinions from those of the Sponsor, as far as this trial is concerned: (1) The gastrointestinal effects of the drug are at least inconviencing, and are also relatively frequent (see Josephkutty & Potter, 1990); and (2) The reduction of plasma vitamin B12 need to be followed in the individual patient eventually treated with this medication, inasmuch as at least a single case of megaloblastic anemia has been reported recently in the literature (See Levesque et al., 1991).

It's more important, however, to emphasize the following: In my opinion, the Company has failed to determine the lowest dose effective in most patients. This is due to the protocolar choice of titrating upward based on FPG values alone during relatively short intervals. As a result, a hodge-podge of doses were used and not a single one was tested for true efficacy. Under the circumstances, it is very difficult to recommend approval of the drug, though its efficacy seems to be real and significant.

7.2. Second Pivotal Study: Study No. 87-2D-6023

7.2.1. Description of Study

7.2.1.1 Title, Objective and Rationale

U.S. Study No. 87-2D-6023: "A Double-Blind, Placebo Controlled, Randomized, Parallel Group, Multi-Center Study to Compare the Safety and Effectiveness of Metformin Alone to Metformin in Combination with a Second Generation Sulfonylurea (Glyburide) to Glyburide Alone in the Control of Obese, Type II, Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Patients who are not Well Controlled at the Maximum Dose of a First or Second Generation Sulfonylurea" was conducted to evaluate the safety and efficacy of metformin as described in the title. The rationale for the study was scientific evidence of the antihyperglycemic effect associated with the drug in this patient population.

7.2.1.2 Experimental Design

U.S. Study No. 87-2D-6023, conducted from Sept., 1988 through July, 1991, was a double-blind, placebo-controlled (placebos for metformin and glyburide), randomized, parallel group (three), multi-center (20 centers) study comparing the efficacy and safety of 29 weeks of treatment with either metformin (M) alone (with placebo for glyburide) vs. metformin in combination with maximum dose glyburide (M + G) vs. maximum dose glyburide (G) alone (with placebo for metformin), in 632 obese (120-170% of ideal body weight) NIDDM outpatients, not achieving acceptable glycemic control despite maximum doses of a sulfonylurea for at least one month, including one month of maximum dose glyburide (20 mg/day), immediately prior to randomization. Potentially eligible patients were randomized if FPG remained >140 mg/dL, despite maximum dose glyburide for at least one month. (All baseline evaluations occurred while patients were on maximum dose glyburide). In this study, the 500 mg dosage strength of metformin was used.

Subsequent to the one month pre-enrollment run-in phase, in which all potential candidates received maximum dose glyburide, eligible patients were randomized and began a five week metformin dose titration phase (weekly increases of metformin [or placebo M] by 500 mg increments [based on FPG and tolerance], starting with 500 mg/day and increasing to a maximum of 2500 mg/day [1000-500-1000, with meals]), followed by a 24 week treatment phase. Glyburide (or placebo G) treatment was continued throughout the study at a daily dose of 20 mg/day (i.e., identical to pre-randomization dose).

7.2.1.3 Demographics

A total of 632 patients were randomized to treatment with 210 receiving metformin alone, 209 receiving glyburide alone and 213 receiving metformin/glyburide combination. The patients ranged in

age from 40 to 70 with a mean age of 55. There were 47% males and 53% females.

7.2.1.4 Safety Considerations

Adverse experiences and intercurrent events (AE/MEs) were recorded at each visit.

7.2.1.5 Efficacy Endpoints

The primary efficacy parameter was the integrated value of glycemic control. i.e., HbA1c values.

Supportive efficacy parameters comprised other measurements of glycemic control, i.e., FPG, and plasma glucose response during a 3-hour oral glucose tolerance test [OGTT]).

Secondary efficacy parameters included: (a) lipid parameters: total cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL) cholesterol, HDL subfractions and apolipoproteins;(b) body weight change; and, (c) Others: blood pressure and insulin and C-peptide effects (measured as part of the 3-hour OGTT).

7.2.1.6 Statistical Approaches

The population of interest was the intent-to-treat population. For the efficacy analysis this was defined as any patient who took study medication and completed at least one post-baseline visit. For the safety analysis this was defined as any patient who took study medication and was assessed for safety. Observed values and change from baseline values were compared for all efficacy and safety laboratory measures to determine if significant differences existed among the three treatment groups, based on a visit-wise analysis and a last observation carried forward analysis. The primary analyses were the within- and between-treatment comparisons of change from baseline values. The incidence of AE/IMEs were tabulated and compared between treatment groups using the Fisher's Exact test.

7.2.2 Results and Conclusions

7.2.2.1 Patient Comparability

Patient groups were well-matched for all demographic features, as well as for baseline values of efficacy parameters.

7.2.2.2 Patient Disposition

A total of 157 (75%) metformin-treated patients, 174 (83%) glyburide-treated and 192 (90%) metformin/glyburide combination treated patients completed the study.

Eleven patients (four patients in the metformin group [1.9%] vs. three patients in the glyburide group [1.4%] vs. four patients in the metformin/glyburide group [1.9%]) withdrew due to an adverse experience.

7.2.2.3 Efficacy Data

The group of greatest interest in this study was the metformin/glyburide group. This treatment combination resulted in very significant improvement in all parameters of glycemic control (i.e., FPG, HbA_{1c} and 2-hour post-glucose load plasma glucose), with addition of metformin to continued glyburide therapy. For FPG, the combination therapy group had a 63.5 mg/dL decrease from baseline whereas the metformin alone group decrease 0.9 mg/dL and the glyburide alone group increased 13.7 mg/dL.

Subgroup analysis of FPG and HbA_{1c} changes at final visit, according to baseline FPG subgroup, indicated that the magnitude of the response for these parameters in the metformin/glyburide group

varied directly with the severity of the baseline hyperglycemia. The metformin/glyburide group also had mean reductions in total cholesterol and LDL cholesterol which were significantly different from glyburide, with a greater effect on total cholesterol as well as total serum triglycerides in patients with higher baseline cholesterol or triglyceride levels.

Patients on metformin alone, after an initial rise in fasting plasma glucose levels during the metformin titration phase (simultaneous with complete withdrawal from maximum dose glyburide) maintained their previous level of glycemic control, without deterioration and, in fact, with slight improvement (which was also statistically significantly superior to glyburide alone) at final visit. The metformin group experienced mean reductions in body weight which were significantly different than either the metformin/glyburide or glyburide groups. In addition, metformin was shown to be statistically significantly superior to glyburide in reducing HbA_{1c} and LDL cholesterol ($p < 0.050$). This significance was also seen with metformin at the later visits for reductions in fasting plasma glucose.

Patients randomized to glyburide (and thus continuing on maximum dose glyburide, without change from the pre-randomization period) had slight deterioration of glycemic control by final visit, with statistically significant increases in both FPG and HbA_{1c} at final visit.

7.2.2.4 Safety Data

When analyzed on the basis of first occurrence by patient, the overall incidence of AE/IMEs was not statistically significantly different between treatment groups, although it approached significance between the metformin/glyburide group and the glyburide group ($p = 0.066$). AE/IMEs were reported by 88% of the patients in the metformin/ glyburide group compared to 82% in the glyburide group and 84% of patients in the metformin group.

As in U.S. Study No. 87-1D-6023, more digestive system events occurred in metformin/glyburide patients and metformin patients than in glyburide patients. These differences were primarily due to diarrhea and nausea/vomiting. The metformin/glyburide group also showed a significantly higher number of patients who reported "hypoglycemia" than both the metformin and glyburide groups (38 vs. 4 and 7, respectively, $p=0.001$), although these were always mild or moderate (spontaneously disappeared or disappeared with food intake) in severity and were not verified by laboratory determination of plasma glucose levels.

There was one patient death during the study from cardiovascular disease (presumed myocardial infarction, with cardiac arrest, Patient 20/06, in the metformin group), which was thought to be unrelated to study drug. For the metformin group, three (1.4%) of the four patients were prematurely terminated due to gastrointestinal problems and two of these three patients reported diarrhea as one of the reasons for the premature termination. One patient discontinued for rash. For the glyburide group, two (1%) of the three patients were prematurely terminated due to gastrointestinal problems and the third patient withdrew due to a hypersensitivity reaction. For the metformin/glyburide group, three (1.4%) of the four patients were prematurely terminated due to gastrointestinal problems and one patient withdrew from the study due to rash.

Fifteen patients (five patients in the metformin group [2.4%] vs. eight patients in the glyburide group [3.8%] vs. two patients in the metformin/glyburide group [1%]) were prematurely terminated due to an intercurrent illness. For the metformin group, one patient each was discontinued due to the following: unstable angina, allergic reaction probably secondary to gastritis, lichen planus, transient ischemic attack and low platelet count (present, however, prior to randomization). For the glyburide group, six patients were discontinued due to cardiovascular events (including three patients who had myocardial infarctions, two patients with angina pectoris and one patient with heart block, present prior to randomization. One patient was discontinued due to infection and one patient was discontinued due to acute depression. For the metformin/glyburide group one patient discontinued for congestive heart failure (secondary to cardiomyopathy) and one patient

discontinued for chronic left flank pain, present prior to randomization.

Sixteen patients (five patients in the metformin group [2.4%] vs. four patients in the glyburide group [1.9%] vs. seven patients in the metformin/glyburide group [3.3%]) were prematurely discontinued due to abnormal lab results. For the metformin group, four patients were discontinued due to elevated liver function tests (for two patients already abnormal also at baseline) and one patient had elevated ketones. For the glyburide group, one patient each was discontinued for abnormal liver function tests, hyperlipidemia, decreased creatinine clearance with increased serum creatinine and increased lactate levels. For the metformin + glyburide group, one patient was discontinued for elevated urine protein, six patients were discontinued due to decreases in creatinine clearance and one patient was discontinued for abnormal liver function tests.

Patients in both the metformin/glyburide and metformin groups showed a mean decrease in vitamin B_{12} from baseline to final visit which was significantly different than the patients in the glyburide group. In the metformin group, the mean serum vitamin B_{12} level decreased from 554 pg/mL at baseline to 411 pg/mL ($p=0.001$). In the group receiving metformin/glyburide, the mean serum vitamin B_{12} level went from 535 pg/mL at baseline to 401 pg/mL at final visit ($p=0.001$). In contrast, there was no significant change in serum vitamin B_{12} level in the glyburide group at final visit ($p=0.270$). Thus, there were highly significant differences among the treatment groups at final visit for vitamin B_{12} even though mean values remained with the normal range of 200-900 pg/mL. Fifteen patients (9%) in the metformin group and 11 patients (6%) in the metformin/glyburide group had normal or high values for vitamin B_{12} at baseline and subnormal values at final visit compared to one patient (<1%) with similar shifts in the glyburide group. None of these patients had any associated hematologic abnormalities. There was no significant change in serum folic acid levels for any of the treatment groups. Overall, few meaningful or consistent differences among the treatment groups were noted for either liver function tests, renal function tests or hematology parameters at any visit, and where noted, differences were relatively small. Lactate levels were similar among the three treatment groups throughout the study and there were no cases of lactic acidosis.

7.2.2.5 Sponsor's Conclusions

The sponsor concluded that, in this randomized, active treatment-controlled, double placebo, double-blind, multicenter study involving obese NIDDM patients considered to have inadequate response to sulfonylurea monotherapy at maximal dose, coadministration of metformin/glyburide (in actuality, *addition* of metformin to *continued* maximal dose glyburide) resulted in a strong and consistent antihyperglycemic activity expressed by a significant decrease from baseline in FPG, 2-hour post-glucose load plasma glucose, HbA_{1c} and glucosuria. The lipid profile for this same treatment group showed a drop in total cholesterol and serum LDL cholesterol and also for the total cholesterol/HDL and LDL/HDL ratios.

The metformin group showed moderate improvements in FPG, 2-hour post-glucose load plasma glucose, and HbA_{1c} by the end of the study, which were significantly different from the glyburide group. The metformin group also demonstrated a significant and consistent decrease in body weight as compared to virtually no change for the other two treatment groups.

The metformin side-effect profile identified in this study confirmed what is already well-established in the literature and was characterized by an increase in frequency of gastrointestinal adverse experiences in both metformin-containing treatment arms, consisting primarily of diarrhea and nausea/vomiting, but with only 1.4% of patients on metformin and 1.4% of patients on metformin/glyburide withdrawing prematurely because of these symptoms. Asymptomatic decreases in serum vitamin B_{12} to subnormal levels were seen in patients in both metformin-containing treatment groups (9% of patients on metformin and 6% of patients on metformin/glyburide). Patients receiving metformin/glyburide had a comparatively higher incidence

ITEM 2 — NDA SUMMARY

Among the non-U.S. randomized studies, AE/IMEs were evaluated by the individual study investigators for severity in only two studies: non-U.S. Study Nos. MET/GB/85/DORNA and MET/S/86/HERMA. The pooled data from these studies are summarized in intext Tables 62 and 63, pages 433 and 434. Intext Table 63 lists those individual AE/IMEs reported by at least 9% of the patients in one or more treatment groups or AE/IMEs that had differences in incidence between any two treatment groups of at least 5%. The incidence of these AE/IMEs which were considered "severe" is provided. (*Note:* Because of the complex nature of the study design for non-U.S. Study No. MET/S/86/HERMA, only those patients reporting AE/IMEs which first occurred while receiving monotherapy or low dose combination therapy are included in AE/IME summary tables).

Although conclusions drawn from the data here were limited by the relatively small number of patients in these two studies, they tended to support the overall conclusion that the highest percentage of *severe* AE/IMEs occurred within the body system showing the highest overall incidence of AE/IMEs, namely, the Digestive System. As with the pooled U.S. studies, the exception to this maxim concerned the symptom of "hypoglycemia", which, although of relatively high incidence in the metformin/sulfonylurea group had no episodes considered to be "severe".

Table 62.
Number of Patients Reporting AE/IMEs by Body System and Severity:
Non-U.S. Randomized Studies:
MET/GB/85/DORNA and MET/S/86/HERMA (Pooled)

	Patients Reporting Severe AE/IMEs/ Patients Reporting AE/IMEs[1]			
Body System	Metformin	Placebo	Sulfonylurea	Met+Sulf
Total Number of Patients	n=68	n=32	n=34	n=72
Body as a Whole	3/15 (20%)	1/5 (20%)	0/4	2/24 (8%)
Cardiovascular	1/4 (25%)	1/1 (100%)	0/4	0/4
Digestive	**16/44 (36%)**	**2/15 (13%)**	**2/12 (17%)**	**3/25 (12%)**
Metabolic & Nutritional Disorders	0/3	0	0/1	1/9 (11%)
Musculoskeletal	1/1 (100%)	0	0	0
Nervous	3/8 (38%)	0/4	2/14 (14%)	5/30 (17%)
Respiratory	1/2 (50%)	1/2 (50%)	0/1	0/1
Skin & Appendages	1/11 (9%)	0/2	0/5	2/8 (25%)
Special Senses	0/7	1/1 (100%)	0/3	2/6 (33%)
Urogenital	0/2	0/2	0/1	0/3

[1] Included only those patients with known severity of the AE/IMEs.

Table 63.
Frequently Reported AE/IMEs by Severity:
Non-U.S. Randomized Studies:
MET/GB/85/DORNA and MET/S/86/HERMA (Pooled)

	Patients Reporting Severe AE/IMEs/ Patients Reporting AE/IMEs[1]			
AE/IME	Metformin	Placebo	Sulfonylurea	Met+Sulf
Total Number of Patients	n=68	n=32	n=34	n=72
Diarrhea	9/35 (26%)	0/7	0	0/11
Nausea/Vomiting	2/12 (17%)	0/1	0/3	1/3 (33%)
Abdominal Discomfort	5/13 (38%)	0/2	0/3	0/8
Indigestion	2/8 (25%)	0/2	0/2	0/2
Asthenia	1/9 (11%)	0/1	0/3	1/18 (6%)
URI	0	1/2 (50%)	0	0
Hypoglycemia	0	0	0/1	0/2
Taste Disorder	0/4	0	0/2	0/1
Constipation	0/4	2/6 (33%)	0/3	0/4
Headache	1/6 (17%)	1/3 (33%)	0	2/7 (29%)
Sweating, Increased	1/7 (14%)	0	0/4	0/4
Dizziness	1/6 (17%)	0/3	1/5 (20%)	4/14 (29%)
Lower Respiratory Tract Infection	1/1 (100%)	0	0	0
Urinary Tract Infection	0/1	0	0	0
Thirst	0/3	0	0	1/5 (20%)
Abnormal Vision	0/3	0	0/1	2/5 (40%)
Pruritus	0/1	0/1	0	2/4 (50%)
Tremulousness	0/2	0	2/14 (14%)	4/23 (17%)
Polyuria	0/1	0	0/1	0/2

[1] Included only those patients with known severity of the AE/IMEs.

Table 63. (cont'd)
Frequently Reported AE/IMEs by Severity:
Non-U.S. Randomized Studies:
MET/GB/85/DORNA and MET/S/86/HERMA (Pooled)

	Patients Reporting Severe AE/IMEs/ Patients Reporting AE/IMEs[1]			
AE/IME	metformin	placebo	sulfonylurea	met+sulf
Appetite Increased	1/1 (100%)	0	2/7 (29%)	2/6 (33%)
Anxiety/Tension	1/1 (100%)	0	1/1 (100%)	0/4

[1] Included only those patients with known severity of the AE/IMEs

Incidence of AE/IMEs by severity for non-U.S. Phase IV Study No. MET/D/86/HAUPT are summarized in intext Table 64, below and Table 65, page 437.

Table 64.
Number of Patients Reporting AE/IMEs
by Body System and Severity:
Non-U.S. Study No. MET/D/86/HAUPT (Phase IV)

	Patients Reporting Severe AE/IMEs/ Patients Reporting AE/IMEs[1]
Body System	**Metformin+Sulf**
Total Number of Patients	*n=3724*
Body as a Whole	17/107 (16%)
Cardiovascular	7/18 (39%)
Digestive	101/497 (20%)
Metabolic & Nutritional Disorders	5/27 (19%)
Musculoskeletal	5/14 (36%)
Nervous	20/91 (22%)
Respiratory	0/2
Skin & Appendages	6/34 (18%)
Special Senses	6/64 (9%)
Urogenital	0/1

[1] Included only those patients with known severity of the AE/IMEs.

Table 65.
Frequently Reported AE/IMEs by Severity:
Non-U.S. Study No. MET/D/86/HAUPT (Phase IV)

	Patients Reporting Severe AE/IMEs/ Patients Reporting AE/IMEs[1]
AE/IME	**Metformin + Sulf**
Total Number of Patients	n=3724
Diarrhea	50/246 (20%)
Nausea/Vomiting	38/186 (20%)
Abdominal Discomfort	29/160 (18%)

[1] Included only those patients with known severity of the AE/IMEs.

Available data on incidence of AE/IMEs for Non-U.S. Phase IV Study No. MET/AM/87/PHASE, according to severity of gastrointestinal AE/IMEs, are shown above in intext Table 59, page 428. In this study, at each visit, at least 78% of the patients reported "no digestive intolerance". Overall, the percentage of patients with any "digestive intolerance" decreased over the course of the study as did the incidence of severe events (from 4% of severe or very severe events at Month 1 to <1% at Month 3).

2.8.6.1.2.4 Serious and Potentially Serious AE/IMEs

The analysis within this section is distinguished from the previous one (AE/IMEs Analyzed with Respect to Severity, Section 2.8.6.1.2.3) by a standardized criterion for a severe AE/IME which permitted an objective assessment of severity. This criterion was taken from CRF 21:312.32(a) which defined a "serious AE/IME" as "... any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer or overdose..." A "potentially serious AE/IME" was defined as a medical event that was potentially fatal or life-threatening.

U.S. Phase III Studies (Pooled): Serious/potentially serious AE/IMEs, by body system, for the pooled U.S. Phase III studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023) are presented in intext Table 66, page 439. Inspection of the data for the number of patients reporting serious/potentially serious AE/IMEs revealed few differences among treatment groups for any body system.

Individual narratives for each patient who experienced a serious/potentially serious event, which includes a description of the event along with other obtainable pertinent information, are located in Section 8.8.15, Volume 1.80.

Table 66.
Serious/Potentially Serious AE/IMEs by Body System:
U.S. Phase III Studies (Pooled)[1]

Treatment Group	Metformin	Placebo	Glyburide	Met + Glyb
Total Number of Patients	n=351	n=145	n=209	n=213
Patients with any AE/IME	303 (86%)	114 (79%)	171 (82%)	188 (88%)
Patients with Serious/Potentially Serious AE/IMEs	26 (7%)	8 (6%)	12 (6%)	8 (4%)
Body as a Whole	6 (2%)	2 (1%)	4 (2%)	1 (<1%)
Cardiovascular	9 (3%)	2 (1%)	5 (2%)	1 (<1%)
Digestive	7 (2%)	1 (<1%)	2 (1%)	2 (<1%)
Metabolic & Nutritional Disorders	3 (<1%)	1 (<1%)	2 (1%)	1 (<1%)
Musculoskeletal	0	1 (<1%)	0	1 (<1%)
Respiratory	4 (1%)	0	1 (<1%)	0
Skin and Appendages	0	0	0	1 (<1%)
Urogenital	3 (<1%)	2 (1%)	0	0
Intercurrent Illness	0	1 (<1%)	0	2 (<1%)

[1] Studies 87-1D-6023 and 87-2D-6023.

Non-U.S. Randomized Studies (Pooled): Serious/potentially serious AE/IMEs, by body system, for the pooled non-U.S. Category II randomized studies (Non-U.S. Study Nos. MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/86/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA) are presented in intext Table 67, page 441. As in the U.S. Category I studies, inspection of the data for the number of patients reporting serious/potentially serious AE/IMEs revealed few differences among treatment groups for any body system. In the metformin/sulfonylurea group (representing patient data from non-U.S. Study No. MET/S/86/HERMA alone) and sulfonylurea treatment groups, 10% and 2% of the patients, respectively, reported a serious or potentially serious AE/IME in the Metabolic and Nutritional Disorders System, vs. <1% of the patients in the metformin group and no patients in the placebo group. This relatively high incidence of reports in the Metabolic and Nutritional Disorders category for the metformin/sulfonylurea treatment group was due solely to reports of hypoglycemia. In the analysis of this study, hypoglycemia was considered to be "potentially serious" if it was reported to occur three or more times throughout the study, even though individual episodes were all mild.

Table 67.
Serious/Potentially Serious AE/IMEs by Body System:
Non-U.S. Randomized Studies (Pooled)[1]

Treatment Group	Metformin	Placebo	Sulfonylurea	Met + Sulf
Total Number of Patients	n=176	n=83	n=87	n=72
Patients with any AE/IME	110 (63%)	32 (39%)	50 (57%)	61 (85%)
Patients with Serious/Potentially Serious AE/IME	20 (11%)	4 (5%)	7 (8%)	14 (19%)
Body as a Whole	6 (3%)	3 (4%)	0	0
Cardiovascular	3 (2%)	1 (1%)	1 (1%)	3 (4%)
Digestive	7 (4%)	1 (1%)	2 (2%)	0
Metabolic & Nutritional Disorders	1 (<1%)	0	2 (2%)	7 (10%)
Musculoskeletal	1 (<1%)	0	0	0
Nervous	3 (2%)	0	1 (1%)	2 (3%)
Respiratory	3 (2%)	0	0	0
Skin & Appendages	1 (<1%)	0	1 (1%)	0
Special Senses	1 (<1%)	0	0	0
Urogenital	1 (<1%)	0	0	2 (3%)

[1] Studies: MET/AM/84/DORF1, MET/AM/86/DORF2, MET/GB/86/DORNA, MET/GB/86/CAMP1, MET/AM/88/DUCHI, and MET/S/86/HERMA

Non-U.S. Phase IV Studies: Serious/potentially serious AE/IMEs, by body system, for non-U.S. Phase IV (Non-U.S. Study No. MET/D/86/-HAUPT) are summarized in intext Table 68, page 443. Of the 3,724 patients who contributed evaluable data, 156 (4%) had serious or potential serious AE/IMEs and 105 (3%) had events that occurred in the Digestive System. All other body systems had an occurrence rate of <1% for serious or potentially serious AE/IMEs. The only particular events with an occurrence rate of ≥1% for serious or potentially serious AE/IMEs were diarrhea (53 patients, 1%) and nausea/vomiting (39 patients, 1%). All other events had an occurrence rate of <1%.

As mentioned previously, the CRF for non-U.S. Study No. MET/AM/87/PHASE was not designed to collect comprehensive AE/IME data. In an effort to be consistent across all studies regarding categorization of AE/IMEs, all serious/potentially serious AE/IMEs were identified by the Primary Medical Officer (PMO) at Lipha and are presented in Table 16.3.0, Section 8.8.14.

From a total of 4,252 patients, 84 AE/IMEs were considered to be either serious or potentially serious according to the PMO. Fifty-six (56) of these patients were also represented as patients who discontinued due to adverse experiences/-intercurrent medical events.

Table 6d.
Serious/Potentially Serious AE/IMEs by Body System:
MET/D/86/HAUPT

Body System	Metformin + Sulf
Total Number of Patients	n=3724
Patients with any AE/IME	684 (18%)
Patients With Any Serious/Potentially Serious AE/IME	158 (4%)
Body as a Whole	17 (<1%)
Cardiovascular	7 (<1%)
Digestive	105 (3%)
Metabolic & Nutritional Disorders	5 (<1%)
Musculoskeletal	5 (<1%)
Nervous	20 (<1%)
Skin & Appendages	6 (<1%)
Special Senses	6 (<1%)

2.8.6.1.2.5 Drug Dose at Time of First Occurrence of AE/IMEs

This analysis considered the drug dose at time of first occurrence of AE/IMEs by body system and by individual AE/IMEs. Only data from patients receiving metformin was considered. Patients receiving metformin monotherapy and those receiving metformin in combination with sulfonylureas were considered separately.

Metformin (Monotherapy):

Analysis of the data for drug dose at time of first occurrence of AE/IMEs for patients on metformin alone in the pooled U.S. Category I studies suggests that, overall, slightly more than half of all first occurrences of AE/IMEs by body system occurred at metformin dose of >2000 mg/day. However, the incidence of Digestive System AE/IMEs was greatest while patients were receiving 500-1000 mg/day of metformin.

The data for drug dose at time of first occurrence of AE/IMEs for patients on metformin alone in non-U.S. randomized studies (Category II) indicated that first occurrences of AE/IMEs were distributed throughout the dosage ranges. This pattern differs somewhat from that seen in the pooled U.S. studies where the overall trend suggested a predominance of first occurrences in the >2000 mg/day range. However, as in the non-U.S. randomized studies, for the Digestive System (which accounted for the greatest incidence of AE/IMEs), 25% of first occurrences were in the 500-1000 mg/day range, 40% were in the 1000-2000 mg/day range,

and 35% were in the >2000-3000 range. This pattern is generally consistent with the pattern seen in the pooled U.S. studies.

Metformin/Sulfonylurea (Combination) Treatment:

In U.S. Study No. 87-2D-6023, for patients on the metformin/glyburide combination therapy, overall, first occurrences of AE/IMEs by body system were slightly more frequent with patients receiving >2000 mg/day of metformin (in combination with glyburide). Among the individual body systems, first occurrences of AE/IMEs were generally spread across the dose ranges.

In randomized non-U.S. Study No. MET/S/86/HERMA, low dose combination therapy, as defined in this study, consisted of metformin in doses of up to 1500 mg/day and glibenclamide (micronized formulation) in doses of up to 5.25 mg/day (approximately half of standard/maximum doses of either drug). In contrast to U.S. Study No. 87-2D-6023, the bulk of first occurrences of AE/IMEs for patients receiving low dose combination therapy in non-U.S. Study No. MET/S/86/HERMA were reported while patients were receiving 500-1000 mg/day of metformin (plus glibenclamide).

In non-U.S. Phase IV Study No. MET/D/86/HAUPT, metformin was administered primarily in combination with glibenclamide. Most of the first occurrences of AE/IMEs were reported while patients were receiving 850 mg/day of metformin.

Thus, in general, the data reflecting the increased incidence of digestive system side-effects at lower doses, is consistent with an increased incidence of such side-effects during treatment initiation, when metformin is started at low dose and increased, thereafter, in step-wise fashion.

2.8.6.1.2.6 Time to First Occurrence of AE/IMEs for Patients on Study Medication

The relationship between time on study medication and the first occurrence of AE/IMEs for the various treatment groups of the U.S. Studies was examined using life table analyses, with grouping of occurrences of AE/IMEs at seven day time intervals.

Analyses of time to first occurrence of *any* AE/IME, irrespective of relationship to drug, for the various treatment groups of the pooled U.S. Phase III pivotal studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023), as can be seen in intext Table 69, page 447, indicated that 50% of the patients in the metformin and in the metformin/glyburide treatment groups reported an AE/IME (first occurrence) within 28 days after starting therapy. This contrasted with 49 days for the placebo group and 35 days for the glyburide group. Similarly, 75% of the patients in the metformin and metformin/glyburide groups reported an AE/IME within 56 days and 42 days, respectively. These times contrasted even more sharply with those for the placebo group (140 days) and the glyburide group (119 days). These results,

together with examination of the hazard rate (i.e., the probability of a response during a given time interval), suggested that patients receiving metformin reported their first occurrence of an AE/IME earlier in treatment relative to patients in the placebo and glyburide treatment groups. (It should be recalled that patients who were randomized to glyburide in U.S. Study No. 87-2D-6023 had been on glyburide, at maximum dose [as had all patients in the study, prior to randomization], and thus, randomization did not result in a change in medication for this group. Thus, a more prolonged time to first occurrence of any AE/IME would not be unexpected.)

Table 69.
Time of First Occurrence of Any AE/IME:
U.S. Phase III Studies (Pooled)[1]

Treatment	Estimated No. of Patients @ Risk (Days 0-7)	Days on study medication until X % of the patients in a treatment group reported an occurrence of an AE/IME		
		25% of patients	50%	75%
All Treatments	907.5	7-14 days	21-28 days	77-84 days
Placebo	142.0	14-21 days	42-49 days	133-140 days
Metformin	346.5	7-14 days	21-28 days	49-56 days
Glyburide	206.5	7-14 days	28-35 days	112-119 days
Met+Glyb	212.5	7-14 days	21-28 days	35-42 days

[1] U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023.

Analyses of time to first occurrence of *any gastrointestinal* AE/IME, irrespective of relationship to drug, for the various treatment groups of the pooled U.S. Phase III pivotal studies, as shown in intext Table 70, page 449, indicated that 50% of the patients in the metformin and in the metformin/glyburide treatment groups reported an AE/IME (first occurrence) within 42 days after starting therapy. This contrasted with >294 days for the placebo group and >238 days for the glyburide group (i.e. less than 50% of the patients in these two groups reported a first occurrence of a Gastrointestinal (GI) AE/IME during the treatment period). These results, together with examination of the hazard rate (i.e. the probability of a response during a given time interval), suggested that patients receiving metformin reported the first occurrence of a gastrointestinal AE/IME earlier than patients receiving placebo and glyburide therapy. This pattern reflected that seen with time to first occurrence of *any* AE/IME, as discussed above. This is consistent with the known increased frequency of gastrointestinal symptoms with metformin treatment initiation, which abate as treatment is continued.

Table 70.
Time of First Occurrence of Any GI AE/IME:
U.S. Phase III Studies (Pooled)[1]

Treatment	Estimated No. of Patients @ Risk (Days 0-7)	Days on study medication until x % of the patients in a treatment group reported the occurrence of a GI AE/IME	
		25%	50%
All Treatments	897.0	21-28 days	77-84 days
Placebo	137.0	35-42 days	(> 294 days)
Metformin	345.5	14-21 days	35-42 days
Glyburide	204.0	35-42 days	(> 238 days)
Met+Glyb	210.5	14-21 days	35-42 days

[1] U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023.

2.8.6.1.2.7 Conclusions Regarding Adverse Experiences

It can be concluded that, across all pooled studies, metformin monotherapy or metformin/sulfonylurea combination therapy resulted in an increased incidence of Digestive System symptoms compared to placebo or sulfonylurea therapy. Within the Digestive System, specific symptoms occurring at greater frequency were diarrhea, nausea/vomiting and abdominal discomfort. In general, when analyzing adverse events by reported severity, Digestive System symptoms also tended to have the greatest incidence of reported "severe" events. Metformin-treated patients experiencing Digestive System events tended to experience them at the

lower dose levels of metformin and earlier in the course of treatment, relative to other AE/IMEs. This most likely reflects the fact that all studies *initiated* metformin therapy at *low* doses, with gradual stepwise increase and that, historically, it is known that digestive system symptoms tend to occur during therapy initiation and abate thereafter.

The only other COSTART body system with both a significant and meaningful difference in occurrence rate of AE/IMEs between metformin-containing and non-metformin-containing treatment groups was the Metabolic and Nutritional Disorders system. This was accounted for by the greater incidence of "hypoglycemia" in the metformin/sulfonylurea treatment groups. Of note, despite the increased incidence of hypoglycemia in both U.S. and non-U.S. pooled randomized studies in the combination therapy groups, there were no reports of "severe" hypoglycemia. Study design features could contribute to the relatively high incidence of hypoglycemia with such therapy, particularly in U.S. Study No. 87-2D-6023.

2.8.6.2 Drug-Drug Interaction

This section reviews the interactions of metformin with other drugs likely to be prescribed for the same patient population.

2.8.6.2.1 Metformin/Sulfonylurea in Combination vs. Metformin Monotherapy

Based on the analysis of U.S. Phase III Study No. 86-2D-6023, metformin/sulfonylurea combination therapy reflected the combined AE/IME profiles of the individual drugs for individual AE/IMEs as well as for body systems. The sole important exception to this overall trend was for the symptom of hypoglycemia, where the incidence of AE/IMEs for the treatment group receiving metformin/sulfonylurea was substantially higher than that of either of the monotherapy treatment groups. An increased incidence of hypoglycemia in this group, however, probably relates to two factors involved in the protocol design.

First, as previously noted, all patients, prior to randomization, were on maximum dose glyburide (20 mg/day), for at least one month, and, despite such therapy, were considered to be "sulfonylurea failures". In fact, the mean fasting plasma glucose of the randomized population, as a whole, while on maximum dose glyburide (i.e., baseline determination) exceeded 250 mg/dL. As seen in the efficacy analysis, the group randomized to glyburide (in reality, *continuation* on

glyburide) had deterioration of glycemic control during the course of the study and, thus, would not have been expected to experience much hypoglycemia.

Secondly, in order to facilitate interpretation of outcome, the protocol was designed to hold the glyburide dose constant at 20 mg/day in both the glyburide alone arm and the metformin/glyburide arm. In the event of hypoglycemia, the metformin dose was modified. This would be contrary to the course taken in clinical practice, where, in the event of hypoglycemia, the dose of sulfonylurea (which stimulates release of insulin) would be the more logical one to modify.

2.8.6.2.2 Review of the Findings of the Clinical Pharmacology Drug Interaction Studies, Relative to Safety

Single dose drug interaction studies were performed in healthy non-diabetic volunteers with metformin and the following drugs, considered to be representative of their class:

- Cimetidine (H_2-receptor antagonist)
- Nifedipine (calcium channel blocking agent)
- Propranolol (β-blocking agent)
- Furosemide (loop diuretic)
- Ibuprofen (non-steroidal anti-inflammatory agent)

A single dose drug interaction study was also performed in healthy diabetic volunteers with metformin and glyburide.

ITEM 2 — NDA SUMMARY

Although there were no clinically relevant AE/IMEs occurring during the conduct of these single dose drug interaction studies, conducted for the most part in healthy volunteers, based on pharmacokinetic analysis, the following general statements can be made:

- Co-administration of cimetidine with metformin significantly increased plasma and whole blood metformin levels. Total and renal clearance of metformin was also decreased with cimetidine co-administration although this was not statistically significant. There was no effect of metformin on cimetidine pharmacokinetics. Theoretically, these observations suggest a potential impact with chronic use of both products, including possible accumulation of metformin.

- Metformin plasma and whole blood concentration-related parameters increased during metformin and nifedipine co-administration, but metformin urinary excretion increased even more and metformin plasma elimination half-life was not affected. It appeared that nifedipine in some way increased the bioavailability of metformin, but without resultant accumulation of metformin. There was no effect of metformin on nifedipine kinetics.

- There were no significant changes in pharmacokinetics of either metformin or propranolol during co-administration of these drugs.

- Pharmacokinetic interactions which might have an impact on chronic use of metformin and furosemide include the observation that furosemide significantly increased metformin concentration-related parameters, while not affecting the plasma or whole blood half-life or clearance. It was considered that furosemide increased the bioavailability of metformin. Conversely, metformin co-administration resulted in a decrease in bioavailability of furosemide. The importance of this interaction (15-22% increase in metformin concentration and 13-31% decrease in furosemide concentration with single dose administration) will depend on the magnitude of the interaction when the two drugs are administered chronically. Currently, such information is not available.

- During the metformin/ibuprofen drug interaction study, no significant pharmacokinetic interaction was noted.

- During the single dose drug interaction study of metformin/glyburide, conducted in subjects with mild-to-moderate NIDDM, no effect of glyburide on metformin pharmacokinetics was noted during co-administration. Metformin decreased glyburide absorption by approximately 25% which was judged to be clinically insignificant.

2.8.6.3 Drug-Demographic Interactions

General considerations: This discussion considers AE/IMEs for subpopulations of patients receiving metformin (either alone or in combination with sulfonylureas), with subpopulation definitions based on the following baseline demographic variables:

- sex (male vs. female);
- age (<65 years vs. ≥65 years for U.S. and non-U.S. randomized studies and <65 years vs. 65-74 years vs. ≥75 years for the non-U.S. Phase IV study);
- race (white vs. black vs. hispanic vs. other - U.S. Phase III studies only).

2.8.6.3.1 Sex

U.S. Phase III Studies: Of the 564 patients who participated in the U.S. Phase III Category I studies and received metformin (either alone or in combination with sulfonylurea [i.e., glyburide]), 255 were males and 309 were females. Overall, 491 patients (87%) reported an AE/IME. AE/IMEs were reported by 223 males (87% of male population) and 268 females (87% of female population). Appreciable differences between males and females were evident for the Digestive, Musculoskeletal, and Urogenital Systems.

For the Digestive system, 222 female patients (72%) versus 158 male patients (62%) had AE/IMEs; this difference could be attributed to the difference in the occurrence of diarrhea (163 [53%] females vs. 109 [43%] males) and nausea/vomiting (104 [34%] females vs. 48 [19%] males).

For the Musculoskeletal system, 85 female patients (28%) vs. 45 male patients (18%) had AE/IMEs and for the Urogenital system, 69 female patients (22%) vs. 26 male patients (10%) had AE/IMEs.

Non-U.S. Randomized Category II Studies (Pooled): Of the 247 patients who participated in the six non-U.S. randomized studies with available AE/IME information and received metformin (either alone or in combination with sulfonylureas), 129 were males and 118 were females. Overall, 170 patients (69%) reported an AE/IME. AE/IMEs were reported by 87 males (67% of male population) and 83 females (70% of female population). Appreciable differences between males and females were noted for the Body as a Whole, Digestive, Metabolic and Nutritional, Nervous, and Respiratory Body Systems.

For Body as a Whole, more males (35 [27%]) than females (22 [19%]) had AE/IMEs; this difference between the gender groups could be attributed, primarily, to the difference in the occurrence of asthenia (21 [16%] males versus 13 [11%] females).

For the Digestive System, more females (60 [51%]) than males (49 [38%]) had AE/IMEs; this difference could be attributed to the difference in the occurrence of diarrhea (38 [32%] females versus 31 [24%] males) and nausea/vomiting (24 [20%] females versus 9 [7%] males).

For the Metabolic and Nutritional System, more males (31 [24%]) than females (19 [16%]) had AE/IMEs; this difference could be attributed to the difference in the occurrence of hypoglycemia (19 [15%] males versus 12 [10%] females).

For the Nervous System, more males (29 [22%]) than females (18 [15%]) had AE/IMEs; this difference could be attributed to the difference in the occurrence of dizziness (16 [12%] males versus 7 [6%] females) and tremulousness (15 [12%] males versus 9 [8%] females).

For the Respiratory System, more males (20 [16%]) than females (11 [9%]) had AE/IMEs; this difference could be attributed to the difference in the occurrence of dyspnea (3 [2%] males versus 0 females) and pharyngitis (3 [2%] males versus 0 females).

Non-U.S. Study No. MET/D/86/HAUPT (Phase IV): Of the 3724 patients who participated in the study, 3722 contributed evaluable data to this analysis; 1496 were males and 2226 were females. More females than males (424 [19%] vs. 240 [16%]) reported AE/IMEs, however, no appreciable differences were seen between

males and females regarding the incidence of AE/IMEs either by body system or by individual events.

2.8.6.3.2 Age

U.S. Phase III Studies: Of the 564 patients who participated in the studies and received metformin (either alone or in combination with sulfonylureas), 495 were in the age group <65 and 69 were in the age group ≥65. Of the 491 patients (87%) who reported an AE/IME, 429 (87% of those in this age group) were in the age group <65 and 62 (90% of those in this age group) were in the age group ≥65. Appreciable differences between the two age groups were evident for the Body as a Whole, Digestive, Musculoskeletal, and Nervous Systems.

For Body as a Whole, 36 (52%) of the patients in the age group ≥65 versus 211 (43%) of the patients in the age group <65 had AE/IMEs; this difference between the groups could be attributed, primarily, to the difference in the occurrence of asthenia (15 [22%] of patients ≥65 versus 53 [11%] of patients <65).

For the Digestive System, 51 (74%) of the patients in the age group ≥65 vs. 329 (66%) of the patients in the age group <65 had AE/IMEs; this difference could be attributed to the difference in the occurrence of diarrhea (38 [55%] of patients ≥65 vs. 234 [47%] of patients <65), nausea/vomiting, (22 [32%] of patients ≥65 vs. 130 [26%] of patients <65), and indigestion (9 [13%] of patients ≥65 vs. 41

[8%] of patients <65).

For the Musculoskeletal System, 20 (29%) of the patients in the age group ≥65 vs. 110 (22%) of the patients in the age group <65 had AE/IMEs. For the Nervous System, 17 (25%) of the patients in the age group ≥65 vs. 79 (16%) of the patients in the age group <65 had AE/IMEs.

Although there was no appreciable difference between the two age groups within the Metabolic and Nutritional Disorders System, 8 (12%) of patients ≥65 versus 37 (7%) of patients <65 had hypoglycemia. No other events within this system showed a greater difference between the groups.

Non-U.S. Category II Randomized Studies (Pooled): Of the 245 patients who participated in the studies and received metformin (either alone or in combination with sulfonylureas), 183 were in the age group <65 and 62 were in the age group ≥65. Of the 169 patients (69%) who reported an AE/IME, 122 (67%) were in the age group <65 and 47 (76%) were in the age group ≥65. Appreciable differences between the two age groups were apparent for the Body as a Whole, Metabolic and Nutritional, Special Senses, and Urogenital Systems.

For Body as a Whole, 18 (29%) of the patients in the age group ≥65 versus 39 (21%) of the patients in the age group <65 had AE/IMEs; this difference could be attributed, primarily, to the difference in the occurrence of asthenia (15 [24%] of

patients ≥65 versus 19 [10%] of patients <65).

For the Metabolic and Nutritional System, 14 (23%) of the patients in the age group ≥65 versus 36 (20%) of the patients in the age group <65 had AE/IMEs; this difference could be attributed to the difference in the occurrence of thirst (5 [8%] of patients ≥65 versus 6 [3%] of patients <65).

For the Special Senses System, 9 (15%) of the patients in the age group ≥65 versus 13 (7%) of the patients in the age group <65 had AE/IMEs; this difference could be attributed to the difference in the occurrence of taste disorder (5 [8%] of patients ≥65 versus 5 [3%] of patients <65) and abnormal vision (3 [5%] of patients ≥65 versus 5 [3%] of patients <65).

For the Urogenital System, 10 (16%) of the patients in the age group ≥65 versus 13 (7%) of the patients in the age group <65 had AE/IMEs; this difference could be attributed to the difference in the occurrence of polyuria (4 [6%] of patients ≥65 versus 3 [2%] of patients <65) and urinary tract infection (4 [6%] of patients ≥65 versus 4 [2%] of patients <65).

Non-U.S. Study No. MET/D/86/HAUPT (Phase IV): Of the 3724 patients who participated in the study, 3708 contributed evaluable data to this analysis; 2294 patients were <65 years old, 1250 patients were 65-74 years old, and 164 patients ≥75 years old. Less patients who were <65 years old reported AE/IMEs than

patients in either of the other two age categories (17% vs. 19% and 20%), however, no appreciable differences were seen among age groups regarding the incidence of AE/IMEs by either body system or individual events. For individual AE/IMEs, only those occurring with a frequency ≥3% are listed.

2.8.6.3.3 Race

U.S. Phase III Studies: Only the U.S. Phase III studies provided racial demographic data and thus this analysis is based on solely on the pooled U.S. Phase III pivotal studies.

Of the 564 patients who participated in the studies and received metformin (either alone or in combination with sulfonylureas), 405 were white, 84 were black, 33 were hispanic, and 42 belonged to other racial groups. Of the 491 patients (87%) who reported an AE/IME, 359 (89%) were white, while 62 (74%) were black, and 33 (100%) were hispanic. Appreciable differences between the white and black groups were apparent for the Body as a Whole, Digestive, Musculoskeletal, Nervous, and Respiratory Systems.

For Body as a Whole, 182 (45%) of the patients who were in the white group vs. 29 (35%) who were in the black group had AE/IMEs; this difference could be attributed, primarily, to the difference in the occurrence of back pain (35 [9%] of patients who were in the white group vs. 1 [1%] in the black group).

For the Digestive System, 280 (69%) of the patients who were in the white group vs. 47 (56%) of the patients who were in the black group had AE/IMEs; this difference could be attributed to the difference in the occurrence of diarrhea (201 [50%] of patients who were in the white group vs. 31 [37%] of patients who were in the black group), abdominal discomfort (56 [14%] of patients who were in the white group versus 6 [7%] of patients who were in the black group), and indigestion (44 [11%] of patients who were in the white group vs. 3 [4%] of patients who were in the black group).

For the Musculoskeletal System, 100 (25%) of the patients who were in the white group vs. 11 (13%) of the patients who were in the black group had AE/IMEs. For the Nervous System, 73 (18%) of the patients who were in the white group vs. 8 (10%) of the patients who were in the black group had AE/IMEs. For the Respiratory System, 152 (37%) of the patients who were in the white group versus 23 (27%) of the patients who were in the black group had AE/IMEs.

2.8.6.3.4 Conclusions Regarding Drug-Demographic Interactions

In general, the overall incidence of AE/IMEs was comparable in males and females in all pooled studies. No clear patterns emerged except that in the U.S. and non-U.S. randomized studies, more females tended to report Digestive System symptoms than did males. This was accounted for by a higher incidence of diarrhea and nausea/vomiting in females.

In the pooled U.S. studies, the percentage of AE/IMEs occurring in those patients <65 and those ≥65 were comparable. The older age group, however, tended to report more asthenia, more Digestive System symptoms and to experience more hypoglycemia in these studies. In the pooled non-U.S. randomized study, the percentage of AE/IMEs occurring in patients ≥65 was greater than in those <65. Older patients in these studies also reported more asthenia. In the large Phase IV study (MET/D/86/HAUPT), somewhat greater percentages of AE/IMEs were reported by older patients, but no patterns of AE/IME occurrence could be detected.

No clear racial differences in occurrence of AE/IMEs were noted excepted for a greater incidence of Digestive System symptoms in whites compared to blacks.

2.8.6.4 Drug-Disease Interactions

This discussion addresses the safety considerations in the administration of metformin to patients with established disease and includes analyses of AE/IMEs for patients receiving metformin alone or in combination with sulfonylureas by:

- baseline severity of NIDDM (as reflected by baseline FPG);
- renal impairment;
- cardiovascular disease;
- alcoholism and chronic hepatic disease.

2.8.6.4.1 Baseline Diabetes Severity

Incidence of AE/IMEs by body system and by baseline value for fasting plasma glucose (<200 mg/dL vs. ≥200 mg/dL) for patients receiving metformin (either as monotherapy or in combination with sulfonylureas) were extracted from for the pooled Phase III U.S. studies. The AE/IME profile, by body system, for patients with FPG <200 mg/dL at baseline was essentially the same as that for patients with FPG ≥200 mg/dL at baseline. The only difference between the two groups of any note (>5%) was observed for the Respiratory System: 40% of the patients with baseline FPG <200 mg/dL reported AE/IMEs for this body system vs. 4% of the patients with baseline FPG ≥200 mg/dL.

2.8.6.4.2 Renal Impairment

Overview: Since metformin's primary elimination pathway is via the kidneys, decreases in renal function have considerable potential for having a negative impact on safety, through resultant metformin accumulation, producing an increased lactate load and risk of lactic acidosis.

Categorization of patients was attempted on the basis of basis serum creatinine (<1.4 mg/dL vs. ≥1.4 mg/dL) for the data generated from the U.S. Phase III controlled studies and the non-U.S. Category II studies. However, there were not enough patients with serum creatinine levels ≥1.4 mg/dL in these data bases to allow meaningful comparisons of these categories.

A published study by Sirtori et al showed that there was a significant prolongation of the half-life of metformin disappearance from plasma (t½ β) in renal-impaired patients (due to significantly reduced total plasma metformin clearance and renal plasma clearance) and a significant correlation between the t½ β and the creatinine clearance ($r=0.88$, $p<0.001$) [see Item 8 — Clinical Data Section, ref. 11].

Tucker et al studied the disposition of single doses of metformin in diabetic and non-diabetic subjects, having a spectrum of creatinine clearances ranging from 47-179 ml/min [see Item 8, ref. 13]. On combining selected plasma and urine pharmacokinetic data from these subjects, a highly significant linear correlation was observed between metformin plasma renal clearance and creatinine clearance ($r=0.85$, $p<0.001$). There was also a significant linear correlation between metformin plasma total oral clearance and creatinine clearance ($r=0.66$, $p<0.01$), as well as between metformin plasma renal clearance and age ($r=0.76$).

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In U.S. Study No. 90-13-6023, decreases in the clearance of metformin with aging resulted in a 76% larger maximum plasma concentration (C_{max}) and an 85% larger maximum whole blood concentration ($C_{max,b}$) in elderly individuals, and a 60% larger extrapolated AUC (AUCX) in plasma and 70% larger AUCX in whole blood in the elderly group. These changes were primarily attributed to declining renal function in older patients, although there may be an independent function of age and suggests that the use of metformin in elderly patients carries a greater risk of potential metformin accumulation and its consequences.

Stocks et al measured trough serum metformin levels, as well as serum lactate levels, in 15 NIDDM patients with normal renal function and in 18 diabetics on long-term metformin who were incidentally found to have renal insufficiency. Metformin serum concentrations were significantly higher in the patients with renal function impairment compared to those with normal renal function, on all dosing levels. Regression analysis indicated a linear relationship between lactate and serum metformin levels ($r=0.51$, $p<0.0001$). Lactate levels, however, were only slightly increased in the renal-impaired group compared to the group with normal renal function [see Item 8, ref. 336].

Post-marketing surveillance reports (since 1984) of serious AE/IMEs in patients on metformin with abnormal renal function reveal that at least 75% of the cases of lactic acidosis had renal dysfunction (primary or contributory factor).

2.8.6.4.3 Cardiovascular and Pulmonary Disease

Acute or chronic cardiovascular disease and acute or chronic pulmonary disease can both be considered independent risk factors for lactic acidosis, since they are conditions with a potential for tissue hypoxia and increased anaerobic metabolism with excess lactate production, on the basis of either poor tissue perfusion or poor tissue oxygen delivery. In addition, patients with such illnesses, particularly chronic cardiac disease, are very likely to be on one or more concomitant medications (e.g., diuretics, ACE-inhibitors) which can cause acute changes in fluid balance and may result in changes in renal perfusion and, consequently, renal function (particularly if the latter is borderline to begin with). This, in turn, could have deleterious consequences as far as the ability of the kidneys to eliminate metformin and resultant metformin accumulation, in turn, can further increase the lactate burden.

Among the 99 cases of lactic acidosis identified through post-marketing surveillance (73 cases from France and 26 cases from other countries), there were 15 patients (15%) with coexistent chronic cardiac disease. Diffuse vascular disease or hypertension, often in association with acute vascular occlusive events, was the background in 19 cases (19%). Six cases (6%) of the 99 cases had acute or chronic respiratory distress as the background for the development of lactic acidosis.

2.8.6.4.4 Chronic Hepatic Disease and Alcoholism

Since the liver is normally the major site of extraction of lactate from the blood, impairment of hepatic function by intrinsic disease or by the excessive acute or chronic ingestion of alcohol may interfere with this process and contribute to or induce hyperlactatemia and lactic acidosis. When increased lactate production and decreased utilization are simultaneously present, such as may occur with metformin plus excess alcohol intake, the extraction capacity of the liver may be even further taxed and lactate accumulation may occur. Cases of lactic acidosis occurring in alcoholics taking metformin have been previously described.

Among the 99 cases of lactic acidosis, identified through post-marketing surveillance, chronic hepatic disease, secondary to chronic ethanol abuse, was associated with 17 of the cases (17%). Nine of these patients had an acute hepatorenal syndrome at the time that lactic acidosis developed.

Ethanol abuse was present in three other cases. In one case, an acute week-long alcoholic binge (with the background of chronic ethanol abuse) resulted in fatal lactic acidosis.

2.8.6.5 Withdrawals Due to AE/IMEs

Withdrawals due to AE/IMEs by body system, for the pooled U.S. Phase III studies (Studies 87-1D-6023 and 87-2D-6023) are presented in intext Table 71, page 470.

Inspection of the data revealed only minor differences among treatment groups for any body system. In the metformin and metformin/glyburide treatment groups, 4% and 1% of the patients, respectively, reported withdrawal from the study due to an AE/IME in the Digestive System vs. <1% of the patients in the placebo group and 1% of the patients in the glyburide group. This difference noted for the metformin group is due mostly to reports of diarrhea that led to discontinuation from the study. Even lesser differences between treatment groups were noted for all other body systems.

Table 71.
Withdrawals Due to AE/IMEs by Body System:
U.S. Phase III Studies (Pooled)[1]

Treatment Group	Metformin	Placebo	Glyburide	Met+Glyb
Total Number of Patients	n=351	n=145	n=209	n=213
Patients with any AE/IME	303 (86%)	114 (79%)	171 (82%)	188 (88%)
Patients who Withdrew due to AE/IME	24 (7%)	5 (3%)	3 (1%)	4 (2%)
Body as a Whole	2 (<1%)	1 (<1%)	0	0
Cardiovascular	5 (1%)	0	1 (<1%)	0
Digestive	15 (4%)	1 (<1%)	2 (1%)	3 (1%)
Metabolic & Nutritional Disorders	2 (<1%)	0	0	0
Musculoskeletal	0	2 (1%)	0	0
Respiratory	0	2 (1%)	0	0
Skin & Appendages	2 (<1%)	0	0	1 (<1%)
Urogenital	0	2 (1%)	0	0

[1] Studies 87-1D-6023 and 87-2D-6023

2.8.6.6 Deaths

Deaths discussed here include those deaths that occurred during metformin treatment (either alone or in combination with sulfonylureas) or within 30 days of discontinuation of metformin treatment. However, for the non-U.S. Phase IV studies, all deaths are noted here regardless of temporal relationship to study medications since precise dates for discontinuation of metformin could not be determined.

A total of 14 patients died during the conduct of the eleven studies comprising the NDA data base and involving 9,526 NIDDM patients (two U.S. Phase III, controlled, randomized Category I studies; seven non-U.S., controlled, randomized Category II Studies; and two non-U.S. uncontrolled Phase IV studies).

There was one death in the U.S. Phase III studies (U.S. Study No. 87-2D-6023), from cardiovascular disease, occurring in a patient who had been randomized to metformin. One patient died of cancer in non-U.S. Study No. MET/GB/86/CAMP1, while on glipizide, and one patient died of an apparent myocardial infarction in non-U.S. Study No. MET/S/86/HERMA, while on glibenclamide/metformin. Eleven patients died in non-U.S. Study No. Phase IV study MET/AM/87/PHASE, involving 4374 patients for a study duration of six months.

2.8.6.7 Clinical Laboratory Data

General Considerations: Analyses of routine clinical chemistry and hematology data, related to safety, were undertaken in order to identify general changes in patient populations and to identify individual patients with clinically significant abnormalities for laboratory parameters. Tests are discussed by organ systems, as follows:

- Liver function tests;
- Kidney function tests (including urinalysis);
- Electrolytes;

- Hematology: RBC parameters;
- Hematology: WBC/platelet parameters.

In addition, because of historical information on the known safety profile of metformin and the class of biguanides, special attention was devoted to analysis of:

- Vitamin B_{12} and folic acid;
- Fasting plasma lactate.

For each laboratory parameter, general changes in values for patient populations were sought through analysis of means and change from baseline data and through analyses of shift tables. Mean values at baseline and final visit and change from baseline values for patient populations must be interpreted with caution since many changes in means, while statistically significant, are not clinically significant and represent small shifts within the normal range. Conversely, small changes in means may mask clinically significant changes for a few individual patients. To help identify trends in patient populations that may not have been apparent from an analysis of mean values, shift tables were used to analyze the distribution of patients at baseline and final visit with respect to the normal range for each laboratory safety parameter.

Overall, few meaningful differences among the treatment groups (metformin, placebo, sulfonylurea, and metformin/sulfonylurea combinations) were noted for

liver function tests, kidney function tests, electrolytes, and hematology parameters, and, where noted, differences were usually small. Therefore, neither extensive analyses nor tabular summaries of these laboratory data are provided in this Item. Rather, the number of patients who experienced laboratory abnormalities within the clinically significant range and any clinically significant difference between the treatment groups will be noted using the U.S. Category I Phase III studies (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023), wherein all laboratory analyses were performed by the same central laboratory (SciCor, Inc). Laboratory profiles with regard to plasma lactate levels, vitamin B_{12} and folic Acid are analyzed in more detail because of the special significant these have for metformin's safety profile.

2.8.6.7.1 Liver Function Tests

Individual patients with clinically significant abnormalities in liver function tests were defined as those patients meeting one or more of the following criteria: SGOT >3x ULN (i.e. upper limit of normal, using the SciCor normal ranges); SGPT >3x ULN; total bilirubin >2x ULN; and alkaline phosphatase >2x ULN.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**) only two patients, one in each treatment group (metformin and placebo), had clinically important abnormalities for liver function tests, both involving alkaline phsophatase. The metformin patient (*Patient 2/23*) (who also had renal function

test abnormalities), was thought to have had either hemorrhagic pancreatitis or viral hepatitis and the abnormalities in liver and kidney function parameters, were attributed to this intercurrent illness. The placebo patient (*Patient 12/08)* had an elevated alkaline phosphatase level at baseline and, intermittently, throughout the course of the study.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), there were eight patients in the metformin group, six patients in the glyburide group, and three patients in the metformin/glyburide group, that had clinically important abnormalities for liver function tests, as follows:

In the metformin group, three patients (*Patients 6/25, 11/29, and 22/02*) had increased levels of liver enzymes that were attributed to poor glycemic control. All three patients were terminated from the study. In addition, three patients had clinically abnormal liver function tests that were attributed to concurrent disease (*Patient 7/14*--increased bilirubin attributed Gilbert's disease; *Patient 8/18*--increased SGOT/SGPT levels attributed to viral hepatitis; *Patient 21/21*--increased alkaline phosphatase levels attributed to fatty infiltration of the liver), and one patient (*Patient 17/33*) had increased liver enzyme levels attributed to concomitant medication. Finally, one patient (*Patient 11/21*) had a transient, unexplained rise in total bilirubin that quickly returned to normal.

In the glyburide group, three patients (*Patients 7/19, 10/30, and 11/03*) had increases in liver enzymes (SGOT/SGPT and/or alkaline phosphatase) that were attributed to fatty infiltration of the liver and one patient (*Patient 3/11*) had increases in liver enzymes that were attributed to study medication (glyburide). In addition, two patients had transient increases in either liver enzymes (*Patient 5/21*; attributed to lab error) or total bilirubin (*Patient 11/16*; unexplained) that quickly returned to normal.

In the metformin/glyburide group, all three patients with clinically significant liver function tests had abnormalities attributed to concurrent diseases: one patient (*Patient 5/06*) had increased liver enzyme levels attributed to fatty liver, one patient (*Patient 8/23*) had increased liver enzyme and bilirubin levels attributed to hepatitis (this patient was terminated from the study due to proteinuria), and one patient (*Patient 7/08*) had fluctuating levels of liver enzymes throughout the study that decreased after starting insulin therapy after the end of the study.

2.8.6.7.2 Renal Function Tests

Individual patients with clinically significant abnormalities in kidney function tests were defined as those patients meeting one or more of the following criteria: blood urea nitrogen >48 mg/dL; serum creatinine >2.0 mg/dL; serum uric acid >10 mg/dL; and urine protein ≥2+ at final determination but negative at baseline.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), two patients in the metformin group had clinically important abnormalities for kidney function. *Patient 2/23*, as previously discussed, with moderate elevation of uric acid level and lesser elevations of urea nitrogen and creatinine, was thought to have either hemorrhagic pancreatitis or viral hepatitis. *Patient 4/15* had clinically important elevations in creatinine levels at Visit 6.1 and lesser elevations in creatinine levels at prior visits and urea nitrogen levels at this visit and prior visits. Data from follow-up visits showing a return to normal creatinine levels after discontinuation of study medication.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), there were no patients in the metformin group, no patients in the glyburide group, and four patients in the metformin/glyburide group with clinically important abnormalities for kidney function.

In the metformin/glyburide group, all four patients had increased uric acid levels that were clinically significant and attributed to concomitant medication (*Patient 1/11*, hydrochlorothiazide; *Patient 2/14*, Maxzide), concurrent illness (*Patient 7/29*, thalassemia minor), or both (*Patient 9/28*, gout/hydrochlorothiazide; this patient also had decreased levels of potassium despite supplementation).

2.8.6.7.3 Hematology: RBC Parameters

Individual patients with clinically significant abnormalities in RBC parameters were defined as those patients meeting one or more of the following criteria: hemoglobin <10 g/dL; hematocrit <30%; RBC count <3.0 x $10^6/\mu L$; and mean corpuscular volume (MCV) ≤70 or >105 fL.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), two patients in the metformin group and three patients in the placebo group met one or more of these criteria.

In the metformin group, Patients *12/19* and *17/02* had significantly higher values for MCV on one or more occasions accompanied by values for RBC count that were generally at the lower limit of the normal range. There were no abnormalities of serum vitamin B_{12} or folic acid levels in these two patients, however.

In the placebo group, *Patients 4/01, 12/20, and 13/08* had significantly lower values for MCV on one or more occasions with values for RBC count that were generally at the upper limit of the normal range.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), one patient in the metformin group, three patients in the glyburide group, and four patients in the metformin/glyburide group met one or more of the above criteria.

In the metformin group, *Patient 16/16* had an increased value for MCV at Visit 0 (Baseline) and a significantly increased value at an initial interim visit (Visit 0.1), values of 99 and 107 fL, respectively, but generally normal values for other hematology parameters. The MCV returned to normal at subsequent visits.

In the glyburide group, two patients had significantly low values for hemoglobin and/or hematocrit on one or more occasions with corresponding values for RBC count that were below the lower limit of the normal range; these anemias were attributed to bleeding from uterine fibroids and menorrhagia (*Patient 4/26*) and post-operative hemorrhage (*Patient 8/20*), respectively. In addition, one patient (*Patient 14/02*) had abnormally low values for hematology parameters at visit 8.0 that were attributed to a laboratory error.

In the metformin/glyburide group, two patients had microcytosis that was present at Baseline and throughout the study that was attributed to unknown etiology (*Patient 5/25*) or thalassemia minor (*Patient 7/29* [also had an increased uric acid level]). In addition, one patient (*Patient 15/14*) had macrocytosis of uncertain etiology that was present at Baseline and throughout the study. Another patient (*Patient 4/07*) had an abnormally low MCV value at Visit 11 that was accompanied by subnormal values for hemoglobin, hematocrit, and serum vitamin B_{12} (this patient was subsequently found to have iron deficiency in addition to subnormal vitamin B_{12} and was begun on iron and vitamin B_{12} supplementation.

2.8.6.7.4 Hematology: WBC/Platelet Parameters

Individual patients with clinically significant abnormalities in WBC/platelet parameters were defined as those patients meeting one or more of the following criteria: WBC count $<2.5 \times 10^3$/uL; neutrophils <1000/uL; lymphocytes >75% in differential WBC; and platelets $<100 \times 10^3$/uL.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), two patients (*Patients 6/14 and 9/05*), both in the placebo group, met one or more of these criteria. Both patients had modest leukopenia due to neutropenia. The changes were persistent in both patients without apparent clinical consequences; etiology was not investigated further.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), there were two patients in the metformin group and three patients in the metformin/glyburide group who met one or more of these criteria.

In the metformin group, one patient (*Patient 6/04*) had repeatedly low platelet counts (present, however, at baseline) that resulted in termination at Visit 7 and one patient (*Patient 19/05*) had a single, isolated clinically abnormal value for platelet count that was attributed to lab error.

In the metformin/glyburide group, one patient (*Patient 7/16*) had repeatedly low platelet counts that were attributed to cirrhosis of the liver and splenomegaly. One patient (*Patient 7/21*) had abnormal values for several WBC parameters at final visit (Visit 11) that were normal on repeat testing and were considered to have been a laboratory error. One patient (*Patient 16/20*) had leukopenia of unknown etiology throughout the study.

2.8.6.7.5 Serum Electrolytes

Individual patients with clinically significant abnormalities in serum electrolytes were defined as those patients meeting one or more of the following criteria: sodium <122 mEq/L; potassium <3.0 or >5.7 mEq/L; bicarbonate <16 or >40 mEq/L; chloride <80 mEq/L; anion gap >22 mEq/L; and calcium <7.5 or >12 mg/dL with albumin ≥4 g/dL.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), only one patient met one or more on these criteria. *Patient 4/22*, in the placebo group, had an elevated value for serum potassium at Visit 8. At the same time, this patient had a value for serum bicarbonate that was slightly below normal. The patient was asymptomatic, was not on potassium supplementation, and the value was not considered clinically significant.

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In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), there were six patients in the metformin group, one patient in the glyburide group, and two patients in the metformin/glyburide group that met one or more of these criteria.

In the metformin group, two patients (*Patients 5/15 and 6/35*) had isolated, abnormally low values for serum bicarbonate but with accompanying anion gap values that were in the acceptable range. Two patients had isolated, abnormally low values for calcium that were either unexplained (*Patient 6/01*) or attributed to laboratory error (*Patient 7/02*). One patient (*Patient 9/04*) had a transient, abnormally high value for potassium that was unexplained, and one patient (*Patient 17/25*) had an increased calculated anion gap of unknown etiology.

In the glyburide group, one patient (*Patient 6/20*) had a transient, abnormally low value for serum bicarbonate that was unexplained (the accompanying anion gap was in the acceptable range, however).

In the metformin/glyburide group, one patient (*Patient 9/28*) had an abnormally low value for serum potassium despite potassium chloride supplementation that may have been related to gout or concomitant medication (hydrochlorothiazide). This patient also had clinically significant laboratory abnormalities for uric acid levels. *Patient 16/06* had electrolyte values at a single visit which were considered to be spurious: the patient was clinically well and repeat evaluations were normal.

2.8.6.7.6 Vitamin B_{12} and Folic Acid

Results for serum vitamin B_{12} and folic acid levels fo. U.S. Phase III studies are summarized in intext Tables 72 (means and changes from baseline) and 73 (shift tables), page 483

In **U.S. Study No. 87-1D-6023**, there was a substantial difference between treatment groups for treatment effects on serum vitamin B_{12}. In the metformin group, the mean serum vitamin B_{12} level decreased from 490 pg/mL at baseline to 384 pg/mL at final visit (Normal Range: 200-900 pg/mL), with a mean change from baseline of -105 pg/mL. In contrast, in the placebo group, the mean vitamin B_{12} level increased slightly from 514 pg/mL at baseline to 528 pg/mL at final visit, with a mean change from baseline of +12 pg/mL.

As shown in intext Table 73, page 483, shift analysis supported the interpretation of decreased serum vitamin B_{12} levels in the metformin group: 13 patients (11%) in the metformin group had normal values for vitamin B_{12} at baseline and subnormal values at final visit compared to 0 patients with similar shifts in the placebo group.

For serum folic acid levels, there was only a small difference between treatment groups and only one patient on metformin went from a normal value at baseline to a subnormal value at final visit.

Table 72. U.S. Phase III Studies: Serum Vitamin B_{12} and Folic Acid Levels: Summary of Means and Changes from Baseline

Study No.	Folic Acid (NR: 2.5-17.0 ng/mL)	Vitamin B_{12} (NR: 200-900 pg/mL)
87-1D-6023		
Metformin		
Baseline Mean	8.9	490
FINAL VISIT	-0.9	-105
Placebo	10.6	514
Baseline Mean	+0.2	+12
FINAL VISIT		
87-2D-6023		
Metformin		
Baseline Mean	10.6	554
FINAL VISIT	+0.3	-144
Glyburide	9.7	522
Baseline Mean	+0.6	+13
FINAL VISIT		
	9.8	535
Met+Glyb	-0.2	-138
Baseline Mean		
FINAL VISIT		

Table 73. U.S. Phase III Studies: Serum Vitamin B_{12} and Folic Acid Levels: Summary of Shift Tables

Study No.	Folic Acid Normal and/or High to Low	Vitamin B_{12} Normal and/or High to Low
87-1D-6023		
Metformin	1 (<1%)	13 (11%)
Placebo	0	0
87-2D-6023		
Metformin	0	15 (9%)
Glyburide	2 (1%)	1 (<1%)
Met+Glyb	1 (<1%)	11 (6%)

U.S. Study No. 87-2D-6023 also showed substantial differences between treatment groups for serum vitamin B_{12} levels. Folic acid levels did not reveal such differences (see intext Table 72, page 483).

In the metformin group, the mean serum vitamin B_{12} level decreased from 554 pg/mL at baseline to 411 pg/dL at final visit, with a mean change from baseline of -144 pg/mL. These data are consistent with data for the metformin treatment group in the U.S. placebo-controlled study described above.

In the metformin/glyburide group, there was a similar decrease; the mean serum vitamin B_{12} level went from 535 pg/mL at baseline to 401 pg/mL at final visit, with a mean change from baseline of -138 pg/mL.

In the glyburide group, in contrast, the mean serum vitamin B_{12} level increased slightly from 522 pg/mL at baseline to 541 pg/mL at final visit, with a mean change from baseline of +13 pg/mL.

Thus, there were substantial differences among the treatment groups at final visit for serum vitamin B_{12} even though mean values remained with the normal range. Shift tables (see intext Table 73, page 483) showed that 15 patients (9%) in the metformin group and 11 patients (6%) in the metformin/glyburide group had normal values for serum vitamin B_{12} at baseline and low (i.e. below the normal range) at final visit, compared to only one patient (<1%) with similar shifts in the

glyburide group. These data support the trend toward lower serum vitamin B_{12} levels in patients treated with metformin, either alone or in combination. In this study, there was no effect of any treatment on serum folic acid levels.

While there appears to be an association between metformin and decreases in serum vitamin B_{12} levels, the data from these studies provide no evidence of a relationship of these decreases to plasma metformin levels. The apparent lack of any relationship was confirmed by regression analysis of data for both studies (U.S. Study No. 87-1D-6023, r^2 <0.10; U.S. Study No. 87-2D-6023, r^2 <0.0117).

Patients with Clinically Significant Abnormalities: Individual patients with clinically significant values for serum vitamin B_{12} and folic acid levels were defined as those patients with vitamin B_{12} levels <200 pg/mL and/or folic acid levels <2.0 ng/mL.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), 16 patients in the metformin group and two patients in the placebo group had clinically significant abnormalities for serum vitamin B_{12} or folic acid.

In the metformin group, 14 patients had serum vitamin B_{12} levels <200 pg/mL at one or more study visits (*Patients 1/14, 2/18, 2/22, 3/12, 5/02, 9/01, 9/08, 9/21, 10/27, 11/14, 12/15, 12/17, 12/21, 13/09*). Of these 14 patients, one patient had an abnormally low baseline value and three others had values which could be

considered "borderline" at baseline. No patients were anemic and only one patient (*Patient 9/21*) had a slightly increased MCV (101 fL).

In the placebo group, one patient (*Patient 5/11*) had an abnormally low serum vitamin B_{12} value at interim Visit 0.1 and Visit 9 (no baseline values available). *Patient 7/07* had an abnormally low serum vitamin B_{12} value at baseline, which was confirmed on repeat testing and the patient was started on parenteral vitamin B_{12} following a Schilling test.

In the metformin group, two patients (*Patients 6/01 and 10/28*) had abnormally low serum folic acid levels. Patient 10/28 also had an abnormally low value at baseline. There were no patients in the placebo group with abnormally low serum folic acid levels.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), 16 patients in the metformin group, three patients in the glyburide group, and 17 patients in the metformin/glyburide group had clinically significant abnormalities for serum vitamin B_{12} or folic acid levels.

In the metformin group, 16 patients (*Patients 1/32, 7/22, 10/10, 11/21, 11/26, 12/09, 12/34, 14/26, 15/13, 15/20, 15/29, 17/14, 17/21, 18/06, 18/26, and 21/07*) had serum vitamin B_{12} levels <200 pg/mL at final visit. Of these 16 patients, six patients had baseline levels of vitamin B_{12} that were "borderline" low and two patients (*Patients 10/10 and 15/13*) were diagnosed as having pernicious anemia.

In the glyburide group, two patients (*Patients 16/08 and 17/24*) had serum vitamin B_{12} levels <200 pg/mL at final visit. One patient (*Patient 16/08*) had a significantly low Vitamin B_{12} level at baseline (114 pg/mL) and the other with a "borderline" low level at baseline.

In the metformin/glyburide group, 16 patients (*Patients 1/17, 2/11, 4/07, 4/21, 8/11, 9/08, 9/13, 9/21, 11/19, 11/24, 13/20, 15/14, 15/25, 16/10, 20/11, and 21/24*) had serum vitamin B_{12} levels <200 pg/mL at final visit. Of these 16 patients, five patients had a significantly low vitamin B_{12} level at baseline and seven patients had baseline levels of vitamin B_{12} that could be considered "borderline" low. In addition, Patient 4/07 was noted to have a concomitant microcytic anemia Patient 15/14 had increased MCV values (macrocytosis) throughout the study, including baseline.

Serum Folic Acid: There were 0 patients in the metformin group, one patient (*Patient 14/21*) in the glyburide group, and one patient (*Patient 18/11*) in the metformin/glyburide group with serum levels of folic acid below 2.0 ng/mL. In neither case was the low serum folic acid level associated with low levels of serum vitamin B_{12} or any other clinically abnormal hematological finding.

2.8.6.7.7 Fasting Plasma Lactate

U.S. Studies: Results for fasting plasma lactate levels for U.S. Phase III studies are summarized in intext Tables 74 (means and changes from baseline) and 75 (shift tables), page 492.

In **U.S. Study No. 87-1D-6023**, a comparison of mean values and change from baseline values for fasting plasma lactate of the metformin and placebo groups revealed no clinically significant differences between the treatment groups at final visit. In fact, mean fasting plasma lactate levels for the two groups remained essentially unchanged throughout the study: mean levels at baseline were 1.41 mmol/L and 1.40 mmol/L for the metformin and placebo groups (Normal Range: 0.3-2.0 mmol/L), respectively, with mean change from baseline values at final visit of +0.04 mmol/L (metformin) and 0.00 mmol/L (placebo).

Shift tables supported the similarity of outcome for this parameter in the two treatment groups: 12 patients (9%) in the metformin group and 13 patients (9%) in the placebo group shifted from normal plasma levels of lactate at baseline to high values at final visit; and 12 patients (9%) in the metformin group and 12 patients (8%) in the placebo group shifted from high levels at baseline to normal levels at final visit.

In this study, there were no patients with fasting plasma lactate levels ≥4 mmol/L. Furthermore, a plot of the maximum metformin plasma level vs. the corresponding lactate level showed no evidence of a relationship.

In **U.S. Study No. 87-2D-6023**, mean values and change from baseline values for fasting plasma lactate also revealed no clinically significant differences among the treatment groups at final visit. However, the metformin and metformin/glyburide treatment groups did show slight mean increases at final visit, in contrast to the slight mean decrease shown by the glyburide group.

For the metformin group, mean fasting plasma lactate level increased slightly from 1.47 mmol/L at baseline to 1.54 mmol/L at final visit, with a mean change from baseline of +0.08 mmol/L.

For the metformin/glyburide group, the mean fasting plasma lactate level increased similarly from 1.45 mmol/L at baseline to 1.51 mmol/L at final visit, with a mean change from baseline of +0.06 mmol/L.

For the glyburide group, on the other hand, the mean fasting plasma lactate level decreased slightly from 1.45 mmol/L to 1.42 mmol/L at final visit, with a mean change from baseline of -0.01 mmol/L.

Shift tables showed that 21 patients (10%) in the metformin group and 22 patients (10%) in the metformin/glyburide group had normal (or low) values at baseline and high values at final visit, compared to 11 patients (5%) with similar shifts in the glyburide group.

Patients with Clinically Significant Abnormalities: Fasting plasma lactate levels ≥4.0 mmol/L were defined as clinically significant.

In the U.S. placebo-controlled study (**U.S. Study No. 87-1D-6023**), there were three patients meeting this criterion at one or more visits: one patient in the metformin group and two patients in the placebo group. In the **metformin group**, *Patient 12/09* had moderately elevated plasma lactate levels at a number of study visits and a level of 4.0 mmol/L at Visit 5. Levels of other electrolytes were within normal limits throughout the study. In the **placebo group**, *Patient 1/19* had a plasma lactate level of 5.3 mmol/L at Visit 5 (possibly due to a difficult venipuncture) and *Patient 5/12* had a plasma lactate level of 4.6 at Visit 7. For both patients, levels of other electrolytes were generally within normal limits throughout the study.

In the U.S. active treatment comparison study (**U.S. Study No. 87-2D-6023**), there were four patients in the metformin group, four patients in the glyburide group, and four patients in the metformin/glyburide group meeting the criterion for clinically significant abnormalities in fasting plasma lactate at one or more visits.

ITEM 2 — NDA SUMMARY

In the **metformin group**, four patients (*Patients 6/35, 12/34, 18/03, and 19/17*) had higher than normal plasma lactate levels at a number of study visits and transient, abnormally high lactate levels (≥4 mmol/L) at one or two visits. In the **glyburide group**, three patients (*Patients 7/05, 10/26, and 15/19*) had transient levels of fasting plasma lactate that exceeded 4 mmol/L. In addition to these three patients, one patient (*Patient 4/33*) had repeatedly high lactate levels without any known etiology. In the **metformin/glyburide group**, three patients (*Patient 2/02, 8/09, and 12/14*) had higher than normal plasma lactate levels at a number of study visits and transient, abnormally high lactate levels (≥4 mmol/L) at one or more visits; all three patients were well, however.

There were no instances of lactic acidosis in either study.

Table 74.
Fasting Plasma Lactate: Summary of Means
and Changes From Baseline
(All Studies with Available Data)

Study No.	Lactate (NR: 0-2 mmol/L)
87-1D-6023	
Metformin	
Baseline Mean	1.41
FINAL VISIT	+0.04
Placebo	
Baseline Mean	1.40
FINAL VISIT	0.00
87-2D-6023	
Metformin	
Baseline Mean	1.47
FINAL VISIT	+0.08
Glyburide	
Baseline Mean	1.45
FINAL VISIT	-0.01
Met+Glyb	
Baseline Mean	1.45
FINAL VISIT	+0.06

Table 75.
Fasting Plasma Lactate:
Summary of Shift Tables
(All Studies with Available Data)

	Fasting Plasma Lactate Shifts	
Study No.	Normal and/or Low to High	High to Normal
87-1D-6023		
Metformin	12 (9%)	12 (9%)
Placebo	13 (9%)	12 (8%)
87-2D-6023		
Metformin	21 (10%)	8 (4%)
Glyburide	11 (5%)	12 (6%)
Met+Glyb	22 (10%)	15 (7%)

2.8.6.8 Summary of Other Safety Assessments

2.8.6.8.1 Vital Signs

In analyzing the pooled U.S. Phase III studies, generally, very few patients had clinically important abnormalities of vital signs at either baseline or final visit. Treatment group differences were minimal.

Individual patients with clinically significant abnormalities for vital signs were defined as those patients meeting one or more of the following criteria: systolic blood pressure ≤100 mm Hg, pulse rate ≤55 or >100 bpm, and body temperature >100° F.

In the U.S. placebo-controlled study (U.S. Study No. 87-1D-6023) there were 28 patients in the metformin treatment group and 29 patients in the placebo group with clinically important abnormal values for vital signs. Generally, these abnormalities were transient. However, there were several patients with consistently (four or more measurements) low systolic blood pressure. Of these, three patients (*Patients 4/17, 10/2, 10/28*) were in the metformin group and eight patients (*Patients 2/20, 4/23, 5/13, 7/4, 8/3, 10/7, 10/12, and 12/16*) were in the placebo group. In addition, there was one patient (*Patient 5/13*) in the placebo group with multiple (three or more) pulse rate measurements of ≤55 bpm.

In the U.S. active treatment comparison study (U.S. Study No. 87-2D-6023), there were 40 patients in the metformin treatment group, 23 patients in the glyburide group, and 40 patients in the metformin/glyburide group with clinically important abnormal values for vital signs. As observed in the U.S. placebo-controlled study (U.S. Study No. 87-1D-6023), these abnormalities were generally transient.

However, consonant with the placebo-controlled study, there were several patients with consistently (four or more measurements) low systolic blood pressure. Of these, one patient (*Patient 4/8*) was in the metformin treatment group, 0 patients were in the glyburide group, and three patients (*Patients 3/17, 10/5, and 14/23*) were in the metformin/glyburide group.

There were also several patients with multiple (three or more) abnormal pulse rate measurements. Of the patients with three or more pulse rate measurement of >100 bpm, two patients (*Patients 6/25 and 9/27*) were in the metformin treatment group and one patient (*Patient 16/30*) was in the glyburide group. Of the patients with three or more pulse rate measurement ≤55 bpm, two patients (*Patients 3/19 and 11/22*) were in the glyburide group and one (*Patient 3/2*) was in the metformin/glyburide group.

2.8.6.8.2 Electrocardiogram (ECG)

A summary of pooled U.S. Phase III ECG data are presented in intext Table 76, page 496.

In **U.S. Study No. 87-1D-6023**, 85% of the patients in the metformin treatment group versus 93% of the patients in the placebo group, had no significant ECG changes from baseline. There were 19 patients (15%) and 9 patients (7%) in the metformin and placebo group, respectively, who had significant ECG changes from baseline.

In **U.S. Study No. 87-2D-6023**, 92% of the patients in the metformin treatment group, versus 93% of the patients in the glyburide group, versus 88% of the patients who received metformin + glyburide, had no significant ECG changes from baseline. There were 14 patients (8%), 13 patients (7%), and 24 patients (12%) in the metformin, glyburide, and metformin + glyburide group, respectively, who had significant ECG changes from baseline. These results were consistent with ECG results found for patients in U.S. Study 87-1D-6023. Moreover, both individual U.S. Phase III study results compared well to the overall ECG results found for the U.S. Pooled Phase III data analysis.

Table 76.

Summary of Electrocardiogram Results

U.S. Phase III Studies (Pooled)

		Significant Change From Baseline	
Study No.	Treatment	Yes	No
87-1D-6023	Metformin	19 (15%)	110 (85%)
	Placebo	9 (7%)	117 (93%)
87-2D-6023	Metformin	14 (8%)	169 (92%)
	Glyburide	13 (7%)	175 (93%)
	Metformin + Glyburide	24 (12%)	180 (88%)
Pooled	Metformin (Monotherapy)	33 (11%)	279 (89%)

2.8.6.9 Overdosage

The consequence of significant overdosage with metformin is overproduction of lactate, with a risk of lactic acidosis, particularly if there is co-existent acute or chronic renal or hepatic damage (e.g., simultaneous ingestion of a nephrotoxin or acute alcohol intoxication).

In contrast to potential overdosages with either oral sulfonylureas or insulin, when metformin has been consumed in excess (without simultaneous ingestion of other glucose-lowering agents), plasma glucose levels do not decrease to hypoglycemic levels, either in diabetics or non-diabetics even with plasma metformin levels as much as 80 or more times the usual therapeutic range.

Cases of intentional overdosage with metformin, reported to Lipha S.A. through post-marketing surveillance, are summarized in tabular form in Section 8.9.2.1.1. There were 14 cases occurring in France since May, 1984 and one case reported from Germany, occurring in 1980. (See Section 8.8.16, for narrative summaries of these cases).

The amount of metformin ingested varied from an unknown quantity (or even questionable ingestion of metformin) to a maximum of 76.5 g, as a single dose. Ten of the 13 patients (for whom the information was available) had taken other drugs, in addition to metformin.

Outcome information was available on all fifteen patients. Twelve of the 15 recovered without sequelae and the other three patients died, all with severe acidosis at presentation (one of whom did not have detectable levels of metformin in plasma).

For one patient, no information is available, except that he "recovered". Of the remaining 14 patients, six patients were asymptomatic at the time they were assessed and all these patients had an uneventful recovery. None of these patients had evidence of lactic acidosis. Of these six, five among five for whom plasma metformin levels were available, had levels which were within the expected therapeutic range for metformin and not consistent with metformin accumulation (i.e., <5 mg/L).

Three patients presented with mild to moderate gastrointestinal or CNS symptoms. All three had significantly elevated plasma metformin levels (67.7, 63.3 and 40 mg/L, respectively). All three had arterial pH levels of 7.36 and were considered to have mild to moderate lactic acidosis, with lactate levels, respectively, of 5.8, 4.2 and 31.3 mmol/L. All three patients recovered completely, with a therapeutic approach consisting of correction of electrolyte problems, gastric lavage, induced vomiting, etc.

Four patients presented in a comatose state, two most likely on the basis of hypoglycemia. (***NOTE:*** *Both of these patients had also taken the sulfonylurea,*

glibenclamide, in excess). One patient, with a plasma glucose level of 25 mg/dL, had no detectable metformin in the plasma and had no evidence of lactic acidosis. The other patient had a very elevated plasma metformin level of 35.1 mg/L but only slight plasma lactate increase (5.7 mmol/L) and no available pH determination. Plasma glucose level was 34 mg/dL. Both of these patients recovered, the latter patient having hemodialysis, in addition to correction of glucose abnormality and anti-benzodiazepine treatment.

The two other comatose patients were most likely comatose from causes other than hypoglycemia. Both were severely acidotic (arterial pH of 6.75 and 6.8, respectively) and both had a fatal outcome.

Of the 11 patients for whom this information was available, eight were diabetics and three were non-diabetics. Among these three non-diabetics, plasma glucose levels were normal in all. For two of the three, plasma metformin levels were also available: Case #612, with a markedly elevated plasma metformin level (63.3 mg/L), had a plasma glucose level of 114 mg/dL; Case #1191, had a plasma metformin level within the therapeutic range (1.99 mg/L) and had a "normal" plasma glucose level, as measured by a qualitative method.

Among the eight known diabetic patients, plasma glucose levels were available in five, with two patients having glucose levels in the hypoglycemic range (the two cases mentioned above). Both had also ingested excessive quantities of the

sulfonylurea glibenclamide. Case #614, with a plasma glucose of 25 mg/dL, as previously noted, had no detectable metformin in plasma and Case #743, with a plasma glucose level of 34 mg/dL, had a very elevated plasma metformin level (35.1 mg/L), but admitted to ingesting 450 mg of glibenclamide (in addition to 76.5 g of metformin).

Since metformin is not protein-bound and is dialyzable, therapy of confirmed overdosage with metabolic manifestations should include hemodialysis. Larcan et al, in 1981, reviewed their experience from 1976-1980 in the treatment of 31 cases of lactic acidosis of diverse etiology with hemodialysis, using a polyacrylonitrile membrane. Two of these cases were due to voluntary metformin overdose. Both patients overdosing on metformin had extremely elevated plasma metformin levels (85 and 65 mg/L). Both patients presented with acidosis, with arterial pH of 7.24 and 7.21 and plasma lactate levels of 12.2 and 12 mmol/L. Both patients recovered without sequelae. The first patient, with normal renal function, who had taken 15 g of metformin as a single dose, along with phenobarbital and belladonna, was successfully treated with intermittent hemodialysis over a 24 hour period, using a bicarbonate bath. The second patient, a 56 year old female diabetic with chronic renal disease and a history of psychiatric problems, had to be intermittently hemodialyzed over 68 hours prior to satisfactory recovery.

ITEM 2 — NDA SUMMARY

The authors pointed out that treatment of lactic acidosis, of any cause, with dialysis is the best approach, since correction of fluid, electrolyte and acid-base problems can take place without the same risk of fluid overload as may occur with attempts at alkalinization by administration of corrective intravenous solutions. This is particularly important in this gravely ill population, since renal function is often compromised. Furthermore, dialysis permits the removal of acidic ions, including lactate (small-sized molecules, which are readily dialyzable) and, in the case of lactic acidosis associated with toxic accumulation of a product such as metformin, simultaneously permits the removal of the product.

They also pointed out, however, that not all forms of dialysis are equivalent. For example, peritoneal dialysis does not permit a clearance rate sufficiently high to keep pace with the production rate of lactate or other acidic molecules and, in cases of lactic acidosis secondary to drug ingestion, may not remove the etiologic agent (e.g., metformin, in the present discussion) with sufficient rapidity. They recommended hemodialysis with a polyacrylonitrile membrane (membrane with high permeability for small and medium-sized molecules) for lactic acidosis occurring in diabetics treated with metformin, whenever possible product accumulation is suspected.

ITEM 2 — NDA SUMMARY

The following conclusions can be drawn regarding metformin overdosage:

- The only severe potential consequence of metformin overdosage is lactic acidosis.

- Metformin, water-soluble and of low molecular weight, is readily dialyzable. Clearance of metformin via dialysis is relatively dependent on hemodynamic status but may be as high as 170 ml/min. Metformin can be measured in body fluids and dialysate, with a highly specific and sensitive HPLC method. Metformin accumulation is confirmed by plasma metformin levels >5 mg/L (usual therapeutic levels in plasma are <2 mg/L, with lower levels in red blood cells).

- In suspected metformin overdosage, monitoring of plasma (and erythrocyte) metformin levels is recommended. Metformin may also be measured in dialysate.

- In suspected metformin overdosage, asymptomatic patients with normal or near-normal arterial pH and lactic acid levels are very likely to recover with only conventional techniques of overdosage treatment (e.g., gavage, induced vomiting, fluid replacement, etc., as indicated).

- In suspected metformin overdosage, patients presenting with mild acidosis (arterial pH >7.2) and minimal symptoms, but with evidence of excessive metformin in plasma (>5 mg/L), are likely to recover, but hemodialysis should be considered.

- In suspected metformin overdosage, patients presenting with coma and/or severe acidosis (arterial pH <7) and lactate accumulation, have a more guarded prognosis, particularly if there is evidence of hepatic injury, and hemodialysis should be promptly instituted. Under such circumstances, coma due to hypoglycemia should be excluded (due to concomitant ingestion or use of other glucose-lowering agents such as sulfonylureas), although metformin alone, even in markedly excessive quantities, does not cause hypoglycemia, either in non-diabetics or diabetics.

- Currently, hemodialysis is recommended for treatment of confirmed metformin overdosage (or when a high level of suspicion of such overdosage exists), since this technique permits treatment of lactic acidosis (removes lactate and other acidic ions), removal of excess metformin and allows correction of fluid and electrolyte imbalance. Hemodialysis should be continued until clinical and hemodynamic stability is achieved and, ideally, until metformin levels in red blood cells are in the usual therapeutic range (<2 mg/L). Premature termination of hemodialysis may result in relapse.

2.8.6.10 Drug Abuse Potential

Glucophage® (brand of metformin hydrochloride) possesses no pharmacodynamic properties, either primary or secondary, which could be construed as conferring on it the potential for abuse as a recreational drug. Metformin has displayed no addictive liability or habit-forming activity in over thirty years of worldwide marketing experience. Consequently, no prospective studies were undertaken to further explore this property and the drug is not being proposed for scheduling as a controlled substance.

2.8.6.11 Relevant Safety Issues

2.8.6.11.1 Lactic Acidosis

Lactic acidosis is appreciated as a safety issue for metformin.

Metformin is distributed to the main tissues involved in lactate metabolism, especially the intestine, kidney and liver. Therapeutic dosages of metformin may cause a small rise in blood lactate concentrations. This is mainly evident postprandially and the rise in blood lactate is usually <2 mmol. Thus, blood lactate concentrations generally remain within the normal physiological range.

Recent clinical and animal studies suggest that the small rise in blood lactate during metformin therapy is due to a net increase in lactate production from the splanchnic bed. Therapeutically relevant concentrations of metformin do not increase lactate production by various non-splanchnic tissues, including muscle, fat, skin and brain. Animal studies have provided evidence, however, that metformin promotes net production of lactate by the intestine in both the basal (interprandial) and postprandial states. Under normal physiological conditions in the basal state, the liver is a net extractor of lactate. This limits the amount of extra-intestinally derived lactate that gains access to the systemic circulation, and restricts excursions of venous blood lactate concentrations. When the liver is confronted with raised lactate and glucose concentrations in the postprandial

state, the liver is not able to sustain net lactate extraction. This accounts for the postprandial nature of the rise in blood lactate. *In vitro* studies with animal tissues have indicated that metformin concentrations in the upper therapeutic range and above may cause some increase in hepatic lactate production, but serious increases in hepatic lactate production only occur at inordinately raised metformin concentrations (as might be present with overdosage or metformin accumulation with renal failure) and in the presence of other complicating factors such as hypoxia or alcohol.

Lactic acidosis is a metabolic acidosis characterized by raised arterial blood lactate (e.g., >5 mM), reduced arterial pH (e.g., ≤pH 7.25), and an increased anion gap (e.g., $[Na^+] - [Cl^- + HCO_3^-]$ >15 mEq/L). Presenting clinical symptoms are usually nonspecific, but typically include hyperventilation, malaise and abdominal discomfort. There can be many different causes of lactic acidosis. Most commonly (type A lactic acidosis), there is severe tissue hypoxia due to cardiac or respiratory failure, septicemia or shock. Much less frequently (type B lactic acidosis), tissue hypoxia is not implicated, and the cause may be liver disease, renal tubular malfunction, malignancy, diabetic ketoacidosis, alcohol-induced acidosis or exposure to chemical toxins or a drug overdose. The occurrence of type B lactic acidosis among the non-diabetic population, and among patients with NIDDM not exposed to biguanides is described as rare, but a reliable quantification is not available. Both type A and type B lactic acidosis carry a high risk of mortality.

ITEM 2 — NDA SUMMARY

Metformin-associated lactic acidosis (MALA) belongs to the type B category of lactic acidosis.

Type B lactic acidosis in general, and MALA in particular, are rare. The estimated overall incidence of MALA is in the region of 0.03 cases per 1000 patient-years of metformin treatment. Mortality risk is about 50%, giving an overall mortality rate of about 0.015 cases per 1000 patient-years.

The incidence and mortality risk of MALA are at least an order of magnitude lower (10- to 20-fold lower) than for phenformin-associated lactic acidosis (PALA). The incidence and mortality risk of PALA were, respectively, estimated to be in the range of 0.25 to 4 cases per 1000 patient-years (incidence) and 0.125 to 2 fatalities per 1000 patient-years (mortality), compared with the previously noted estimates of 0.03 cases per 1000 patient-years (incidence) and 0.015 fatalities per 1000 patient-years (mortality) for MALA.

The ability to predict patients at particular risk of MALA is much greater than for PALA. Metformin is more rapidly and more predictably eliminated than phenformin. Metformin is not metabolized, whereas there is genetic variability in the capacity to metabolize phenformin. Other important differences between metformin and phenformin are now established which emphasize, at both a structural and functional level, that the two drugs must not be confused.

These include the following key differences:

- **different structural organization** (*protonation site, cyclical formation and planar configuration; phenformin has greater hydrophobicity and greater liphophilicity*);
- **differences of membrane binding** (*positioning within membrane; greater binding affinity for phenformin*);
- **different potency of effects on mitochondria** (*electron chain conductance, ATP production, redox state disturbed by phenformin*);
- **different concentration in muscle** (*relatively higher for phenformin*);
- **different fate of glucose metabolism in muscle** (*greater propensity for lactate production with phenformin*);
- **different metabolism** (*phenformin metabolism with variable efficiency, metformin not metabolized*);
- **different protein binding** (*phenformin circulates partly protein bound*);
- **different elimination characteristics** (*less rapid and less predictable with phenformin*);
- **different incidence of lactic acidosis** (*10- to 20-fold higher with phenformin*).

It is worthwhile considering some of the more recent information on MALA. Based on the careful review contained within this NDA, it appears that the total number of *known* cases worldwide of MALA during the twenty year period 1972 through 1992, although varying somewhat by source and author, is approximately 150-200 cases. Total worldwide incidence is not known.

The period following 1977 is more useful in assessing incidence, owing to growing recognition of MALA following withdrawal of phenformin from the market; the availability of a new blood test for measurement of lactate levels; and more widespread measurement of blood metformin levels.

In various countries, at varying time periods, the incidence of MALA has varied from zero to 0.084 per 1000 patient-years (see intext Table 77, page 511).

The most recent and largest set of data are from France, where metformin is most widely used and reporting of toxic effects of drugs is mandatory. These data comprise almost 2.5 million patient-years of treatment and 73 cases of MALA. The incidence of MALA in this group was 0.03 per 1000 patient-years (France, 1984-1992), within the range of other countries. The mortality rate in France during the 1984-1992 period averaged 0.013 per 1000 patient-years (33 of the 73 cases or 45%). An overall mortality rate from all sources worldwide is approximately 50%, with variations in different countries and at different time periods ranging from zero to 63%.

It is important to note that metformin concentrations have not been measured in many diagnoses of MALA, and clinical information is often insufficient to assess other potential causes. Thus, the figures provided in intext Table 77 include reported cases of lactic acidosis in patients receiving or purporting to receive metformin, irrespective of whether the diagnosis could be substantiated. The figures cited herein for MALA, allowing for under-reporting and other uncertainties, contrast strikingly with the incidence of phenformin-associated lactic acidosis (PALA). The incidence of PALA estimated by the FDA in 1977, varied from 0.25 to 4.0 cases per 1000 patient-years. Thus, the reported incidence of PALA was considerably much greater than for MALA. With a mortality for PALA of approximately 50% (the same as with MALA), the incidence of death for PALA ranged from 0.125 to 2.0 per 1000 patient-years. It does not seem possible to be more precise than this. There is no reason to believe that reporting was either more or less accurate with phenformin as compared to metformin. The comparative safety of metformin compared with phenformin is clearly distinguishable and is considered in detail within Section 8.8.13.1.7 of this NDA. ***(NOTE:*** *Section 8.8.13.1 considers the topic of Lactic Acidosis in great detail, including in-depth comparison of metformin and phenformin).*

Table 77. Reported Incidence and Mortality Risk of Metformin-associated Lactic Acidosis (MALA)*

Country	Years	Approximate numbers of patient-years of treatment	Total Cases (nonfatal/fatal)	Incidence of Cases per 1000 patient-years	Mortality Rate (fatal cases per 1000 patient-years)
U.K.	1976-1986	400,000	11(4/7)	0.027	0.017
Switzerland	1972-1977	29,800	2(2/0)	0.067	-----
Sweden	1972-1981	83,500	7(5/2)	0.084	0.024
	1987-1991	100,100	3 (1/2)	0.03	0.02
Canada	1972-1982	56,000	0	0	0
France	1984-1992	2,476,061	73(40/33)	0.03	0.013

* Data in this table derive from the following sources: Campbell 1985 [260], Wiholm and Myrhed [289], Bailey and Nattrass 1989 [305], Berger 1985 [306], Cohen 1979 [311], Lucis 1983 [312], Campbell 1984 [313], and The French National Drug Adverse Effect Surveillance Commission, 1985-1991 (Reference numbers for Item 8).

With growing usage of metformin in most countries since the 1970s and with increased awareness of the lactic acidosis issue, the trends in incidence and mortality are important to assess. In France, the incidence has been remarkably constant, at approximately 0.03 cases/1,000 patient-years, for each year from mid-1984 through 1992 (French National Adverse Effect Surveillance Commission, 1984-1992). The mortality rate for this same eight and one-half year period was

somewhat more variable (see below), ranging from 0.005 to 0.02 cases per 1,000 patient-years, but, as can be seen below, no upward trends in either incidence or mortality in France are apparent:

Reporting Period	Total Cases of MALA/*Fatal Cases* per 1,000 Patient-Years
May 24, 1984 through June 30, 1985	0.04/*0.02*
July 1, 1985 through June 30, 1986	0.03/*0.008*
July 1, 1986 through June 30, 1987	0.025/*0.017*
July 1, 1987 through June 30, 1988	0.038/*0.011*
July 1, 1988 through Dec. 31, 1989	0.032/*0.014*
Jan. 1, 1990 through Dec. 31, 1990	0.032/*0.019*
Jan. 1, 1991 through Dec. 31, 1991	0.030/*0.015*
Jan. 1, 1992 through Dec. 31, 1992	0.017/*0.005*

In the 1993 publication of Wiholm and Myrhed (Division of Drug Epidemiology, Information and Inspection, Medical Products Agency, Uppsala, Sweden and Karolinska Institute), it is noted that the reported incidence of acidosis and lactic acidosis occurring in patients taking metformin is decreasing in Sweden, declining from 0.15/1,000 patient-years during the period 1972-1981 to 0.024/1,000 patient-years during 1987-1991. This decline has been attributed (at least in part) to the use of lower average daily dosages of metformin and to restrictions on its use in the very elderly.

Thus, in those countries where reliable data on drug exposure and post-marketing surveillance are available, the frequency of known cases of lactic acidosis has not increased over time and with usage, but has either remained constant or declined.

It is noted here again that there were no cases of MALA during the conduct of studies reported on in this NDA, including the U.S. Phase III and related U.S. studies (clinical pharmacology and pharmacokinetic), or the non-U.S. studies (both Categories II and III and including two large Phase IV studies).

Considering further the pathophysiology of MALA, it should be noted that virtually all cases of lactic acidosis, of any etiology, appear to involve a combination of increased production and decreased utilization of lactate. As discussed above, in individuals with normal hepatic and renal function, the hyperlactatemic effect of metformin is modest. In the absence of other functional or pathological disorders, the elevations of blood lactate appear to be insufficient to cause lactic acidosis. Some additional condition, disturbance or disorder is apparently necessary to induce acidosis, either by increasing metformin blood and tissue levels, by an augmentation of the hyperlactatemic effect of the drug, by further alterations in cellular redox state, by inability of the liver to adequately extract lactate or by increased hepatic (or other tissue) lactate production. In fact, some of these conditions are capable of causing lactic acidosis by their direct effects on cellular metabolism in patients not receiving metformin.

Almost all known cases of MALA have been accompanied by concomitant acute or chronic illness, multiple medications which may impact upon renal hemodynamics or metformin disposition, or other conditions in which the drug is clearly contraindicated. From analysis of published or reported cases, the most commonly overlooked or disregarded contraindication is renal dysfunction, acute or chronic.

Based on review of the literature as well as cases of MALA reported during post-marketing surveillance, the most frequently encountered disorders which may predispose or contribute to MALA, either as preexisting conditions or which appear during treatment, are as follows:

1. ***Renal failure***, due to acute or chronic renal disease or renal functional impairment resulting from a variety of causes, including circulatory failure, the administration of intravascular radiocontrast media while metformin treatment continues, nephrotoxic drugs concomitantly administered with metformin, and dehydration resulting from vigorous diuresis, inadequate fluid intake and vomiting and/or diarrhea associated with acute illnesses or other conditions.

2. ***Impaired liver function***, acute or chronic.

3. ***Hypoxia***, acute or chronic, of any cause, including serious

cardiovascular disease, cardiopulmonary insufficiency, myocardial or peripheral infarction, shock, severe infections, septicemia, other complications of diabetes and severe trauma.

4. ***Alcoholism***, acute or chronic.

Multiple disorders, including those listed above, are characteristic of diabetic populations, and appear in various combinations. Although this multiplicity might result in more profound effects on lactate metabolism, any one of these conditions may suffice to elicit or contribute to lactic acidosis in patients receiving metformin. Whether these disorders are considered as causal, contributory or predisposing to the development of MALA, they may convert an innocuous hyperlactatemic state into a critical one.

In addition to a thorough review of 95 published cases of MALA (which have been carefully scrutinized to identify cases which have been published in more than one report), Item 8 provides detailed information on the 73 cases of MALA reported to the French National Adverse Effect Surveillance Commission from 1984 through 1992, as noted above.

From an analysis of these 73 cases from France, the following general statements can be made: The average age was 66 years (range: 42 to 87 years), with almost 40% of cases occurring in patients >70 years of age. Forty patients were female

and 33 were male. On average, patients were taking 3.5 concomitant medications (range: 0 to 11). Seven cases followed an intravascular radiocontrast study (preceding which, metformin had not been discontinued). All patients had associated acute or chronic illnesses. Fifty-five patients (75%) had acute or chronic renal insufficiency at presentation, among which 11 had both hepatic and renal problems. Seven additional patients had acute or chronic hepatic decompensation, without apparent renal problems. Thirty-one patients (42%) had chronic cardiovascular disease, frequently in association with acute or chronic renal dysfunction. Four patients had chronic pulmonary disease or acute respiratory insufficiency.

Thirty-three of the 73 cases (45%) had a fatal outcome (although two of these patients had recovered from the lactic acidosis and died of other intercurrent illness). The average age of those patients who died was 70 years. Six of the deaths were assessed as being unrelated to the adverse event. Fifty-three of 73 patients (68%) had measurements of plasma metformin levels (metformin levels in erythrocytes were also measured on occasion). Thirty-four of the 53 (64%) patients had metformin levels ≥5 μg/mL(i.e., abnormally elevated) and 28 of the 53 (53%) had metformin levels ≥10 μg/mL. Nineteen of the 53 patients (36%) in whom measurements of plasma metformin levels were made had either non-detectable plasma levels or levels that were within the expected therapeutic range.

It can be further said, upon review of the published literature and the reported cases of MALA from post-marketing surveillance, that in probably every instance, a fundamental error in clinical judgement was made: that is to say, metformin was administered in conditions/circumstances known to be contraindicated to its use. The fact that these reports contain instances in which patients with acute renal failure and anuria or patients on peritoneal dialysis or awaiting renal transplant continued to receive metformin illustrates how profound the errors can be.

The same conclusions have been drawn by Hermann and Melander, Bailey, Luft et al and Campbell, based on their respective reviews of the literature (*see Item 8 reference numbers 20,190,258,260*).

Furthermore, criteria for the diagnosis of MALA have not been consistently applied, and clinical information is often incomplete, in many instances lacking measurement of plasma metformin concentrations. Moreover, as noted above, the background incidence of lactic acidosis in diabetes mellitus is not accurately established, and diabetics are at greater risk for lactic acidosis of other etiologies (type A lactic acidosis), such as cardiovascular collapse and septicemia. Thus, it is likely that a proportion of cases of lactic acidosis attributed to metformin result, in fact, from other causes.

In this regard, of particular interest is the observation that in studies in which sufficient data are available, a proportion (up to 30%) of patients with MALA had

metformin plasma concentrations within the therapeutic range (<5 μg/mL) or which were undetectable. The consistency with which at least some patients with these characteristics are found in a variety of reviews indicates that attribution cannot be made to faulty clinical judgement, improper techniques or laboratory errors.

Several explanations have been offered: failure of compliance by patients to therapeutic directions; a prolonged interval between the last dose of metformin and blood sampling; failure to exclude ketoacidosis and erroneous diagnosis of lactic acidosis. To this must be added, erroneous diagnosis of MALA.

To clarify this situation, Lambert et al conducted a prospective study of 20 metformin-treated diabetic patients with hyperlactatemia and a serious acute condition (coma, shock, respiratory distress, anuria). Two groups could be distinguished:

1. **Group 1**: Seven patients had classical features of MALA: high blood lactate concentrations, high plasma metformin concentrations and, with one exception (a patient who had been rehydrated), all had evidence of renal impairment as indicated by an elevated blood urea nitrogen. Acute renal failure was the predominant renal disorder. The authors ascribed the clinical condition of these patients to metformin treatment error or to reduced renal excretion of metformin.

2. **Group 2**: Thirteen patients did not fully comply with the classical pattern of MALA, as seen in Group 1. That is, none of the patients had elevated plasma metformin levels (the levels were near zero in five patients). Three of the 13 patients had normal or modestly elevated blood urea nitrogen levels. High blood lactate levels were found in nine patients and modest elevations (below 6 mmol) were present in four. Lambert et al attributed the hyperlactatemia in this group to serious hypoxic disorders: hemorrhagic, toxic/infectious or post-operative shock, hypoxic bronchopneumonia, hyperosmolar coma, evolving ketosis or an acute complication of chronic alcoholism.

The role of metformin, if any, in the pathogenesis of lactic acidosis in these Group 2 patients was not (and is not) clear, but Lambert et al suggest that the drug played no role whatsoever. These authors concluded that hyperlactatemia may result from renal failure and metformin retention (Group 1) or to tissue hypoxia caused by serious clinical disorders (Group 2). According to Lambert et al, the use of metformin therapy would not add any significant risk in Group 2 patients in whom lactic acidosis is attributed to hypoxia. The finding of normal or very low levels of metformin is offered as support for this interpretation and further substantiated by the lack of clinical benefit derived in this group by removal of metformin from the blood by dialysis (*see reference 265, item 8*).

If the presence of normal plasma levels of metformin does not incriminate this drug in the genesis of lactic acidosis in these circumstances, it may well be that a considerable proportion of patients alleged to have MALA have not been correctly diagnosed. This interpretation must cast serious doubts about the reliability of many previous cases of MALA in which the cause was attributed to metformin. The study by Lambert et al further serves to highlight that diabetics develop lactic acidosis for reasons other than metformin.

Furthermore, if we consider the other currently available oral anti-diabetic agents in the United States, namely, the sulfonylureas, it should be noted that they also carry a liability. That is, the risk of inducing hypoglycemia, which is sometimes fatal. Metformin does not carry the risk of hypoglycemia.

Data collected over a period of 25 years (1960-1984) in Switzerland, in obese and non-obese patients with NIDDM, and analyzed by Berger in 1986, have indicated that the incidence of serious hypoglycemia with sulfonylureas is greater than the incidence of lactic acidosis in patients receiving metformin, but the mortality risks of the sulfonylureas and metformin, for these respective side-effects, are almost identical. The incidence of hypoglycemia in Switzerland by drug, in order of frequency, was:

glyburide	0.38/1,000 treatment-years
chlorpropamide	0.34/1,000 treatment-years

glipizide	0.15/1,000 treatment-years
tolbutamide	0.07/1,000 treatment-years

The average mortality risk due to hypoglycemia, considering all of the above sulfonylureas together, was 0.020/1,000 patient-years over this 25-year time period and showed no tendency toward reduction in incidence (see Ref. 306, Item 8).

This compares with a mortality risk from lactic acidosis, in the same population over the same period of time, for metformin of 0.024/1,000 patient-years.

In a separate analysis of glibenclamide and metformin from Swedish data, during the period of 1972-1981, Campbell (Ref.260, Item 8) reported that the incidence of serious hypoglycemia with glibenclamide was 0.19/1,000 treatment-years, compared with an incidence of MALA of 0.084/1,000 treatment-years. Although the incidences were quite different, the relative mortality risks of the two drugs were not significantly different:

glibenclamide	0.032/1,000 treatment-years
metformin	0.024/1,000 treatment-years

Despite different mechanisms of action and safety profiles, the mortality risks of the sulfonylureas and of metformin are virtually the same, although the reasons differ: metformin alone does not induce hypoglycemia--it is an anti-hyperglycemic drug; and sulfonylureas are not recognized as a cause of lactic acidosis.

In addition to mortality risks there are other similiarities. The predisposing factors for development of hypoglycemia with sulfonylureas in many respects resemble those for metformin and lactic acidosis: renal disease, hepatic disease, cardiovascular disease, intercurrent illness and possibly age.

It cannot confidently be said of metformin, as was the case with phenformin, that the relative frequency of lactic acidosis (the only possible serious adverse event with metformin use) "...is considerably higher than that being reported for any other treatment for diabetes.." (see Ref. 304, Item 8).

2.8.6.11.2 Hypoglycemia

Metformin, at therapeutic doses and even at greatly increased doses, when used alone, is not known to cause hypoglycemia in man in the absence of another antidiabetic drug or other agent that, in and of itself, can cause the lowering of blood glucose by itself. Thus, hypoglycemia is not a safety problem with metformin monotherapy.

Hypoglycemia due to sulfonylureas (or insulin) is a well appreciated safety risk of these drugs, worldwide. Fundamental differences in the mechanism of action of metformin compared with these other antidiabetic drugs account for the fact that metformin alone does not cause hypoglycemia.

However, because the use of metformin in combination with sulfonylureas for non-insulin-dependent diabetes is also an important aspect of this NDA submission, the potential for developing hypoglycemia is addressed in this section of the NDA, based largely on the clinical experience comprising the NDA data base.

Of drugs used for the treatment of non-insulin-dependent diabetes, sulfonylureas stimulate insulin release, at least during the initial months of therapy, and this is held to be the main mechanism through which these agents maintain their blood glucose-lowering efficacy. Sulfonylureas may also potentiate certain actions of insulin, and exert some separate effects which can lower glycemia (e.g., a direct

anti-gluconeogenic effect on the liver). Whatever the mechanism(s) of action are, it is well recognized that the sulfonylureas can cause hypoglycemia and that it can occur fairly often with standard doses of oral sulfonylurea agents. In an excellent brief review, Ferner and Neil pointed out that in one large series of patients, the highest incidence of hypoglycemia occurred in patients taking glyburide, followed by (in order) chlorpropamide, glipizide, and tolbutamide. The risk of sulfonylurea-induced hypoglycemia increases with age and with concomitant use of aspirin, β-blockers, and sulfonamide antibiotics. In some patients taking chlorpropamide or glyburide, hypoglycemia may be prolonged and fatal cases have been reported even with very low doses of these agents.

In contrast to sulfonylureas, metformin does not stimulate insulin release, and metformin does not raise plasma insulin concentrations. Indeed, metformin may actually reduce the day-long plasma insulin profile in hyperinsulinemic patients.

In fact, because of its multifactorial mechanism of action, metformin may well offer a built-in safety net to counter hypoglycemia through the production of lactate by the intestine, which provides an extra substrate to help maintain gluconeogenesis.

Aside from antidiabetic agents, other drugs also can exert a hypoglycemic effect, particularly when taken in excess and in the absence of an exogenous supply of glucose. Alcohol itself can cause hypoglycemia and it can do so to an even greater extent in people with diabetes who use insulin or sulfonylureas. Of

interest, Hermann has reported that alcohol can even potentiate the blood glucose-lowering effect of metformin. Thus, a number of medical conditions and chemical agents can cause hypoglycemia by decreasing blood glucose to subnormal physiological levels. Since metformin acts, in part, by enhancing insulin utilization, any concomitant use of such drugs, including hypoglycemic antidiabetic agents, may induce a hypoglycemic attack.

The world literature on metformin, comprising experience for more than thirty years in many countries, testifies that metformin monotherapy is not associated with hypoglycemia. Even when metformin has been taken for attempted suicide, in diabetics or non-diabetics, the drug has not resulted in hypoglycemia (*see above Section 2.8.6.9 on Overdosage*). In a recent U.S. pharmacokinetic and pharmacodynamic study of metformin, which included a week of metformin administration at the maximum daily dose of 850 mg t.i.d., conducted in nine diabetic and nine healthy, non-diabetic subjects **(U.S. Study No. 89-12-6023)**, no hypoglycemic events occurred in either group and daily monitoring of fasting glucose levels indicated that blood glucose remained within the normal range for all non-diabetic subjects while approaching normoglycemic levels in the diabetic group. Finally, hypoglycemia has not been found in patients being treated with metformin when metformin plasma levels are well beyond the therapeutic range.

It must be appreciated that diabetic patients receiving metformin may, on occasion, complain of symptoms similar to those experienced during

hypoglycemia. This may correspond with low glucose concentrations at the lower end of the euglycemic range, especially if the patient is not consuming an adequate diet or has incurred an intercurrent illness with temporary loss of appetite. However, when simultaneous blood glucose measurements have been made, a true condition of hypoglycemia has not been found.

When metformin is taken by patients, in whom its use is contraindicated due to acute or chronic alcoholism or hepatic dysfunction, the potential for development of hypoglycemia should be anticipated. Isolated cases involving multiple medications can be identified, but the complexity of the clinical complications does not allow the conclusion to be drawn that metformin itself could be responsible for the hypoglycemia.

In diabetic patients taking metformin in combination with sulfonylurea, the risk for development of hypoglycemia appears to be at least as great as that with sulfonylurea alone and provides the rationale for stepwise addition of the second agent to an ongoing monotherapeutic program, when combined therapy is required (i.e., stepwise addition of metformin to continued sulfonylurea therapy or stepwise addition of sulfonylurea to continued metformin therapy).

In **U.S. Study No. 87-2D-6023**, discussed in previous sections above, 49 patients reported at least one episode of "hypoglycemia" (four patients in the metformin [M] group, seven patients in the glyburide [G] group, and 38 patients in the

metformin/glyburide [M/G] group), for a respective occurrence rate of 2%, 3% and 18% (M vs. G, p = 0.355; MG vs. M, p = 0.001; MG vs. G, p = 0.001). According to the above-described definitions of hypoglycemia, all episodes of hypoglycemia experienced during this 29 week study would be considered "mild". There were no patients in any of the treatment groups that reported severe "hypoglycemia".

In the metformin + glyburide group, 23 patients reported experiencing a single episode of hypoglycemia without sequelae and 15 patients reported more than one episode of hypoglycemia. Of the 23 patients who reported one episode, ten of the patients did not require active intervention (the hypoglycemia disappeared shortly after the patients ate or spontaneously resolved), while 11 of the patients were managed with subsequent study drug dose reductions (11 patients had their metformin dose reduced [as per protocol instructions] while one patient had the glyburide dose reduced). Two patients had no information listed regarding treatment of the hypoglycemic symptoms. All of these patients completed the study successfully except for one patient who was discontinued for other reasons. In no case was there concomitant laboratory verification of hypoglycemia, based on plasma glucose measurements.

Fifteen patients receiving metformin + glyburide reported more than one episode of hypoglycemia. Of these, five patients had their hypoglycemic symptoms disappear shortly after eating. Five patients were subsequently managed with metformin dose reductions and two additional patients had metformin dose

reductions after previous acute management of their hypoglycemic symptoms with food intake. One patient had both metformin and glyburide dose reductions after previous acute management of symptoms with the ingestion of food. One patient was treated with Glucola 75 mg, after previous management of his symptoms with food intake and in response to an FPG level at the final visit consistent with hypoglycemic symptoms (the *site* obtained a value of 53 mg/dL whereas the *central laboratory* result, run on the same sample, was 73 mg/dL). One patient had no information listed regarding treatment of the hypoglycemic symptoms. All of these patients successfully completed the study with the exception of one patient who discontinued for unrelated reasons. Excluding the patient discussed above, there were no cases of concomitant laboratory verification of hypoglycemia, based on plasma glucose measurements.

As noted above, in this study, there was a statistically significantly greater occurrence of mild hypoglycemia in the metformin/glyburide combination group. However, it would appear that this may very well have been related to the protocol design, in which the glyburide dose was held at maximum dose, whereas, in usual clinical practice, the recommendation would be to keep doses of both medications as low as possible, consistent with good glycemic control and tolerance. Furthermore, it could have been predicted that the occurrence of hypoglycemia in the comparator arms of this study (i.e., metformin alone or glyburide alone) would be low. Metformin, as presented in earlier discussions of its mechanism of action, does not stimulate insulin release and thereby was not expected to

cause hypoglycemia as monotherapy. Glyburide, although certainly capable of causing hypoglycemia, would appear less likely to do so in this patient population, since all patients had been exposed to maximum dose glyburide for at least a month, with poor glycemic control (as witnessed by the mean baseline fasting plasma glucose level for the total randomized population of approximately 250 mg/dL). In addition, no changes in glyburide dose were made during the course of the study (or could be made, according to protocol design), since patients were already on (and continued on) maximum dose glyburide.

In **non-U.S. Category II Study No. MET/S/86/HERMA**, as summarized in previous sections, patients were initially randomized to monotherapy (38 patients on metformin [MM]; 34 patients on glibenclamide [GG]) or low dose combination therapy (72 patients on MGL). During a titration period, patients not adequately controlled with either agent as monotherapy could have the second agent added, with stepwise increases (M/G or G/M) and those not controlled on low dose combination therapy, could receive high dose combination therapy (MGH).

While patients were on monotherapy or low dose combination therapy, the relative occurrence of "hypoglycemia" was 8 cases (21%) with metformin monotherapy, 12 cases (35%) with glibenclamide monotherapy, and 24 cases (33%) with low dose combination therapy. Thus, in this relevant comparison, the incidence of hypoglycemia with metformin + sulfonylurea was comparable to that with sulfonylurea alone.

In patients advancing to the higher dose combination groups (M/G, G/M and MGH), there was no statistically significant difference in occurrence of "hypoglycemia", being present in 33% of the M/G group, in 31% of the G/M group and in 17% of the MGH group.

In **non-U.S. Category II Study No. MET/D/86/HAUPT**, summarized above in previous sections, 3724 NIDDM patients, already on on sulfonylurea therapy, were additionally administered metformin. In this study, much more akin to a clinical practice situation, the incidence of recorded episodes of hypoglycemia was <1% (nine recorded AEs), with three episodes considered to be "slight", four "moderate" and two "severe" (no further definition provided).

From the above, the following conclusions can be drawn:

- Hypoglycemia is not a recognized risk in diabetics treated with metformin monotherapy.

- **The possible risk of hypoglycemia must, however, be considered in patients with contraindications to the use of metformin or in those taking multiple medications or abusing alcohol.**

- Combination therapy of metformin + sulfonylurea carries a risk of hypoglycemia which is comparable to that of sulfonylurea alone and can be minimized by judicious use of each agent in such a combination therapy program.

2.8.6.11.3 Effects of Metformin on Vitamin B_{12} and Folic Acid

Published foreign experience, as well as results from controlled, double-blind U.S. studies reported in this NDA, reveal that metformin use is associated with an increased incidence of decreased or subnormal serum vitamin B_{12} levels, generally thought to be reversible with discontinuation of metformin.

Although changes in serum vitamin B_{12} levels have been attributed by some investigators to reduced intestinal absorption of vitamin B_{12}, the mechanism of interference with absorption is still unknown and is unlikely to be either a "classical" malabsorption problem or an anti-intrinsic factor effect. The time-course and pathogenesis of decreased serum vitamin B_{12} levels with metformin are currently under investigation in the U.S. **(Study No. 92-05-6023)**. Preliminary information suggests that an interaction of metformin with calcium reduces the availability of ionic calcium, which is necessary for the binding of the vitamin B_{12}-intrinsic factor complex to its ileal receptor and that this may be easily overcome with simple proprietary or dietary calcium supplementation (*Personal communication from V. Herbert, M.D., August 26, 1993*).

ITEM 2 — NDA SUMMARY

Changes in serum folic acid levels in association with metformin, if any, are less consistent and, in fact, serum folic acid levels may even be increased with metformin. No significant shifts from normal to abnormal serum folic acid levels occurred during the course of the U.S. Phase III studies reported in this NDA.

Even though metformin's effects on serum vitamin B_{12} absorption appear to be relatively common, reported cases of megaloblastic anemias have been extremely uncommon and, to Lipha's knowledge, no neurologic disease attributable to metformin has been reported.

In the U.S. Phase III controlled, double-blind, multicenter studies reported in this NDA, an average of 7% of 566 patients receiving metformin for up to six months, either alone or in combination with a sulfonylurea, developed subnormal serum vitamin B_{12} levels, based on comparison of pre-treatment and end-of-treatment measurements (**U.S. Study Nos. 87-1D-6023 and 87-2D-6023**). No trend toward macrocytosis nor megaloblastic anemia was observed during the course of these U.S. studies, although the relatively short-term nature of these studies (29 weeks' duration) would make this unlikely, given the time-course of development of vitamin B_{12} deficiency.

When published foreign experience of long-term (>2 years) metformin administration is pooled, an average incidence of subnormal serum vitamin B_{12} levels of 13% is obtained (29 of 215 patients).

ITEM 2 — NDA SUMMARY

Despite the recognized effect of metformin on vitamin B_{12} absorption, reported cases of macrocytic anemia related to metformin use are exceedingly uncommon (three published cases and two cases reported to Lipha S.A. in post-marketing surveillance), especially considering the more than three decades of metformin's availability. Furthermore, among these cases, where sufficient information was provided to adequately assess the time-course of events, eight to 15 years of metformin treatment had been given, prior to development of anemia. As already noted, no cases have been reported either during U.S. or non-U.S. Lipha-sponsored studies.

Until further information is available as to pathogenesis and based on currently available data, it is considered advisable to monitor serum vitamin B_{12} levels on an annual basis in patients receiving metformin, either alone or in combination with sulfonylureas. In the presence of subnormal serum vitamin B_{12} levels, vitamin B_{12} supplementation is recommended.

2.8.6.11.4 Gastrointestinal Side-Effects

As previously noted, it was recognized early on in the clinical experience with metformin, that there was a high incidence of relatively minor gastrointestinal side-effects, consisting primarily of diarrhea, nausea and abdominal discomfort, particularly during initial use of metformin. Management of such side-effects has included the recommendation that metformin tablets be taken with meals (or immediately before or after a meal, in some studies), symptomatic treatment when required or metformin dose reduction (generally, temporary). On occasion, for persistent symptoms, it may be necessary to discontinue metformin therapy.

Based on recent controlled studies reported in this NDA, the prevalent concept of an increased incidence of gastrointestinal side-effects occurring in metformin-treated patients, has been confirmed. Controlled, double-blind U.S. studies of metformin, either used alone or with sulfonylurea, suggest that metformin results in a net occurrence of gastrointestinal side-effects of approximately 30%, consisting primarily of mild intermittent diarrhea and, to a lesser extent, nausea.

In analyzing the data from **U.S. Study No. 87-1D-6023** (metformin vs. placebo) relative to the frequency of nausea/vomiting and diarrhea by visit, it was noted that 80% of the 42 patients in the metformin group experiencing nausea/vomiting and 90% of the 79 patients in this group experiencing diarrhea, had their first occurrence by Visit 4 (end of Metformin Dose Titration Phase) of the study.

With regard to severity, the vast majority of diarrheal episodes were rated as being mild (50 to 57%) or moderate (31 to 46%) in severity and the diarrhea was primarily intermittent in occurrence (63 to 89% of reported events). Among patients experiencing nausea/vomiting, the *worst* severity was "mild" for 20 patients (49%), "moderate" for 15 patients (37%) and "severe" for six patients (15%).

In the *metformin group*, 11 of 19 patients (7.8% of randomized patients) who prematurely terminated study participation did so because of gastrointestinal problems (G-I) and nine of these 11 patients reported diarrhea as at least one of the reasons for the premature termination.

In the *placebo group*, six patients (4.1% of those randomized) were prematurely terminated for various medical events, none of which were G-I in origin.

In an analysis of the frequency of nausea/vomiting and diarrhea by visit in **U.S. Study No. 87-2D-8023** (metformin vs. glyburide vs. metformin/glyburide), it was noted that approximately two-thirds of patients with such symptoms in either the metformin or the metformin/glyburide group, experienced them by Visit 5 (i.e., end of the Metformin Dose Titration Phase).

With regard to severity, the vast majority of diarrheal episodes were rated as being mild (ranging from 38 to 82% of all such episodes experienced by the metformin

group and from 51 to 81% of those experienced by the metformin/glyburide group) or moderate (ranging from 9 to 58% of all such episodes experienced by the metformin group and from 19 to 46% of those experienced by the metformin/glyburide group) in severity and the diarrhea was primarily intermittent in occurrence (36 to 92% of reported events in the metformin group and 48 to 88% of events in the metformin/glyburide group).

Eleven patients (four patients in the metformin group [1.9%] vs. three patients in the glyburide group [1.4%] vs. four patients in the metformin/glyburide group [1.9%]) withdrew due to an adverse experience (AE).

For the *metformin group*, three of four patients (1.4%) who prematurely terminated study participation did so because of gastrointestinal problems and two of these three patients reported diarrhea as one of the reasons for the premature termination.

For the *glyburide group*, two of the three patients (1%) who prematurely terminated study participation did so because of gastrointestinal problems.

For the *metformin/glyburide group*, three of the four patients (1.4%) who prematurely terminated study participation did so because of gastrointestinal problems.

Thus, in this study, as in U.S. Study No. 87-1D-6023, there was a net difference in occurrence of digestive tract symptoms in metformin-treated patients (either alone or with sulfonylurea) of approximately 30% compared to the active treatment (glyburide) control group. In this study, however, there was no difference between treatment groups in percentage of patients terminating prematurely for adverse events related to the digestive tract and, in fact, the percentage of such terminations was very low for all treatment groups (approximately 1%). (This compares to the 8% discontinuation rate for gastrointestinal side-effects in the metformin arm in U.S. Study No. 87-1D-6023).

In the two uncontrolled non-U.S. Phase IV studies which, together, involved more than 8000 diabetic subjects, although details on side-effects are quite limite, they confirmed the prominence of Digestive System symptoms.

In **non-U.S. Phase IV Study No. MET/D/86/HAUPT**, involving 3724 patients with NIDDM, treated with metformin/sulfonylurea, patients reporting AE/IMEs affecting the digestive system (473 patients or 13% of total enrolled population) outnumbered those reporting AE/IMEs affecting other body systems. Within this body system, the most frequently reported AE/IMEs were diarrhea (250 patients, 7%), nausea (168 patients, 5%), epigastric distress (112 patients, 3%), and vomiting (47 patients, 1%).

Although complete information was sometimes lacking, of these 473 patients, Digestive System symptoms regressed as therapy continued in 279 patients (59% of those experiencing Digestive System symptoms), 44 patients had symptom regression with dose reduction (9% of those experiencing Digestive System symptoms) and 113 had symptoms which resulted in their premature termination from study participation (3% of enrolled patients, 24% of those experiencing Digestive System symptoms). Of those patients who withdrew due to an adverse event/intercurrent medical event (AE/IME), the three major events were diarrhea, nausea and epigastric distress.

In **non-U.S. Category II Study No. MET/AM/87/PHASE**, involving 4374 NIDDM outpatients, specific information concerning gastrointestinal side-effects was sought. Of the 4374 enrolled patients, more than 78% of patients, at each visit, for whom information was recorded, had no Digestive System intolerance. The overall incidence of digestive intolerance of all categories of severity decreased from 22% (901 patients of 4183 for whom information was recorded) at Month 1 to 11% at Month 6 (413 of 3825 patients for whom information was recorded), suggesting an adjustment to this type of side-effect.

Approximately half of the digestive intolerances (50% of events) were "moderate" to "very severe" at Month 1, compared to 50% which were "mild", whereas at Month 6, "mild" events comprised the severity of almost 75% of events, again suggesting that the side-effects decreased not only in frequency but also in

severity with time. Events rated as "severe" or "very severe" comprised 19% of events at Month 1 compared to only 4% of events at Month 6.

One hundred forty-four patients of 168 patients who did not complete the study were discontinued prematurely due to digestive intolerance (3.3% of enrolled patients), 24 for other adverse experiences/intercurrent medical events.

From these studies, it can be concluded that metformin, either as monctherapy or when coadministered with sulfonylurea causes an increased incidence of minor gastrointestinal side-effects. These studies also confirm that the symptoms tend to be mild, tend to be single events of intermittent occurrence and tend to decrease in both frequency of occurrence and severity with time. Between 1% and 8% of patients discontinue the use of metformin due to such side-effects.

There was no difference in gastrointestinal side-effect incidence in patients taking metformin alone or patients taking metformin with a sulfonylurea, and thus, it can be concluded that there was no additive gastrointestinal intolerance under such circumstances.

In the controlled, double-blind U.S. studies reported on in this NDA, no consistent approach to potential counter-measures for gastrointestinal side-effects was recommended, other than that metformin be taken with meals and that metformin dose reduction be tried (temporary or permanent). However, this approach and

the generally mild nature of the side-effects resulted in good patient/physician acceptability and few patients required therapy to be interrupted or discontinued. The above-reported incidences and outcomes are consistent with those obtained in the large uncontrolled European experience also reported herein.

2.9 CONCLUDING DISCUSSION

2.9.1 Integrated Summary of Benefits and Risks

Metformin has been in clinical use for more than 30 years and is currently commercially available in more than 80 countries worldwide, including all major western European and Scandinavian countries and Canada. Glucophage brand of metformin hydrochloride has never been withdrawn from any commercial market for either safety or efficacy reasons.

2.9.1.1 Benefits of Metformin

- Metformin is an oral anti-hyperglycemic agent whose multifactorial mechanism of action does not depend on stimulation of insulin release. It can, therefore, be effectively used for the treatment of NIDDM, either alone or in conjunction with sulfonylureas.

- The use of metformin monotherapy in patients with NIDDM, who are not satisfactorily responsive to dietary management alone, results in effective and significant improvement in parameters of glycemic control, including FPG, PPG and HbA_{1c}. The magnitude of change in glycemic control parameters is comparable to that achieved with sulfonylurea monotherapy. Advantages of metformin over sulfonylurea monotherapy include lack of risk

of hypoglycemia, lack of significant body weight gain and lack of increased insulin stimulation (which may have long-term implications for cardiovascular disease risk).

- The use of metformin plus an oral sulfonylurea can result in excellent improvement in parameters of glycemic control in patients with NIDDM and may be very useful when the response to either agent alone is suboptimal. Such combination therapy increases the therapeutic options available for patients with NIDDM and may permit a significant number of them to avoid or postpone parenteral insulin therapy (which for many patients carries an undesirable stigma and which may have a negative impact on patients' abilities to pursue certain careers or activities, due to the real or perceived risk of severe hypoglycemia). Since the side-effect profiles of metformin and sulfonylureas are significantly different, there is no increase in incidence of any side-effect unique to either agent, including hypoglycemia, when metformin and sulfonylurea are used in combination. The risk of hypoglycemia when metformin is used with sulfonylurea is comparable to that with sulfonylureas alone. In the experience reported herein of such combination therapy, all episodes of hypoglycemia reported can be categorized as mild.

- Because metformin does not stimulate insulin output, body weight gain is less likely to occur, which can be very meaningful in obese patients with NIDDM.

- In general, metformin, either alone or in combination with a sulfonylurea, has a beneficial effect on fasting serum lipid profiles. Modest lowering of total serum cholesterol levels (2-5% from baseline) and total fasting serum triglyceride levels (3% to 16%) is seen, with the magnitude of change being greatest in patients with higher initial levels of these lipids. Uncontrolled studies suggest that the effect of metformin on postprandial lipid levels (triglycerides, free fatty acids and intestinally-derived lipoproteins) may be greater than the effect on fasting lipid levels. This is currently an area of considerable interest in terms of cardiovascular disease risk.

2.9.1.2 Risks of Metformin

- As is the case for all biguanides, metformin use can be associated with the occurrence of lactic acidosis. However, as has been discussed in this NDA, the incidence of such occurrence is vastly different among the biguanides, with metformin having the lowest incidence of any biguanide which is or has been commercially available. Reflective of this improved safety profile for metformin and, simultaneously bespeaking its efficacy in the treatment of diabetes, is the fact that metformin has been in clinical use for more than 30 years and is commercially available in more than 80 countries worldwide. Glucophage brand of metformin has never been withdrawn from a commercial market for either reasons of safety or efficacy.

Biguanides, although members of the same family of compounds, must be and can be distinguished from each other (as has been discussed in depth in this NDA) on the basis of significant structural differences, significant pharmacokinetic and metabolic differences and significant differences in their actions and reactivity on a molecular level.

- Metformin use in France since 1984 accounts for approximately 2.5 million patient-years of exposure to metformin. Cases of metformin-associated lactic acidosis (MALA) occurring in France, from 1984 to the present, where the use of metformin is the greatest and where detailed pharmacovigilance information is available, have shown a remarkable pattern of constancy over this time period. Per 1,000 patient-years, there has been an average of 0.03 cases of MALA each year (approximately 1 case per 33,000 patient-years), with 0.015 fatal cases per 1,000 patient-years. In Sweden, where, likewise, very careful adverse event reporting and usage information is available, have shown a very similar incidence rate (0.024 cases per 1,000 patient-years), with 0.012 fatalities directly attributable to the acidosis per 1,000 patient-years. There is no indication that this incidence is increasing, despite steady increases in metformin usage and, in fact, in Sweden, the incidence has *decreased* more than threefold compared to an earlier five-year period of evaluation. Furthermore, a number of cases considered to be MALA do not have supportive evidence (i.e., blood metformin levels) to unequivocally establish this diagnosis and, thus, the incidence of MALA

may be even less than these figures indicate. Finally, comparative risk estimates for fatal adverse reactions for products which continue to be widely used include a death rate from anaphylaxis with penicillin use of 0.02 patients per 1,000 patients treated and a death rate from thromboembolism amongst oral contraceptive users of 0.01 to 0.03 per 1,000 patient-years. Estimates of fatal hypoglycemic reactions due to use of oral sulfonylureas average 0.020 per 1,000 patient-years.

(For purposes of comparison, it should be noted that at the time of phenformin's withdrawal from most world markets, estimates of phenformin-associated lactic acidosis in the U.S. varied from 0.25 to 4.0 cases per 1,000 patient-years, with a mortality rate of from 0.125 to 2.0 per 1,000 patient years).

- All cases of MALA have occurred in the setting of at least one or more acute or chronic illnesses, known to be either a direct risk factor for the development of lactic acidosis in patients taking metformin (e.g., acute or chronic renal impairment) or an independent risk factor for lactic acidosis (acute or chronic cardiovascular disease, pulmonary disease with hypoxia, sepsis or acute or chronic hepatic disease with or without associated alcoholism). Patients >70 years of age appear to be at greatest risk for development of MALA, probably due to the presence of borderline or frank renal impairment, greater likelihood of associated illnesses, more diagnostic

or surgical interventions and multiple concomitant medications, often inappropriately combined. (These issues are appropriately and comprehensively addressed in the proposed labeling for Glucophage).

- Except for the very rare occurrence of lactic acidosis, the side-effect profile of metformin is remarkably uncomplicated and patient acceptance is generally very good. In controlled clinical trials of metformin vs. placebo, the only body system with an increased incidence of treatment-emergent events was the Digestive System. Mild to moderate gastrointestinal symptoms, consisting primarily of intermittent diarrhea, nausea and abdominal discomfort (alone or in combination) tend to occur when metformin therapy is first started and disappear, for the most part, spontaneously, as therapy is continued. The incidence of such symptoms is comparable in patients treated with metformin as monotherapy and in patients treated with metformin plus a sulfonylurea. In controlled clinical trials reported herein, between 1% and 8% of patients terminated study participation prematurely because of gastrointestinal side-effects. In large open-label non-U.S. Phase IV studies of metformin monotherapy or metformin plus continued sulfonylurea therapy, involving more than 7,000 patients (approximately half of whom were treated for three months and the remainder for six months), approximately 3% of patients discontinued study participation prematurely because of gastrointestinal side-effects.

ITEM 2 — NDA SUMMARY

- A subclinical side-effect of metformin use, for which the current data base provides more information than heretofore available, is that of depression of serum vitamin B_{12} levels in patients receiving metformin, either alone or in combination with sulfonylureas. In the U.S. controlled clinical trials presented in this NDA, 7% of 566 patients exposed to metformin for 29 weeks developed subnormal serum vitamin B_{12} levels. Combining published information of long-term (>2 years) metformin use, it appears that approximately 13% of patients receiving metformin for such a duration will have subnormal serum vitamin B_{12} levels. Despite this, reported cases (published and unpublished) of megaloblastic anemias have been extremely rare (five cases, including three published cases; none in U.S. studies) and there is no known report of neurologic disorders on the basis of vitamin B_{12} deficiency and metformin use.

Although it is known that metformin decreases vitamin B_{12} absorption both in man and in animals, the mechanism of this decrease is not completely understood. Recent information from an ongoing Lipha-sponsored study suggests that it may be due to interaction of metformin with ionic calcium which, in turn, interferes with receptor binding of the vitamin B_{12}/intrinsic factor complex at its ileal absorptive site. This absorptive defect appears rapidly but also reverses rapidly with metformin discontinuation.

Until further information becomes available, it is recommended that patients receiving metformin, either alone or in combination with sulfonylureas, have serum vitamin B_{12} levels monitored annually, with implementation of parenteral vitamin B_{12} treatment, should a subnormal serum vitamin level be identified.

- Metformin's side effect profile does *not* include hypoglycemia, when metformin is used alone (unless, theoretically, other extenuating circumstances are present, such as acute alcohol excess). However, since metformin can be used in combination with sulfonylureas, hypoglycemia can and does occur under such circumstances. From the data analyzed in this NDA, the incidence of hypoglycemia in patients newly exposed to either sulfonylurea or metformin plus sulfonylurea appears to be comparable. All cases of hypoglycemia that have occurred during the course of the studies reported in this NDA in patients receiving both metformin and a sulfonylurea would be categorized as mild, since they either spontaneously disappeared or were relieved by food intake. For the most part they were also single occurrences. In no instance was there a hypoglycemic episode which could be considered severe (i.e., requiring assistance of another person and/or resulting in coma or seizures).

2.9.1.3 Summary and Conclusions

Metformin is an effective oral anti-hyperglycemic agent which has been available for many years in all major countries with strong scientific and medical ties to the United States. Availability of metformin in the United States will provide U.S. physicians and the U.S. public with an additional therapeutic option for the treatment of NIDDM, which is currently not available and which may significantly contribute to the desired goal of improved glycemic control in U.S. NIDDM patients.

The advantages of metformin are its multifactorial mode of action, which is very different from that of the currently available oral hypoglycemic sulfonylureas, and which permits it to be not only useful as monotherapy but also permits it to be used in combination with sulfonylureas. Metformin is particularly useful in patients who have both NIDDM and obesity, since it does not stimulate insulin secretion and thus does not promote body weight gain or increase the insulin burden. Higher insulin levels, endogenous or exogenous, and obesity are both integral parts of the syndrome implicated as increasing cardiovascular risk, so-called Syndrome X.

Metformin also has the considerable advantage over oral sulfonylurea therapy of not causing hypoglycemia, when used as monotherapy, and thus can be used by NIDDM patients for whom the risk of hypoglycemia would have a negative impact

on either their employment or life-style or both. Metformin is also of great effectiveness when used in combination with an oral sulfonylurea, in NIDDM patients who are not responding optimally (on either a primary or secondary basis) to either drug as monotherapy. In such patients, the need for insulin therapy may be either significantly delayed or indefinitely postponed, which, for many patients, could be a very meaningful contribution to their sense of quality of life as well as having long-term implications in terms of cardiovascular risk. The risk of hypoglycemia when a sulfonylurea and metformin are used in combination is comparable to that of sulfonylurea use alone.

The side-effect profile of metformin is quite straightforward and patient acceptance is very good. Metformin, either when used alone or with sulfonylureas, causes mild digestive system side-effects in about 30% of patients, consisting primarily of mild to moderate intermittent diarrhea, nausea and abdominal discomfort. These tend to resolve spontaneously, as treatment is continued and result in discontinuation of metformin therapy in less than 10% of patients.

Metformin causes asymptomatic decreases of serum vitamin B_{12} to subnormal levels in about 7% of patients exposed for six months and may cause such decreases in as many as 13% of patients exposed to metformin for two years or more, but very rarely causes any hematologic manifestations. Because of this, it is advised that patients on metformin have serum vitamin B_{12} levels monitored annually, with vitamin B_{12} supplementation if required.

ITEM 2 — NDA SUMMARY

Based on post-marketing surveillance, there is a risk of occurrence of lactic acidosis with metformin use, which is estimated at 0.03 cases per 1,000 patient years and which has an associated mortality rate of close to 50%. The mortality risk is comparable to that of several other widely used products, including the risk of fatal hypoglycemia with oral sulfonylurea agents. Patients with any degree of renal function impairment and patients >70 years of age should not receive metformin, nor should patients with any coexistent illnesses that place them at risk for lactate accumulation (acute or chronic cardiovascular disease, acute or chronic pulmonary disease with hypoxia, acute or chronic hepatic disease, including acute or chronic alcohol abuse).

In summary, the data analyzed in this NDA bespeak to the effectiveness of metformin as a blood glucose-lowering agent without the disadvantages of insulin stimulation and increased insulin burden. The goal of strict glycemic control has significantly gained in importance, based on the recent DCCT results. Metformin, either when used alone or in combination with sulfonylureas, can contribute significantly to achieving that goal for an increased proportion of NIDDM patients, relative to present therapeutic options. Although metformin carries a risk of a serious, potentially fatal, side-effect, namely lactic acidosis, the magnitude of risk for a serious, potentially fatal side-effect is acceptable and no greater than that for other currently available products, including oral hypoglycemic agents.

The recent publication of the results of the DCCT trials in IDDM patients confirm that maintenance of normoglycemia prevents or delays all major complications of diabetes. Although these data cannot be directly extrapolated to NIDDM patients, there is no reason to believe that the beneficial effects of better control of blood glucose levels in IDDM would not be applicable to NIDDM also, since complications involving the eye, kidney and peripheral nervous system appear similar and are likely to be of the same pathogenesis. Although genetic and environmental factors probably contribute to the pathogenesis of such complications, the DCCT results definitively confirm that glycemic control is a meaningful goal, with long-term beneficial implications in diabetes. From a negative perspective, patients on intensive therapy in the DCCT trials gained more weight and had three times more episodes of severe hypoglycemia than patients in the standard treatment group, because of the increased daily insulin use. Neither of these consequences occur with Glucophage.

2.9.2 Proposed Postmarketing Clinical Studies

Since Lipha S.A. (and, accordingly, Lipha Pharmaceuticals, Inc.) is currently in negotiations with potential licensees for the commercialization of Glucophage, proposed postmarketing clinical studies will be left to the discretion of said licensee. Ongoing clinical pharmacology studies and investigator-initiated clinical pharmacology and clinical studies, proposed and initiated prior to finalization of such licensing arrangements, will be concluded under Lipha's supervision.

STATISTICAL REVIEW

STATISTICAL REVIEW AND EVALUATION

MAR 1 1994

NDA# 20-357/Drug Class 1P

APPLICANT: Lipha Pharmaceuticals, Inc.

NAME OF DRUG: Glucophage (metformin hydrochloride) Tablets

INDICATION: Non-Insulin Dependent Diabetes (NIDDM)

DOCUMENTS REVIEWED: Volumes 1.1, 1.205-1.208, 1.221-1.224, 1.237-1.240 of NDA 20-357 dated September 29, 1993.

MEDICAL REVIEWER: This review has been discussed with the clinica reviewer, John L. Gueriguian, M.D., (HFD-510)

RELEVANT ISSUES DISCUSSED IN THE REVIEW:

1. The results of Study 87-1D-6023 indicate that metformin patients experience significantly greater mean reductions in FPG and HbA_{1c} levels than do placebo patients.

2. The results of Study 87-2D-6023 indicate that metformin patients experience significantly greater mean reductions in FPG and HbA_{1c} levels than do glyburide patients. However, the magnitude of the metformin treatment effect was not nearly as great as that experienced by the Study 87-1D-6023 patients. Combination (metformin plus glyburide) patients experienced reductions similar to those experienced by the Study 87-1D-6023 metformin patients.

3. The results of both studies indicate that metformin is statistically associated with the occurrence of diarrhea and nausea/vomiting.

4. The minimally effective metformin dose cannot be determined due to the design and conduct of these studies.

KEY WORDS: combination, cholesterol, diarrhea, diet, fasting plasma glucose, glyburide, glycemic, intent-to-treat, lipids, minimally effective dose, nausea/vomiting, non-insulin dependent diabetes, obese, placebo, sulfonylurea, titration, triglycerides, weight

The sponsor has submitted the results of two Phase III, U.S., double-blind, randomized, multi-center studies which were conducted to evaluate the safety and efficacy of metformin in the treatment of obese, type II, non-insulin dependent diabetes mellitus (NIDDM). A statistical review and evaluation of each of these studies follows.

STUDY 87-1D-6023

This double-blind, randomized, multi-center (13 centers) U.S. placebo-controlled study was conducted to compare the safety and efficacy of metformin relative to placebo in the treatment of obese, type II, NIDDM outpatients who are not adequately controlled with diet alone. These patients had either never received pharmacologic antidiabetic therapy or had not received such treatment for two months prior to randomization. These patients had neither achieved acceptable glycemic control nor experienced significant weight loss despite being on a weight-reduction diet for two months prior to randomization.

A two-month prebaseline phase to assess weight loss and glycemic control response to a weight-reduction diet was followed by a five-week double-blind dose titration phase and a six-month double-blind treatment phase. Based on their diet history, patients were advised to follow a diet designed to maintain their body weight throughout the duration of the study.

Eligible patients (eligibility criteria included a fasting plasma glucose (FPG) in excess of 140 mg/dl, moderate obesity and stable weight) were randomized to receive double-blind treatment at the start of the dose titration phase.

Patients commenced treatment with one 850mg tablet of metformin or matching placebo with their evening meal. Based on FPG levels and clinical tolerance, patients were titrated biweekly to 850mg bid and 850mg tid of metformin or matching placebo during the dose titration phase. At the conclusion of the dose titration phase, patients were either at the maximum permitted (2550mg/day) dose of metformin or matching placebo or at "their effective or maximally tolerated dose" of study medication.

Subsequent dose adjustments could also be made during the six-month double-blind treatment phase based on glycemic control and tolerance.

Patients were assessed at weeks 2, 4, and 5 of the titration phase and monthly (weeks 9, 15, 17, 21, 25, and 29) during the treatment phase.

The primary efficacy parameters included an assessment of glycemic

control (FPG, HbA_{1c}), lipid profile parameters (total cholesterol, triglycerides, LDL, HDL) and body weight changes.

FPG levels were assessed at baseline as well as at weeks 2, 4, and 5 of the dose titration phase and at weeks 9, 13, 21, and 25 of the treatment phase.

HbA_{1c} levels were assessed at baseline as well as at every visit of the treatment phase.

Lipids were assessed at baseline and at weeks 17 and 29 of the treatment phase. Body weight was assessed at baseline as well as at each titration and treatment visit.

The primary analysis was an intent-to-treat (ITT) last observation carried forward (LOCF) analysis where the final visit (last observation on blinded study medication) was the primary endpoint. The sponsor's intent-to-treat efficacy population consisted of patients who had taken study medication and completed at least one post-baseline visit. Visit-wise analyses which used the actual efficacy measurements at each visit without employing the LOCF procedure were also conducted by the sponsor.

REVIEWER'S COMMENTS ON STUDY 87-1D-6023

A total of 289 patients (143 metformin, 146 placebo) were randomized to receive double-blind treatment. Seventy-two (31 metformin, 41 placebo) of these patients failed to complete the study. The primary early termination reasons were treatment failure (2 metformin, 18 placebo, $p<.001$) and adverse experiences (14 metformin, 2 placebo, $p<.01$).

A total of 241 (127 metformin, 114 placebo, $p<.01$) patients experienced at least one adverse experience during the study with diarrhea and nausea/vomiting being the most frequently reported adverse experiences. A significantly greater proportion of metformin patients experienced diarrhea (56.0%, $p<.001$), nausea/vomiting (29.8%, $p<.001$), flatulence (12,8%, $p=.033$), taste disorder (5.0%, $p=.013$) and otitis media (4.3%, $p=.027$) than did placebo patients (diarrhea: 14.5%, nausea/vomiting: 9.7%, flatulence: 5.5%, taste disorder: 0.0%, otitis media: 0.0%).

The results of the sponsor's LOCF FPG and HbA_{1c} analyses are displayed in Tables 1 and 2 respectively. In examining these tables, one notes that the metformin patients experienced significantly ($p<.001$) greater mean reductions (placebo patients experienced a mean increase) in FPG and HbA_{1c} levels than did placebo patients.

The above mention FPG results are very representative of the visit-

wise results obtained throughout the titration and efficacy phases as the metformin patients experienced significantly ($p<.001$) greater FPG decreases than did placebo patients at each evaluation.

In fact, the FPG metformin mean reduction was already 52.5 mg/dl by the conclusion of the titration phase.

Similarly, metformin patients experienced significantly ($p<.001$) greater HbA_{1c} decreases than did placebo patients at each evaluation. In fact, the HbA_{1c} metformin mean reduction was already 1.47% at the week 17 evaluation.

Consequently, this study was successful in demonstrating that metformin patients experience significantly greater FPG and HbA_{1c} mean reductions than do placebo patients over the duration of the study.

The results of the sponsor's total cholesterol, triglyceride, LDL, and HDL LOCF analyses are displayed in Tables 3-6. In examining these tables, one notes that the metformin patients experienced significantly greater mean total cholesterol ($p=.024$) and LDL ($p=.021$) reductions than did placebo patients. Significant treatment group differences were not detected with regard to the change in triglyceride or HDL levels. The sponsor's visit-wise analyses yielded similar results.

Consequently, these lipid results indicate that metformin patients experience significantly greater mean total cholesterol and LDL reductions than placebo patients and that there is not a significant detrimental metformin treatment effect with regard to triglyceride and HDL levels.

The body weight results which are displayed in Table 7 indicate that both treatment groups experienced, a small decease in body weight by study's end.

Ninety-five (84.8%) of the 112 metformin patients who completed the study were receiving 2550mg/day at the conclusion of the double-blind treatment phase. (All but two of the 105 placebo completers completed the treatment phase at the "maximum" dose).

Consequently, it is apparent that the investigators believed that titrating to the maximum dose was essential for most of the patients. However, it is unclear to this reviewer what <u>specific</u> guidelines were followed in deciding whether or not to titrate a patient to a higher dosage level.

The sponsor stated that "there is no fixed dosage regimen for the management of diabetes mellitus with metformin or any other anti-diabetic agent" and that the "dosage of metformin must be individualized on the basis of both effectiveness and tolerance

while not exceeding the maximum recommended daily dose of 2550mg".

As it stands, the lack of an explanation regarding the dosage titration decision making process employed by the investigators, as well as the study design itself, precludes one from drawing any conclusions regarding a minimally effective dose.

Consequently, although the results of the study indicate statistically that metformin has an anti-hyperglycemic effect, it is not possible to determine a minimally effective dose based on these results.

STUDY 87-2D-6023

This double-blind, randomized, multi-center (20 centers) U.S. study was conducted "to compare the effectiveness of metformin alone to metformin in combination with a maximum dose of the second generation sulfonylurea, glyburide, to maximum dose of glyburide alone in obese type II non-insulin dependent diabetes mellitus (NIDDM) patients who do not have acceptable glycemic control despite having received maximum doses of sulfonylurea (first or second generation) for at least one month, including one month of maximum dose glyburide (20mg/day)".

A seven-week open prebaseline phase in which potential study candidates, all of whom had been on a maximum sulfonylurea dose and a maximum glyburide dose for one month was followed by randomization into a five-week double-blind metformin (or placebo for metformin) dose titration phase and a six-month double-blind treatment phase. Based on their diet history, patients were advised to follow a diet designed to maintain their body weight throughout the study.

Eligible patients (eligibility criteria included a fasting plasma glucose in excess of 140mg/dl, and moderate obesity) were randomized to receive double-blind treatment at the start of the dose titration phase.

Patients were randomized to metformin and placebo for glyburide, metformin in combination with maximum dose glyburide, or maximum dose glyburide and placebo for metformin at the start of the dose titration phase.

All patients received either glyburide 20mg/day or matching placebo for the duration of the study. However, the metformin or placebo for metformin dose was escalated weekly during the dose titration phase (based on FPG levels and clinical tolerance) from 500mg/day to 2500mg/day in 500mg increments.

At the conclusion of the dose titration phase, patients were either at the maximum permitted (2500mg/day) dose of metformin or matching

placebo or at "their effective maximally tolerated dose if less than 2500mg/day". As previously noted, patients were on maximum dose glyburide or matching placebo throughout the double-blind dose titration and treatment phases.

Subsequent metformin or matching placebo dose adjustments could also be made during the six-month double-blind treatment phase based on glycemic control and tolerance.

Patients were assessed weekly (week 1-5) during the titration phase and monthly (weeks 9, 13, 17, 21, 25, and 29) during the treatment phase.

The primary efficacy parameters included an assessment of glycemic control (FPG, HbA_{1c}), lipid profile parameters (total cholesterol, triglycerides, LDL, HDL) and body weight changes.

FPG levels were assessed at baseline, weekly during the titration phase and at weeks 9, 13, 21, and 25 of the treatment phase.

HbA_{1c} levels were assessed at baseline as well as at every treatment phase visit.

Lipids were assessed at baseline and at weeks 17 and 29 of the treatment phase.

Body weight was assessed at baseline as well as at each visit during the titration and treatment phases.

The primary analysis was an intent-to-treat (ITT) last observation carried forward (LOCF) analysis where the final visit (last observation on blinded study mediation) was the primary endpoint. The sponsor's intent-to-treat efficacy population consisted of patients who had taken study medication and completed at least one post-baseline visit.

Visit-wise analyses which used the actual efficacy measurements at each visit without employing the LOCF procedure were also conducted by the sponsor.

REVIEWER'S COMMENTS ON STUDY 87-2D-6023

A total of 632 patients (210 metformin, 209 glyburide, 213 combination) were randomized to receive double-blind treatment. A significantly greater proportion of combination patients (192/213,90.1%) completed the study than did glyburide (174/209,83.3%, p=.04) or metformin (157/210,74.8%, p<.001) patients. Also, a significantly (p=.03) greater proportion of glyburide patients completed the study than did metformin patients. The primary reason for early termination was treatment failure (21

metformin, 6 glyburide, 1 combination) as a significantly greater proportion of the metformin patients withdrew for this reason than did glyburide ($p<.01$) and metformin ($p<.001$) patients. Only 14 patients (5 metformin, 5 glyburide, 4 combination) withdrew due to adverse experiences.

A total of 535 (176 metformin: 83.8%, 171 glyburide: 81.8%, 188 combination: 88.5%) patients experienced at least one adverse experience during the study. As in Study 87-1D-6023, diarrhea, and nausea/vomiting were the most frequently reported adverse experiences. This is reflected in Table 8 which displays adverse experiences in which pairwise treatment group comparisons yielded p-values less than five percent.

The results of the sponsor's LOCF FPG and HbA_{1c} analyses are displayed in Tables 9 and 10 respectively. In examining these tables, one notes that the metformin patients experienced significantly greater mean reductions in FPG and HbA_{1c} levels than did glyburide patients. However, the magnitude of the metformin effect is not as great as it was in Study 87-1D-6023 (Tables 1 and 2). This could be due to the fact that at baseline, the open-label glyburide 20mg/day dose taken during the prebaseline phase was discontinued while simultaneously the dose-titration phase of metformin was begun or to the fact that the dose-titration procedure differed from that employed in Study 87-1D-6023.

The combination patients experienced significantly greater mean FPG and HbA_{1c} reductions than did the metformin and glyburide patients. But in this case the magnitude of the combination effect was somewhat higher than that experienced by the Study 87-1D-6023 metformin patients. Unlike the metformin patients, the combination patients were not withdrawn from glyburide after the prebaseline phase.

Metformin patients experienced (Table 11) a significantly greater reduction in body weight than did the combination and glyburide patients.

The results of the sponsor's total cholesterol, triglyceride, LDL, and HDL LOCF analyses are displayed in Tables 12-15. In examining these tables, one notes that the metformin and combination patients experienced significantly greater mean triglyceride and LDL reductions than did glyburide patients. Statistical trends were also noted in favor of metformin over glyburide with regard to total cholesterol and HDL levels. Consequently these results are supportive of the Study 87-1D-6023 lipid results.

As with regard to Study 87-1D-6023, most (145/157, 92.4%) of the patients who were randomized to the metformin treatment group completed the treatment phase at the maximum permitted study dose

which in this case was 2500mg/day. (Sixty-eight percent of the combination patients also completed the treatment phase at the 2500mg daily metformin dose). Consequently, as in Study 87-1D-6023, the investigators believed that titration to the maximum metformin dose was essential for most of the patients. Once again, it is unclear to this reviewer what specific guidelines were followed in deciding whether or not to titrate a patient to a higher metformin dosage level.

Thus, although the results of this study indicate statistically that metformin and metformin in combination with glyburide have an anti-hyperglycemic effect, it is not possible to determine a minimally effective dose based on these results.

REVIEWER'S CONCLUDING COMMENTS (may be conveyed to the sponsor)

The results of Study 87-1D-6023 indicate that metformin patients experience a significantly greater mean reduction in the glycemic control parameters (FPG, HbA_{1c}) than do placebo patients. These results were supported by the Study 87-2D-6023 results which indicate that metformin patients experience a significantly greater mean reduction in FPG and HbA_{1c} levels than do glyburide patients. However, the magnitude of the metformin treatment effect was not near as great in Study 87-2D-6023 as it was in Study 87-1D-6023 which could be due to the difference between the metformin dose titration procedures employed in these studies or to the withdrawal of glyburide subsequent to the prebaseline phase. In fact, the magnitude of the combination (metformin plus glyburide) treatment effect in Study 87-2D-6023 was similar to that of the Study 87-1D-6023 metformin treatment effect.

Similar statements may be made with regard to the lipid parameters.

The results of both studies indicate that metformin is statistically associated with the occurrence of diarrhea and nausea/vomiting.

Consequently, in the opinion of this reviewer, Studies 87-1D-6023 and 87-2D-6023 have demonstrated that the administration of metformin and metformin in combination with glyburide results in a statistically significant reduction in the glycemic control parameters FPG and HbA_{1c}.

However, the minimally effective dose cannot be determined due to the design and conduct of these studies.

David N. Marticello

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 2-28-94

Dr. Dubey 3-1-94

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Original: NDA 20-357
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HFD-510/Dr. Sobel
HFD-510/Dr. Gueriguian
HFD-510/Ms. Galliers
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/Mr. Marticello
Chron.

This review consists of 9 pages of text and 15 pages of tables

D.MARTICELLO/MEG/WP51WINDOWS/C:\STAT.REV\20357.DM/2-9-94

TABLE 1

STUDY 87-1D-6023

MEAN FASTING PLASMA GLUCOSE (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

	FPG		
	Metformin	Placebo	P-value
N	139	143	
Baseline	241.5	238.1	.72
Change	-53.0	6.3	<.001*

* P<.001 IN FAVOR OF METFORMIN OVER PLACEBO
TREATMENT-BY-CENTER INTERACTION P-VALUE=.33

TABLE 2

STUDY 87-1D-6023

MEAN HEMOGLOBIN A_{1C} (%) LEVELS

SPONSOR'S LOCF ANALYSES

	HbA_{1c}		
	Metformin	Placebo	P-value
N	135	135	
Baseline	8.4	8.2	.267
Change	-1.4	.4	<.001*

* P<.001 IN FAVOR OF METFORMIN OVER PLACEBO
TREATMENT-BY-CENTER INTERACTION P-VALUE=.193

TABLE 3

STUDY 87-1D-6023

MEAN TOTAL CHOLESTEROL (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

TOTAL CHOLESTEROL

	Metformin	Placebo	P-value
N	130	138	
Baseline	212.4	212.6	.937
Change	-9.5	1.8	.024*

* P=.024 IN FAVOR OF METFORMIN OVER PLACEBO
TREATMENT-BY-CENTER INTERACTION P-VALUE=.862

TABLE 4

STUDY 87-1D-6023

MEDIAN TRIGLYCERIDE (mg/dl) LEVELS +

SPONSOR'S LOCF ANALYSES

	TRIGLYCERIDES		
	METFORMIN	PLACEBO	P-VALUE
N	130	138	
BASELINE	161.0	162.5	.484
CHANGE	-10.0	4.0	.085#

P=.085
TREATMENT-BY-CENTER INTERACTION P-VALUE=.617

+ A FEW OUTLIERS SKEWED THE DATA. CONSEQUENTLY, THE MEDIAN VALUES ARE A MORE VALID ASSESSMENT OF THE TREATMENT GROUP RESPONSES.

TABLE 5

STUDY 87-1D-6023

MEAN LDL (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

	LDL		
	METFORMIN	PLACEBO	P-VALUE
N	117	125	
BASELINE	137.5	138.5	.794
CHANGE	-11.1	-2.0	.021*

* P=.021 IN FAVOR OF METFORMIN OVER PLACEBO

TABLE 6

STUDY 87-1D-6023

MEAN HDL (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

	HDL		
	METFORMIN	PLACEBO	P-VALUE
N	130	137	
BASELINE	38.7	40.8	.175
CHANGE	.8	-.3	.303

TABLE 7

STUDY 87-1D-6023

MEAN BODY WEIGHT (lbs)

SPONSOR'S LOCF ANALYSES

BODY WEIGHT

	METFORMIN	PLACEBO	P-VALUE
N	141	144	
BASELINE	201.0	206.0	.200
CHANGE	-1.4	-2.4	.207

TABLE 8

STUDY 87-2D-6023

ADVERSE EXPERIENCES+

	TREATMENT GROUP#			P-VALUES		
ADVERSE EXPERIENCE	M	G	C	M vs G	M vs C	G vs C
Anorexia	14(6.7%)	2(1.0%)	9(4.2%)	<.01	.27	.04
Diarrhea	98(46.7%)	25(12.0%)	95(44.6%)	<.001	.67	<.001
Indigestion	9(4.3%)	8(3.8%)	25(11.7%)	.81	<.01	<.01
Nausea/Vomiting	56(26.7%)	17(8.1%)	54(25.4%)	<.001	.76	<.001
Hypoglycemia	4(1.9%)	7(3.3%)	38(17.8%)	.36	<.001	<.001
Anxiety/Tension	1(0.5%)	9(4.3%)	4(1.9%)	.01	.37	.15
Tremulousness	5(2.4%)	2(1.0%)	9(4.2%)	.45	.29	.04
Pharyngitis	8(3.8%)	10(4.8%)	19(8.9%)	.62	.03	.09
URTI++	40(19.0%)	46(22.0%)	67(31.5%)	.45	<.01	.03
Vaginitis	8(3.8%)	16(7.7%)	5(2.3%)	.09	.38	.01

\+ ADVERSE EXPERIENCES FOR WHICH A PAIRWISE TREATMENT COMPARISON P-VALUE I LESS THAN .05

++ UPPER RESPIRATORY TRACT INFECTION

\# M = METFORMIN
G = GLYBURIDE
C = COMBINATION

TABLE 9

STUDY 87-2D-6023

MEAN FASTING PLASMA GLUCOSE (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

		FPG		P-VALUES (change from baseli		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	213	250.5	-63.5	<.001**	<.001**	.025*
Metformin (M)	209	253.9	-.9			
Glyburide (G)	207	247.5	13.7			

* P=.025 IN FAVOR OF METFORMIN OVER GLYBURIDE

** P<.001 IN FAVOR OF THE COMBINATION OVER METFORMIN AND GLYBURIDE

TREATMENT-BY-CENTER INTERACTION P-VALUE = .199

TABLE 10

STUDY 87-2D-6023

MEAN HEMOGLOBIN A_{1C} (%) LEVELS

SPONSOR'S LOCF ANALYSES

		HbA_{1C}		P-VALUES (change from baseli		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	200	8.8	-1.7	<.001*	<.001*	<.001*
Metformin (M)	200	8.9	-.4			
Glyburide (G)	191	8.5	.2			

* P<.001 IN FAVOR OF METFORMIN OVER GLYBURIDE AND IN FAVOR OF COMBINATION OVER METFORMIN AND GLYBURIDE

TREATMENT-BY-CENTER INTERACTION P-VALUE = .667

TABLE 11

STUDY 87-2D-6023

BODY WEIGHT (lbs)

SPONSOR'S LOCF ANALYSES

		BODY WEIGHT		P-VALUES (change from baseli		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	212	202.2	.9	.001**	.011*	<.001**
Metformin (M)	208	204.0	-8.4			
Glyburide (G)	206	203.0	-.7			

* P=.011 IN FAVOR OF GLYBURIDE OVER COMBINATION

** P<.001 IN FAVOR OF METFORMIN OVER COMBINATION AND GLYBURIDE

TREATMENT-BY-CENTER INTERACTION P-VALUE = .420

TABLE 12

STUDY 87-2D-6023

MEAN TOTAL CHOLESTEROL (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

		TOTAL CHOLESTEROL		P-VALUES (changes from baseli		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	207	215.2	-9.3	.139	<.001*	.087
Metformin (M)	195	213.4	-4.0			
Glyburide (G)	194	220.4	2.8			

* P<.001 IN FAVOR OF COMBINATION OVER GLYBURIDE

TREATMENT-BY-CENTER INTERACTION P-VALUE = .797

TABLE 13

STUDY 37-2D-6023

MEDIAN+ TRIGLYCERIDE (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

		TRIGLYCERIDES		P-VALUES (changes from baseli		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	207	170.0	-14.0	.888	.004*	.007*
Metformin (M)	196	197.5	-6.5			
Glyburide (G)	194	184.0	6.5			

* P<.01 IN FAVOR OF COMBINATION AND METFORMIN OVER GLYBURIDE
TREATMENT-BY-CENTER INTERACTION P-VALUE = .752

+ A FEW OUTLIERS SKEWED THE DATA. CONSEQUENTLY, THE MEDIAN VALUES
A MORE VALID ASSESSMENT OF THE TREATMENT GROUP RESPONSES

TABLE 14

STUDY 87-2D-6023

MEAN LDL (mg/dl) LEVELS

SPONSOR'S LOCF ANALYSES

		LDL		P-VALUES (change from baseli		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	190	137.2	-8.0	.466	<.001**	.003*
Metformin (M)	168	135.4	-6.0			
Glyburide (G)	177	138.1	3.8			

* P<.01 IN FAVOR OF METFORMIN OVER GLYBURIDE

** P<.001 IN FAVOR OF COMBINATION OVER GLYBURIDE

TABLE 15

STUDY 87-2D-6023

MEAN HDL (mg/dl) LEVELS

		HDL		P-VALUES (change from baseline		
TREATMENT GROUP	N	BASELINE	CHANGE	C vs M	C vs G	M vs G
Combination (C)	207	39.0	1.1	.303	.361	.056
Metformin (M)	194	37.0	1.8			
Glyburide (G)	193	37.2	.4			

PHARM AND TOX REVIEW

NDA 20-357 14 April 1994

Lipha Pharmaceuticals, Inc.
9 West 57th Street, Suite 3825
New York, NY 10019-2701

MAY 3 1994

Submission: Received 30 Sep 93

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Glucophage Tablets (Brand of Metformin hydrochloride)

Antihyperglycemic Agent

Indicated Use: As monotherapy, as an adjunct to diet to lower blood glucose in patients with non-insulin dependent diabetes (NIDDM) whose hyperglycemia cannot be satisfactorily managed on diet alone. Glucophage Tablets are also indicated in patients with NIDDM whose hyperglycemia cannot be satisfactorily managed by diet and maximum dosage of a sulfonylurea.

Table of Contents

* OI = Original IND Review 11 Apr 86; Attachment C
OIA-# = Original IND Review 11 Apr 86 Attachment (#)
I = IND 27,966 Review 7 Aug 90 & 14,22 Feb 90; Attachments A & B
2,4 etc. = pages of this review (NDA 20-357)

cc: Original NDA 20-357; IND HFD-502 ATaylor;
HFD-400 JContrera; HFD-510 NDA 20-357, IND
HFD-345; HFD-510 AJordan; HFD-510 DHertig

David H. Hertig
Pharmacologist

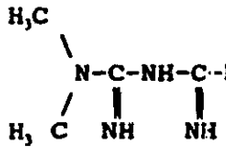
5/3

Related: IND - Lipha Chemicals, Inc.
IND - Metformin -
IND - Metformin -
DMFs

Supplier: Bulk drug substance produced by Lipha S.A., Lyon, France at their manufacturing plant Lipha Calais, in Calais, France. The drug product (tablets) will be manufactured, packaged and labeled by Lipha Pharmaceuticals Limited, United Kingdom, at their facilities in Hitchin, Herfordshire and Letchworth, Herfordshire, respectively, in England.

Dosage and Form: Supplied as 500 and 850 mg Tablets for oral administration. Dosage of Glucophage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. Blood glucose and glycosylated hemoglobin should be periodically monitored.

Structure:



MW 165.63

N,N-dimethylimidodicarbonimidic diamide
or N,N-Dimethylbiguanide

Foreign Studies: Yes - See Individual Studies.

Preclinical Studies:
Pharmacology: See also previous reviews.

The major effect of the biguanides appears to be a potentiation of insulin effectiveness. Several review articles are present in the literature which summarize the pharmacological activity of metformin and discuss its mechanism of action which is not completely understood. The effects of metformin are probably due to multiple actions which have included the following suggestions of the mechanism of action: 1) increased insulin receptor binding; 2) decreased intestinal glucose absorption; 3) increased cellular glucose uptake; 4) decreased hepatic gluconeogenesis; 5) stimulation of anaerobic glycolysis; and 6) potentiation of insulin action at the receptor or post-receptor level. Cellular level studies indicate that metformin potentiates insulin action and in vitro studies support a post-receptor mechanism of action.

Metformin improves glucose tolerance, however, therapeutic doses do not reduce basal glucose concentrations below the normal physiological range in diabetic or non-diabetic animals or humans. When given orally metformin effectively lowers plasma glucose levels in genetically diabetic KK mice, streptozotocin-induced diabetic mice, obese female fa/fa rats and alloxan-induced diabetic rats. Glucose lowering does not appear to be due to effects on plasma insulin or glucagon concentrations. Although the evidence is not entirely conclusive it is generally accepted that metformin's antihyperglycemic effects are poorly correlated with insulin binding and its effects on receptor binding and number are not directly related to its metabolic and clinical effects. Metformin does not increase circulating insulin levels and does not appear to stimulate insulin secretion.

Although concentrations are usually higher than the therapeutic range, metformin inhibits intestinal glucose absorption in normal and diabetic animals, however, other mechanisms of action probably also play a role.

Metformin in general potentiates insulin-mediated glucose uptake into tissues, especially skeletal muscle (may be due to facilitation of a post-receptor sensitivity to insulin). No effect was seen on basal or insulin-stimulated glucose oxidation in non-diabetic mouse muscle. Glucose oxidation was potentiated, however, in streptozotocin-diabetic mouse muscle in the presence of insulin. Basal glucose oxidation in adipocytes from non-diabetic rats was also increased by metformin. Metformin has produced either no effect or an increase in insulin-stimulated glycogen synthesis in non-diabetic and diabetic animal skeletal muscle.

Metformin enhanced the rate of lactate production in vitro in isolated male Wistar rat parenchymal liver cells but did not affect lactate production in male Sprague-Dawley rat isolated pancreas. Metformin significantly increased in vivo blood lactate levels in male Hartley guinea pigs at doses from 125-500 mg/kg i.p., at 100-400 mg/kg p.o. in male Wistar rats, at 50-400 mg/kg p.o. in male streptozotocin-diabetic Wistar rats, and 50-200 mg/kg i.v. and p.o. in alloxan-diabetic rats. However, in other studies metformin p.o. produced no significant blood lactate effects. The following showed no significant lactate production effects: 150 mg/kg/day x 4 in male Wistar rats; skeletal muscle from normal or streptozotocin-diabetic mice after 250 mg/kg/day p.o. for 3-weeks; diaphragm from normal and hyperglycemic mice or epididymal fat from normal mice after 250 mg/kg orally; normal mice after 500-200 mg/kg i.v. and p.o.; normal, hyperglycemic obese mice and hyperinsulinemic DBM mice after 200 mg/kg p.o..

Metformin has also been shown to have hypolipidemic effects and to significantly improve the progression and regression of atherosclerotic lesions. Although metformin does not appear to show any significant effects on normal Sprague-Dawley rat cholesterol levels, it inhibits fructose and fat-induced hypertriglyceridemia. No effects were seen on hypercholesterolemia induced in Fauve de Bourgogne rabbits by a high-fat diet. [Metformin has been reported to be an effective hypolipidemic agent in humans - a 38% decrease in triglyceride levels in various types of lipid disorders has been noted. Metformin appears to inhibit the transfer of dietary triglyceride from the gastrointestinal tract into plasma and to reduce the uptake of absorbed lipid by adipose tissue.

Various studies indicate that metformin produces lipoprotein changes in cholesterol-fed animals toward a more normal composition. Structural modification of VLDL leads to a rapid turnover and decreased interaction with binding components of the arterial wall. Aortic wall lipid metabolism is altered with inhibition of intramural lipid biosynthesis.

Metformin showed a noticeable prophylactic effect on development of atherosclerotic lesions throughout the entire arterial trunk of cholesterol-fed animals. Significant reductions were seen in cholesterol content of the aorta, coronary arteries, and pulmonary artery, and arterial lesions were decreased. Elimination of lipid deposits after cessation of the high cholesterol diet was greatly accelerated by metformin.

Effects of metformin on the microcirculation were studied in several different animal models and it is reported that they suggest that metformin may play a beneficial role in prevention and/or development of diabetic microangiopathy with a reduction in the incidence of glomerulosclerosis.

250 mg/kg i.p. reduced food in lean and genetically obese mice (more sensitive). On the other hand, 50 or 250 mg/kg/day p.o. for 15 days did not produce significant changes in body weight or daily food intake in lean or obese mice. Male rats showed an antidipsic effect when 20-100 µg metformin was implanted in the hypothalamus.

Metformin did not produce any effect on liver microsomal enzymes in rat studies, however liver blood flow was significantly increased. Metformin has also been reported to counteract the hyperglycemic effects of diazepam and nifedipine in rats.

ADME, Plasma Kinetic Studies: [Radioactive labeling on the two biquanide carbons.] Summaries - See also Tables p. 8a and Comments.

Studies with [^{14}C]-Metformin in Charles River CD Sprague-Dawley Rats: Inveresk Research International, Scotland. IRI Project 151738 Report 8656. Completed: Dec 92. Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 6.88 MBq·mg^{-1}, 186 μCi·mg^{-1}. Non-radiolabeled Batch 21889.

Target dose levels for oral and i.v. administration were 50 mg·kg^{-1} and 25 mg·kg^{-1}, respectively.

[^{14}C]-Metformin was fairly well absorbed following **oral administration** to rats. Urinary excretion was ca. 66% for males and ca. 51% for females; fecal excretion was 31 and 44%. Urinary excretion following **i.v. administration** was ca. 93 and 92%; fecal excretion was 5 and 3.7% By 24 h the majority of the dose by both routes had been recovered in excreta. Total radioactive dose recovered after the oral dose was 99.05% for males and 96.53% for females, and after the i.v. dose 105.8% for males and 86.4% for females. There was little or no radioactivity in expired CO_2 from either route.

Single Dose Plasma Kinetics:

Single 50 mg·kg^{-1} oral dose: Peak mean levels of total radioactivity in plasma were 2.804 μg equiv·ml^{-1} for males at 1 h and 2.361 μg equiv·ml^{-1} for females at 1.5 h. At 4 hrs. levels were 1.270 μg equiv·ml^{-1} for males and 1.027 μg equiv·ml^{-1} for females and near background by 12 hrs. The $AUC_{0-4\,h}$ was 7.93 μg equiv·h·ml^{-1} for males and 6.49 μg equiv·h·ml^{-1} for females. The whole blood to plasma ratio of mean values of total radioactivity at 4 hrs. was 1.39 for males and 1.42 for females.

Single 25 mg·kg^{-1} i.v. dose: Plasma radioactivity was highest at 5 min. being 19.410 μg equiv·ml^{-1} for males and 24.991 μg equiv·ml^{-1} for females. Values had decreased to 0.346 and 0.561 μg equiv·ml^{-1} by 3 hrs. and near background by 6 hours. The $AUC_{0-4\,h}$ was 13.59 and 16.99 μg equiv·ml^{-1} for males and females. Whole blood to plasma ratio of mean values was ca. 0.9 at 0.5 h for both sexes and 1.7 and 1.4 for males and females at 4 hours.

Multiple Dose Excretion Studies:

7 Daily 50 mg·kg^{-1} oral administrations: Pattern of excretion was broadly similar to that of a single dose.

Dose 1: (24 h post dose) Urinary recovery was 47 21% for males and 43.66% for females and for feces 47.41 and 55.31%.

Dose 7: (24 h post dose) Urinary recovery was 47.72 and 45.50% for males and females and fecal recovery was 49.60 and 50.02%.

At 24 h post daily dose >97% of the total radioactivity administered up to that time point had usually been excreted.

Multiple Dose Plasma Kinetics:

Dose 1: Peak mean total radioactivity levels at 1 and 2 hrs. were 2.755 μg equiv·ml^{-1} for males and 2.389 μg equiv·ml^{-1} for females.
The $AUC_{0-4\,h}$ was 8.13 μg equiv·ml^{-1} for males and 8.02 μg equiv·ml^{-1} for females.

Dose 7: Peak levels were seen 1 hr. post dose - mean values of 3.329 and 3.971 μg equiv·ml^{-1} for males and females.
The $AUC_{0-4\,h}$ was 8.77 and 10.23 μg equiv·ml^{-1} for males and females.

At 24 h following each dose, radioactivity was generally at or near background with no significant accumulation of radioactivity.

Quantitative Tissue Distribution:

Male rats - Levels of total radioactivity in tissues and organs examined were usually highest 2 h post dose. Except for the GI tract radioactivity was highest in kidney (21.038 μg equiv$\cdot g^{-1}$) and liver (14.655 μg equiv$\cdot g^{-1}$).

By 6 h radioactivity in general decreased significantly except for adrenals (6.259 μg equiv$\cdot g^{-1}$) and heart (5.448 μg equiv$\cdot g^{-1}$). Thyroid increased slightly to 3.116 μg equiv$\cdot g^{-1}$.

By 12 h except for the GI tract levels were highest in adrenals, heart and thyroid (3.857, 2.413 and 2.357 μg equiv$\cdot g^{-1}$).

By 12 h except for the GI tract levels were in general at or near background.

Qualitative Tissue Distribution:

Whole body radiography: Total radioactivity in tissues and organs were highest at 1.5 h in the stomach and small intestine, with lower levels in liver, lungs, heart, spleen, kidneys and adrenals, and testes. Levels decreased by 4 h. At 48 h levels were detectable only in the GI tract.

Placental Transfer:

Single oral dose Day 16 of gestation: Total radioactivity was higher in maternal tissues than in the fetus (some placental barrier). Levels in fetus, placenta and amniotic fluid at the time of peak (2 h) were lower than those in plasma. At 6 h levels in plasma and placenta were broadly similar (1.529 μg equiv$\cdot ml^{-1}$ for plasma, 1.542-1.970 μg equiv$\cdot g^{-1}$ for placenta). At 12 h levels in placenta (0.387-0.443 μg equiv$\cdot g^{-1}$) were higher than in plasma (0.200 μg equiv$\cdot ml^{-1}$). At 120 h maternal and fetal levels were at or near background.

Milk Transfer:

Variable results with relatively low levels of total radioactivity in milk compared to plasma at 1.5 h (milk:plasma ratio <1). Levels in milk were greater than those in plasma by 8 h and this difference increased significantly by 24 hours.

Studies with [^{14}C]-Metformin in Mice: Inveresk Research International, Scotland. Report 8799. IRI Project 151785. Completed: May 92. Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 6.88 MBq$\cdot mg^{-1}$, 186 $\mu Ci \cdot mg^{-1}$.
Non-radiolabeled Batch 21889.

Target dose levels for oral and i.v. administration were 50 mg$\cdot kg^{-1}$ and 25 mg$\cdot kg^{-1}$, respectively. Each mouse received ca. 5 μCi. Radioactivity excretion kinetics were similar for both sexes by both routes.

Oral Administration: Elimination of radioactivity was rapid with 83-99% of the dose recovered by 48 hrs. The main route of elimination was urinary being 34-56% in males and 38-61% for females at 120 hrs. 9.54-9.65% was also recovered in the cage wash (associated with urine). Fecal elimination accounted for 29-43% in males and 21-37% in females. At 120 hrs. there was no significant retention of radioactivity in the carcass or GI tract.

I.V. Administration: Urine was the main route of elimination of radioactivity accounting for 83-101% for males and 51-89% for females. Fecal excretion accounted for another 2-9% for males and 4-32% for females. Recovery from cage wash was 7.02% for males and 11.58% for females.

Plasma and Whole Blood Kinetics:

Oral Administration: Males - Rapid absorption with peak mean levels of total radioactivity in plasma at 0.5 h (3.59 μg equiv$\cdot ml^{-1}$). Elimination from plasma was rapid mean levels being 0.14 μg equiv$\cdot ml^{-1}$ at 8 hrs. after dosing. Total radioactivity was below the limit of reliable measurement at 24 hrs.

Females - Total radioactivity peak mean plasma levels also at 0.5 h were 4.22 $\mu g \cdot equiv \cdot ml^{-1}$. They fell to 0.20 $\mu g \cdot equiv \cdot ml^{-1}$ at 8 hrs. and by 24 hrs. were below the limit of reliable measurement.

For whole blood the profile of total radioactivity was in general similar to that observed in plasma, although levels were slightly lower.

Studies with [^{14}C]-Metformin in New Zealand White Rabbits: Inveresk Research International, Scotland. IRI Project 151759 Report 9092 Completed Oct 92. Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 6.88 $MBq \cdot mg^{-1}$, 186 $\mu Ci \cdot mg^{-1}$. Non-radiolabeled Batch 21889.

Target dose was 50 $mg \cdot kg^{-1}$ such that each animal received a radioactive dose of ca. 50 μCi (1.85 MBq) orally by gavage.

Studies did not show any apparent sex differences.

Single oral dose: Recovery was 52-61% in the urine and 31-42% in the feces. Total recovery of radioactivity including GI tract, carcass and cage wash during the 5 day collection period was 95-104%. Less than 3% was recovered during the 96-120 h period. Radioactivity peaked at 1.5 h at a mean of 5.26 $\mu g \cdot equiv \cdot ml^{-1}$ and rapidly fell to 10% of peak levels at 6 h. They then fell slowly and were below the limit of detection at 48 h.

7 Days administration: The excretion pattern was similar to that after single administration with the majority of the dose being recovered in the urine (47-61%) and an additional 29-46% in the feces. Total recovery up to 120 h post Dose 7 was 95-101%. Less than 2% was recovered during the 96-120 h period. It appears that either absorption is not complete or some excretion via bile into the feces exists.

Plasma Kinetics:

Radioactivity peaked at 1.5 h (3.09-6.28 $\mu g \cdot equiv \cdot ml^{-1}$) after the first dose and fell to ca. 10% of initial levels at 6 h. At 24 h after Dose 1 and 24 h after Dose 6 levels of total radioactivity were fairly constant (mean 0.42-0.77 $\mu g \cdot equiv \cdot ml^{-1}$). The pattern after Dose 7 was similar to that after Dose 1 declining more slowly after 8 h and not being significantly above background 72 h after Dose 7.

There appeared to be a movement of radiolabeled components across the cell membrane into the red cells. Levels in whole blood after the 7th dose were similar to that of plasma with a peak at 1 h. The ratio of radioactivity in whole blood to plasma was 61% at 1 h and 134% at 24 hours after Dose 7.

Tissue Radioactivity:

Administration on Day 18 of gestation.

Radioactivity highest at 2 h for kidney (24-111 $\mu g \cdot equiv \cdot g^{-1}$), liver (19-65 $\mu g \cdot equiv \cdot g^{-1}$), heart and lung fell to 1-3 and 1-2 $\mu g \cdot equiv \cdot g^{-1}$ at 48 h.

The maximum total radioactivity in placenta and whole fetus declined after 6 h. Total radioactivity in amniotic fluid increased from 2-48 h resulting in a change in the ratio in amniotic fluid to maternal plasma, from 0.02 at 2 h to 4.47 at 48 h.

Fetal radioactivity remained fairly constant. The ratio of radioactivity in fetus:maternal heart tissue increased from 0.09 at 2 h to 0.66 at 48 h. The partial barrier to radiolabeled components crossing the placenta to the fetus is not as complete as that preventing their return to the maternal circulation.

Studies with [^{14}C]-Metformin in Dogs: Inveresk Research International, Scotland. IRI Project 151743 Report 8778. Study Completed Jun 92.
Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 6.88 MBq·mg^{-1}, 186 μCi·mg^{-1}. Non-radiolabeled Batch 21889.

Target dose levels of 50 mg·kg^{-1} after oral administration and 25 mg·kg^{-1} after i.v. administration. Target radioactive dose 100 μCi per dog for each route.

Single oral dose: Mean peak plasma concentrations of total radioactivity were seen at 1.5 h for male and 2 h for females; peak values ranged between 0.75 and 3 h. $AUC_{0\infty}$ was 43.2 μg equiv·h·ml^{-1} for males and 44.2 for females.
Urinary excretion: ca. 86% for males and ca. 87% for females at 120 h.
Fecal excretion: For males ca. 19% and for females ca. 17%.
Excretion was rapid with ca. 100% recovered by 24 h.

Single I.V. dose: Peak plasma radioactivity levels were seen at the first 5 min. sampling being 68 and 78 μg equiv·ml^{-1} for males and females respect. $AUC_{0\infty}$ was 45.8 and 51.6 μg equiv·ml^{-1} for males and females.
Urinary excretion: ca. 98% for males and ca. 99% for females at 120 h.
Fecal excretion: Males ca. 2% and females ca. 1%.
Excretion was rapid with ca. 95% recovered by 24 h.

Both routes - Plasma: Later time points (up to 120 h) levels of total radioactivity in plasma were at or near background. Levels in whole blood were generally less than in plasma.

7-Daily Oral Administrations: Excretion was again mainly urinary with a pattern similar to that seen after single oral administration.
Plasma: Peak plasma levels were seen at 1 and 1.5 h for males and females, Post Dose 1 (ca. 13 and 13 μg equiv·ml^{-1}) and Post Dose 7 (ca. 12 and 10 μg equiv·ml^{-1}). $AUC_{0\infty}$ for males and females were Post Dose 1 ca. 55 and 50 μg equiv·ml^{-1} and Post Dose 7 ca. 44.8 and 50.3 μg equiv·ml^{-1}. Steady state levels were achieved after 2-3 days of dosing.
Urinary excretion: 24 h after Dose 1 urinary recovery was ca. 71% for males and ca. 65% for females. At 120 h Post Dose 7 values were ca. 67% for males and ca. 78% for females.

No significant accumulation of total radioactivity appeared to occur (it is reported however, that such radioactivity data should be interpreted with caution).

Studies with [^{14}C]-Metformin in Rhesus Monkeys: Inveresk Research International, Scotland., IRI Project 151764 Report 8737. Study Completed May 92.
Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 1.14 GBq·mmol^{-1}, 31 mCi·mmol^{-1}. Non-radiolabeled Batch 21889.

Target dose levels of 50 mg·kg^{-1} after oral administration and 25 mg·kg^{-1} after i.v. administration. Target radioactive dose 100 μCi per animal for each route. 3M;3F

Single oral dose: Peak mean plasma radioactivity showed a large variability with values at 2 h (range 1-2 h) of 5.97 μg equiv·ml^{-1} for males and at 0.75 h (range 0.75-3 h) of 7.26 μg equiv·ml^{-1} for females. By 24 h plasma decreased significantly to means of 0.09 and 0.06 μg equiv·ml^{-1} for males and females. Later time periods (up to 168 h) showed plasma radioactivity

to be at or near background. $AUC_{0-24\ h}$ was 26.5 and 35.1 μg equiv·ml^{-1} for males and females. Whole blood radioactivity was generally less than that of plasma with mean concentrations at 4 h for males of 2.34 μg equiv·ml^{-1} and at 1 h for females of 4.48 μg equiv·ml^{-1}.

Urinary excretion: For males ca. 48% of the dose and for females ca. 42% of the dose at 168 hrs. plus additional ca. 7 and 9% in cage wash and debris.

Fecal excretion: At 168 h ca. 44% for males and 40% for females. By 24 h a mean of ca. 70% was recovered in excreta.

I.V. Administration: Mean plasma radioactivity for males and females of ca. 55 and 62 μg equiv·ml^{-1} at 5 min. decreased to a mean of 0.13 and 0.19 μg equiv·ml^{-1} at 8 hours. Radioactivity was near background by 168 hours. $AUC_{0-24\ h}$ for males and females were 21.5 and 27.3 μg equiv·h^{-1}.

Radioactivity in whole blood was lower than in plasma being 5.51 and 7.38 μg equiv·ml^{-1} at 5 h for males and females.

Urinary excretion: At 168 hours ca. 90 and 77% of the dose plus ca. 8 and 20% in cage wash and debris.

Fecal excretion: ca. 1 and 2% for males vs females.

It appears that following oral administration, absorption of radiolabeled drug may be at least 50%.

Metabolite Profiling Studies in Samples from Rats, Dogs, Mice, Rabbits and Cynomolgus Monkeys Following Oral or Intravenous Administration of [^{14}C]-Metformin: Inveresk Research International, Scotland. Report 9089. IRI Project 151790. Completed: Oct 92. Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 1.14 GBq·$mmol^{-1}$, 31 mCi·$mmol^{-1}$. Non-radiolabeled Batch 21889. Combination of the following projects:

IRI Project 151738 - Rats; IRI Project 151764 - Rhesus Monkeys;
IRI Project 151743 - Dogs; IRI Project 151759 - Rabbits;
IRI Project 151785 - Mice.

Pooled samples from rats, dogs, mice, and rhesus monkeys were subjected to TLC analysis which indicated the presence of a single radioactive component in all three solvent systems examined which co-chromatographed with [^{14}C]-Metformin. There did not appear to be any apparent differences between males and females.

Rabbits were an exception. Two radioactive components were observed in urine and plasma - one component co-chromatographed with [^{14}C]-Metformin. Autoradiography confirmed two distinct radioactive components.

Identification of the Major Unknown Radioactive Component in Rabbits Following Single Oral Administration of [^{14}C]-Metformin: Inveresk Research International, Scotland. IRI Project 153583. Report 9753. Issued Aug 93. Study dates Apr - Jun 93. Batch: CFQ 6664 [^{14}C]-labeled Metformin specific activity 1.14 GBq·$mmol^{-1}$, 31 mCi·$mmol^{-1}$. Non-radiolabeled Batch 21889.

20 mg·kg^{-1} [ca. 1.85 MBq (50 μCi)] [^{14}C]-Metformin was administered to 3 female New Zealand White rabbits with collection of urine and plasma for up to 24 h.

Pooled samples of urine and plasma analyzed by TLC (supported by mass spectra analysis) showed the presence of 2 radioactive components, one co-chromatographing with [^{14}C]-Metformin and the other with 1-Methyl biguanide.

HFD-510

Statistical Review and Evaluation
of Carcinogenicity Studies

JUN - 2 1994

NDA #: 20-357 Date:

Applicant: Lipha Pharmaceuticals, Inc.

Name of Drug: Glucophage Tablets (Metformin Hydrochloride)

Documents Reviewed:

1. NDA submission volumes 1.14 to 1.19, "Metformin Hydrochloride: 91 week (dietary administration) carcinogenicity study in the mouse", Report No. 7352-537/11, Report Date: December, 1992, Date of Document: Sep. 29, 1993.

2. NDA submission volume 1.21, "Chronic toxicity, hormone and oncogenicity study with Metformin Hydrochloride in rats", HWA study No. B2613-101, Report Date: Sep. 17, 1992, Date of Document: Sep. 29, 1993.

3. NDA submission volumes 1.26 to 1.31, "Metformin Hydrochloride: 104 week oral (dietary administration) carcinogenicity study in the rat", Report No. 7476-537/12, Report Date: May, 1993, Date of Document: Sep. 29, 1993.

4. NDA Special Submission, Date of Document, Feb. 24, 1994 and March 22, 1994, Data Diskettes for two animal tumorigenicity studies.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) and one 52-week rat toxicity study were included in this NDA submission. The purpose of these studies was to assess the toxicity and oncogenicity of the test article, Metformin hydrochloride (Glucophage), when given by oral administration to the rats and mice for 104 and 91 weeks. Mr. John R. Short, HFD-511, who is the reviewing CSO of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses.

II. The Rat Study

II. a. Design

In this study, Metformin hydrochloride was orally administered to groups of Crl:CD(SD)BR rats at the following dose levels for 104 weeks. However, owing to reduced survival in females, the necropsies of the females were performed after 99 weeks of dosing when their survival was of the order of 50%.

Group number	Group Description	Dose level mg/kg/day	Number of animals Male	Female
1	Control	0	60+20#	60+20#
2	Low	150	60+20#	60+20#
3	Intermediate I	300	60	60
4	Intermediate II	600	60	60
5	High	900	60+20#	60+20#

satellite animals for laboratory investigations.

The concentration of the test article in the diet was adjusted weekly for the first 16 weeks and then every four weeks on the basis of the group mean body weight and an estimate of the food consumption of main study animals. Blood samples were withdrawn from satellite animals in weeks 7, 25, and 52. The animals were killed and discarded after each bleed.

All animals were examined twice daily to detect any abnormalities. Animals found dead or killed moribund were removed and necropsied to prevent autolysis or cannibalism. In addition each animal was given a detailed clinical examination at weekly intervals. Body weight and food consumption were measured weekly to week 16 and at a 4-week interval thereafter and at necropsy. Treatment was started on July 30, 1990. Necropsies were completed on June 24, 1992 (females) and August 3, 1992 (males). Tissues of all animals in control and high dose groups and of animals that died or were killed in extremis were evaluated by the study pathologist using light microscopy. In addition, the kidneys of males, testes, uterus, ovaries and other tissues with gross lesions and masses of animals in low, intermediate I and intermediate II animals were also examined microscopically.

II. b. Sponsor's Analyses

Kaplan-Meier technique was applied to estimate the survival probability functions. Survival curves were compared by the log-rank procedure. Results of the statistical analyses showed that survival was increased in males treated at 300, 600, and 900 mg/kg/day but in females this increase was at the high dose only (900 mg/kg/day). The survival rates at the end of the treatment period were 47%, 45%, 63%, 60%, and 75% for control, low, medium-1, medium-2, and high dose groups, respectively for males, and 48%, 43%, 47%, 52%, and 63% for control, low, medium-1, medium-2, and high dose groups for females. In males, the decrease in morbidity/mortality in treated groups was due to reductions in various conditions, including skin/appendage lesions and glomerulonephropathy, together with a reduction in deaths due to pituitary tumors (high dose only). In females, the decrease was mainly due to a reduction in mammary tumors. The Kaplan-Meier estimates of survival data are presented in Figures 1 and 2 for males and females, respectively.

The methods described in Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the linear trend in the tumor data. Permutation tests were used to establish the significance of findings wherever fatal or non-fatal tumors were observed with a total incidence of at least 3 but less than 10, or wherever the total combined incidence of both fatal and non-fatal tumors was less than 10 but at least 3. The above test results showed that there was an increase in benign testicular leydig cell tumors in intermediate I and high dose males ($p < 0.01$ and $p < 0.05$, respectively), with no apparent linear trend relationship ($p = 0.037$). There was also an increase in the incidence of benign uterine stromal polyps in high dose females ($p < 0.05$) and linear trend ($p = 0.004$). The sponsor provided the following historical control data of leydig cell tumors and uterine stromal polyps for Crl:CD(SD)BR rats from studies conducted during 1988 to 1993:

Study	1	2	3	4#	5	6#
Animals examined	100	100	70	100	100	100
Finding						
B-Leydig cell tumor	8	4	7	1	7	4
P -tromal Polyp	6	15	7	6	15	3

data not yet audited by Quality Assurance

Comparing the incidence rates of leydig cell tumors and uterine stromal polyps of this study with those of historical control data, the sponsor indicated that the incidence of testicular leydig cell tumor exceeded the historical control range (1% - 10%) only for the intermediate I dose group (15%). The incidence of uterine stromal polyps in high dose group (20%) slightly exceeded the historical control range (3% - 15%).

Table 1 listed the numbers of animals examined microscopically in each group and incidence rates of selected tumors/organs. Noted that only kidneys and testes in male rats and ovaries and uterus in female rats have 95% of the animals examined microscopically. Results of statistical analyses for selected tumors/organs were shown in Table 2.

Based on the above analyses, the sponsor concluded that "treatment with Metformin hydrochloride to rats at doses up to and including 900 mg/kg/day was associated with a marked reduction in body weight gain which had a pronounced effect on the age-related pathology of the

animals, including their overall survival. There were no tumor types of an unusual nature or incidence to suggest a direct carcinogenic or anti-carcinogenic effect of the test article. At the high dose of 900 mg/kg/day, there was an increased incidence of uterine stromal polyps and an increased incidence of unilateral testicular atrophy but the toxicological significance of this latter finding remains unclear."

II.c. Reviewer's Analyses and Comments

The following results are the statistical analyses of two-year carcinogenic study. Since the sponsor did not submit the data of the 52-week rat toxicity study on the computer-readable diskette, the statistical analysis of 52-week study was not performed.

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.0101 and 0.2633 for males and females, respectively. No significant difference in the survival distribution was detected in female rats. However, there is a significant difference in the survival distribution in male rats. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values of the test were 0.0233 and 0.3938 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 3) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-99 weeks for female rats and 0-50, 51-80, and 81-104 weeks for male rats. The actual dose levels 0, 150, 300, 600, and 900 mg/kg/day were the scores assigned to the control, low, medium-1, medium-2, and high dose groups, respectively. The results of the analyses showed that there were significant (at 0.05 level) linear trends in the intercurrent mortality rate in female ($p = 0.0402$) and male rats ($p = 0.0006$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in uterus stromal polyps ($p = 0.0024$) in female rats. The tumor incidence rates between control and high dose females of uterus stromal polyps are significant ($p = 0.0226$; two sided test) different. There was a marginally statistically significant linear trend in testis leydig cell tumor ($p = 0.0997$) in male rats. The pairwise comparison between control and high dose males in testis leydig cell tumor was not significant ($p = 0.1201$; two-sided) different. The incidence rates of uterus stromal polyps in female rats and testes leydig cell tumor in male rats are given in Tables 4 and 5.

As mentioned previously, not all tissues of all animals were examined microscopically. The sponsor listed the tumor incidences and number of animals evaluated for each tumor types in Table 1. Due to the constraint of the format of the data sent by the sponsor, the above analyses are assumed that all of animals are examined microscopically for selected tumor/organ types. For example, there are 60, 59, 60, 60, and 60 male rats which were examined microscopically for testes in control, low, medium-1, medium-2, and high dose groups. However, the reviewer assumed that there were 60 male rats examined microscopically for testes for each group.

III. The Mouse Study

III. a. Design

In this study, 240 male and 240 female Charles River Crl:CD-1(SD) BR mice were equally and randomly assigned into three treated groups and one control group. Metformin hydrochloride was orally administered at doses of 150, 450, and 1500 mg/kg/day to the mouse for 91 weeks. Additional 24 animals/sex were selected in the control, low, and high dose groups used as satellite animals for proof of absorption only. All animals were examined twice daily to detect any abnormalities. Animals found dead or killed moribund were removed and necropsied to prevent autolysis or cannibalism. In addition each animal was given a detailed clinical examination at weekly intervals. Body weight and food consumption were measured at weekly intervals to week 16 and at 4-week intervals thereafter and at necropsy. The animals were received on 27 June 1990, treatment was started on 16 July 1990 and necropsies were completed on 23 April 1992. Tissues of all animals in control and high dose groups and of animals of other groups that died or were killed in extremis were evaluated by the study pathologist using light microscopy. In addition, the kidneys of low and intermediate dose animals were examined microscopically after macroscopic findings were seen at necropsy in the high dose animals.

III. b. Sponsor's Analyses

Kaplan-Meier technique was applied to estimate the survival probability functions. Survival curves were compared by the log-rank procedure. Results of the statistical analyses showed that morbidity and mortality was slightly increased in intermediate and high dose males ($p < 0.05$ for both). At the end of the treatment period, the survival was 57%, 47%, 42%, and 38% for control, low, medium, and high dose groups, respectively for males, and 55%, 57%, 55%, and 65% for control, low, medium, and high dose groups for females. The Kaplan-Meier estimates of survival data are presented in Figures 3 and 4 for males and females, respectively.

The procedures of Peto et al. (1980) and exact permutation trend test were used to test any dose-dependent trend in the number of tumor carriers. The above test results showed that there was a reduced incidence of liver tumors in high dose males compared with control

males ($p < 0.05$). This decrease, in animals which were probably physiologically abnormal because of cystic kidney changes, was considered not to be of any biological significance. Table 6 listed the numbers of animals examined microscopically in each group and incidence rates of selected tumors/organs. Noted that only kidneys have 95% of the animals examined microscopically. Table 7 listed the statistical analyses results for selected tumors/organs.

Based on the above analyses, the sponsor stated that "treatment with Metformin Hydrochloride by oral (dietary) administration at dose levels 150, 450, and 1500 mg/kg/day in mice was associated with cystic nephropathy in all male treated groups and intermediate and high dose females. The incidence of tumors, however, was considered not to have been affected by treatment."

III.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.1839 and 0.7022 for males and females, respectively. Hence, no statistically significant difference (at 0.05 level) in the survival distribution was detected in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.1859 and 0.76 for males and females, respectively.

The intercurrent mortality rates for both male and female mice (see Table 8) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-91 weeks. The actual dose levels 0, 150, 450, and 1500 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female mice ($p = 0.1588$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male mice ($p = 0.0307$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was a marginally statistically significant (at 0.05 level) linear trend in the kidney adenoma in male mice ($p = 0.0575$). No significant difference in the incidence rates between control and high dose males of kidney adenoma ($p = 0.4786$) was detected. The incidence rates of this tumor are listed in Table 9.

IV. Summary

IV. a. The Rat Study

The oncogenic potential of Metformin hydrochloride was evaluated in

this rat study when orally administered to Crl:CD(SD)BR rats at the following concentrations: 0, 150, 300, 600, and 900 mg/kg/day for 104 weeks for males and 99 weeks for females.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no significant difference in the survival distribution in female rats. However, there is a significant difference in the survival distribution in male rats.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. The results of the analyses showed that there were significant (at 0.05 level) linear trends in the intercurrent mortality rate in female ($p = 0.0402$) and male rats ($p = 0.0006$).

Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in uterus stromal polyps ($p = 0.0024$) in female rats. The tumor incidence rates between control and high dose females of uterus stromal polyps are significant ($p = 0.0226$; two sided test) different. There was a marginally statistically significant linear trend in testis leydig cell tumor ($p = 0.0997$) in male rats. The pairwise comparison between control and high dose males in testis leydig cell tumor was not significant ($p = 0.1201$; two-sided) different.

IV. b. The Mouse study

The oncogenic potential of Metformin hydrochloride was evaluated in this mouse study when orally administered to the animals at doses of 150, 450, and 1500 mg/kg/day for 91 weeks.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. No statistically significant difference (at 0.05 level) in the survival distribution was detected in both sexes in both tests.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female mice ($p = 0.1588$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male mice ($p = 0.0307$).

Results of tumor data analyses showed that there was a marginally statistically significant (at 0.05 level) linear trend in the kidney adenoma in male mice ($p = 0.0575$). No significant difference in the

incidence rates between control and high dose males of kidney adenoma ($p = 0.4786$) was detected.

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 6/1/94
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA 20-357
HFD-510/Dr. Sobel
HFD-510/Mr. Short
HFD-510/Dr. Hertig
HFD-710/Chron
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-502/Assistant Director (Pharmacology)
HFD-715/DRU 2.1.1, Glucophage, Lipha Pharm. Inc.

FIGURE 1

Group survival (%) – males

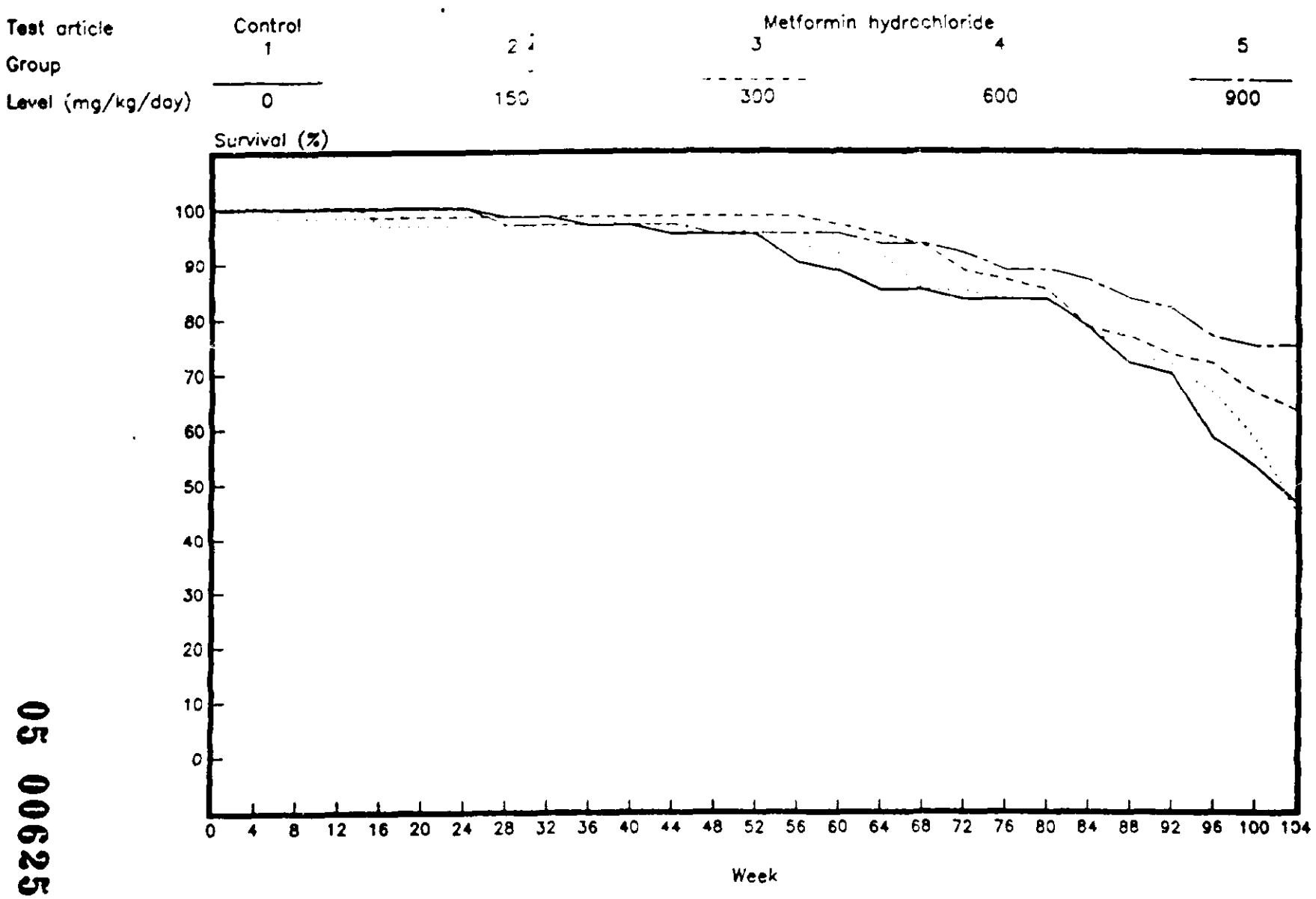


Figure 1

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FIGURE 2

Group survival (%) – females

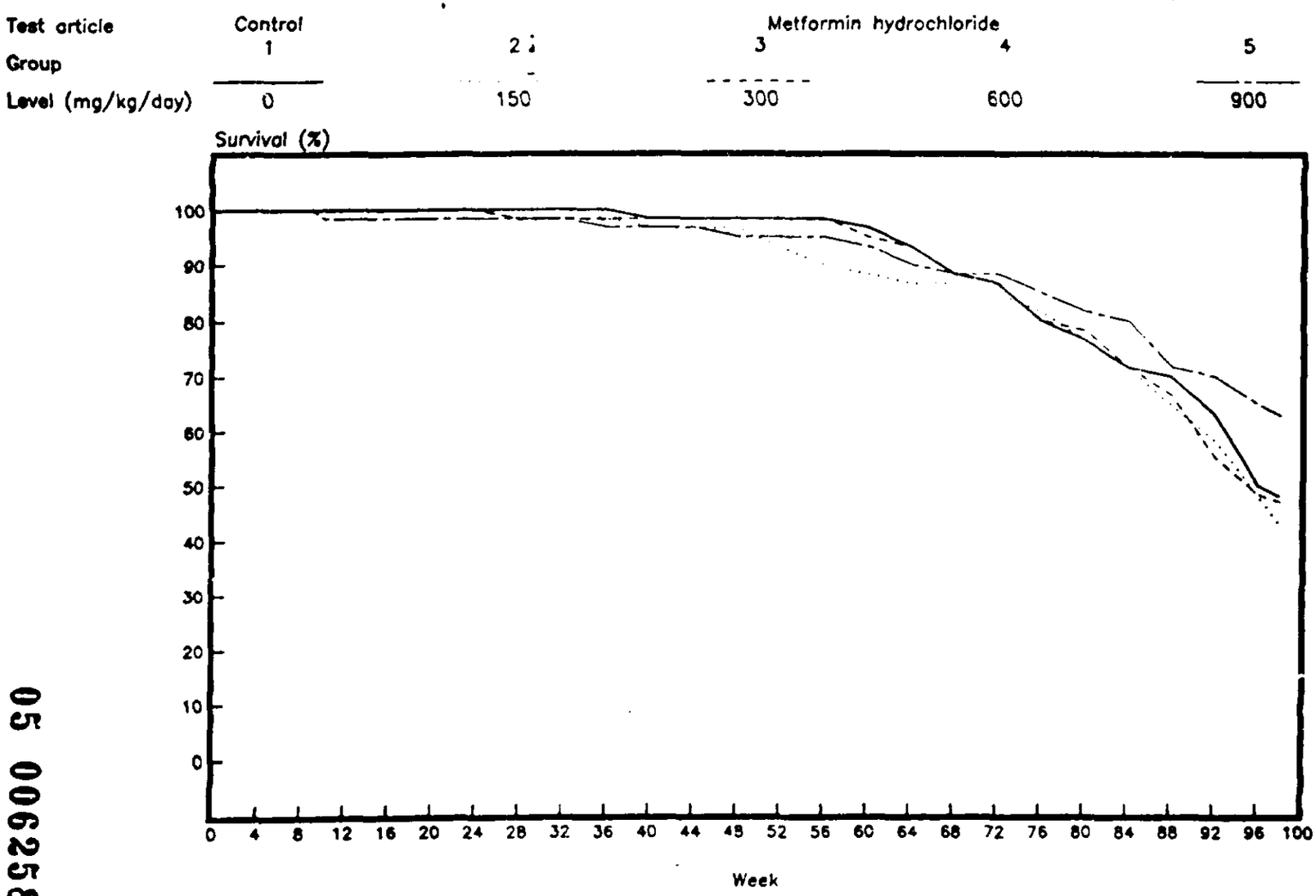

Figure 2

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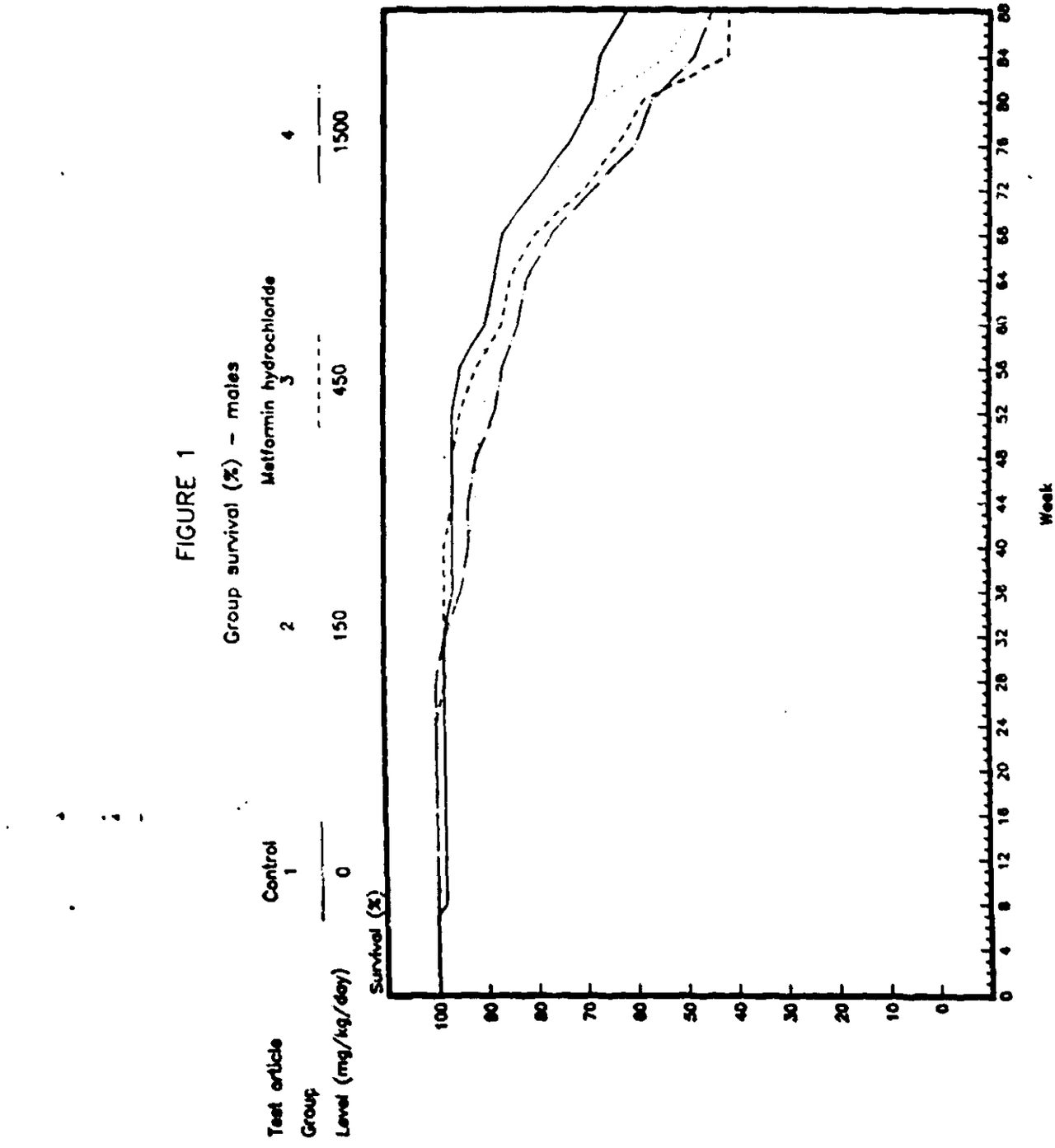
FIGURE 1
Group survival (%) - males
Test article
Group
Level (mg/kg/day)
Control
1
0
2
150
Metformin hydrochloride
3
450
4
1500
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72
76
80
84
88
Week

Figure 4

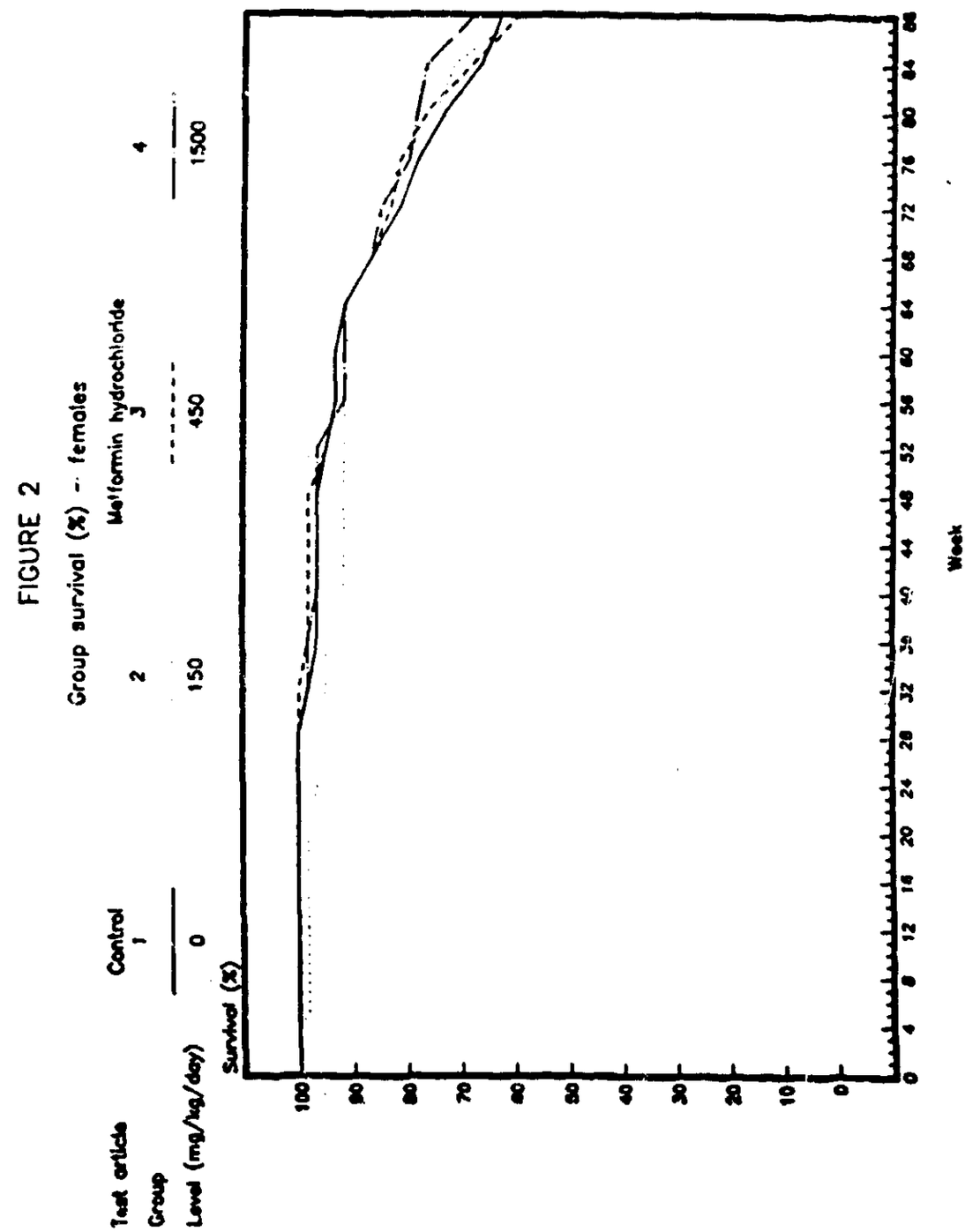
FIGURE 2
Group survival (%) - females
Test article
Group
Level (mg/kg/day)
Control
1
0
Metformin hydrochloride
2
150
3
450
4
1500
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72
76
80
84
88
Week

TABLE 10.7
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

DOSE LEVELS (MG/KG/DAY): GP 1=0, GP 2=150, GP 3=300, GP 4=600, GP 5=900

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

PRINTED: 24-MAR-93
PAGE: 1

STUDY NUMBER: 53712

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		MALE					FEMALE				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** TOP OF LIST **											
BRAIN	NUMBER EXAMINED:	60	32	22	24	60	60	36	32	31	60
--M-LYMPHOMA-LYMPHOCYTIC		0	0	0	0	1	0	1	0	0	0
--B-MENINGIOMA		1	0	0	0	0	1	0	0	1	0
--M-GLIOMA		0	2	0	1	0	0	0	0	0	0
PITUITARY	NUMBER EXAMINED:	60	47	27	28	59	60	48	50	39	60
--B-ADENOMA		27	24	21	15	18	45	38	36	26	36
SKIN SUBCUTIS	NUMBER EXAMINED:	60	44	45	34	60	60	53	56	48	60
--B-LIPOMA		4	8	2	0	1	2	0	2	0	0
--B-DERMAL FIBROMA		12	0	6	3	3	0	0	0	0	0
--B-FIBROLIPOMA		1	0	0	0	0	0	0	0	0	0
--B-FIBROMA		10	4	6	5	4	0	2	0	0	0
--B-NEUROFIBROMA		0	0	0	0	1	0	0	0	0	0
--B-SEBACEOUS TUMOUR		1	0	0	0	0	0	0	0	0	0
--B-KERATOACANTHOMA		10	0	5	1	0	0	2	0	0	0
--B-PAPILLOMA		3	2	1	1	1	0	0	0	0	1
--B-BASAL CELL TUMOUR		0	1	2	0	1	0	0	1	0	0
--B-HAEMANGIOMA		0	0	0	0	1	0	0	0	0	0
--M-SARCOMA		2	0	3	2	4	1	1	2	0	0
--M-LIPOSARCOMA		0	1	0	0	0	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA		0	1	0	0	0	0	0	1	0	0
--M-SQUAMOUS CARCINOMA		0	0	1	1	0	0	0	0	1	0
--M-BASAL CELL CARCINOMA		0	0	1	0	0	0	1	0	0	0
--M-HAEMANGIOSARCOMA		1	0	0	1	0	0	0	0	0	0
MAMMARY GLAND	NUMBER EXAMINED:	2	0	1	0	1	60	52	49	45	60
--B-FIBRO/ADENOMA		2	0	1	0	1	38	37	31	26	26
--M-CARCINOMA		0	0	0	0	0	4	4	10	10	8
--M-SARCOMA		0	0	0	0	0	0	1	1	0	0

Table 1
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TABLE 10.7
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

DOSE LEVELS (MG/KG/DAY): GP 1=0, GP 2=150, GP 3=300, GP 4=600, GP 5=900

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

STUDY NUMBER: 53712

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
LIVER	NUMBER EXAMINED:	60	48	32	33	60	60	44	42	35	60
--B-ADENOMA		1	2	0	2	1	2	0	0	0	0
--M-CARCINOMA		0	1	0	1	0	0	0	1	0	0
SPLEEN	NUMBER EXAMINED:	60	35	27	26	60	60	37	34	32	60
--M-HAEMANGIOSARCOMA		0	0	0	0	0	0	1	0	0	0
PANCREAS	NUMBER EXAMINED:	60	33	21	24	60	60	35	32	31	60
--B-EXOCRINE ADENOMA		1	0	2	0	1	0	0	0	0	0
--B-ISLET CELL ADENOMA		1	1	1	0	1	1	0	1	0	1
--M-ISLET CELL CARCINOMA		0	0	0	0	0	0	0	0	1	0
MES.LYMPH NODE	NUMBER EXAMINED:	60	32	22	24	60	60	36	32	30	59
--B-HAEMANGIOMA		2	0	0	0	1	0	0	0	0	0
--B-LYMPHANGIOMA		0	0	0	0	0	1	0	0	0	0
STOMACH	NUMBER EXAMINED:	60	35	25	27	60	59	37	36	31	60
--B-PAPILLOMA		0	1	0	0	0	0	0	0	0	0
ADRENAL	NUMBER EXAMINED:	60	36	24	27	60	60	45	41	39	60
--B-ADENOMA		0	0	0	1	1	0	0	1	1	0
--B-PHAEOCHROMOCYTOMA		12	9	2	2	3	2	2	1	2	0
--M-PHAEOCHROMOCYTOMA		0	1	1	0	0	0	0	1	0	2
--M-CARCINOMA		1	0	0	0	0	0	0	0	0	0
KIDNEY	NUMBER EXAMINED:	59	60	50	60	60	60	37	34	33	60
--B-LIPOMATOUS TUMOUR		0	0	0	1	0	0	0	0	0	0
--M-RENAL LIPOSARCOMA		0	1	1	1	0	0	0	0	0	0

TABLE 10.7
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

DOSE LEVELS (MG/KG/DAY): GP 1=0, GP 2=150, GP 3=300, GP 4=600, GP 5=900

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

STUDY NUMBER: 53712

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE---------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
OVARY	NUMBER EXAMINED:	0	0	0	0	0	60	60	60	59	60
--B-GRANULOSA THECA TUMOUR		0	0	0	0	0	1	0	0	0	0
--B-TUBULAR ADENOMA		0	0	0	0	0	0	0	0	1	1
--M-GRANULOSA-THECA TUMOUR		0	0	0	0	0	0	0	0	1	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	60	57	60	57	60
--B-LEIOMYOMA		0	0	0	0	0	0	0	0	0	1
--B-STROMAL POLYP		0	0	0	0	0	3	4	4	7	12
--M-SARCOMA		0	0	0	0	0	0	1	0	1	0
--M-STROMAL SARCOMA		0	0	0	0	0	1	0	0	0	0
TESTIS	NUMBER EXAMINED:	60	59	60	60	60	0	0	0	0	0
--B-LEYDIG CELL TUMOUR		1	2	9	2	7	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	54	27	17	22	58	57	34	30	30	57
--B-THYMOMA		0	0	0	0	1	0	0	0	0	0
--M-CARCINOMA		0	0	0	0	0	0	0	0	0	1
HEART	NUMBER EXAMINED:	60	34	22	24	60	60	36	32	31	60
--B-SCHWANN CELL TUMOUR		3	0	0	0	0	0	0	0	0	0
THYROID	NUMBER EXAMINED:	60	28	22	23	60	60	34	30	34	60
--B-FOLLICULAR ADENOMA		3	2	0	1	3	0	0	0	0	0
--B-C-CELL ADENOMA		12	3	2	2	8	9	2	1	3	6
PARATHYROID	NUMBER EXAMINED:	55	29	20	19	56	56	30	31	26	53
--B-ADENOMA		0	0	0	0	0	0	0	0	1	0
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	4	2	2	3	4	0	1	1	0	2
--M-LYMPHOMA LYMPHOCYTIC		2	0	0	0	0	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

TABLE 10.7
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

DOSE LEVELS (MG/KG/DAY): GP 1=0, GP 2=150, GP 3=300, GP 4=600, GP 5=900

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

STUDY NUMBER: 53712

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	4	2	2	3	4	0	1	1	0	2
--M-LEUKAEMIA		0	1	1	0	0	0	0	0	0	0
--M-LEUKAEMIA GRANULOCYTIC		0	0	0	0	0	0	1	0	0	1
--M-LEUKAEMIA LYMPHOCYTIC		2	1	1	3	3	0	0	1	0	1
--M-LYMPHOMA HISTIOCYTIC		0	0	0	0	1	0	0	0	0	0
ORAL CAVITY	NUMBER EXAMINED:	7	4	2	1	4	5	6	4	6	4
--M-SARCOMA		1	0	0	0	0	0	0	0	0	0
ABDOMINAL CAVITY	NUMBER EXAMINED:	2	1	2	2	0	1	2	1	0	1
--M-SARCOMA		0	1	0	0	0	0	0	0	0	0
--M-CARCINOMA		1	0	0	0	0	0	0	0	0	0
TAIL	NUMBER EXAMINED:	22	21	38	36	28	20	17	17	35	30
--B-PAPILLOMA		0	1	1	1	0	0	1	0	0	0
BONE	NUMBER EXAMINED:	1	0	0	0	2	0	1	0	1	0
--M-OSTEOSARCOMA		0	0	0	0	1	0	0	0	0	0
--B-CHONDROMA		0	0	0	0	1	0	0	0	0	0
CONNECTIVE TISS	NUMBER EXAMINED:	0	1	0	0	1	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA		0	1	0	0	1	0	0	0	0	0
HEAD	NUMBER EXAMINED:	0	3	2	0	0	0	0	0	0	0
--B-FIBROMA		0	0	1	0	0	0	0	0	0	0
ZYMBAL GLAND	NUMBER EXAMINED:	1	1	0	0	0	0	0	0	0	0
--M-CARCINOMA		1	1	0	0	0	0	0	0	0	0

** END OF LIST **

TABLE 10.8

TUMOUR INCIDENCE - STATISTICAL ANALYSIS
KEY TO CLASSIFICATION

Skin 1	skin B-lipoma
	skin M-liposarcoma
Skin 2	skin B-dermal fibroma
	skin B-fibrolipoma
	skin B-fibroma
	skin B-neurofibroma
	head B-fibroma
	skin M-sarcoma
	oral cavity M-sarcoma
Skin and tail	skin B-keratoacanthoma
	skin B-papilloma
	skin M-squamous carcinoma
	tail B-papilloma
Skin and mesenteric lymph node	skin M-haemangiosarcoma
	skin B-haemangioma
	mesenteric lymph node B-haemangioma
	mesenteric lymph node B-lymphangioma
B	benign
M	malignant

TABLE 10.8

Tumour incidence males - statistical analysis
Results of tests for a decreasing and increasing incidence

Tumour Type		Number of tumour bearing animals Gp 1	Gp 5	Included in analysis	p-values for increased tumour incidence Group 1 vs Group 5	p-values for decreased tumour incidence Group 1 vs Group 5	Method of analysis
Skin 1	F	1	0	ALL	0.927	0.350	P
	NF	3	1				
	ALL	4	1				
Skin 2	F	6	5	ALL	0.992	0.008**	L
	NF	17	7	F	0.699	0.301	L
	ALL	23	12	NF	0.999	0.001**	L
Skin and Tail	F	0	1	ALL	0.991	0.009**	L
	NF	13	1	NF	0.999	0.001***	L
	ALL	13	2				
Skin and Mes lymph node	F	0	1	ALL	0.767	0.595	P
	NF	3	1				
	ALL	3	2				
Adrenal phaeochromocytoma	NF	12	3	NF	0.982	0.018*	L
Haem/lymph/retic all sites	F	4	1	ALL	0.751	0.513	P
	NF	0	3				
	ALL	4	4				
Heart schwann cell tumour	F	1	0	ALL	1.000	0.128	P
	NF	2	0				
	ALL	3	0				
Thyroid follicular adenoma	NF	3	3	NF	0.672	0.670	P
Thyroid c-cell adenoma	NF	12	8	NF	0.922	0.078	L
Pituitary adenoma	F	6	2	ALL (U as F)	0.965	0.035*	L
	NF	20	16	ALL (U as NF)	0.956	0.044*	L
	U	1	0	NF (U as F)	0.915	0.085	L
	ALL	27	18	NF (U as NF)	0.926	0.074	L
				F (U as F)	0.989	0.058	P
				F (U as NF)	0.979	0.098	P

KEY

F = Fatals
NF = Non-fatals
L = Large sample tests
P = Permutation tests

TABLE 10.8

Tumour incidence females - statistical analysis
Results of tests for a decreasing and increasing incidence

Tumour Type		Number of tumour bearing animals Gp 1	Gp 5	Included in analysis	p-values for increased tumour incidence Group 1 vs Group 5	p-values for decreased tumour incidence Group 1 vs Group 5	Method of analysis
Mammary all sites	F	18	10	ALL	0.939	0.061	L
	NF	21	20				
	ALL	39	30				
Adrenal phaeochromocytoma	F	0	1	ALL	0.718	0.665	P
	NF	2	1				
	ALL	2	2				
Thyroid c-cell adenoma	NF	9	6	ALL	0.791	0.209	L
Pituitary adenoma	F	11	8	ALL	0.891	0.109	L
	NF	34	28				
	ALL	45	36				

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9
Tumour incidence males - statistical analysis
Results of tests for increasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
Testis leydig cell tumour	NF	1	2	9	2	7	NF	0.037*	0.264	0.005**	0.356	0.032*	L
Kidneys all sites	F	0	0	1	0	0	ALL	0.317	0.500	0.523	0.167		P
	NF	0	1	0	2	0							
	ALL	0	1	1	2	0							

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence males - statistical analysis
Results of tests for decreasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals					Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
		Gp 1	Gp 2	Gp 3	Gp 4	Gp 5							
Testis leydig cell tumour	NF	1	2	9	2	7	NF	0.963	0.736	0.995	0.644	0.968	L
Kidneys all sites	F	0	0	1	0	0	ALL	0.757	1.000	1.000	1.000		P
	NF	0	1	0	2	0							
	ALL	0	1	1	2	0							

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence females - statistical analysis
Results of tests for increasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
Uterus stromal polyp	F	0	0	0	0	1	ALL	0.004**	0.371	0.340	0.118	0.013*	L
	NF	3	4	4	7	11	NF	<0.001***	0.371	0.340	0.118	0.013*	L
	ALL	3	4	4	7	12							
Uterus sarcoma and stromal sarcoma	F	1	1	0	1	0	F	0.795	0.735	1.000	0.739	1.000	P

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence females - statistical analysis
Results of tests for decreasing dose response and pairwise tests

Tumour Type	Number of tumour bearing animals						Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
		Gp 1	Gp 2	Gp 3	Gp 4	Gp 5							
Uterus stromal polyp	F	0	0	0	0	1	ALL	0.996	0.629	0.660	0.882	0.987	L
	NF	3	4	4	7	11	NF	>0.999	0.629	0.660	0.882	0.987	L
	ALL	3	4	4	7	12							
Uterus sarcoma and stromal sarcoma	F	1	1	0	1	0	F	0.251	0.764	0.531	0.760	0.466	P

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

Table 3
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Med-1			Med-2			High		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	3	5	60	2	3.3	60	1	1.6	60	4	6.6	60	3	5
51-80	57	7	12.3	58	10	17.2	59	8	13.5	56	5	8.9	57	4	7.0
81-104	50	22	44.0	48	21	43.7	51	13	25.5	51	15	29.4	53	8	15.1
Term.	28			27			38			36			45		

Female Rats

Weeks	Control			Low			Med-1			Med-2			High		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	1	1.6	60	4	6.6	60	1	1.6	60	4	6.6	60	3	5
51-80	59	13	22.0	56	10	17.8	59	12	20.3	56	13	23.2	57	8	14.0
81-99	46	17	36.9	46	22	47.8	47	19	40.4	43	14	32.5	49	11	22.4
Term.	29			24			28			29			38		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 4
Tumor Incidence Rates
Female Rats, Uterus Stromal Polyps

Weeks	Control		Low		Med-1		Med-2		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	4	0	1	1	4	0	3
51-80	0	13	0	10	0	12	0	13	1	8
81-99	1	17	3	22	0	19	2	14	3	11
terminal	2	29	1	24	4	28	4	29	8	38
Total	3	60	4	60	4	60	7	60	12	60

Trend test: p = 0.0024
Pairwise Comparison: Control vs. High: p = 0.0226

Table 5
Tumor Incidence Rates
Male Rats, Testes Leydig Cell Tumor

Weeks	Control		Low		Med-1		Med-2		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	2	0	1	0	4	0	3
51-80	0	7	0	10	0	8	0	5	0	4
81-104	0	22	1	21	3	13	0	15	1	8
terminal	1	28	1	27	6	38	2	36	6	45
Total	1	60	2	60	9	60	2	60	7	60

Trend test: p = 0.0997
Pairwise Comparison: Control vs. High: p = 0.1201

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

TABLE 10.8
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

Dose levels (mg/Kg/day): Group 1 = 0, 2 = 150, 3 = 450, 4 = 1500

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

PRINTED: 14-DEC-92
PAGE: 1

STUDY NUMBER: 53711

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:		60	60	60	60	60	60	60	60
** TOP OF LIST **									
PITUITARY	NUMBER EXAMINED:	54	29	28	54	57	25	24	57
--B-ADENOMA		0	0	0	0	0	1	0	0
SKIN SUBCUTIS	NUMBER EXAMINED:	60	39	40	60	59	36	38	60
--B-FIBROMA		0	0	0	1	0	0	0	0
--B-PAPILLOMA		0	0	0	0	0	0	1	0
--M-SARCOMA		1	3	0	1	1	0	2	0
--M-HAEMANGIOSARCOMA		0	0	0	1	0	0	1	0
MAMMARY GLAND	NUMBER EXAMINED:	0	0	1	0	56	25	23	53
--M-CARCINOMA		0	0	0	0	0	1	0	1
FEMUR + MARROW	NUMBER EXAMINED:	60	32	35	60	59	26	26	60
--B-HAEMANGIOMA		1	0	0	1	0	0	0	0
--M-OSTEOSARCOMA		0	0	1	0	0	0	0	0
--M-HAEMANGIOSARCOMA		0	1	0	0	0	0	0	0
LIVER	NUMBER EXAMINED:	60	44	43	60	59	33	31	60
--B-ADENOMA		20	11	10	8	0	0	1	0
--B-HAEMANGIOMA		2	1	1	0	0	0	0	0
--M-CARCINOMA		2	3	2	0	0	0	0	1
SPLEEN	NUMBER EXAMINED:	60	35	38	60	59	34	35	59
--B-HAEMANGIOMA		0	0	0	1	1	0	0	1
--M-HISTIOCYTIC SARCOMA		0	0	0	0	0	0	1	0
PANCREAS	NUMBER EXAMINED:	58	32	33	60	58	24	25	59
--B-ISLET CELL ADENOMA		1	0	0	0	0	0	0	0

Table 6

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TABLE 10.8
GROUP INCIDENCE: HISTOPATHOLOGY ALL ANIMALS: NEOPLASTIC DATA

Dose levels (mg/Kg/day): Group 1 = 0, 2 = 150, 3 = 450, 4 = 1500

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

PRINTED: 14-DEC-92
PAGE: 2

STUDY NUMBER: 53711

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:		60	60	60	60	60	60	60	60
MES:LYMPH NODE	NUMBER EXAMINED:	58	32	36	57	55	24	25	56
--B-HAEMANGIOMA		0	0	1	0	0	0	0	0
DUODENUM	NUMBER EXAMINED:	52	26	33	52	56	21	24	58
--B-ADENOMATOUS POLYP		0	0	0	0	0	1	1	0
CAECUM	NUMBER EXAMINED:	51	28	28	48	50	19	22	53
--M-LEIOMYOSARCOMA		0	0	0	0	1	0	0	0
ADRENAL	NUMBER EXAMINED:	60	33	35	60	59	27	26	59
--B-PHAEOCHROMOCYTOMA		0	0	0	0	1	0	0	0
KIDNEY	NUMBER EXAMINED:	60	60	60	60	59	60	59	59
--B-ADENOMA		0	0	0	2	0	0	0	0
TESTIS	NUMBER EXAMINED:	60	38	36	60	0	0	0	0
--B-LEYDIG CELL TUMOUR		0	5	2	2	0	0	0	0
PROSTATE	NUMBER EXAMINED:	57	31	33	55	0	0	0	0
--B-ADENOMA		1	0	0	0	0	0	0	0
OVARY	NUMBER EXAMINED:	0	0	0	0	59	58	48	58
--B-PAPILLARY ADENOMA		0	0	0	0	0	0	0	1
--B-HAEMANGIOMA		0	0	0	0	0	0	0	1
--B-LUTEOMA		0	0	0	0	0	2	1	2
UTERUS	NUMBER EXAMINED:	0	0	0	0	59	53	52	57
--B-GRANULAR CELL TUMOUR		0	0	0	0	1	0	0	0
--B-HAEMANGIOMA		0	0	0	0	2	6	1	1
--B-STROMAL POLYP		0	0	0	0	1	0	3	2

** CONTINUED ON NEXT PAGE **

TABLE 10.8
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

Dose levels (mg/Kg/day): Group 1 = 0, 2 = 150, 3 = 450, 4 = 1500

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

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STUDY NUMBER: 537.1

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---							
SEX:		-------MALE-------				-----FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:		60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **									
UTERUS	NUMBER EXAMINED:	0	0	0	0	59	53	52	57
--B-LEIOMYOMA		0	0	0	0	6	0	0	2
--M-SARCOMA		0	0	0	0	0	0	1	0
--M-HISTIOCYTIC SARCOMA		0	0	0	0	3	0	3	1
LUNG	NUMBER EXAMINED:	60	39	44	60	60	32	30	60
--B-ADENOMA		13	13	11	15	7	5	5	4
--M-CARCINOMA		1	1	3	2	1	0	1	0
OESOPHAGUS	NUMBER EXAMINED:	60	33	35	60	60	26	26	60
--B-PAPILLOMA		0	1	0	0	0	0	0	0
ABDOMINAL CAVITY	NUMBER EXAMINED:	4	4	5	1	4	5	4	2
--M-OSTEOSARCOMA		0	0	0	1	0	0	0	0
TAIL	NUMBER EXAMINED:	22	23	23	28	27	28	27	26
--B-SCHWANNOMA		0	0	0	1	0	0	0	0
EAR	NUMBER EXAMINED:	17	7	4	9	3	1	1	1
--B-HAEMANGIOMA		1	0	0	0	0	0	0	0
BONE	NUMBER EXAMINED:	0	3	0	0	0	0	0	0
--M-SQUAMOUS CARCINOMA		0	1	0	0	0	0	0	0
FOOT/LEG	NUMBER EXAMINED:	2	0	0	1	0	1	0	1
--M-HAEMANGIOSARCOMA		1	0	0	0	0	0	0	0
HARDERIAN GLAND	NUMBER EXAMINED:	0	1	0	0	0	0	0	0
--B-ADENOMA		0	1	0	0	0	0	0	0

TABLE 10.8
GROUP INCIDENCE: HISTOPATHOLOGY: ALL ANIMALS: NEOPLASTIC DATA

Dose levels (mg/Kg/day): Group 1 = 0, 2 = 150, 3 = 450, 4 = 1500

HAZLETON UK
HARROGATE, NORTH YORKSHIRE, ENGLAND

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PAGE: 4

STUDY NUMBER: 53711

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	60	60	60	60	60	50	60	60
CONNECTIVE TISS	NUMBER EXAMINED:	0	0	0	1	0	0	0	0
--M-HISTIOCYTIC SARCOMA		0	0	0	1	0	0	0	0
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	2	3	1	3	9	10	5	8
--M-LYMPHOMA		0	0	0	0	0	1	0	0
--M-LYMPHOMA LYMPHOCYTIC		2	3	1	2	8	5	4	5
--M-LYMPHOMA MIXED		0	0	0	1	1	3	1	2
--M-LYMPHOMA-HISTIOCYTIC SARCOMA		0	0	0	0	0	1	0	1

** END OF LIST **

TABLE 10.9

Tumour incidence males
Statistical analysis for an increasing dose response and pairwise tests

Test article	Control	Metformin hydrochloride		
Group	1	2	3	4
Level (mg/kg/day)	0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Liver adenoma and carcinoma	F	1	3	0	0	ALL	0.959	0.894	0.940	0.976	L
	NF	20	9	11	8	F	0.941	0.295	1.000	1.000	P
	C	21	12	11	8	NF	0.996	0.980	0.952	0.985	L
Liver haemangioma	NF	2	1	1	0	NF	0.903	0.891	0.816	1.000	P
Haem/lymph/retic all sites	F	2	2	0	1	ALL	0.357	0.471	0.845	0.644	P
	NF	0	1	1	2						
	C	2	3	1	3						
Lung adenoma and carcinoma	F	1	2	3	2	ALL	0.224	0.491	0.514	0.267	L
	NF	13	12	9	13						
	C	14	14	12	15						
Skin subcutis sarcoma and fibroma	F	0	3	0	1	ALL	0.362	0.289	1.000	0.384	P
	NF	1	0	0	1						
	C	1	3	0	2						
Testis Leydig cell tumour	NF	0	5	2	2	NF	0.454	0.017	0.324	0.247	P

KEY: F - fatals
NF - non-fatals
C - combined

L - large sample tests
P - permutation tests

N.B. The pairwise comparison for group 2 versus control for testis Leydig cell tumour is not significant when using Bonferroni adjustments

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TABLE 10.9

Tumour incidence females
Statistical analysis for an increasing dose response and pairwise tests

Test article		Control	Metformin hydrochloride		
Group		1	2	3	4
Level (mg/kg/day)		0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Haem/lymph/retic all sites	F	2	7	2	3	ALL (U as NF)	0.685	0.406	0.860	0.638	L
	NF	7	3	2	5	ALL (U as F)	0.688	0.406	0.862	0.638	L
	U	0	0	1	0						
	C	9	10	5	8						
Lung adenoma and carcinoma	F	1	0	0	0	ALL	0.828	0.772	0.700	0.886	L
	NF	7	5	6	4						
	C	8	5	6	4						
Skin subcutis sarcoma and fibroma	F	1	0	2	0	F	0.699	1.000	0.508	1.000	P
Uterus haemangioma	NF	2	5	1	1	NF	0.983	0.076	0.721	0.769	L
Uterus histiocytic sarcoma, sarcoma and stromal polyp	F	1	0	4	1	ALL	0.704	0.999	0.769	0.937	L
	NF	9	0	3	4						
	C	10	0	7	5						
Ovary luteoma	NF	0	2	1	2	NF	0.194	0.254	0.500	0.228	P

KEY: F - fatals
NF - non-fatals
C - combined
U - uncertain

L - large sample tests
P - permutation tests

TABLE 10.10

Tumour incidence males
Statistical analysis for a decreasing dose response and pairwise tests

Test article	Control	Metformin hydrochloride		
Group	1	2	3	4
Level (mg/kg/day)	0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Liver adenoma and carcinoma	F	1	3	0	0	ALL	0.041 *	0.106	0.060	0.024 *	L
	NF	20	9	11	8	F	0.098	0.943	0.504	0.527	P
	C	21	12	11	8	NF	0.004 **	0.020 *	0.048 *	0.015 *	L
Liver haemangioma	NF	2	1	1	0	NF	0.159	0.482	0.615	0.352	P
Haem/lymph/retic all sites	F	2	2	0	1	ALL	0.671	0.831	0.558	0.720	P
	NF	0	1	1	2						
	C	2	3	1	3						
Lung adenoma and carcinoma	F	1	2	3	2	ALL	0.776	0.509	0.486	0.733	L
	NF	13	12	9	13						
	C	14	14	12	15						
Skin subcutis sarcoma and fibroma	F	0	3	0	1	ALL	0.668	0.945	0.576	0.927	P
	NF	1	0	0	1						
	C	1	3	0	2						
Testis Leydig cell tumour	NF	0	5	2	2	NF	0.549	1.000	1.000	1.000	P

KEY: F - fatals
NF - non-fatals
C - combined

L - large sample tests
P - permutation tests

* p<0.05
** p<0.01
*** p<0.001

TABLE 10.10

Tumour incidence females
Statistical analysis for a decreasing dose response and pairwise tests

Test article	Control	Metformin hydrochloride		
Group	1	2	3	4
Level (mg/kg/day)	0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Haem/lymph/retic all sites	F	2	7	2	3	ALL (U as NF)	0.315	0.594	0.140	0.362	L
	NF	7	3	2	5	ALL (U as F)	0.312	0.594	0.138	0.362	L
	U	0	0	1	0						
	C	9	10	5	8						
Lung adenoma and carcinoma	F	1	0	0	0	ALL	0.172	0.228	0.300	0.114	L
	NF	7	5	6	4						
	C	8	5	6	4						
Skin subcutis sarcoma and fibroma	F	1	0	2	0	F	0.347	0.489	0.871	0.478	P
Uterus haemangioma	NF	2	6	1	1	NF	0.017 *	0.924	0.279	0.231	L
Uterus histiocytic sarcoma, sarcoma and stromal polyp	F	1	0	4	1	ALL	0.296	0.001 **	0.231	0.064	L
	NF	9	0	3	4						
	C	10	0	7	5						
Ovary luteoma	NF	0	2	1	2	NF	0.835	1.000	1.000	1.000	P

KEY: F - fatals
NF - non-fatals
C - combined
U - uncertain

L - large sample tests
P - permutation tests

* p<0.05
** p<0.01
*** p<0.001

N.B. Bonferroni adjustment applied to comparison between control and group 2 for uterus histiocytic sarcoma, sarcoma and stromal polyp

Table 8
Intercurrent Mortality Rates
Male Mice

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	2	3.3	60	6	10	60	2	3.3	60	7	11.6
51-80	58	17	29.3	54	14	25.9	58	23	39.6	53	19	35.8
81-91	41	7	17.1	40	12	30	35	10	28.6	34	11	32.4
Term.	34			28			25			23		

Female Mice

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	2	3.3	60	5	8.3	60	1	1.6	60	2	3.3
51-80	58	14	24.1	55	10	18.2	59	13	22.0	58	11	18.9
81-91	44	11	25	45	11	24.4	46	13	28.3	47	9	19.1
Term.	33			34			33			38		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 9
Tumor Incidence Rates
Male Mice, Kidney Adenoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	2	0	6	0	2	0	7
51-80	0	17	0	14	0	23	0	19
81-91	0	7	0	12	0	10	1	11
terminal	0	34	0	28	0	25	1	23
Total	0	60	0	60	0	60	2	60

Trend test: p = 0.0575
Pairwise Comparison: Control vs. High: p = 0.4786

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Mean Plasma Kinetics of [^{14}C]-Metformin after Oral or Intravenous Administration in Mouse, Rat, Rabbit, Dog, and Monkey

	Tmax (hrs)				Cmax (µg equiv/ml)				AUC* (µg equiv/ml)			
		Multiple PO Dose[b]				Multiple PO Dose[b]				Multiple PO Dose[b]		
Species	PO[c]	1	7	IV	PO[c]	1	7	IV	PO[c]	1	7	IV
Mouse	0.50	ND	ND	ND	3.80	ND	ND	ND	ND	ND	ND	ND
Rat	1.25	1.50	1.00	0.08	2.58	2.58	3.65	22.30	7.21	8.08	9.50	15.29
Rabbit	1.50	1.50	1.00	ND	5.25	4.26	4.04	ND	ND	ND	ND	ND
Dog	1.75	1.75	1.75	0.08	10.57	12.78	10.83	73.00	43.70	52.50	47.55	48.70
Monkey	1.38	ND	ND	0.08	6.82	ND	ND	58.20	30.80	ND	ND	24.4[illegible]

* AUC for rat over 0-4 hours, for dog over 0-8 hours, for monkey over 0-24 hours
[b] Multiple PO dose = 50 mg/kg/day for 7 days
[c] PO = single oral administration of 50 mg/kg
IV dosage = 25 mg/kg
ND = not determined

Mean Excretion of Radioactivity in Mice, Dogs, and Monkeys Treated with a Single Intravenous Dose of [^{14}C]-Metformin (25 mg/kg)

		% of Dose			
Species	Time (h)	Urine	Feces	Other*	Total
Mouse	0-24	76.97	7.12	7.94	92.03
	0-120	78.92	7.85	9.35	96.12
Rat	0-24	90.52	3.65	6.95	101.12
	0-120	92.46	4.35	8.38	105.19
Dog	0-24	92.62	0.86	1.95	95.44
	0-120	98.04	1.16	3.21	102.40
Monkey	0-24	79.76	0.86	8.54	89.16
	0-120	83.39	1.42	12.94	97.76

* Values include cage wash, carcass, and GI tract for mice; cage wash and cage debris for dogs and monkeys

Mean Excretion of Radioactivity in Mice, Rats, Rabbits, Dogs, and Monkeys Treated with a Single Oral Dose of [^{14}C]-Metformin (50 mg/kg)

		% of Dose			
Species	Time (h)	Urine	Feces	Other*	Total
Mouse	0-24	46.07	32.68	8.30	87.05
	0-48	48.02	34.02	9.14	91.18
	0-120	48.39	34.22	9.64	92.25
Rat	0-24	56.10	34.43	1.15	91.68
	0-48	57.99	37.31	1.44	96.74
	0-120	58.42	37.50	1.87	97.79
Rabbit	0-24	38.38	18.22	2.56	58.16
	0-48	49.45	21.30	3.63	82.38
	0-120	57.38	34.80	5.38	97.56
Dog	0-24	82.71	15.66	2.42	100.79
	0-48	85.24	17.56	3.64	106.44
	0-120	86.90	17.72	4.86	109.48
Monkey	0-24	41.42	24.48	4.02	69.92
	0-48	43.78	41.04	5.04	89.86
	0-120	44.82	41.72	6.00	92.54

* Values include cage wash, carcass, and GI tract for mice, rats, and rabbits; cage wash and cage debris for dogs and monkeys

(Modification of Sponsor's Tables)

Toxicity Studies:

52-Week Toxicity, Hormone and Oncogenicity Study with Metformin Hydrochloride in Rats: Hazleton Washington, Inc. Study HWA B2613-101.
Study Dates: Dec 90 - Jan 92. Lot: 3835

Dose: 0, 150, 300, 600, 900 mg/kg Groups 4-8 for 52 weeks
[Based on food consumption: Males 0, 144, 291, 583, 875 mg/kg and Females 0, 147, 297, 590 and 900 mg/kg.]

No. Animals: 20 per/sex/group Crl:CDBR rats
About 43 days old. 153.1 to 232.0 g for males; 133.6 to 185.2 g for females.

Clinical pathology parameters evaluated included hematology, serum chemistry, and urinalysis Weeks 14, 27 and 53. Levels of specific metabolic hormones were determined Weeks 17, 30, and 50. TSH, T3, T4, GH and corticosterone were determined in 1/2 of the animals and ACTH in the other half. During Weeks 30 and 50, LH levels were determined in males chosen for ACTH.

Results:

Mortality: Deaths included 2-Gp 4 males, 1-Gp 7 male, 2-Gp 8 males and 1 female each in Gps 6-8 (accidental).

Clinical Signs: Group 7 and 8 animals appeared thin. Other findings appeared to be sporadic. Tissue masses were noted spuriously throughout all groups with no dose or treatment relationship. Treated groups showed no evidence of endocrine tumors.

Body Weights: Mean body weights were significantly decreased beginning Week 12 for males and females of Groups 7 and 8. Percent body weight change Week 52 for Groups 7 and 8 were 19 and 29% for males and 23 and 28% for females. Mean body weights were also slightly lower for Groups 5 and 6 beginning about Week 16.

Food Consumption: Sporadic - Compared to controls treated Groups 5-8 showed no statistically significant differences.

Ophthalmoscopic Exam: No apparent treatment related changes.

Hematology: Sporadic, low magnitude changes without consistent occurrence were considered incidental to treatment. These included:
Increases - Hemoglobin Gp 7 & 8 females (Wks 14, 53);
Hematocrit - Control females (Wk 14), Gp 7 & 8 females (Wks 14, 53);
Seg Neutrophil - Gp 8 Males (Wk 27) and females (Wk 14).
Platelets - Gp 7 (Wk 53) & 8 (Wk 27) females
Decreases - WBC Gp 8 males (Wk 14); Lymph Gp 8 males (Wk 14,53).

Blood Chemistry:
Mild treatment-related significant decreases:
Total protein - males in Gps 7 & 8 Week 53; females in Gp 5 (Wk 14), Gp 7 & 8 (Wks 14, 27).
Albumin - females in Gp 5 & 6 (Wk 14), Gp 7 (Wks 14, 27) and Gp 8 Wks 14, 27, 53).
Albumin/globulin ratio - females in Gp 8 (Wks 14, 27).
Other significant decreases included:
Glucose - Gp 8 males (Wk 53)
ALT - Gp 6 & 8 males (Wk 14)
ALK P - Gp 6 males (Wks 14, 53), Gp 7 & 8 males (Wks 14, 27, 53)
T BILI - Gp 8 males (Wk 27)
Increased: ALT Gp 8 males (Wk 27).

Urinalysis: Generally unremarkable. Volumes including controls quite variable.

Organ Weights: Various significant increases noted in mean organ weight ratios including that of adrenals, ovaries, brain, heart, spleen, kidney, liver, testis, uterus, thyroid and pituitary, were attributed by the sponsor to decreased body weight values. Among others, absolute Gp 7 & 8 female kidney weights were decreased.

Gross Pathology: Sporadic with no apparent treatment related alterations.

Histopathology: (control, high dose and decedents)
No apparent treatment related lesions reported. However, compared to controls, there was a marginal decrease in the incidence and severity of pituitary hyperplasia and degenerative cardiomyopathy for Gp 8 males. [It is reported that lesions are frequently small and focal in rats of this age and any differences may have been due to sectioning.]
Histopathology of the kidney appeared to be comparable with that of controls.

Metabolic Hormonal Data: Values generally quite variable with large standard deviations of the means. Findings were unremarkable with no apparent effect on hypophyseal balance. Male LH values did not show endocrine imbalance secondary to body weight loss. High dose male ACTH increased at week 50 was due to a single animal.

52-Week Toxicity Study of Metformin in Mice: Hazleton Washington, Inc. Study HWA 2613-100. Study Dates: Jan 1991 - Jan 1992. Lot 3835.

Dose: 0, 150, 450, 1500 mg/kg/day (Groups 1-4) in the diet for at least 52 consecutive weeks.

No. Animals: 42M;42F per Group Crl:CD-1 (ICR)BR mice ca. 6 wks. of age. Males 23.9-32.7 gms. Females 16.0-26.1 gms.

Sacrifice: 10 animals/sex/group during Weeks 14 (1st Interim) and 27 (2nd Interim). All surviving animals were sacrificed during Week 53.

Results:
Clinical Signs: Clinical signs gave no indication of a treatment related effect. The incidence and type of tissue masses was reported normal for the age and strain.
Mortality: Six mice died: 1-Gp2 male; 1-Gp4 male; 2-Gp3 females; 2-Gp4 females. One Gp3 female death Week 30 was accidental.
Body Weights: Gp4 male mean body weights were significantly decreased (5.3-7.6%) at various time periods from ca. Weeks 14-52. Also beginning at week 14 Gp4 females also showed lower mean body weights (usually nonsignificant) ranging from 5.9 to 10.9% of concurrent control values. Absolute mean body weight values were increased for Gp2 males at various time periods Weeks 2-44.
Food Consumption: Various statistically significant differences in mean food consumption were considered by the sponsor to be spurious and unrelated to drug administration. Values were similar for treated and controls except for the following: Significantly increased mean food consumption was seen for Gp2 males at various periods through week 15; Gp3 males at Week 5; Gp4 males weeks 5 and 8; Gp2 females at various times through week 16; and Gp4 females at week 48.
Ophthalmoscopic Exam: No apparent drug-related changes.
Hematology: Treated males showed dose-related increases in mean erythrocyte counts at Weeks 14, 27 and 53 which were usually accompanied by increases in mean hemoglobin concentration and hematocrit. Gp4 males showed a slight but significant decrease in mean eosinophil counts at Week 14.
Blood Chemistry: Spurious significant changes for a few parameters at various time periods with no apparent drug-related effects.
Urinalysis: Generally comparable with controls.

Organ Weights: Significant increases in various organ weights (Gp4 body weight ratios were increased for male brains, male and female kidneys, male testes and female liver) were attributed to decreased terminal body weights. (See histopath. re kidneys.)

Gross Pathology: Findings of those that died or were sacrificed (including interims) showed no apparent drug-related findings.

Histopathology: [Terminal - Control and high dose and those that died. Interim sacrifices only grossly abnormal tissues/organs saved for histopath.] The incidence and severity of Gp4 male and female kidney cystic tubular dilation and Gp4 male kidney tubular vacuolization showed a drug-related increase.

100-Week Chronic Toxicity, Hormone and Oncogenicity Study with Metformin Hydrochloride in Rats: Hazleton Washington, Inc. Study HWA A2613-101 Study Completion: May 1993. Lot: 3835

This study was designed to characterize the potential effects on the reproductive hormone profile resulting from exposure to Metformin Hydrochloride.

Dose: 0, 150, 900 mg/kg/day in the diet. Groups 1-3.
[Correspond to 147 and 856 mg/kg/day based on food consumption data.]

No. Animals: 52, 52, 60 female Crl:CDBR rats Groups 1-3.
Beginning treatment ca. 43 days old and 128.9 to 193.1 g.

Reproductive hormonal parameters evaluated included estradiol, estrone, prolactin, progesterone, follicle stimulating hormone, and luteinizing hormone during weeks 14, 27, 53, 79 and 100 for all surviving animals. Vaginal smears were evaluated for estrous stage approximation. The indicated females were bled when cytology demonstrated vaginal cornified cells and/or leukocytes.

Results.

Mortality: Control, low and high dose = 54, 45, 42%. Unscheduled deaths were reported to be incidental and considered unrelated to drug administration.

Clinical Signs: Treated females showed a higher incidence of thin appearance consistent with lower body weights compared to controls. The high dose group also had a slightly higher incidence of sores, chromodacryorrhea, and tail desquamation. Tissue masses were reported to show no dose or treatment related relationship.

Body Weights: The high dose group showed significantly decreased mean body weights. Body weights were lower than those of controls weeks 0-52 by 7% for Groups 2 and 39% for Group 3. Values for 0-99 weeks were lower by 7% for Group 2 and 40% for Group 3.

Food and Water Consumption: [Week 1 was 0 due to spillage in all groups.] Absolute food consumption data for Weeks 28 and 52 gave values comparable with controls. Group 3 females showed mean food consumption to be significantly higher than that of controls at weeks 13 and 99.

Ophthalmoscopic Exam: No apparent drug related abnormalities.

Gross Pathology: Reported to be sporadic with no distinct drug related findings. However, there were slightly higher incidences of speckled adrenal cortices and uterine cysts for Gp 3 and ovarian cysts for Groups 2 and 3 when compared to controls.

Organ Weights - Histopathology: Organ weights were not obtained and histology was not performed.

Drug Consumption: Within 20% of target value through Week 8 (except for spillage in Week 1) and except for Group 2 within 12% up to Week 92 at which time this group was within 19%. At Week 96, values were within 23% for Gp2 and 19% for Gp3. Both groups were within 10% at Week 99.

Drug Plasma Analysis: During week 6. Metformin HCl was absorbed in a dose-related fashion. [It is reported that extremely low levels of drug were found in controls - appeared to be due to contamination at bleeding.]

Hormone Analysis: The significant decreases (with low magnitudes of change) seen in the mean estrone value in Gp2 females at Week 14 and in mean progesterone in high dose females at Weeks 53 and 79 were thought to be incidental. Although not significant, Gp3 progesterone values were also decreased at week 100.

Segment II - Dosage-Range Pilot Study of Metformin HCl in New Zealand White Rabbits: Argus Research Laboratories, Inc., Horsham, PA. Protocol 812-001P. Study 91-T1-6023P. Study Dates: Jan 91 - Feb 91. Lot 3900.

Dose: 0, 50, 100, 200, 300, 400 mg/kg/day. Vol. 2 ml/kg
Days 6 - 18 of presumed gestation.

No. Animals: 5 per group presumed pregnant (artificially inseminated)

Sacrifice: Day 29 of gestation.

Results:

During the dosage period, 200 mg/kg and higher caused deaths, other clinical observations (soft, liquid or dried feces, ataxia, impaired righting reflex) and reduced body weight gains and absolute and relative food consumption values. 200, 300 and 400 mg/kg caused deaths in 3, 4, and 5 rabbits. Compared to controls, post dosage days 19-29 caused body weight gain increases at 200 and 300 mg/kg and increased feed consumption at 300 mg/kg. It is reported that there were no adverse effects on C-sectioning or litter observations. For does in the surviving dosage groups litter averages for corpora lutea, implantations, litter sizes, early and late resorptions, fetal weights, percent male fetuses and percent resorbed conceptuses were comparable. No gross fetal external alterations were reported - fetuses were then discarded.

Rabbit Historical Control Data was provided for 53 Studies consisting of 585 pregnant does at C-sectioning.

Segment II - Oral Teratology Study of Metformin HCl in Female New Zealand White Rabbits: Argus Research Laboratories, Inc., Horsham, PA. Study 91-T2-6023. Protocol 812-001. Study Dates: Mar 91 - Apr 91. Lot: 3900

Dose: 0, 50, 100, 140 mg/kg orally by stomach tube Days 6-18 of gestation.
Conc. 0, 25, 50, 70 mg/ml. Vol. 2 ml/kg. Vehicle - H_2O.

No. Animals: 20 per group presumed pregnant (artificially inseminated 4x).
3.00 to 4.10 kg.

Sacrifice: Day 29 of gestation.

Results:

Deaths: Low dose: 1 on Day 8 due to intubation error (litter - one normal conceptus); 1 on Day 18 - weight loss, extremely reduced feed consumption after day 7 (litter - one early resorption).

High dose: 1 on Day 10 (soon after intubation) had tonic extensor convulsions, body jerks, decreased motor activity, ataxia, impaired righting reflex. Weight loss and reduced feed after day 6. No gross lesions. Litter - one normal conceptus.

1 on Day 15 - no clinical observations but body weight remarkably reduced day 15 and feed consumption reduced days 13 and 14. Necropsy - black raised area in liver. Litter - 6 normals.

1 on Day 14 - no clinical or necropsy observations. Body wt. unremarkable; food consumption reduced day 12. Litter - 8 normals.
1 on Day 18 - body wt. and food consumption reduced after day 11. Aborted (and found dead) - 5 normals and 3 early resorptions.

Abortions:
Control: 1 on day 20 (litter-1 aborted conceptus) Reported that abortion of a one conceptus litter is common in this strain of rabbit. No clinical observations before abortion and no necropsy observations.
Mid dose: 1 on day 26 (litter of 3 - 2 conceptuses and 1 late resorption partially cannibalized). Dried feces days 20-25. Necropsy red genital area and hemorrhagic area in pyloric region of stomach.
High dose: 1 on day 25 (litter of 5 - 4 normal and 1 cannibalized). Red substance in cage pan day 24, weight loss and reduced feed consumption after day 8. No gross lesions at necropsy.
1 on day 25 (litter - 7 partially cannibalized). Dried feces days 19-24; reduced body weights and feed consumption after day 16. Mottled cecum with hemorrhagic areas at necropsy.

Premature Delivery:
High dose - 1 on day 29 (11 fetuses - 10 normal and 1 partially cannibalized). Weight loss and reduced feed consumption after day 10 and dried feces days 19-29. No gross lesions at necropsy.

Clinical and Necropsy Observations:
Increased numbers of mid and high dose had dried feces considered a test article effect. Other possible drug related effects in those that died or aborted included decreased motor activity, ataxia, impaired righting reflex, tonic extensor convulsions, body jerks, mucoid feces and a red substance in the cage pan. Other non-dose related findings were not considered dose related.
There were no apparent treatment related gross findings.

Maternal Body Weights:
Mid and high dose showed weight losses days 15-19. Reported that weight gains days 6-19 did not show a significant difference among the 4 groups.
Days 19-29 (post dose): Treated groups showed increased weight gains. Body weight gains showed significant increases days 24 to 29 for the mid and high dose groups. Body weights for the 4 groups were reported to be comparable throughout the study.

Food Consumption: Comparable pre-dosing. Dosing period (days 6 to 19) - absolute and relative maternal feed consumption was reduced for the mid and high dose groups. Post dosing absolute and relative feed consumption was slightly increased in the treated groups compared to controls.

Caesarean-Sectioning and Litter Observations:
Pregnancy: control through high dose - 17 (85%), 18 (90%), 15 (75%) and 19 (95%). C-section observations based on 16, 16, 14, 12 pregnant rabbits. (One low and one mid dose had only resorbed litters - included in analysis.
Comparable litter averages were found for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions and the number of does with any resorptions and viable fetuses.
Also comparable were litter averages for percent male fetuses, fetal body weights and percent conceptuses resorbed.

Fetal Alterations: No apparent drug related gross external, soft tissue or skeletal alterations. The significant increases in fetal incidences of irregular skull ossification occurred in all treated groups. However, it

is reported that values were not dose dependent, were within historical control range, and the litter values were not significantly increased. Reductions rather than increases in incidences of angulated hyoid ala(e) were also probably not drug related.

There were 101, 89, 95, 70 live Caesarean delivered fetuses from 16, 15, 13, and 12 litters. 10 delivered pups were from 1 high dose doe - 2 had variations in skull ossifications.

104-Week Oral (Dietary Administration) Carcinogenicity Study of Metformin HCl in the Rat: Hazleton UK. Report 7476-537/12 dtd. May 1993.
Study Dates: Jul 90 - Aug 92. Batch 3221

Dose: 0, 150, 300, 600, 900 mg/kg (control, low, Intermediate I, II and high dose)

No. Animals: 60M;60F per group plus 20/sex/group for control, low and high dose satellite animals for laboratory investigations.
Weight: Males 202.0 to 334.1 g. Females 141.6 to 239.8 g.
Crl:CD(SD)BR strain rats.

Proof of Absorption:
Blood samples were withdrawn from satellite animals in weeks 7, 25 and 52. Animals were killed and discarded after each bleed.

Sacrifice: Females at 99 weeks due to survival in the order of 50%.

Results:
Clinical Signs: Reported that none were considered to be treatment related.
Mortality: Mortality for males was 53, 55, 37, 40 and 25% for control through high dose males and 52, 57, 53, 48 and 37% for control through high dose females. [Increased high dose survival was considered by sponsor to be due to treatment-associated decreases in body weight gain and consequent reduction in age-related pathology.]
Body Weights: Males - Intermediate I, II and high dose gained less than controls ($p<0.01$, $p<0.001$ and $p<.001$ respectfully wks. 0-104). At end of study difference for these groups compared to controls was 13, 28, 31% respectfully. Females - Intermediate I, II and high dose gained less than controls ($p<0.05$, $p<0.001$, $p<0.001$ respectfully wks. 0-96. Compared to controls at week 96 differences were 10, 21, and 32% respectfully. During the latter part of study low dose females had a difference of 6% (not significant).
Food and Water Consumption: Intermediate I, II, and high dose males consumed less food than controls [6% ($p<0.01$), 13% ($p<0.001$) and 15% ($p<0.001$) respectfully. Females were similar to controls. Water consumption was similar to that of controls.
Compound Consumption: In general in agreement with nominal dose levels.
Hematology: Mean total white cell blood count: Males - Intermed. I, II and high dose were slightly lower than that of controls. ($p<0.05$, $p<0.001$ and $p< 0.001$ respectively.) Females - High dose lower than controls ($P<0.05$).
Blood Chemistry: There was no difference in glucose concentration between groups and little difference with time for control, low and high dose measured week 7 at three different times of the day coinciding with the measurement of Metformin plasma levels.
Organ Weights: Variable with few significant differences. Although there was no apparent dose relationship male kidney/body weight ratios of treated males exceeded that of controls 11 to 23 % and females 6 to 18%. Also with no dose relationship, relative adrenal weights of treated males exceeded that of controls by 12 to 32% and females from 16 to 26%. High dose ovary weights exceeded that of controls ($p<0.05$).

Gross Pathology: Findings with increased incidence included: soft and enlarged testis; uterine distension and ovarian cysts. Those with **decreased incidence** included: liver discoloration; enlarged and masses in pituitary; fur loss, scres and skin masses; thickened stomach; enlarged thyroid; enlarged and sore foot/leg and **enlarged kidneys**. Such findings were considered by the sponsor to be treatment-related and correlated with histopathology findings.

Histopathology: (control and high dose; kidneys, testes, uterus and ovaries of Gps 2, 3, 4.)

High dose animals showed **decreases of incidence and/or severity** of inflammatory and degenerative lesions in various organs including degeneration/fibrosis of the heart various liver lesions and **glomerulonephropathy**. Such findings in non-endocrine dependent organs were attributed by the sponsor to treatment associated decrease in body weight gain. Atrophy of the spleen was increased in the intermediate II males only.

Findings in endocrine/endocrine dependent tissues were also attributed by the sponsor to reduced body weight gain. These included reductions in adrenal medullary hyperplasia and increased pituitary altered cell foci in males. Pituitary tumors tended to be reduced in number and size. Intermediate I and high dose groups had an increased incidence of testicular Leydig cell hyperplasia and Leydig cell tumors. There was also a slight increase in unilateral testicular atrophy in high dose males (there was no clear-cut explanation and the relationship to treatment is uncertain). Ovaries of treated females tended to be less atrophic compared to controls. The incidence of ovarian cysts appeared to be more prevalent in treated. The incidence of uterine cystic glands was greater in treated and the incidence of stromal polyps was greater in the Intermediate II and high dose groups. [According to the sponsor, the tendency of less atrophic ovaries was suggestive of prolongation of hormonal activity in the dosed groups and correlated with the increase in cystic uterine glands in Intermediate I, II and high dose animals.] (See also below regarding neoplastic findings.)

Neoplastic Findings: Findings in controls were those expected for the age and strain with more frequent tumors involving skin, mammary gland, thyroid, pituitary, adrenal medulla, testis and uterus. Findings in high dose rats were similar to that of controls with incidence variations. The decreased incidence of pituitary tumors in high dose animals ($P<0.05$, males only) was attributed by the sponsor to decreased body weight gain. The incidence of high dose adrenal medullary tumors (medullary hyperplasia and pheochromocytoma) was decreased in high dose males ($p<0.05$) and the incidence of mammary tumors was decreased in high dose females, however the incidence of mammary carcinomas was greatest for the intermediate I group. Benign testicular Leydig cell tumors were increased in the Intermediate I and high dose males ($p<0.01$ and $p<0.05$, respectfully) with no apparent dose-response relationship. Only the intermediate I dose group exceeded historical controls.

The increased incidence of benign uterine stromal polyps of high dose females ($p<0.05$) slightly exceeded the range of historical controls.

There was a treatment-related decrease in benign skin tumors, including fibromas and keratoacanthomas, in high dose males ($p<0.01$). The spectrum of other tumor types was similar to that of controls.

[See Tables pages 24-30.]

Proof of Absorption: **Rat Plasma: Weeks 7, 16, 24, 8 hrs.**
Plasma concentrations of Metformin hydrochloride for low dose were within the range of 919 to 2598 ng/ml for males and 411 to 2692 ng/ml for females. For the high dose concentrations ranged from 2183 to 11299 ng/ml for males and 4978 to 7469 ng/ml for females.

91-Week Oral (Dietary Administration) Carcinogenicity Study of Metformin HCl in the Mouse: Hazleton UK, North Yorkshire, England. Report 7352-537/11 dtd Dec 92. Protocol P5745d. Batch: 3221. Study Dates: Jul 90 - Apr 92.

Dose: 0, 150, 450, 1500 mg/kg/day Groups 1-4.

No. Animals: 60/sex/group plus 24/sex/control, low and high dose groups for proof of absorption only. Crl:CD-1(SD)BR mice
Wt. Males: 22.6 to 37.0 g. Wt. Females: 18.8 to 29.4 g

Results:

Mortality: Groups Control through High Dose (60/sex/gp).
Males: 26 (43%), 32 (53%), 35 (58%), 37 (62%);
Females: 27 (45%), 26 (43%), 27 (45%), 22 (37%).
Amyloid cystic nephropathy caused deaths (Gps 1-4) in 0, 0, 7, 11 males and 0, 0, 5, 10 females. Urogenital tract lesions (Gps 1-4) caused demise in 6, 7, 12, 15 males but no females. Amyloidosis was more prevalent in control males and females (also low dose) that died .

Clinical Signs: No apparent drug related findings were observed.

Body Weights: The high dose gained less weight than controls. Findings were statistically significant weeks 0-13 for females and weeks 0-88 for males. For the high dose by 88 weeks the difference was 7% for males and 13% for females. Low dose males gained more weight than controls being statistically significant ($p<0.05$) weeks 13-24 with a difference of 7% by week 88.

Food and Water Consumption: In general high dose males ate about 5% less than controls. The difference was statistically significant ($p<0.05$) weeks 14-24. Mid dose males ate ca. 10% more than controls week 84 to end of study (reported possibly due to isolation after cage mates had died). Water consumption reportedly showed no visual assessment differences from controls.

Drug Consumption: About 13% above nominal levels for mid dose males week 84 to end of study.

Hematology: Mid and high dose female (but not males) white blood cell counts were less (high dose - $p<0.05$ week 90) than that of controls, however there was variation within each group.

Organ Weights: Kidney: high dose males greater than controls by 15% ($p<0.05$). Female: absolute greater than control by 20% ($p<0.01$) and relative greater than control by 35% ($p<0.001$).
Liver: Females Gps 1-3 = 4%, 5% and 10%.
Thyroid: mid and high dose females less than controls by 18% and 27% ($p<0.05$).

Gross Pathology: Findings were in general those expected for this age and strain of mice. However, the incidence of the following findings was increased: cysts and enlarged kidneys in mid and high dose males and females; pale kidneys and urinary bladder distension in treated males; sore and enlarged penis in mid and high dose; enlarged preputial glands in high dose males. Urogenital tract findings were probably treatment related and correlated with histopathological changes.

Histopathology: (control and high dose and those killed or died in extremis and gross lesions and tissue masses ex all groups; also kidneys of low and intermediate dose).
A number of background histopathological findings not unexpected for the age and strain were seen.
Kidneys however, showed treatment related changes. Cystic nephropathy (cystic tubular dilation), although increasing in severity over controls but not necessarily increasing in severity within individual groups, showed a dose related increase Gps 1-4 as follows: Males 5 (8%), 17

(28%), 36 (60%), 53 (88%); Females 14 (24%), 12 (20%), 25 (42%), 43 (73%). Minimal to slight increased tubular vacuolation seen in males but not females was as follows for Gps 1-4: 0, 4 (7%), 10 (17%), 7 (12%).

Controls showed occasional minimal distended/cystic tubes in the renal cortex. **All male treatment groups and intermediate and high dose females showed an increased incidence and severity of cystic nephropathy.** A polycystic appearance (usually present at necropsy), often accompanied by a shortening of the renal papilla and dilation of the renal pelvis (hydronephrosis) was present in the more extensive cases. **Cystic nephropathy was frequently associated with amyloidosis. Deaths of several were attributed to amyloid/cystic nephropathy and renal papillary necrosis. Increased mortality was also associated with an increase of lower urogenital tract lesions in treated males.** Compared to controls, vacuolation of proximal tubular epithelium of mid and high dose males was increased.

The incidence of diffuse hepatocyte microvacuolation, presumably fat, of the liver was increased for high dose females but not males as follows Gps 1 and 4: Males 18 (30%), and 10 (17%); Females 23 (39%) and 27 (45%). This finding was considered by the sponsor to be due to a physiological response to reduced bodily condition. Low and intermediate dose livers were not examined.

Neoplastic Findings:

Neoplastic findings for controls were generally those expected for this age and strain of mice with more frequent tumors involving liver, lung, uterus and hemolymphoreticular system. Common spectrum tumor types for high dose females were in general similar to that of controls. Compared to controls high dose males showed a reduced incidence of liver tumors ($p<0.05$). **Two** high dose males had **kidney adenomas** which the sponsor considers not unusual at doses causing major kidney cystic changes and unlikely evidence of direct genotoxic effects.

Although reported as not significant the incidence of Leydig cell tumors was 0, 5, 2, 2, control through high dose.

[See Tables pages 31-34.]

Proof of Absorption: Satellite animals week 6. Six males and six females from each satellite group were bled at 16.00, 24.00 and at 08.00 h on the following day. Additional samples from the high dose animals at 24 h in week 52.

Concentrations of drug in the low dose group were typically greater than 1000 ng/ml vs ca 5000 ng/ml for the high dose at 6 weeks. Findings for the high dose at 52 weeks were similar. [The source of contamination leading to the detection of drug in two controls could not be determined.]

Estrogenic analysis of diet: Showed no estrogenic activity.

Mutagenicity Studies:

Bacterial Mutation Assay (Ames Test) With Metformin HCl: Huntingdon Research Centre Ltd., UK. LPA 161/89819 Study dates: Apr-May 89. Batch/Lot: ?

Histidine dependent auxotrophic mutants of Salmonella typhimurium (strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100) were exposed to test material, diluted in water which was also used as a negative control. Tests were performed in the presence and absence of liver preparations from Aroclor 1254-induced rats. Concurrent positive controls demonstrated the sensitivity of the assay and the metabolizing activity of the liver preparations.

Metformin HCl was not mutagenic in this system at dose levels up to 5000 µg/plate in water.

Mouse Lymphoma TK Locus Assay With Metformin HCl: Huntingdon Research Centre Ltd., UK. LPA 178/911534 Study dates: Oct-Nov 91. Batch/Lot: ?

Using the mouse lymphoma thymidine kinase assay, four independent in vitro tests were carried out, two in the absence of exogenous metabolic activation (S-9 mix) and two in the presence of S-9 mix (derived from homogenized livers of rats previously treated with Aroclor 1254). Concentrations of test substance ranged up to 5000 µg/ml.

All tests both in the absence and presence of S-9 mix produced some toxicity, however, increases in mutant frequency indicative of a positive response were not produced. Thus, Metformin HCl did not demonstrate mutagenic potential in this system.

Assay to Assess the Ability of Metformin HCl to Induce Chromosomal Aberrations in Human Lymphocytes Cultured In Vitro: Huntingdon Research Centre Ltd., UK. LPA 179/911645 Study dates: Oct-Dec 91. Batch/Lot: ?

Doses selected for metaphase analysis were up to 313 µg/ml in the absence of S-9 and up to 5000 µg/ml in its presence.

The significant increases in the proportion of aberrant cells seen in the absence of S-9 mix with 156 and 313 µg/ml were within historical control range and were not considered to be treatment related.

Metformin HCl in the presence of S-9 mix did not cause a significant increase in the proportion of metaphase figures containing chromosomal aberrations compared to solvent controls at any dose level.

Positive controls caused large statistically significant increases in the proportion of aberrant cells.

Metformin HCl showed no evidence of clastogenic activity in this in vitro system.

Mouse Micronucleus (bone marrow erythrocytes) Test With Metformin HCl: Huntingdon Research Centre Ltd., UK. LPA 180/911635

Study dates: Oct-Dec 91. Batch/Lot: ?

Mice were SPF CD-1 outbred of Swiss origin ca. 39 days old. The positive control was Mitomycin C (produced large highly significant increases in the frequency of micronucleated polychromatic erythrocytes). The dose of Metformin HCl was 2000 mg/kg.

Metformin HCl did not cause any statistically significant increases in the number of micronucleated polychromatic erythrocytes, in the incidence of micronucleated normochromatic erythrocytes or any significant decreases in the ratio of polychromatic to normochromatic erythrocytes

No evidence of chromosome damage or bone marrow cell toxicity was seen when Metformin HCl was administered orally in this in vivo test procedure which was thus determined to be negative.

Literature: A considerable number of literature reprints and references were submitted, some of which have been covered under previous reviews.
See also Pharmacology and Comments sections.

Labeling: **The Precautions section is satisfactory from the standpoint of Pharmacology except that multiples of the human dose should be rounded off to whole numbers.**

Comments and Conclusion:

Glucophage brand of metformin hydrochloride is an oral anti-diabetic, antihyperglycemic agent currently in use in some eighty plus countries throughout the world. A considerable number of articles have appeared in the literature since its discovery by the French in the late 1950's. Many of these articles have been submitted or referred to in this and previous submissions. A number of pharmacology and toxicology studies were previously reviewed under G.D. Searle and Company's IND 5934 (discontinued in 1972 - see attached reviews) as well as under IND 27,966 of Lipha Chemicals, Inc.

Chemically Metformin (N,N-Dimethylbiguanide) is only slightly different from the biquanide Phenformin (1-phenethylbiguanide) which was marketed as an anti-diabetic agent under the trade name of DBI until, due to the production of an unacceptably high risk of lactic acidosis, it was removed from the market in October of 1977.

Results of in-vitro and in-vivo animal studies on metformin and lactate production have provided conflicting results.

According to the sponsor, there are a number of fundamental differences between metformin and phenformin that may influence the potential of each drug to produce lactic acidosis.

Different structural organization (different location of protonation site; formation of intramolecular hydrogen bonds and cyclical formation with phenformin compared to planar configuration of metformin; phenformin is 50-fold more lipophilic than metformin, whereas metformin is hydrophilic);

Differences of membrane binding (phenformin has greater membrane binding affinity than metformin, it positions itself deeply into membranes and is more disruptive to membranes than the hydrophilic metformin);

Different potency of effects on mitochondria (electron chain conductance, ATP production, redox state disturbed by phenformin);

Different concentration in muscle (relatively higher for phenformin);

Different fate of glucose metabolism in muscle (greater propensity for lactate production with phenformin);

Different metabolism (metformin is not metabolized whereas phenformin is metabolized and there is genetic variability in the capacity to metabolize phenformin such that phenformin can accumulate in so-called "Poor Metabolizers");

Different protein binding (phenformin circulates partly protein-bound whereas metformin is not protein-bound);

Different elimination characteristics (metformin has a considerably shorter plasma half-life than phenformin; metformin is eliminated entirely via the renal route, unchanged, with a very high renal clearance and is thus much more rapidly and predictably eliminated than phenformin. Phenformin depends on hepatic metabolism as well as renal elimination of both parent compound and metabolite).

The major effect of the biguanides appears to be a potentiation of insulin effectiveness. Several review articles are present in the literature which summarize the pharmacological activity of metformin and discuss its mechanism of action which is not completely understood. The effects of metformin are probably due to multiple actions which have included the following suggestions of the mechanism of action: 1) increased insulin receptor binding; 2) decreased intestinal glucose absorption; 3) increased cellular glucose uptake; 4) decreased hepatic gluconeogenesis; 5) stimulation of anaerobic glycolysis; and 6) potentiation of insulin action at the receptor or post-receptor level. Cellular level studies indicate that metformin potentiates insulin action and in vitro studies support a post-receptor mechanism of action.

Most studies suggest that the basis for the hypoglycemic effect of metformin is probably at the level of skeletal muscle by increasing glucose transport across the cell membrane; also multifactorial basis. Diabetes Care 13:696-704, 1990.

At therapeutic doses, Metformin does not lower plasma glucose levels in non-diabetic animals or humans or reduce basal glucose concentrations below the normal physiological range in either diabetic animals or humans. Oral Metformin effectively lowers plasma glucose in several different animal models of hyperglycemia, including streptozotocin-induced diabetic mice, genetically diabetic KK mice, obese female fa/fa rats, and alloxan-induced diabetic rats.

Hypolipidemic effects have been seen in animals fed an atherogenic diet. It has been reported that there are favorable effects on VLDL composition, lipid metabolism, and intramural lipid biosynthesis. A significant effect has been reported on both the development and regression of atherosclerotic lesions in cholesterol-fed animals.

The effect of Metformin on the microcirculation has been studied in several different animal models and suggests that Metformin may play a beneficial role in the prevention and/or development of diabetic microangiopathy and reduce the incidence of glomerulosclerosis.

[^{14}C]-metformin was used to determine the absorption, distribution, kinetics, metabolism, and excretion of metformin in mice, rats, rabbits, dogs, and monkeys. Fetal distribution was studied in pregnant rats and rabbits.

Absorption was rapid - peak plasma levels were obtained in 30 min. in mice, 1-2 hrs. in rats, 1.5 hrs. in dogs, and 0.75-2 hrs. in monkeys. There was about 50% absorption in rats.

After a single oral dose in mice radioactivity first appeared in the stomach, urinary tract, and bladder and later in the salivary gland and intestinal walls. The highest radioactivity was found in the kidneys, adrenals, pancreas, liver, lungs and intestinal wall with little localized in brain or fat. Multiple doses showed no apparent accumulation in the tissues. Rats were similar to mice with highest levels observed in kidneys, liver, adrenals, lungs and GI track by 2 hrs. Levels were highest in rabbit kidney and liver at 2 hrs.

After oral single or multiple doses, plasma radioactivity decreased by 5-22 fold within 8 hrs. Oral administration to hyperglycemic obese and hyperinsulinemic mice (DBM strain) produced a plasma half-life of 2.7 hrs. which was similar to that found in normal mice (2.5 hrs.) and humans (2.8 hrs.). Following 7-days dosing of rats no significant accumulation of total radioactivity was observed in the plasma.

No metabolites were found in urine, fecal, and/or plasma from mice, rats, dogs, or monkeys - reported to be consistent with human studies. One metabolite occurred in rabbits - N-desmethyl metformin [N-monomethylbiguanide].

Recovery of radioactivity was almost complete by 120 hrs. After oral administration excretion of metformin in the dog is mainly in the urine, with the monkey excreting almost equal amounts in the urine and feces after 24 hrs. In the mouse, rat and rabbit the main route is via the urine although a significant amount is excreted in the feces (probably unabsorbed Metformin).

Following oral administration to pregnant rats, levels of radioactivity were generally lower in the fetus than in maternal tissue. When given to lactating rats the ratio of total radioactivity in milk to plasma was generally increased at later time points.

Acute toxicity studies (Food and Drug Research; Hazleton Labs.) were conducted in the mouse, rat, rabbit, dog, and monkey. Rabbits and dogs appeared to be more sensitive to the effects of Metformin than mice or rats. Dogs showed salivation, emesis, diarrhea, and CNS effects including convulsions. LD_{50} ranged from 0.375 g/kg in dogs to 2.4 g/kg in mice. A single oral dose of 250 mg/kg produced no clinical signs in the monkey; 693.75 mg/kg was fatal.

Chronic toxicity studies were carried out in the rat, mouse, dog and monkey.

Studies in rats up to 78 weeks showed the non-toxic dose to be 120 mg/kg which on a mg/kg basis for a 50 kg person is about 2.4 x the HTD (max. 2550 mg).

Higher doses in the rat resulted in depression of weight gain and food consumption and after long term administration a dose related incidence of uterine polyps (increased at 300 mg/kg and higher) and a decrease in ovarian activity. [See special review (IND 5,934 of 6/4/79) by the Supervisory Pharmacologist (1979), Dr. V. R. Berliner (Found as Attachment VII in IND 27,966 review 11 Apr 86), in which he stated the following: "I cannot get excited over the noted induction of uterine polyps in the rat with the high (toxic) doses because the rat is peculiar in its response to drugs by its reproductive system, that also might be the cause for the depression of ovarian functions, and these might also be caused by the general, drug induced toxic milieu in these animals."]

A 52-week study in mice reported no adverse effects at doses up to and including 450 mg/kg/day. The highest dose of 1500 mg/kg decreased body weight gain compared with controls and drug related lesions in the kidney - consisting of tubular dilation in both sexes and increased tubular vacuolization [in males].

In 6-month and 78-week oral studies in the dog, the minimal toxic dose was 50 mg/kg or about equal to the max. proposed HTD (2550 mg) on a **mg/kg basis**. Higher doses produced a 50-100% mortality with symptoms of GI distress and vascular lesions and degenerative changes in the brain, heart, kidney and skeletal muscle. (Brain cell degenerations are believed by the sponsor to be secondary to vascular changes characterized by an impairment of the nuclei and a thickening of the cerebral walls.)

Rhesus monkeys tolerated 180 mg/kg or ca. **3.6 x** HTD without apparent toxic effects in a 2-year oral study. The 360 mg/kg (**ca. 7.2 x HTD**) high dose, however caused a 75% mortality, severe GI distress, weight gain depression and cytoplasmic changes in hepatocytes and some cells of the adrenal gland. Brains of monkeys also showed some effects of the drug.

The 104-week carcinogenicity study in rats was reported to have findings similar to those of a 78-week study, with an increased incidence of uterine polyps in female rats at 900 mg/kg. [Metformin was reported to produce no apparent effect on reproductive hormone levels in a separate 99-week study in female rats.] The increased incidence of benign uterine stromal polyps of high dose females ($p<0.05$) slightly exceeded the range of historical controls. Overall, there did not appear to be any unusual tumor types or incidences suggestive of a direct carcinogenic effect. However, There was an increased incidence of Leydig cell hyperplasia and Leydig cell tumors. The tumors had a $p<0.01$ for the Intermediate I (300 mg/kg) group and $p<0.05$ for the high dose (900 mg/kg) group. Only the incidence for the Intermediate I (300 mg/kg) group was reported to exceed historical controls.

Findings in the 91-week carcinogenicity study in mice were similar to those seen in the 52 week study. Males showed increased tubular dilation at the lowest dose studied (150 mg/kg). Females were affected at 450 and 1500 mg/kg. 450 and 1500 mg/kg males showed increased mortality, primarily due to an increase in urogenital lesions resulting from renal toxicity. There did not appear to be any evidence of any direct carcinogenic effect.

Segments I, II and III Reproduction studies were carried out in rats, as well as, a Segment II Teratology study in rabbits. Doses of Metformin were up to 600 mg/kg (on a mg/kg basis about 12 times and on a mg/m^2 about 2.1 times the maximum recommended daily dose) in rats and up to 140 mg/kg in rabbits. [Doses of 200 mg/kg and higher caused deaths in a pilot rabbit teratology study.] **Findings in rats were in general comparable with controls; there were no significant effects on teratology, or adverse effects on gestation, parturition, lactation, pup size, viability, fertility or reproductive performance or perinatal/postnatal development. No teratology was produced in rabbits although there were a greater number of deaths (4) in the high dose.**

A battery of Mutagenicity studies was negative.

Recommendation:

Preclinical studies show that there is a considerable species variation with regard to the type of toxicity expressed in response to Metformin, however, with adequate labeling Pharmacology can recommend approval of this NDA for the proposed indication to lower blood glucose.

The Precautions section of the labeling appears satisfactory from the standpoint of Pharmacology except that multiples of the human dose should be rounded off to whole numbers.

D. Hertig

David H. Hertig
Pharmacologist

A Jordan 5/3

cc:
Original NDA 20-357;
HFD-502 ATaylor
HFD-400 JContrera
HFD-345
HFD-510 NDA 20-357;
HFD-510 AJordan
HFD-510 DHertig

Calculation of Multiple of Human Dose
(Labeling)

Based on: Freireich, E. J., et al., 1966. Quantitative comparison of toxicity of anticancer agents in mouse, rat, dog, monkey and man. Cancer Chemother. Repts. 50 (4): 219-244.

Representative Surface Area to Weight Ratios (km) for Various species.

	Body Weight (kg)	Surface Area (Sq. m.)	km factor
Man	60	1.6	37
Man*	50*	1.4*	34*
Rat	.15	.025	5.9 (=6)
Mouse	.02	.0066	3.0

* Reviewers calculated estimate (apparently also used by the sponsor).

Human: [Based on a 50 kg person (as used by the sponsor).]
Maximum HTD from Labeling: 2550 mg

2550 mg ÷ 50 kg person = 51 mg/kg maximum HTD

51 mg/kg x 34 (km factor) = 1734.0 mg/m^2

Rat:

900 mg/kg x 6 (km factor) = 5400 mg/m^2

600 mg/kg x 6 (km factor) = 3600 mg/m^2

Mouse:

1500 mg/kg x 3 (km factor) = 4500 mg/m^2

Multiple of max. HTD (2550 mg):

Rat:

For 900 mg/kg:
5400 mg/m^2 ÷ 1734 mg/m^2 = **3.11 times**

For 600 mg/kg:
3600 mg/m^2 ÷ 1734 mg/m^2 = **2.1 times**

Mouse:

For 1500 mg/kg:
4500 mg/m^2 ÷ 1734 mg/m^2 = **2.6 times**

RAT - CA STUDY

Text table 3: Incidence of selected endocrine-related microscopic findings

Organ and finding		Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Pituitary	Number examined	60	47	27	28	59	60	48	50	39	60
altered cell focus		9	6	1	4	15	7	2	5	4	8
B-adenoma		27	24	21	15	18	45	38	36	26	36
Adrenal	Number examined	60	36	24	27	60	60	45	41	39	60
medullary hyperplasia		10	6	3	1	1	2	4	4	0	3
B-phaeochromocytoma		12	9	2	2	3	2	2	1	2	0
Testis	Number examined	60	59	60	60	60	-	-	-	-	-
Atrophy											
Bilateral		5	8	6	6	6	-	-	-	-	-
Unilateral		4	7	6	7	10	-	-	-	-	-
Leydig cell hyperplasia		1	5	7	3	7	-	-	-	-	-
B-Leydig cell tumour		1	2	9	2	7	-	-	-	-	-
Mammary gland	Number examined	2	0	1	0	1	60	52	49	45	60
mammary tumours#		2	0	1	0	1	39	40	35	34	30
Ovary	Number examined	-	-	-	-	-	60	60	60	59	60
atrophy		-	-	-	-	-	15	7	6	6	5
Uterus	Number examined	-	-	-	-	-	60	57	60	57	60
cystic glands		-	-	-	-	-	13	16	28	18	33
B-stromal polyp		-	-	-	-	-	3	4	4	7	12

animals bearing benign and/or malignant tumours

Text table 4: Histopathology findings: Leydig cell tumours and uterine stromal polyps. Control data from 2 year rat carcinogenicity studies using Charles River UK, Crl:CD(SD)BR rats (during the period 1988 to 1993)

Study	1	2	3	4#	5	6#
Animals examined	100	100	70	100	100	100
Finding						
B-Leydig cell tumour	8	4	7	1	7	4
B-stromal polyp	6	15	7	6	15	3

data not yet audited by Quality Assurance

TABLE 10.8

Tumour incidence males - statistical analysis
Results of tests for a decreasing and increasing incidence

Tumour Type	Number of tumour bearing animals	Gp 1	Gp 5	Included in analysis	p-values for increased tumour incidence Group 1 vs Group 5	p-values for decreased tumour incidence Group 1 vs Group 5	Method of analysis
Skin 1	F	1	0	ALL	0.927	0.350	P
	NF	3	1				
	ALL	4	1				
Skin 2	F	6	5	ALL	0.992	0.008**	L
	NF	17	7	F	0.699	0.301	L
	ALL	23	12	NF	0.999	0.001**	L
Skin and Tail	F	0	1	ALL	0.991	0.009**	L
	NF	13	1	NF	0.999	0.001***	L
	ALL	13	2				
Skin and Nes lymph node	F	0	1	ALL	0.767	0.595	P
	NF	3	1				
	ALL	3	2				
Adrenal phaeochromocytoma	NF	12	3	NF	0.982	0.018*	L
Naem/lymph/retic all sites	F	4	1	ALL	0.751	0.513	P
	NF	0	3				
	ALL	4	4				
Heart schwann cell tumour	F	1	0	ALL	1.000	0.128	P
	NF	2	0				
	ALL	3	0				
Thyroid follicular adenoma	NF	3	3	NF	0.672	0.670	P
Thyroid c-cell adenoma	NF	12	8	NF	0.922	0.078	L
Pituitary adenoma	F	6	2	ALL (U as F)	0.965	0.035*	L
	NF	20	16	ALL (U as NF)	0.956	0.044*	L
	U	1	0	NF (U as F)	0.915	0.085	L
	ALL	27	18	NF (U as NF)	0.926	0.074	L
				F (U as F)	0.989	0.058	P
				F (U as NF)	0.979	0.098	P

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.8

Tumour incidence females - statistical analysis
Results of tests for a decreasing and increasing incidence

Tumour Type		Number of tumour bearing animals Gp 1	Gp 5	Included in analysis	p-values for increased tumour incidence Group 1 vs Group 5	p-values for decreased tumour incidence Group 1 vs Group 5	Method of analysis
Mammary all sites	F	18	10	ALL	0.939	0.061	L
	NF	21	20				
	ALL	39	30				
Adrenal phaeochromocytoma	F	0	1	ALL	0.718	0.663	P
	NF	2	1				
	ALL	2	2				
Thyroid c-cell adenoma	NF	9	6	ALL	0.791	0.209	L
Pituitary adenoma	F	11	8	ALL	0.891	0.109	L
	NF	34	28				
	ALL	45	36				

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9
Tumour incidence males - statistical analysis
Results of tests for increasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
Testis leydig cell tumour	NF	1	2	9	2	7	NF	0.037*	0.264	0.005**	0.356	0.032*	L
Kidneys all sites	F	0	0	1	0	0	ALL	0.317	0.500	0.523	0.167		P
	NF	0	1	0	2	0							
	ALL	0	1	1	2	0							

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence males - statistical analysis
Results of tests for decreasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals					Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
		Gp 1	Gp 2	Gp 3	Gp 4	Gp 5							
Testis leydig cell tumour	NF	1	2	9	2	7	NF	0.963	0.736	0.995	0.644	0.968	L
Kidneys all sites	F	0	0	1	0	0	ALL	0.757	1.000	1.000	1.000		P
	NF	0	1	0	2	0							
	ALL	0	1	1	2	0							

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence females - statistical analysis
Results of tests for increasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
Uterus stromal polyp	F	0	0	0	0	1	ALL	0.004**	0.371	0.340	0.118	0.013*	L
	NF	3	4	4	7	11	NF	<0.001***	0.371	0.340	0.118	0.013*	L
	ALL	3	4	4	7	12							
Uterus sarcoma and stromal sarcoma	F	1	1	0	1	0	F	0.795	0.735	1.000	0.739	1.000	P

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence females - statistical analysis
Results of tests for decreasing dose response and pairwise tests

Tumour Type		Number of tumour bearing animals					Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Gp 1 v Gp 5	Method of analysis
		Gp 1	Gp 2	Gp 3	Gp 4	Gp 5							
Uterus stromal polyp	F	0	0	0	0	1	ALL	0.996	0.629	0.660	0.882	0.987	L
	NF	3	4	4	7	11	NF	>0.999	0.629	0.660	0.882	0.987	L
	ALL	3	4	4	7	12							
Uterus sarcoma and stromal sarcoma	F	1	1	0	1	0	F	0.251	0.764	0.531	0.760	0.466	P

KEY

F = Fatals
NF = Non-Fatals
L = Large sample tests
P = Permutation tests

TABLE 10.9

Tumour incidence males
Statistical analysis for an increasing dose response and pairwise tests

	Test article	Control	Metformin hydrochloride		
	Group	1	2	3	4
	Level (mg/kg/day)	0	150	450	1500

Tumour Type	Number of tumour bearing animals	Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Liver adenoma and carcinoma	F	1	3	0	0	ALL	0.959	0.894	0.940	0.976	L
	NF	20	9	11	8	F	0.941	0.295	1.000	1.000	P
	C	21	12	11	8	NF	0.996	0.980	0.952	0.985	L
Liver haemangioma	NF	2	1	1	0	NF	0.903	0.891	0.816	1.000	P
Haem/lymph/retic all sites	F	2	2	0	1	ALL	0.357	0.471	0.845	0.644	P
	NF	0	1	1	2						
	C	2	3	1	3						
Lung adenoma and carcinoma	F	1	2	3	2	ALL	0.224	0.491	0.514	0.267	L
	NF	13	12	9	13						
	C	14	14	12	15						
Skin subcutis sarcoma and fibroma	F	0	3	0	1	ALL	0.362	0.289	1.000	0.384	P
	NF	1	0	0	1						
	C	1	3	0	2						
Testis Leydig cell tumour	NF	0	5	2	2	NF	0.454	0.017	0.324	0.247	P

KEY: F - fatals
NF - non-fatals
C - combined

L - large sample tests
P - permutation tests

N.B. The pairwise comparison for group 2 versus control for testis Leydig cell tumour is not significant when using Bonferroni adjustments

TABLE 10.9

Tumour incidence females
Statistical analysis for an increasing dose response and pairwise tests

	Test article	Control	Metformin hydrochloride		
	Group	1	2	3	4
	Level (mg/kg/day)	0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Haem/lymph/retic all sites	F	2	7	2	3	ALL (U as NF)	0.685	0.406	0.860	0.638	L
	NF	7	3	2	5	ALL (U as F)	0.688	0.406	0.862	0.638	L
	U	0	0	1	0						
	C	9	10	5	8						
Lung adenoma and carcinoma	F	1	0	0	0	ALL	0.828	0.772	0.700	0.886	L
	NF	7	5	6	4						
	C	8	5	6	4						
Skin subcutis sarcoma and fibroma	F	1	0	2	0	F	0.699	1.000	0.508	1.000	P
Uterus haemangioma	NF	2	6	1	1	NF	0.983	0.076	0.721	0.769	L
Uterus histiocytic sarcoma, sarcoma and stromal polyp	F	1	0	4	1	ALL	0.704	0.999	0.769	0.937	L
	NF	9	0	3	4						
	C	10	0	7	5						
Ovary luteoma	NF	0	2	1	2	NF	0.194	0.254	0.500	0.228	P

KEY: F - fatals
NF - non-fatals
C - combined
U - uncertain

L - large sample tests
P - permutation tests

TABLE 10.10

Tumour incidence males
Statistical analysis for a decreasing dose response and pairwise tests

	Test article	Control	Metformin hydrochloride		
	Group	1	2	3	4
	Level (mg/kg/day)	0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Liver adenoma and carcinoma	F	1	3	0	0	ALL	0.041 *	0.106	0.060	0.024 *	L
	NF	20	9	11	8	F	0.098	0.943	0.504	0.527	P
	C	21	12	11	8	NF	0.004 **	0.020 *	0.048 *	0.015 *	L
Liver haemangioma	NF	2	1	1	0	NF	0.159	0.482	0.615	0.352	P
Haem/lymph/retic all sites	F	2	2	0	1	ALL	0.671	0.831	0.558	0.720	P
	NF	0	1	1	2						
	C	2	3	1	3						
Lung adenoma and carcinoma	F	1	2	3	2	ALL	0.776	0.509	0.486	0.733	L
	NF	13	12	9	13						
	C	14	14	12	15						
Skin subcutis sarcoma and fibroma	F	0	3	0	1	ALL	0.668	0.945	0.576	0.927	P
	NF	1	0	0	1						
	C	1	3	0	2						
Testis Leydig cell tumour	NF	0	5	2	2	NF	0.549	1.000	1.000	1.000	P

KEY: F - fatals
NF - non-fatals
C - combined

L - large sample tests
P - permutation tests

* p<0.05
** p<0.01
*** p<0.001

TABLE 10.10

Tumour incidence females
Statistical analysis for a decreasing dose response and pairwise tests

	Test article	Control	Metformin hydrochloride		
	Group	1	2	3	4
	Level (mg/kg/day)	0	150	450	1500

Tumour Type		Number of tumour bearing animals Gp 1	Gp 2	Gp 3	Gp 4	Included in analysis	Dose response	Gp 1 v Gp 2	Gp 1 v Gp 3	Gp 1 v Gp 4	Method of analysis
Haem/lymph/retic all sites	F	2	7	2	3	ALL (U as NF)	0.315	0.594	0.140	0.362	L
	NF	7	3	2	5	ALL (U as F)	0.312	0.594	0.138	0.362	L
	U	0	0	1	0						
	C	9	10	5	8						
Lung adenoma and carcinoma	F	1	0	0	0	ALL	0.172	0.228	0.300	0.114	L
	NF	7	5	6	4						
	C	8	5	6	4						
Skin subcutis sarcoma and fibroma	F	1	0	2	0	F	0.347	0.489	0.871	0.478	P
Uterus haemangioma	NF	2	6	1	1	NF	0.017 *	0.924	0.279	0.231	L
Uterus histiocytic sarcoma, sarcoma and stromal polyp	F	1	0	4	1	ALL	0.296	0.001 **	0.231	0.064	L
	NF	9	0	3	4						
	C	10	0	7	5						
Ovary luteoma	NF	0	2	1	2	NF	0.835	1.000	1.000	1.000	P

KEY: F - fatals
NF - non-fatals
C - combined
U - uncertain

L - large sample tests
P - permutation tests

* $p<0.05$
** $p<0.01$
*** $p<0.001$

N.B. Bonferroni adjustment applied to comparison between control and group 2 for uterus histiocytic sarcoma, sarcoma and stromal polyp

CHEMISTRY REVIEW

short

DEC 19 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-357 **CHEMISTRY REVIEW #: 6** **DATE REVIEWED:** 16-DEC-1994

Submission:	Original	Doc. 29-SEP-1993	Rec. 29-SEP-1993	
	Amendment	Doc. 16-DE-1994		(amendment # 36)

Applicant: Lipha Pharmaceutical Inc.
9 West 57th. Street, Suite 3825
New York, NY 10019-2701 (212) 223-1392

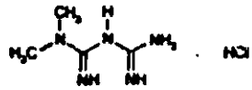
Drug Product Name

Proprietary:	Glucophage®
Nonproprietary/Established/USAN:	Metformin Hydrochloride Tablets
Code Name/#:	LA-6023
Chem.Type/Ther.Class:	1 P

Pharmacological Category/Indication: Antihyperglycemic Agent

Dosage Form:	Tablet
Strengths:	500 and 850 mg
Route of Administration:	Oral
Dispensed:	_X_ Rx __ OTC

Chemical Name, Structural Formula, and Molecular Weight:



$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride, or *N,N*-Dimethylbiguanidine hydrochloride

Remarks: Metformin is a USAN name, but Metformin hydrochloride is not. The lack of a USAN for Metfomin Hydrochloride will not hold up approval of the NDA. However, the firm should request a separate name as soon as possible. We asked a commitment from the applicant, Lipha Pharmaceutical Inc., to request a separate USAN name for the hydrochloride salt. This amendment fulfils satisfactorily the Agency request.

Conclusions & Recommendations: The amendment addresses adequately the concerns regarding the applicant commitment to include Metformin Hydrochloride as a USAN separate name. The two CMC pending issues pertaining Glucophage (Metformin Hydrochloride) Tablets approval have been satisfactorily resolved. An acceptable cGMP dated December 7, 1994, has been received, and a Finding of No Significant [Environmental] Impact for NDA 20-357 was approved on November 23, 1994. This information is incorporated in the NDA 20-357 16-DEC-1994 CMC Summary (20357sme.nda attached). The application is approvable from the Chemistry viewpoint.

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510/Ysern

R/D Initialed: 12/19/94

Xavier Ysern, PhD
Review Chemist

filename: 20537_6.nda

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS HFD-510
NDA Summary of Chemistry Review

NDA 20-357 Glucophage (Metformin Hydrochloride) Tablets Lipha S.A. Date: 16-DEC-1994

A. Drug Substance:

1. Other Firm:	(*Satisfactory*, Review #1)
2. Synthesis:	(*Satisfactory*, Review #1)
3. Structure Characterization:	(*Satisfactory*, Review #1)
4. Specifications and Analytical Methods:	(*Satisfactory*, Review # 2)
5. Stability:	(*Satisfactory*, Review #2)

B. Drug Product:

1. Components and Composition:	(*Satisfactory*, Review #1)
2. Raw Material Control:	(*Satisfactory*, Review # 1)
3. Manufacturer:	(*Satisfactory*, Review #1)
4. Manufacturing Processing:	(*Satisfactory*, Review # 1)
5. Packaging and Labeling:	(Polypropylene body and polyethylene cap *Satisfactory*, Review # 1 Blister units *Satisfactory*, Review # 5)
6. Laboratory Controls and Specifications:	(*Satisfactory*, Review # 2)
7. Containers:	(Polypropylene body and polyethylene cap *Satisfactory*, Review # 1 Blister units *Satisfactory*, Review # 5)
8. Stability:	(Satisfactory, Review # 2) Expirating Dating: 5 years
C. Investigational Formulations:	(*Satisfactory*, Review #1)
D. Environmental Impact Analysis:	(*Satisfactory*, Consult acceptable 23-NOV-1994, attached)

E. Samples and Results: *Pending*

Method validation found acceptable (attached) on July 11, 1994, by Winchester Engineering and Analytical Center, WEAC HFR-NE 400. WEAC is the second field servicing laboratory; the opinion of the other validating laboratory (NYK-DO, HFR-NE 500) still pending.

F. Labeling: (*Satisfactory*, Review # 2)

Request for Trademark Review send on January 19, 1994. Labeling and Nomenclature Committee has no reason to find the proposed name unacceptable (consult # 278, 7-MAR-1993). Regarding the labels used for Glucophage Tablets, we prefer that the tablet designation appear as part of the established name (Metformin Hydrochloride Tablets instead of Metformin Hydrochloride). *Metformin is an USAN name, the applicant should request toUSAN a separate name for Metformin Hydrochloride. Commitment from the applicant to request the inclusion of "Metformin Hydrochloride" as a separate name in the USAN and International Drug Names was received on December 16, 1994 (attached).*

G. Established Inspection: *Satisfactory*

Drug Substance:	Drug Product:	Packaging:
Lipha Calais	Lipha Pharmaceutical Limited	Lipha Pharmaceutical Limited
Zone Industrialle Du Beau Marais	Cadwell Lane	Unit 2-5, Amor Way
5-7, Rue Clement Ader	Hitchin, Hertfordshire 564 OSF	Letchworth, Hertfordshire SG6 1UG
62100 Calais FRANCE	United Kingdom	United Kingdom

Drug product packaged in containers with polypropilene body and polyethylene cap (EER ID # 5918, acceptable May 3, 1994). Blister pack units (amendment June 22, 1994) the corresponding EER was originated on August 9, 1994, and found acceptable on August 16, 1994 (EER ID # 6568).

As sixty days have elapsed from the date of inspection approval, a final update request (FUR) was requested on July 6, 1994. FUR found acceptable (EER ID # 6568) on July 18, 1994. As sixty days have elapsed from the date of first FUR, a second FUR was requested on November 17, 1994., and found acceptable on December 7, 1994 (EER ID # 7306, attached)

Issues Pending: (1) Satisfactory Method Validation from a second validating laboratory (post approval)

Xavier Ysern, PhD
Review Chemist/HFD-510

filename: 20357sme.nda
Date: 16-DEC-1994

Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

ST TYPE (Check One) ( ) Original [ ] Follow-Up [X] FUR	DATE Nov 17, 1994	PHONE NO. 443-3510	EER ID # 7306
REQUESTOR'S NAME Y. Chiu for Xavier Ysern	DIVISION Metabolism and Endocrine Drug	MAIL CODE HFD- 510	
APPLICATION AND SUPPLEMENT NUMBER NDA 20-357 Original Submission			
BRAND NAME Glucophage	ESTABLISHED NAME Metformin HCl Tablets		
DOSAGE AND STRENGTH Tablets 500 mg and 850 mg	STERILE [ ] YES [X] NO		
PROFILE CLASS TCM	PRIORITY CLASSIFICATION (See SMG CDER-4820.3) 1P		
APPLICANT'S NAME Lipha Pharmaceutical, Inc.			
ADDRESS 9 West 57th Street Suite 3825 New York, NY 10019-2701			
COMMENTS Acceptable original EER and FUR attached User fee goal date : Dec 29, 1994 Estimated action date : Mid December, 1994			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID		HFD-324 USE ONLY
1. Lipha Labaz, Zone industrielle Du Bois Marais, 5-7 Rue Clement Ader, 69120 Colaix, France	Drug Substance	5451			
		CCS	18074	AC	5/10/93
2. Lipha Pharmaceutical Limited Cadwell Lane, Hitchin, Hertfordshire SG4 0SP, United Kingdom	Drug Product	5919	LPHH		
		TCM	18075	AC	5/13/93
3. Lipha Pharmaceutical Limited Unit 3-5, Amor Way, Letchworth, Hertfordshire SG6 1ZA, United Kingdom	Packaging		LPHL		
		TCM	18076	AC	5/13/93
4.					
5.					

FOR HFD-324 USE ONLY:	CSO Sherrette Ferguson	DATE RECEIVED 11/21/94
	CGMP/COMPLIANCE STATUS Acceptable	DATE 12/7/94

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office 3/15

CM 12/4/94

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date November 16, 1994

From Generic Drugs Compliance Branch, HFD-325
Division of Manufacturing & Product Quality

Subject EIR 9/5-9/8/94
NDA 20-357 METFORMIN HCl TABLETS
500 mg and 850 mg

Firm Lipha Pharmaceutical Limited
Hitchin, Hertfordshire, England
United Kingdom

To Chief, Inv and Comp Eval Branch, HFD-324
Division of Manufacturing & Product Quality

We have reviewed the above referenced inspection report and the written response from the firm on the subject inspection findings for profile class Tablets, Prompt Release(TCM). We conclude that the inspection findings, together with the corrective actions taken, do not require any other regulatory action at this time. The recommendation for withholding of approval of the subject NDA based on compliance with CGMPs is not necessary.

Deficiencies in CGMP were found and presented to the firm in a list of Inspectional Observations. In its written response to the Inspectional Observations, the firm exhibits the ability and the willingness to make necessary corrections.

We find the corrections described in the letter response to the Inspectional Observations to be adequate to effect corrections. However, some of the corrective actions have not been carried through to completion. We have written to the U.S. agent for the firm requesting the documentation showing completion of these items as described in the letter response to the Inspectional Observations.

Also, we have requested reports on the progress of accurate recording of data in the equipment usage logs and in laboratory data, a special report on the examination/evaluation of tablets rejected for foreign matter, and the firms first annual product review for this product completed in accordance with the new procedure for doing such reviews.

The inspection report and the Inspectional Observations contained a number of deficiencies regarding documents and information, e.g. manufacturing steps, testing procedures, specifications, and Master Record inadequacies, submitted in the New Drug Application. Some of the items may require deficiency correspondence to the firm.

1/15

November 16, 1994

A copy of the inspection report should be forwarded to the NDA reviewing chemist for use in connection with the review of the NDA. The firm already has sent a copy of their letter response to the Inspectional Observations to ODE II/Division of Metabolism and Endocrine Products.

Nicholas Buhay

5/15

November 16, 1994

cc:

HFD-322 Rivera
HFC-134
HFC-240
HFA-224
HFD-320 R/F
HFD-325 Chron
HFD-325 Buhay
Concur:JDietrick: _____ Date: 11/16/94
NBuhay:11/16/94:sb
Control #320-94-11-03
WP LIPHA.EVL

HFD-324 Distribution

orig: HFD-324 EER 5918 File
cc: HFD-510
cc: HFD-324 R/F
cc: MAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Center for Drug Evaluation & Research
Office of Compliance
Division of Manufacturing Product Quality
Metro Park North I Room 266 (HFD-325)
7520 Standish Place
Rockville, Maryland 20855

NOV 17 1994

Mr. Bruce E. Goddard
Director of Compliance and Regulatory Affairs
Lipha Pharmaceuticals, Inc.
9 West 57th Street Suite 3825
New York, New York 10019

Dear Mr. Goddard:

We have reviewed the report of the FDA inspection of your firm's facilities at Hitchin, Hertfordshire during September 5-8, 1994 and Dr. Daniel's letter dated October 17, 1994 responding to the Inspectional Observations issued in the course of the inspection. In order to follow up the inspection findings completely, we request additional information and clarifications.

Dr. Daniel's letter response stated that certain corrective actions remain to be completed and are scheduled to be completed before the end of 1994. Further it states you will supply further documentation as it becomes available. Specifically, we await

* a copy of the In House Training Summary for the training session covering specific requirements relating to equipment usage logs scheduled during October 1994, (p. 4, Equipment Observations 2-7 Response)

* a copy of the calibration program for temperature monitoring gauges on the driers to be drawn up in liaison with external specialists before the end of 1994, (p 4. Equipment Observation #8 Response)

* a copy of the validation update being formulated and to be submitted to the FDA prior to the end of 1994, (p. 9 Validation Observation #2 Response)

* a copy of the new procedure for Product Annual Reviews, (p. 9, PAR Observation #1 Response).

Your new Standard Operating Procedure for the Correction of Errors in Batch Documentation and Associated Documents, 1029/Revision 02 dated 4 October 1994 includes a provision for the use of a standard reason for a record alteration called

"entry error". We believe a definition of this is necessary, as any other standard should be defined, and should be added to the procedure. Please provide a copy of the revised SOP.

The inspection report has produced concern about the accurate and complete recording of data in Lipha. So much of the assurance of quality in manufacturing pharmaceuticals is derived from the keeping of accurate and complete records that it is impossible to overemphasize its importance. While we note and accept as an adequate beginning your corrective actions as provided in Dr. Daniel's letter response, we believe additional steps need to be taken to alleviate this concern. To this end we request that you conduct special internal audits to measure the compliance of your employees with the new provisions of procedure 4055/01 for equipment logs, and the provisions of Procedure 2037/00 and 1029/02 for laboratory data. An appropriate time point for the audits would be 6 months after the implementation of the procedures. We request copies of each of the reports of audit.

Another area of concern is the report of foreign materials noted in or on tablets or granulate during visual examination. The report documents the presence of "hairs", "fibers", "dirt spots", "yellow spots", and "yellow globules" in product. Dr. Daniel's letter response refers to these as "foreign materials arising from the normal production process". We note and accept as appropriate that Procedure 2095/02 provides for the measurement of the presence of "gross contamination", "grease/oil spots", and "grease spots" and action limits for them. We request additional information. Please provide a report of your determination of what were the materials in the 5 remarks above, what were their sources, and what steps are being taken to eliminate or reduce their presence as appropriate, and how the action limits for each of the 3 categories above were determined.

Additionally, we request a copy of the report on the first annual product review for Metformin HCl Tablets upon completion.

With these added steps and information we can consider complete the correction of the findings of the inspection. Looking forward to your early response, we thank you for your cooperation.

Please contact me with any question you may. Telephone (301) 594-0098; Telefax (301) 594-2202.

Nicholas Buhay
Compliance Officer

2/15

cc:

HFD-320 Firm file
HFD-324 20-357
HFD-325 Chron
HFC-134
HFA-224
HFD-325 Buhay
Concur:JDietrick: _____ Date: 11/16/94
NBuhay:11/16/94:sb
WP LIPHA.LTR

HFD-324 Distribution

orig: HFD-324 EER 5918 File
cc: HFD-510
cc: HFD-324 R/F
cc: MAL

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE : **November 23, 1994**

ORIGINAL

FROM : **Phillip G. Vincent, Ph. D.**
ENVIRONMENTAL ASSESSMENT OFFICER

SUBJECT: ENVIRONMENTAL : EA & FONSI

TO : John Short HFD-510

The FONSI for metformin hydrochlorid (Glucophage) has been signoff and transmitted with this memorandum.

Please note that your division needs to obtain an USAN name for the hydrochloride salt. Please advise HFD-102 on this matter.

Thanks.

CC: Reader File HFD-102/Vincent
MDJones HFD-5

F/T 11-23-94

20357L01.LPV

10/15

12/1/94

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-357 **CHEMISTRY REVIEW #: 5** **DATE REVIEWED:** 30-NOV-1994

Submission:	Original	Doc. 29-SEP-1993	Rec. 29-SEP-1993
	Amendment	Doc. 11-NOV-1994	Rec. 14-NOV-1994

Applicant: Lipha Pharmaceutical Inc.
9 West 57th. Street, Suite 3825
New York, NY 10019-2701 (212) 223-1392

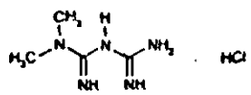
Drug Product Name

Proprietary:	Glucophage®
Nonproprietary/Established/USAN:	Metformin Hydrochloride Tablets
Code Name/#:	LA-6023
Chem.Type/Ther.Class:	1 P

Pharmacological Category/Indication: Antihyperglycemic Agent

Dosage Form:	Tablet
Strengths:	500 and 850 mg
Route of Administration:	Oral
Dispensed:	_x_ Rx __ OTC

Chemical Name, Structural Formula, and Molecular Weight:



$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride, or *N,N*-Dimethylbiguanidine hydrochloride

Remarks: The purpose of this amendment is to provide the information requested on September 8, 1994, pertaining the blister pack information submitted on June 22, 1994.

Conclusions & Recommendations: The amendment addresses adequately the concerns described in our correspondence dated September 8, 1994. Regarding the labels used for Glucophage Tablets, we prefer that the tablet designation appear as part of the established name (Metformin Hydrochloride Tablets instead of Metformin Hydrochloride). This change can be made at some time after introduction of the drug and reported in the first annual report. From the Chemistry viewpoint application will become approvable when satisfactory response to the EIA concerns and acceptable response to the [FUR] EER originated on November 17, 1994, are received. See updated NDA 20-357 summary (20357smd.nda) review dated November 30, 1994.

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510//Ysern

R/D Initialed: 12/1/94

Xavier Ysern, PhD
Review Chemist

filename: 20357_5.NDA

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS HAD-510
NDA Summary of Chemistry Review

NDA 20-357 Glucophage (Metformin Hydrochloride) Tablets Lipha S.A. Date: 30-NOV-1994

A. Drug Substance:

1. Other Firm:	(*Satisfactory*, Review #1)
2. Synthesis:	(*Satisfactory*, Review #1)
3. Structure Characterization:	(*Satisfactory*, Review #1)
4. Specifications and Analytical Methods:	(*Satisfactory*, Review # 2)
5. Stability:	(*Satisfactory*, Review #2)

B. Drug Product:

1. Components and Composition:	(*Satisfactory*, Review #1)
2. Raw Material Control:	(*Satisfactory*, Review # 1)
3. Manufacturer:	(*Satisfactory*, Review #1)
4. Manufacturing Processing:	(*Satisfactory*, Review # 1)
5. Packaging and Labeling:	(Polypropylene body and polyethylene cap *Satisfactory*, Review # 1 Blister units ***Satisfactory***, Review # 5)
6. Laboratory Controls and Specifications:	(*Satisfactory*, Review # 2)
7. Containers:	(Polypropylene body and polyethylene cap *Satisfactory*, Review # 1 Blister units ***Satisfactory***, Review # 5)
8. Stability:	(Satisfactory, Review # 2) Expirating Dating: 5 years

C. Investigational Formulations: (*Satisfactory*, Review #1)

D. Environmental Impact Analysis: *Not Satisfactory*

Meeting with the industry regarding EA concerns took place on May 26, 1994. Amendments submitted on 19-AUG-1994 and on 31-OCT-1994. Pending.

E. Samples and Results: *Pending*

Method validation found acceptable (attached) on July 11, 1994, by Winchester Engineering and Analytical Center, WEAC HFR-NE 400. WEAC is the second

field servicing laboratory; the opinion of the other validating laboratory (NYK-DO, HFR-NE 500) still pending.

F. Labeling: (*Satisfactory*, Review # 2)

Request for Trademark Review send on January 19, 1994. Labeling and Nomenclature Committee has no reason to find the proposed name unacceptable (consult # 278, 7-MAR-1993). Regarding the labels used for Glucophage Tablets, we prefer that the tablet designation appear as part of the established name (Metformin Hydrochloride Tablets instead of Metformin Hydrochloride)

G. Established Inspection: *Pending*

Drug Substance:	Drug Product:	Packaging:
Lipha Calais	Lipha Pharmaceutical Limited	Lipha Pharmaceutical Limited
Zone Industrialle Du Beau Marais	Cadwell Lane	Unit 2-5, Amor Way
5-7, Rue Clement Ader	Hitchin, Hertfordshire 564 OSF	Letchworth, Hertfordshire SG6 1UG
62100 Calais FRANCE	United Kingdom	United Kingdom

Drug product packaged in containers with polypropilene body and polyethylene cap (EER ID # 5918, acceptable May 3, 1994). Blister pack units (amendment June 22, 1994) the corresponding EER was originated on August 9, 1994, and found acceptable on August 16, 1994 (EER ID # 6568).

As sixty days have elapsed from the date of inspection approval, a final update request (FUR) was requested on July 6, 1994. FUR found acceptable (EER ID # 6568, attached) on July 18, 1994. As sixty days have elapsed from the date of first FUR, a **second FUR was requested on November 17, 1994.**

A copy of the FD-483 (Robert Coleman/Investigator; September 5 to 8, 1994) was received via facsimile on September 12, 1994. The 483 form described departures from GMP found in the Hitchin (UK) facility. An EER to follow-up this report was requested on September 28, 1994. The response to that request, assigned as EER ID # 6983, gave an acceptable cGMP (4-OCT-1994) to the blister packaging facility at Letchworth, UK (attached). The firm's response to the 483 form (pertaining drug product manufacture at the facility located in Hitchin, Herts, UK) was sent on October 17, 1994, addressed to the Director of International & Technical Operations Branch. Pending FUR initiated 17-NOV-1994.

Issues Pending: *(1) Adequate Environmental Impact Assessment* *(required for approval)*
(2) Results of FUR originated on November 17, 1994. *(required for approval)*
(3) Satisfactory Method Validation from a second validating laboratory *(post approval)*

ATTACHED:	(1) EER ID # 6983 (includes copy of EER ID # 6568)	(6 pages)	page 3
	(2) EER (FUR) initiated November 17, 1994	(1 page)	page 9

filename: 20357smd.nda
Date: 30-NOV-1994

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One) ☐ Original ☑ Follow-Up ☐ FUR	DATE SEP 28 '94	PHONE NO. 301 443 3510	EER ID [redacted] 6983
REQUESTOR'S NAME Xavier Ysern		DIVISION METABOLISM & ENDOCRINE D.P.	MAIL CODE HFD- 510
APPLICATION AND SUPPLEMENT NUMBER NDA 20-357 (amendment 22-JUN-1994)			
BRAND NAME GLUCOPHAGE Tablets		ESTABLISHED NAME METFORMIN HCl Tablets	
DOSAGE AND STRENGTH Tablets 500 and 850 mg			STERILE ☐ YES ☒ NO
PROFILE CLASS TCM	PRIORITY CLASSIFICATION (See SMG CDER-4820.3) 1 P		
APPLICANT'S NAME LIPHA PHARMACEUTICAL, INC			
ADDRESS 9 WEST 57th. Street, Suite 3825 New York, NY 10019-2701			
COMMENTS - This follow-up is requested to accomodate the recent report from Robert Coleman (ATTACHED) (one page memo, four pages form FD483) - Previous EER, EER ID#6568 is also attached (one page)			

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	[redacted] ONLY
1. LIPHA PHARMACEUTICAL LIMITED UNITS 2-5 AMOR WAY LETCHWORTH HERTFORDSHIRE	Blister Pkg.		[redacted]	[redacted] 9/13/93
2. SGL IUG UNITED KINGDOM		TCM	[redacted]	
3.			[redacted]	
4.				
5.				

FOR HFD-324 USE ONLY:	CSO Shurnette Ferguson	DATE RECEIVED [redacted] OCT 3 1994
	CGMP COMPLIANCE STATUS Acceptable	DATE 10/4/94

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date September 12, 1894

From Robert C. Coleman
Investigator, ITOB, ATL-DO

Subject EI of Lipha Pharmaceuticals

To Peter D. Smith
Associate Director, ITOB, HFC-134

Our inspection of Lipha Pharmaceuticals, Hitchin, UK, on 9/6-8/94, found several significant objectionable conditions concerning pending NDA 20-357, Metformin HCl Tablets 500 & 850 mg. We found problems in the firm's raw material testing and specifications, equipment usage logs, batch production records, handling of rejected tablets, visual inspection of finished tablets, cleaning, validation of manufacturing, product annual reviews, and laboratory controls.

We issued a FD-483 (attached). Management promised correction of all items as soon as possible. Management stated they will respond in writing as soon as possible.

We recommend WITHHOLDING approval pending a satisfactory response from the firm.

Methods validations samples were collected.

Robert C. Coleman

LT

AUG 16 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-357 **CHEMISTRY REVIEW #: 4** **DATE REVIEWED: 10-AUG-1994**

Submission:	Original	Doc. 29-SEP-1993	Rec. 29-SEP-1993
	Amendment	Doc. 22-JUN-1994	Rec. 23-JUN-1994

Applicant: Lipha Pharmaceutical Inc.
9 West 57th. Street, Suite 3825
New York, NY 10019-2701 (212) 223-1392

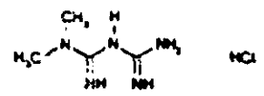
Drug Product Name

Proprietary:	Glucophage®
Nonproprietary/Established/USAN:	Metformin Hydrochloride Tablets
Code Name/#:	LA-6023
Chem.Type/Ther.Class:	1 P

Pharmacological Category/Indication: Antihyperglycemic Agent

Dosage Form:	Tablet
Strengths:	500 and 850 mg
Route of Administration:	Oral
Dispensed:	_x_ Rx __ OTC

Chemical Name, Structural Formula, and Molecular Weight:



$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride, or *N,N*-Dimethylbiguanidine hydrochloride

Related Documents: DMF
DMF

Remarks: The purpose of this amendment is to include a blister pack presentation for both the 500 and 850 mg tablets.

Conclusions & Recommendations: The information provided in the June 22, 1994, amendment is not adequate (incomplete). The application is not approvable from the Chemistry viewpoint. The deficiencies are delinated in the draft letter. Satisfactory response to EIA concerns and EER originated on August 9, 1994, are also pending. See updated NDA 20-329 summary (20344smc.nda) review dated August 15, 1994.

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510//Ysem

R/D Initialed:
M. Davis
YY Chen
8/16/94

Xavier Ysern, PhD
Review Chemist

filename: 20357_4.NDA

John copy

JUL 20 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-357 **CHEMISTRY REVIEW #: 3** **DATE REVIEWED:** 20-JUL-1994

SUBMISSION ORIGINAL Doc. 29-SEP-1993 Rec. 29-SEP-1993

APPLICANT: Lipha Pharmaceutical Inc.
9 West 57th. Street, Suite 3825
New York, NY 10019-2701 (212) 223-1392

DRUG PRODUCT NAME

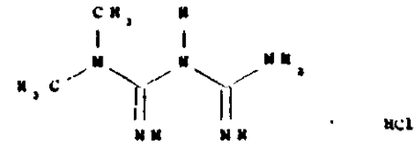
Proprietary:	Glucophage®
Nonproprietary/Established/USAN:	Metformin Hydrochloride Tablets
Code Name/#:	LA-6023
Chem.Type/Ther.Class:	1 P

PHARMACOLOGICAL CATEGORY/INDICATION: Antihyperglycemic Agent

DOSAGE FORM:	Tablet
STRENGTHS:	500 and 850 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_x_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, AND MOLECULAR WEIGHT:

$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride, or
N,N-Dimethylbiguanidine hydrochloride



REMARKS: This review incorporates the FUR since sixty days have elapsed from date of inspection approval (previous EER # 5918, initiated on February 8, 1994, was found acceptable on May 3, 1994). The FUR has been acceptable on July 17, 1994 (EER # 6568 originated on July 6, 1994). This review also incorporates the results of the Method Validation from one of the two servicing laboratories. The Winchester Engineering and Analytical Center (HFR-NE 400) validated the firm proposed methods (assay and identification of glipizide and related substance A, dissolution: cumulative and average release) for the drug product and found them acceptable on July 11, 1994.

CONCLUSIONS & RECOMMENDATIONS: The sponsor has answered satisfactorily the requested CMC information. The application is approvable from the Chemistry viewpoint, pending satisfactory response from the sponsor regarding the EIA concerns. See updated NDA 20-357 summary review dated July 20, 1994. FUR and Method Validation from HFR-NE 400 are attached to the summary.

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510//Ysern

R/D Initialed: 7/20/94

Xavier Ysern, PhD
Review Chemist

filename: 20357_3.NDA

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS HFD-510
NDA Summary of Chemistry Review

NDA 20-357 **Date: 20-JUL-1994**

Glucophage (Metformin Hydrochloride) Tablets Lipha S.A.

A. Drug Substance: *Satisfactory*

1. Other Firm: *Satisfactory*	(Review #1)
2. Synthesis: *Satisfactory*	(Review #1)
3. Structure Characterization: *Satisfactory*	(Review #1)
4. Specifications and Analytical Methods: *Satisfactory*	(Review # 2, DS comment 1)
5. Stability: *Satisfactory*	(Review #2, DS comment 2)

B. Drug Product: *Satisfactory*

1. Components and Composition: *Satisfactory*	(Review #1)
2. Raw Material Control: *Satisfactory*	(Review # 1)
3. Manufacturer: *Satisfactory*	(Review #1)
4. Manufacturing Processing: *Satisfactory*	(Review # 1)
5. Packaging and Labeling: *Satisfactory*	(Review # 1)
6. Laboratory Controls and Specifications: *Satisfactory*	(Review # 2, DP comments 1 and 3)
7. Containers: *Satisfactory*	(Review # 1)
8. Stability: *Satisfactory* Expirating Dating: 5 years	(Review # 2, DP comment 2)

C. Investigational Formulations: *Satisfactory* (Review #1)

Xavier Ysern, PhD

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510/JShort/XYsern
R/D Init

filename: 20357smb.nda

D. Environmental Impact Analysis: *Not Satisfactory*

Meeting with the industry regarding EA concerns took place on May 26, 1994.

E. Samples and Results: *Pending*

MV Package to be send to FDA laboratories.
Method validation found acceptable (attached) on July 11, 1994, by Winchester Engineering and Analytical Center, WEAC HFR-NE 400.
WEAC is the second field servicing laboratory; **the opinion of the other validating laboratory (NYK-DO, HFR-NE 500) still pending.**

F. Labeling: *Satisfactory* (Review # 2)

Request for Trademark Review send on January 19, 1994. Labeling and Nomenclature Committee has no reason to find the proposed name unacceptable (consult # 278, 7-MAR-1993).

G. Established Inspection: *Satisfactory*

EER ID # 5918	Acceptable May 3, 1994
Drug Substance:	Lipha Calais Zone Industrialle Du Beau Marais 5-7, Rue Clement Ader 62100 Calais FRANCE
Drug Product:	Lipha Pharmaceutical Limited Cadwell Lane Hitchin, Hertfordshire 564 OSF United Kingdom
Packaging:	Lipha Pharmaceutical Limited Unit 2-5, Amor Way Letchworth, Hertfordshire SG6 1UC United Kingdom

As sixty days have elapsed from the date of inspection approval, a final update request (FUR) was requested on July 6, 1994. FUR found acceptable (EER ID # 6568, attached) on July 18, 1994.

Issues Pending: *(1) Adequate Environmental Impact Assesment (required for approval)*
(2) Satisfactory Method Validation from a second validating laboratoy (post approval)

Date: 20-JUL-1994 **filename:** 20357smb.nda

ATTACHED: (1) EER ID # 6568
(2) Method Validation/ Verification from WEAC HFR-NE 400

Public Health Service
FOOD AND DRUG ADMINISTRATION

J

ESTABLISHMENT EVALUATION REQUEST

TEST TYPE (Check One) Original ☐ Follow-Up ☑ FUR	DATE 6 JUL 1994	PHONE NO. 301 443 3510	EER ID # 6568
REQUESTOR'S NAME XAVIER YSERN		DIVISION METABOLISM AND ENDOCRINE D. P.	MAIL CODE HFD- 510
APPLICATION AND SUPPLEMENT NUMBER NDA 20357 Original Submission			
BRAND NAME Glucophage Tablets		ESTABLISHED NAME Metformin HCl Tablets	
DOSAGE AND STRENGTH Tablets 500 mg and 850 mg			STERILE ☐ YES ☑ NO
PROFILE CLASS TCM		PRIORITY CLASSIFICATION (See SMG CDER-4820.3) 1 P.	
APPLICANT'S NAME LIPHA PHARMACEUTICAL, INC.			
ADDRESS 9 WEST 57th. Street Suite 3325 New York, NY 10019-2701			
COMMENTS SIXTY DAYS ATTACHED EER ID # 5918 (acceptable 5/3/94)			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID		HFD-324 USE ONLY
1. LIPHA CALAIS ZONE INDUSTRIALLE DU BEAU MARAIS 5-7, RUE CLEMENT ADER 62100 CALAIS FRANCE	DRUG SUBSTANCE	5951			
		CCS	16599	AC	5/10/93
2. LIPHA PHARMACEUTICAL LIMITED CADWELL LANE HITCHIN, HERTFORDSHIRE SG4 0SF UNITED KINGDOM	DRUG PRODUCT	5959	LPHH		
		TCM	16577	AC	5/13/93
3. LIPHA PHARMACEUTICAL LIMITED UNIT 2-5, AMOR WAY LETCHWORTH, HERTFORDSHIRE SG6 1UG UNITED KINGDOM	PACKING		LPHL		
		TCM	16578	AC	5/13/93
4.					
5.					

FOR HFD-324 USE ONLY:	CSO Melissa J Egan	DATE RECEIVED JUL 8 1994
	CGMP COMPLIANCE STATUS Acceptable	DATE 7/18/94

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

MAY 25 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-357 **CHEMISTRY REVIEW #: 2** **DATE REVIEWED:** 24-MAY-1994

SUBMISSION ORIGINAL	Doc. 29-SEP-1993	Rec. 29-SEP-1993	
AMENDMENT	Doc. 13-MAY-1994	Rec. 16-MAY-1994	(Serial # 23)

APPLICANT: Lipha Pharmaceutical Inc.
9 West 57th. Street, Suite 3825
New York, NY 10019-2701 (212) 223-1392

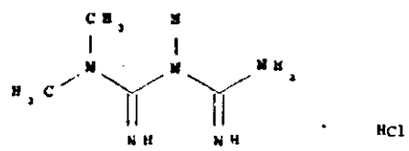
DRUG PRODUCT NAME

Proprietary:	Glucophage®
Nonproprietary/Established/USAN:	Metformin Hydrochloride Tablets
Code Name/#:	LA-6023
Chem.Type/Ther.Class:	1 P

PHARMACOLOGICAL CATEGORY/INDICATION: Antihyperglycemic Agent

DOSAGE FORM: Tablet
STRENGTHS: 500 and 850 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __x__ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_4H_{11}N_5 \cdot HCl$
MW = 129. 7 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride, or *N,N*-Dimethylbiguanidine hydrochloride

REMARKS: This amendment provides the response to the requests delineated on the March 24, 1994, communication. The pending EER (# 5918, initiated on February 8, 1994) has been found acceptable on May 3, 1994. Dr. Phil Vince, CDER Environmental Officer, has expressed concerns regarding the Environmental Impact Assessment (EIA). A meeting with the sponsor regarding EIA issues will take place on May 26, 1994.

CONCLUSIONS & RECOMMENDATIONS: The sponsor has answered satisfactorily the requested CMC information. The manufacturing facilities are acceptable (May 3, 1994, EER # 5918). The application is **approvable from the Chemistry viewpoint, pending satisfactory response from the sponsor regarding the EIA concerns.**

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510//Ysern

R/D Initialed: 5/25/94

Xavier Ysern, PhD
Review Chemist

filename: 20357_2.NDA

MAR 10 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-357 **CHEMISTRY REVIEW #: 1** **DATE REVIEWED:** 10-MAR-1994

SUBMISSION ORIGINAL Doc. 29-SEP-1993 Rec. 29-SEP-1993

APPLICANT: Lipha Pharmaceutical Inc.
9 West 57th. Street, Suite 3825
New York, NY 10019-2701 (212) 223-1392

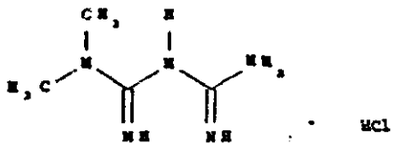
DRUG PRODUCT NAME

Proprietary:	Glucophage®
Nonproprietary/Established/USAN:	Metformin Hydrochloride Tablets
Code Name/#:	LA-6023
Chem.Type/Ther.Class:	1 P

PHARMACOLOGICAL CATEGORY/INDICATION: Antihyperglycemic Agent

DOSAGE FORM:	Tablet
STRENGTHS:	500 and 850 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_x_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride, or *N,N*-Dimethylbiguanidine hydrochloride

REMARKS: Metformin hydrochloride is an oral antihyperglycemic agent (rather than hypoglycemic agent) of the biguanide [structural] group. The other mebers of this class are buformin and phenformin, both have been withdrwn from the market in most countries because of the risk of lactic acidosis. Metformin hydrochloride (which is commercialized outside USA) is under clinical study under treatment IND

CONCLUSIONS & RECOMMENDATIONS: The appplication is approvable from the Chemistry viewpoint pending the acceptable decision for the manufacturing facilities with respect to cGMP compliance by the Division of Manufacturing and Product Quality, and the sponsor response to the deficiencies delineated in draft letter. See Draft Defieciency Letter.

Orig. NDA 20-357
cc: HFD-510/Division File
HFD-510/Gueriguian/Hertig/Innerfield/Short/Ysern
HFD-102/CKumkumian
R/D Initialed: 3/10/94

Xavier Ysern, PhD
Review Chemist

filename: 20357_1.NDA

DOCUMENTS:

IND	Metformin Hydrochloride Oral	Lipha Pharmaceutical Inc., New York, NY	24-FEB-1986
DMF	Type II Original Submission	Metformin Hydrochloride Drug Substance (including Type I information) Lipha Pharmaceutical Inc., New York,NY	
		Superseded see below	9-AUG-1985
	Amendment 1	*Superseded see below*	28-MAR-1987
	Amendment 2	*Supersedes and replaces all Type II data contained in the original submission and Amendment 1*	15-MAR-1993
DMF	Type I Calais (DMF	& SERPA Surenes (DMF	in France Lipha S.A.
DMF	*Supersede Type I data in original DMF .*	*and amendment*	17-NOV-1992
DMF	Type II Original Submission	Metformin Hydrochloride Drug Product (including Type I information) Lipha Pharmaceutical Inc., New York, NY	
		Superseded see below	9-AUG-1985
	Amendment 1	*Superseded see below*	28-MAR-1987
	Amendment 2	*Superseded see below*	28-MAR-1988
	Amendment 3	*Supersedes and replaces all Type II data contained in the original submission and its amendments*	14-FEB-1992
	Amendment 4	*Annual Report*	26-APR-1993
DMF	Type I	Facilities, etc. data for Lipha Pharmaceuticals, Ltd, UK Lipha SA, Lyon, France	
		Supersedes and replaces all Type I data in original DMF and amendments	20-DEC-1991
	Amendment 1	*Annual Report*	14-JAN-1993

ENVIRONMENTAL ASSESSMENT AND FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

GLUCOPHAGE®
[METFORMIN HYDROCHLORIDE]

TABLETS

NDA 20-357

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-510

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-357

Glucophage®

[Metformin Hydrochloride]

Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues. not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Glucophage®, Lipha Pharmaceuticals, Incorporated** has conducted a number of environmental studies and prepared an environmental assessment in accordance with (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Glucophage is a synthetic drug, indicated for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) when hyperglycemia cannot be managed with dietary measures and exercise alone and in conjunction with continued oral sulfonylurea therapy, diet and exercise in NIDDM patients whose hyperglycemia is not or is no longer adequately controlled with sulfonylurea therapy, diet and exercise. Bulk drug substance will be manufactured by Lipha S.A. (production site - Calais, France). Final drug product will be manufactured and packaged by Lipha Pharmaceuticals Limited (production site: Hitchin, Hertfordshire, United Kingdom - packaging site: Letchworth, Hertfordshire, United Kingdom. The finished drug product will be used throughout the United States under a physician's direction.

Waste products generated at the production facility in France will be disposed of in accordance with applicable national and local environmental regulations. Lipha S.A. has received authorization from the appropriate authorities to operate the plant and has certified that operation is in accordance with applicable French environmental regulations. Waste products generated at the production facilities in the United Kingdom will be disposed of in accordance with applicable national and local environmental regulations. Lipha Pharmaceuticals Limited has received authorization from the appropriate authorities to operate the plants and has certified that operation is in accordance with applicable British environmental regulations.

Waste products generated in the United States will consist of expired, rejected or returned drug product. Disposal shall be accomplished by incineration through a contract disposal company. The incinerator has two stages (Rotary Kiln: 1600 - 2400°F, Afterburner: 2000 - 2400°F) and is operated under permits granted by the applicable state and local agencies.

Chemical and physical testing results indicate that the product will most likely be restricted to the aqueous compartment with no appreciable partitioning into the atmospheric or terrestrial environments. The product does not appreciably hydrolyze or biodegrade (mineralize to CO_2) under aerobic conditions. Indirect aqueous photodegradation studies showed that the product breaks down with an observed half-life of approximately 28 days, indicating that the Expected Environmental Concentration (EEC) for the product will be less than half the Maximum Expected Emitted Concentration (MEEC).

Microbial inhibition studies indicated that environmental organisms were not inhibited at concentrations of at least five orders of magnitude (10^5) greater than the EEC values. Acute toxicity studies for *Daphnia magna* yielded a No Observed Effects Concentration (NOEC) of at least five orders of magnitude greater than the EEC values. Acute toxicity studies for freshwater fish (*Lepomis macrochirus*) yielded NOEC values at least six orders of magnitude greater than the EEC values.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

DATE

Glen Jon Smith
Review Chemist
Center for Drug Evaluation and Research

11-22-94
DATE

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

11/23/94
DATE

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)
Letters from foreign governments

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

3.5 Environmental Assessment for Metformin Hydrochloride Tablets

ITEM 3 – CHEMISTRY, MANUFACTURING AND CONTROLS

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METFORMIN HYDROCHLORIDE **LIPHA PHARMACEUTICALS, INC.**

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

EXECUTIVE SUMMARY

This amendment (#32) to our NDA #20-357 for Glucophage® (metformin hydrochloride) reflects a revision as well as additional data to our earlier Environmental Assessment submitted in our NDA application of September 29, 1993 and to its revision (Amendment #27) submitted August 19, 1994. The document format is arranged as required in 21 CFR 25.31(a). The proposed action will provide a new oral antihyperglycemic drug for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) as first-line therapy in selected patients and when hyperglycemia cannot be otherwise managed with available treatments.

The manufacture of metformin HCl will not adversely impact the environment either directly or indirectly. Drug substance will be manufactured in Calais, France and drug product will be manufactured in Hitchin, Hertfordshire, United Kingdom; both sites operate in compliance with all applicable environmental regulations and are currently approved for manufacturing for worldwide distribution. Thus, no additional environmental impact is anticipated by this action.

Metformin HCl is in the protonated form (monohydrochloride). Metformin itself is a strong base with a pK_a of 12.4. The hydrochloride salt is a freely water-soluble compound (~30% wt/vol) with an undetectable vapor pressure at ambient temperatures due to its high melting point of 225°C. The estimated sorption coefficient (K_{oc}), calculated from the octanol/water partition coefficient, is 4.97.

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

Upon use, metformin HCl is excreted unchanged and, based on the calculated K_{oc} of 4.97, it is concluded that it will reside as the hydrochloride salt in the aquatic environmental compartment within the sewage treatment plant and outside in the environment when released as wastewater effluent. Therefore, the effects testing was directed towards the aqueous compartment.

The maximum emitted environmental concentration (MEEC) was calculated to be 1.4×10^{-3} mg/L (1.4 ppb). The results of environmental fate studies demonstrate that there is no hydrolysis (pH 5, 7, and 9) after 5 days and limited aerobic biodegradation in water (approximately 0.6% $^{14}CO_2$ production) after 28 days. No absorption was detected in the ultraviolet-visible absorption spectra in the range of 290 to 800 nm at pH 5, 7, and 9; hence, no direct photolysis study was conducted. Nonetheless, an indirect photolysis study was conducted using acetone as a sensitizer. Metformin degraded into three quantifiable components, with the calculated half-life of the parent being 28.3 days. Based on this calculated half-life, the expected environmental concentration (EEC) may be half of the MEEC. In addition, the wastewater effluents from the sewage treatment plants are expected to be released into waterways and because of the continuous, naturally occurring dilution, the EEC will be still lower.

Extensive toxicity testing, from acute to chronic/carcinogenicity studies, demonstrated that toxicity to mammals is very low. Effects studies in representative microorganisms and aquatic species, such as *Daphnia* and fish,

demonstrated no observable effects at concentrations about 10^5 to 10^6 times the MEEC. The results of these studies are summarized in the following table.

Study Name	Species	Results
Microbial Growth Inhibition (FDA 4.02)	*Aspergillus, Penicillium, Chaetomium* (fungi), *Pseudomonas, Bacillus*	No inhibition @ 1000 ppm **(~10^6 X MEEC)**
	Anabaena (alga)	MIC = 100 ppm **(~$7x10^4$ X MEEC)**
	Azotobacter (N_2-fixing bacterium)	MIC = 800 ppm **(~$5.7x10^5$ X MEEC)**
Daphnia Acute Toxicity (FDA 4.08)	*Daphnia magna*	NOEC = 78 mg/L **(~$5.6x10^4$ X MEEC)** EC_{50} (calc.) = 130 mg/L **(~10^5 X MEEC)**
Freshwater Fish Acute Toxicity (FDA 4.11)	Bluegill (*Lepomis macrochirus*)	NOEC = 982 mg/L **(~10^6 X MEEC)**

NOEC = No-observed-effects concentration
MEEC = Maximum emitted environmental concentration
MIC = Minimum inhibitory concentration
EC_{50} = Concentration producing 50% immobilization

Based on the results of the physicochemical, fate, and effects testing conducted with metformin HCl, no adverse environmental impact is anticipated.

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

3.5 Environmental Assessment for Metformin Hydrochloride (HCl) Tablets

1.	**Date**	*November 8, 1994*
2.	**Name of Applicant**	Lipha Pharmaceuticals, Inc.
3.	**Address**	9 West 57th Street New York, N.Y. 10019-2701

4. **Description of the Proposed Action**

This Environmental Assessment (EA) is part of the New Drug Application (NDA #20-357) requesting approval for the manufacturing, packaging, and marketing of metformin hydrochloride tablets. The document format is arranged as required in 21 CFR 25.31(a).

A. **Requested Action**

Lipha Pharmaceuticals, Inc. has filed a New Drug Application for Glucophage® (brand of metformin hydrochloride) Tablets containing the drug metformin hydrochloride (metformin HCl). These tablets are available in dosage strengths of 500 and 850 mg. The New Drug Application requests approval for the use of metformin HCl as 1) monotherapy, in conjunction with diet and exercise, in patients with non-insulin-dependent diabetes mellitus (NIDDM) when hyperglycemia cannot be managed with dietary measures and

exercise alone, and 2) in conjunction with continued oral sulfonylurea therapy, diet and exercise in NIDDM patients whose hyperglycemia is not or is no longer adequately controlled with sulfonylurea therapy, diet and exercise.

B. **Need for Action**

Approval of this application will result in the distribution of metformin HCl in the United States (U.S.). Oral sulfonylureas are currently the only available oral glucose-lowering agents in the U.S. As a consequence, parenteral insulin is the sole pharmacologic therapeutic agent available to patients with NIDDM who do not respond to oral sulfonylureas or who no longer respond to such agents. However, since the mechanism(s) of action of metformin HCl and oral sulfonylureas are different, the substitution of metformin HCl for oral sulfonylurea monotherapy or their concomitant use in such patients, considered to be sulfonylurea "failures," can result in substantial improvement in glycemic control. Commercial availability of metformin HCl would thereby provide physicians and patients with an alternative therapeutic option.

Because metformin HCl monotherapy does not produce hypoglycemia, it may have advantages over currently available glucose-lowering agents which, by virtue of their mechanism of action, can cause hypoglycemia when used alone. NIDDM patients involved in potentially hazardous or critical occupations may, therefore, be better managed with metformin HCl as monotherapy.

Obesity contributes significantly to the increased morbidity and mortality in NIDDM. Currently available glucose-lowering agents (oral sulfonylureas and insulin) tend to cause weight gain and, thus, metformin HCl may have advantages over such therapies in overweight NIDDM patients since metformin HCl does not result in weight gain and may even result in desirable weight loss, particularly when used as monotherapy. Additional benefits of metformin HCl therapy include improvement in the lipid profile (total cholesterol, LDL-cholesterol and triglycerides), particularly when such lipid fractions are abnormally increased at therapy initiation.

C. **Location of Production — Environmental Conditions at the Site**

Manufacturer of Drug Substance: Metformin HCl is synthesized by Lipha S.A., with headquarters in Lyon, France, in one of their chemical synthesis plants at:

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Lipha Calais
5/7, rue Clement Ader
62100 Calais, France

Manufacturer of the Drug Product: The dosage forms are formulated and produced by:

Lipha Pharmaceuticals Limited
Cadwell Lane
Hitchin, Hertfordshire, SG4 0SF
United Kingdom

Packager of the Drug Product: Drug product will be packaged by:

Lipha Pharmaceuticals Limited
Units 2-5 Amor Way
Letchworth, Hertfordshire, SG6 1UG
United Kingdom

The environmental settings of these facilities, all located in a temperate climate, are as follows:

1) **Calais, France:** The Lipha manufacturing, packaging and warehousing facilities are located in one of Calais' industrial parks (Zone Industrielle de Beau Marais), east of Calais (pop. 70,000), adjacent to the Calais-Dunkirk Road (French National

Route 1), approximately 150 miles north of Paris. The park occupies an area of about acres, not including a planned expansion of acres. The site consists of buildings covering an area of square feet. It employs an average work force of people. The surrounding neighborhood includes other light industries.

Land Resources: The site is situated on a maritime plain with a soil composed primarily of sand. The principal buildings on this site are three manufacturing buildings, several storage buildings, a waste disposal zone, and an office building.

2) **Hitchin, Hertfordshire, U.K.:** This Lipha facility is located on approximately 0.7 acres of land in the city of Hitchin (pop. 30,000), approximately 30 miles north of London. The site consists of one building covering square feet on two floors, and employs an average work force of people. The building includes manufacturing areas, laboratories and offices. It is located in the corridor between motorways M1 and A1, the principal highways between London and the north. The surrounding neighborhood includes sports facilities, light industry, businesses and private residences.

Land Resources: The site is situated on chalk-based soil.

3) **Letchworth, Hertfordshire, U.K.:** Two separate Lipha facilities are located in the city of Letchworth (pop. 32,000), approximately 30 miles north of London. The sites consist of two independent buildings in the same industrial park off Dunhams Lane. Dunhams Court occupies acres of land and comprises one unit with square feet of floor space. It employs an average work force of people. Dunhams Court is primarily a warehouse which is used for receiving, sampling and distribution. The second, Amor Way, is situated on acres of land and involves a combination of light industrial units including warehousing and packaging areas. It covers square feet and employs an average work force of people. Both sites are in the same corridor between the two principal motorways from London to the north, as is Hitchin. The surrounding neighborhood includes sports facilities, light industry, retail businesses and private residences.

Land Resources: Both sites are situated on chalk-based soil.

References to the drug master files for these facilities are included in the NDA.

After approval of the proposed action, the drug product that will be manufactured is as follows:

Glucophage® (brand of metformin hydrochloride)
500- and 850-mg Tablets

D. **Locations of Use and Disposal**

As a prescribed treatment for non-insulin-dependent diabetes mellitus (NIDDM), this drug will be ingested in locations throughout the United States (U.S.). The amount that is eliminated or excreted will enter the wastewater stream as unchanged drug since it is not metabolized.

After commercialization of the drug, all returned, recalled, or expired goods will be disposed of in an appropriate manner by the product distributor under contract with the following company:

Rollins Environmental Services (N.J.) Inc.
Route 322, Bridgeport N.J. 08014
EPA I.D. No. NJD 053 288 239

This facility is permitted to accept and incinerate N,N-dimethyl-biguanide hydrochloride (metformin hydrochloride) and the materials

used in its marketing and distribution, including polypropylene bottles, polyethylene caps and polyvinyl chloride film.

All wastes are processed through a rotary kiln and afterburner at temperatures from 1600° to 2400°F. The residuals are tested to ensure that all Destruction Removal Efficiencies have been met prior to landfill.

Copies of correspondence from Mr. Stephen J. DeLussa, Technical Representative of Rollins, attesting to the above dated November 2, 1994, permit requirements and other related topics, are provided in **Appendix 1**.

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

5. Identification of Chemical Substances that are Subject to this Proposed Action

This NDA is for Glucophage® Tablets. The relevant drug substance and active ingredient is metformin HCl.

A. Nomenclature

1) **Chemical Name (CAS Name)**

N,N-Dimethylimidodicarbonimidic diamide, hydrochloride

2) **Common Name**

N,N-Dimethylbiguanide hydrochloride

3) **Non-Proprietary Name**

Metformin (USAN, INN, BAN) hydrochloride

4) **Synonyms (Base)**

1,1-Dimethylbiguanide

N'-Dimethylguanylguanidine

5) **CAS Registry Numbers**

657-24-9 (base)

1115-70-4 (Hydrochloride)

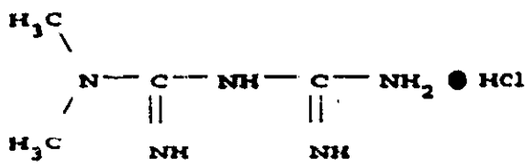
6) **Merck Index (Eleventh Ed.)**

Monograph No. 5845

7) **Molecular Formulas and Molecular Weights**

Base: $C_4H_{11}N_5$	M.W. (base):	129.17
HCl salt: $C_4H_{12}ClN_5$	M.W. (salt):	165.63

8) **Structural Formula**



9) **Material Safety Data Sheet**

The Material Safety Data Sheet for metformin HCl is provided in **Appendix 7.**

B. Physical Description

Metformin HCl is a white, crystalline powder, odorless or with a slight amine odor, with melting point (capillary) between 222°C and 226°C. It is freely soluble in water, sparingly soluble in methanol and 96% ethanol, slightly soluble in ethanol, and practically insoluble in acetonitrile, ether, hexane, and toluene.

A summary table of physicochemical properties is provided in **Appendix 8.**

C. Impurities and Additives

Six impurities have been found in the drug substance using high-performance liquid chromatography (HPLC). Five of these have been identified, and the sixth has been characterized by its elution time, position of its peak in relation to the known compounds eluted, and the percentage of its peak area with respect to the peak area of metformin HCl.

The total amount of impurities, in both the drug substance and the drug product, may not exceed 0.5% of the metformin HCl content, of which none may be present at greater than 0.1% of the metformin

HCl peak area on the chromatogram. One compound, cyanoguanidine (dicyandiamide), may not exceed 0.02% of the metformin HCl content. In practice, each of these impurities is present in much smaller quantities, *i.e.*, on the order of 10^1 ppm to 10^2 ppm (0.001% to 0.01%) of the drug substance, based on actual HPLC analyses of a number of recent lots. The description and characterization of the known impurities are presented in **Appendix 9.**

Additives present in the drug product are comprised of widely used excipients and water-based tablet coating. These additives make up approximately 5.5% of the total tablet weight.

Information concerning the raw materials used in synthesis of the drug substance and the components used in formulation of the drug product that are the subject of the proposed action can be found in **Appendix 10** and **Appendix 11**, respectively.

D. **Drug Product Packaging**

The tablets are packaged in polypropylene bottles with polyethylene caps, which are sealed for protection from tampering. The 500-mg dosage form will also be distributed in blister packs. The container size for each dose is as follows:

500-mg Glucophage® Tablets

- 100-mL (child-resistant) TraCer Pack
  100 tablets/container
- 75-mm x 106 mm Securitainer (about 460 mL)
  500 tablets/container
- 450-mL Snap Secure
  500 tablets/container
- Blister Packs
  21 tablets/sheet

850-mg Glucophage® Tablets

- 150-mL (child-resistant) TraCer Pack
  100 tablets/container
- 75-mm x 106 mm Securitainer (about 460 mL)
  300 tablets/container
- 450-mL Snap Secure
  300 tablets/container

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

6. Introduction of Substances into the Environment

A. Substances Generated During Production of Drug Substance

The manufacturer of the drug substance, identified specifically in Item 4, paragraph C, is located in France. The synthesis of metformin HCl is carried out in compliance with French government environmental laws. Whenever possible, the raw material, by-products, and/or emissions from manufacturing are reused/-regenerated/recycled back into the process. Where reuse/recycling is infeasible, the materials in question are disposed of or emitted in accordance with appropriate laws and regulations. Manufacturing controls and permit information are as follows:

Air Controls: All air emissions from the chemical manufacturing operations are controlled by means of a scrubber system which precipitates any airborne particles and dissolves them in water or in NaOH solution. These are then treated as "other" liquid waste as described below.

Liquid Controls: The principal liquid waste consists of an aqueous solution of metformin HCl plus small amounts of starting materials and non-recyclable solvents. These are

collected on site and incinerated by an outside contractor, resulting in the production of carbon dioxide, water and nitrogen. All of these are naturally occurring substances which pose no environmental hazards.

Xylene, used as a solvent in the synthesis, is recovered, dried and analyzed. If the resultant material meets specifications, it is placed in a tank labeled "recycled xylene" and reused in manufacture. Any material not meeting specifications is disposed of as described above for non-recyclable solvents.

"Other" liquid process waste is sent to Lipha's effluent station where it is handled in accordance with applicable national codes and environmental protection laws (see Appendix 2).

Solids Controls: All solid process residuals (dusts, rejected production materials) are sent off site for incineration, in full compliance with all applicable environmental regulations by qualified outside waste disposal companies.

Outside contractors transferring both liquid and solid waste are all qualified disposal companies for the type of refuse

transferred, operating in full compliance with all applicable environmental regulations. All such companies have to be authorized by the *Direction Régionale de l'Industrie, de la Recherche et de l'Environment (DRIRE)* [Regional Management of Industry, Research and the Environment], the French government body that regulates environmental protection laws.

Therefore, any increase in production using this process is not reasonably expected to adversely affect the compliance status of this facility.

B. **Substances Generated During Production of Drug Product**

The manufacturer of the drug product, identified specifically in Item 4, paragraph C, is located in the United Kingdom (U.K.). The manufacturing of metformin tablets is done in compliance with British government environmental laws. Manufacturing controls and permit information for that facility are described in the following:

Air Controls: The main source of air contamination during production results from tableting dust generated during manufacture. This is minimized by the use of local dust

extraction points linked to the main dust extraction system which collect the tableting dust in a removable receptacle. This is then treated as solid waste.

Liquid Controls: Process liquid wastes, aqueous solutions or suspensions, resulting from manufacture of metformin HCl tablets, consist of negligible wastes from equipment washing plus small amounts of aqueous coating solution remaining in the coating pans after coated tablets are removed to drying trays. In addition, laboratory chemical waste (analytical reagents and the like) is generated during analyses. All waste is handled in accordance with applicable municipal and national codes and environmental protection laws. All waste is further identified, classified and separated as required into reagents, organic solvents, water-miscible solvents, toxic solutions and flammable liquids. Each of these wastes is then handled according to specific disposal procedures.

Solids Controls: All solid waste is categorized for handling and identified as toxic, non-toxic, or controlled substance, and stored in appropriate containers until removal by approved outside contractors. The tableting dust is classified

and treated as toxic waste and deep-buried, although it is recognized as essentially non-toxic.

The accumulated waste, in the designated containers and areas for transfer, is removed daily from manufacturing areas by approved contractors. All waste is removed from the site by outside contractors that are qualified disposal companies for the type of refuse transferred.

Therefore, any increase in production using this process is not reasonably expected to adversely effect the compliance status of this facility.

C. Compliance of Proposed Action with Applicable Emission Requirements

1) Drug Substance Manufacturer

In France, the regulations governing the disposal of all wastes and the protection of the environment are set by the *Direction Régionale de l'Industrie, de la Recherche et de l'Environment (DRIRE)* [Regional Management of Industry, Research and the Environment]. Before an establishment

such as Lipha Calais can begin operations, it must submit documentation in a prescribed format to apply for an authorization permit, called an *Arrêté d'Autorisation préfectoral* [Prefectoral Order of Authorization]. Permits are issued only after inspection of the facility to ensure compliance with all applicable environmental regulations, including those governing waste disposal, effluent and emission limits. *DRIRE* inspectors visit each site on a regular basis to confirm compliance. A formal report is not provided unless a non-conformity is noted during a visit which could put the site and/or the environment at risk, for which a demand for corrective action is issued. Site closure usually results after a major incident. In addition to these regulations, a signed, written agreement between Lipha Calais and the mayor of Calais is in place to resolve any problems associated with waste disposal.

The specific permits in effect for Lipha Calais include the *Arrêtés préfectoraux* of Oct. 28, 1966, of June 16, 1977, of March 29, 1979, of Nov. 12, 1984, and of Oct. 25, 1993 as well as the above-mentioned agreement between the Calais plant and the Mayor of Calais of Jan. 17, 1992. A letter from Dr. Monique Bellevegue, Corporate Director of Quality

Assurance of Lipha, dated August 16, 1994, confirms that compliance is assured through regular inspections by *DRIRE*, with reports issued only if nonconformity is noted. In addition, a letter from Jean-Jacques Barthe, Mayor of Calais, dated October 3, 1994, attests to compliance of the Lipha Calais facilities with environmental regulations. Copies of these documents, together with their certified English translations, as applicable, are provided in **Appendix 2.**

2) **Drug Product Manufacturer**

Within the U.K., authorization to carry out certain industrial processes is required and is the responsibility of Her Majesty's Inspectorate of Pollution (HMIP). These processes are defined in the Environmental Protection (Prescribed Processes and Substances) Regulations 1991 (SI 1991/472). However, Lipha U.K. is not involved in primary chemicals production, nor are organic solvents used in any of the manufacturing operations, including tablet coating. As a result of the above and the small scale of production, Lipha U.K. is not covered by the regulations. Memoranda dated May 25, 1994 and August 12, 1994 from Dr. Brian Curl, Pharmaceutical Director of Lipha Pharmaceuticals, Ltd., to

Lipha Pharmaceuticals, Inc., attesting to the foregoing are provided in **Appendix 3.**

Appendix 4 provides a copy of a letter dated October 14, 1994 from Dr. Phil Heaton of Her Majesty's Inspectorate of Pollution, U.K. to Dr. Brian Curl following an inspection of the Hitchin plant by him and Inspector R. Green on October 11, 1994. Results of the inspection indicate that "the premises do not require authorisation under the 1991 Environmental Protection Act", as detailed in the letter.

All waste is handled and disposed of by contract registered haulers operating under permit. **Appendix 5** contains copies of the two Certificates of Registration controlling waste disposal for the contract waste haulers used by Lipha, U.K.

The Manufacturer's "Specials" License, issued by the Department of Health, Medicines Control Agency, for the Lipha, U.K. manufacturing facilities is:

Lic. No. ML/3759/01.

The product license numbers by strength are as follows:

Metformin 500 mg — Lic. No. 3759/0012,
Metformin 850 mg — Lic. No. 3759/0013.

3) **Occupational Safety Considerations**

Potential emissions into the workplace are associated with dusts from active and additive materials and equipment washing. Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and local, regional, and national standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure containment of chemicals and minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

Both the Lipha Calais and the Lipha U.K. facilities were inspected by the Food and Drug Administration in May 1993 prior to approval of a Treatment Investigational New Drug Application for metformin HCl.

D. Introduction and Concentration of Metformin HCl in the Environment from Product Use

Because metformin HCl is not metabolized in humans, it enters the environment through patient ingestion and elimination. The amount of drug substance (as tablets) forecast for use in the U.S. for the first five years after approval is provided in **Appendix 12.**

The pharmacokinetics of metformin HCl have been defined after oral and intravenous dosing of unlabeled and ^{14}C-labeled drug. It is approximately 50% bioavailable. Absorption of the drug is slow relative to elimination, raising the possibility of absorption rate-limited terminal elimination. It is not excreted in the feces after intravenous dosing. Oral dosing produces maximum plasma concentrations within 3 hours. After a single oral dose, more than 80% of absorbed drug is excreted unchanged in the urine within the first 24 hours.

For purposes of this Environmental Assessment, the drug substance is used for evaluating environmental release mechanisms and estimated environmental concentrations.

1. **Maximum Emitted Environmental Concentration**

Based on estimated 5-year production data, the MEEC is equal to:

1.4×10^{-3} mg/L (1.4 ppb).

(The calculation of this value assumes the maximum environmental emission situation, *i.e.*, that all product manufactured is consumed by patients and is 100% eliminated into the environment.)

The MEEC value was calculated using the following equation:

$$MEEC = (A)/(B)(C)(D)$$

where:

A	=	5th yr production estimate, in mg/yr
B	=	365 days/year
C	=	682 L/person-day (average sewer flow)
D	=	246 million persons (population of U.S.)

The figures used for calculation of the MEEC are also contained in **Appendix 12.**

7. Fate of Emitted Substances in the Environment

A. Molecular Species in Environment

Metformin HCl is normally found in protonated form (monohydrochloride). Metformin itself is a strong base, having a pK_a of 12.4. The hydrochloride salt is freely soluble in water as defined by the USP (~30%, wt/vol) and an undetectable vapor pressure at ambient temperatures due to its high melting point of 225°C.

The octanol/water partition coefficient (K_{ow}) of metformin HCl is 0.056. An estimated sorption coefficient, (K_{oc}), of 4.97 was calculated from log K_{ow} (-1.25), using the following equation:

$$0.544 \times \log K_{ow} + 1.377 = \log K_{oc}$$
$$0.544 \times -1.25 + 1.377 = 0.696;\ K_{oc} = 4.966$$

Based on these data, it is expected that the unchanged drug excreted from patient use will exist as the hydrochloride salt in the aquatic environmental compartment. Therefore, the effects testing strategy was directed toward the aqueous compartment.

A summary of relevant physicochemical properties is provided in Table 1. The studies which yielded the data are contained in **Appendix 13.**

ITEM 3 – CHEMISTRY, MANUFACTURING AND CONTROLS

Table 1. Physicochemical Properties of Metformin HCl

Description:	White crystals
Melting Point:	222 - 226°C
Solubilities:	Please refer to the table below

Some Solubilities of Metformin HCl	
Solvent	**Solubility (%)**
Water	30.555
Octanol	0.012
THF	0.008
Ethyl alcohol	0.311
Acetonitrile	0.005
0.1 N Sodium hydroxide	Unstable

UV Absorption Maximum (H_20):	233 nm
Vapor Pressure: (at ambient temperatures)	Virtually nil
Density:	~1 g/cc
pKa Values:	pKa_1: 12.988 pKa_2: 12.306
pH Values:	6.68 (1% aqueous solution) 6.22 (0.01 M aqueous solution)
Partition Coefficient, K_{ow}:	0.056
log K_{ow}:	-1.25
Sorption coefficient, K_{oc} (est.): (Calculated from log K_{ow})	4.97

As previously discussed in Item 4.D, all returned, recalled or expired product will be incinerated by a licensed contractor, resulting in emission into the atmosphere of small amounts of carbon dioxide, water and nitrogen, all naturally occurring substances which pose no environmental hazard.

The foregoing data on physicochemical properties provide evidence that metformin HCl will not adsorb to organic substances and will reside in the aquatic environment.

B. **Chemical Degradation**

Metformin HCl has been shown to be stable under manufacturing and storage conditions. A study of chemical degradation under agressive conditions in cold and hot (reflux) acid, alkali and oxidant solutions resulted in the following conclusions:

- The metformin molecule is converted by the action of strong hot acid (1 N HCl), with cyclization to give known products: melamine and dimethylmelamine.

- The metformin molecule is less resistant to the action of bases, it is totally degraded into simple substances such as ammonia; the products of degradation would seem to be intermediates of degradation and are, in any event, present in minor amounts.

- The action of oxidizing agents leads to a predominant product different from those obtained by other routes, with an unknown structure.

This study is presented in its entirety in **Appendix 14.**

C. Environmental Degradation

Studies of the fate of metformin HCl in the environment have been carried out by ABC Laboratories, Columbia, MO, in accordance with the FDA Environmental Assessment Technical Assistance Handbook, under GLP regulations. Before beginning the fate studies, all analytical methods to be used (HPLC, radiopurity, etc.) were validated as required.

The results of the environmental fate studies are as follows:
No absorption was detected between 290 nm and 800 nm in the **Ultraviolet-Visible (UV-Vis) Absorption Spectrum** of metformin HCl

at pH values of 5, 7 and 9. Earlier UV-Vis absorption studies in the spectral range of 190-340 nm were conducted by Lipha as part of the characterization of the drug substance. The results showed the absorption maximum in pure water to be 233 nm, with a shift to lower wavelengths at pH values below 5. (See **Appendix 13.**)

In view of the lack of absorption at 290-800 nm, no **Direct Photolysis** study was done.

The preliminary **Hydrolysis Study**, conducted at 50°C for five days, yielded no hydrolysis at pH values of 5, 7 or 9.

In the **Aerobic Biodegradation in Water** study, about 0.6% evolved $^{14}CO_2$ was observed after 28 days.

It was then decided to carry out a 5-day preliminary **Indirect Aqueous Photodegradation** study using 1% acetone as the sensitizer. The UV-Vis spectra at 290 to 800 nm of metformin HCl in the presence of the sensitizer showed an absorption peak at 290 nm. About 14% degradation of the parent compound occurred in five days. Small amounts of three degradation products were detected, none of which was >5% of the parent compound. Using the analytical values obtained at the interim time points, a regression curve was plotted to yield a first-order half-life ($t_{1/2}$) of 28.3 days. The

individual environmental fate studies discussed above are provided in **Appendix 15.**

Summary — Environmental Fate Studies

The results of environmental fate testing showed that there was no degradation of metformin HCl due to hydrolysis at pH values of 5, 7 and 9 at 50°C. Limited aquatic biodegradation of the parent compound occurred, with approximately 0.6% $^{14}CO_2$ detected after 28 days. No absorption was seen in the UV-Visible spectra at 290 to 800 nm, hence, no direct photolysis study was done. However, results of an indirect aqueous photolysis study using acetone as a sensitizer showed it to be a significant removal pathway, with detection of three minor, quantifiable degradates and a degradation half-life of 28.3 days.

Based on the indirect photolysis study, it is estimated that the expected environmental concentration (EEC) will be less than half of the maximum emitted environmental concentration (MEEC) of 1.4 ppb. The EEC will be lowered further due to release of wastewater effluents into waterways. The concentration of metformin HCl in the environment from use is quite low because of: 1) the limited patient population eligible for treatment (*i.e.*, selected NIDDM patients);

2) because of a degradation half-life of 28.3 days; and 3) because of the continuous, naturally occurring dilution in waterways.

8: Environmental Effects of Released Substances

A. Aquatic Toxicology

The drug is non-toxic to the environment, relative to the maximum emitted environmental concentration (MEEC), as shown in acute toxicity studies in the representative aquatic species *Daphnia magna* and bluegill (*Lepomis macrochirus*). The tests were conducted under GLP regulations at ABC Laboratories in accordance with the tests described in the FDA Environmental Assessment Technical Assistance Handbook. The no-observable-effects concentration (NOEC) or the LC_{50} found or estimated in these studies was about 10^5 to 10^6 times the MEEC of 1.4×10^{-3} mg/L (1.4 ppb).

The **Microbial Growth Inhibition** test produced no inhibition in any of the representative microorganisms at less than 100 ppm, about 10^5 times the MEEC.

The results of the environmental effects studies are summarized in Table 2 below. The individual studies are provided in **Appendix 16.**

Table 2.
Environmental Effects Testing

TAD #	Study Name	Species	Time (Hrs)	Results
4.02	Microbial Growth Inhibition	*Aspergillus, Penicillium, Chaetomium* (fungi): *Pseudomonas, Bacillus* (bacteria)	Variable, as req.	No inhibition @ 1000 ppm **(~10^6 times MEEC = 1.4 ppb)**
		Anabaena (alga)		MIC = 100 ppm **(~7 x 10^4 times MEEC)**
		Azotobacter (N_2-fixing bacterium)		MIC = 800 ppm **(~5.7 x 10^5 times MEEC)**
4.08	*Daphnia* Acute Toxicity	*Daphnia magna*	48	NOEC = 78 mg/L **(~5.6 x 10^4 times MEEC)** EC_{50} (calc.) = 130 mg/L **(~10^5 times MEEC)**
4.11	Freshwater Fish Acute Toxicity	Bluegill (*Lepomis macrochirus*)	96	NOEC = 982 mg/L **(~10^6 times MEEC)**

NOEC = No-observed-effects concentration
MEEC = Maximum emitted environmental concentration
MIC = Minimum inhibitory concentration
EC_{50} = Concentration producing 50% immobilization

B. Mammalian Toxicology

Oral Acute Toxicity in Laboratory Animals

The local and systemic toxicity of metformin HCl has been shown to be very low in numerous studies of various laboratory animals following oral administration.

- LD_{50} in mice: 2400 mg/kg
- LD_{50} in rats: 1770 mg/kg
- LD_{50} in rabbits: 552 mg/kg
- LD_{50} in dogs: 375 mg/kg

Oral Subchronic and Chronic Toxicity

"No-effect" levels several times the maximum therapeutic dose in man were identified in four species (mice, rats, dogs and monkeys). A dose-related effect on body weight was observed in rats and mice at doses higher than 300 mg/kg/day. Poor gastrointestinal tolerance following oral administration was observed in dogs at 100 mg/kg/day and in monkeys at 180 mg/kg/day.

No consistent or specific laboratory/necropsy findings or histology abnormalities were noted at the dose ranges used.

Reproductive Toxicity

Reproduction studies in rats and rabbits did not reveal any teratological effects of metformin.

Carcinogenicity and Mutagenicity

Assessment of the oncological potential was performed through four mutagenicity tests (*in vitro* and *in vivo*). These were negative in comparison to a positive control.

Carcinogenicity studies have been completed in rats and mice and have demonstrated no increase in malignant tumors associated with drug treatment in either species.

Results of longer term chronic tests are provided in Table 3.

Table 3. Summary of Chronic Animal Toxicity Data

Species	Year of Study	Duration	Dosage mg/kg per day	Principal Findings
Mice	1993	80 wks	150-1500	No consistent drug-related organ or tissue alterations
Rats	1993	104 wks	150-900	No consistent drug-related organ or tissue alterations
Mice	1989	3 mos.	500-1500	No mortality or drug related clinical signs
Rats	1989	3 mos.	100-900	No mortality or drug related clinical signs
Rats	1989	6 mos.	120-300	Dose related growth retardation at 300 mg
Rats	1969	6 mos.	900	Kidney changes
Dogs	1969	6 mos.	50-150	50 mg: No effects 100 mg: Drug-related organ toxicity; 150 mg: 100% mortality by 8th week
Rats	1970	18 mos.	120-900 (diet)	Dose related growth suppression at 300-900 mg. No severe damage at any dose.
Dogs	1970	18 mos.	1. 50; 2. 50 (1st 3 mo, then 100 to end of study)	50% mortality at 100 mg; no consistent findings in the surviving animals
Monkeys	1971	24 mos.	60-180	No consistent drug related organ or tissue alterations
Monkeys	1971	24 mos.	360	Emaciated at death or sacrifice

C. **Potential Environmental Toxicity Effects**

The extensive toxicological studies which have been conducted indicate that metformin HCl is not toxic to environmental species.

The environmental effects studies do not show toxicity to microbes, *Daphnia* and fish. *Aspergillus, Penicillium, Chaetomium* (fungi), *Pseudomonas* and *Bacillus* (bacteria) were not inhibited at 1000 ppm. *Anabaena* (blue-green alga) and *Azotobacter* (nitrogen-fixing bacterium) were inhibited at 100 ppm and 800 ppm, respectively. The no-effect levels for *Daphnia* and fish, based on the results of the definitive studies, are 78 mg/L and 982 mg/L, respectively. These levels, in all organisms tested, are on the order of 10^5 to 10^6 times the MEEC of metformin HCl.

D. **Potential Effects on the Environment**

Metformin HCl, a drug which is new to the U.S., is well-known in large areas of the world, marketed in over 80 countries, including all of the EEC countries, for periods of up to 30 years. During that time there have been no reports of adverse effects on the environment from its presence, either from use of the drug product or from manufacture of the drug substance or the drug product.

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

As mentioned in Item 7, environmental fate testing shows that metformin HCl degrades *via* indirect aqueous photolysis as a significant removal pathway, with a half-life of 28.3 days. No accumulation in the environment is expected. The concentration of unchanged drug, expected to be exclusively in the aquatic compartment, is quite low because of the limited patient population eligible for treatment (*i.e.*, selected NIDDM patients), because of the degradation half-life of 28 days and because of the continuous, naturally occurring dilution of waterways. As a result, it is estimated that the expected environmental concentration (EEC) leaving the waste water system will be approximately half of the maximum emitted environmental concentration (MEEC) of 1.4 ppb after about a month.

All of the fate and toxicity data, taken together, indicate that no adverse effects on the environment are expected.

9. Use of Resources and Energy

The raw materials utilized to manufacture metformin HCl tablets are common compounds, all of which are in ample commercial supply. The energy commitment for bulk chemical in France and dosage form in the U.K. is nominal and not excessive. Only very small increases in the utilization of energy are anticipated since production occurs at existing facilities. The expected product volume will not significantly increase the consumption of these resources beyond levels currently employed.

No effects on endangered or threatened species are anticipated.

10. Mitigation Measures

Lipha Pharmaceuticals, Inc. has taken all necessary measures (described in Item 6) to achieve compliance with the regulations governing the proposed manufacture of metformin HCl drug substance and of metformin HCl tablets, as well as disposal of returned, recalled or expired goods. In light of the information presented, no mitigation measures are necessary.

11. Alternatives to the Proposed Action

No negative impact on the environment is expected from use of metformin HCl tablets through elimination by patients or from disposal of returned goods. The alternative of no action would deprive eligible Type II diabetic patients of an effective oral therapy with a unique mechanism of action which permits it to be used alone or in combination with existent oral antidiabetic therapies. The latter is of particular importance to non-responders to oral antidiabetic monotherapies and may delay the requirement for parenteral insulin therapy in such patients.

ITEM 3 – CHEMISTRY, MANUFACTURING AND CONTROLS

12. Preparers

Barbara H. Weil, Ph.D.
Senior Director, Science & Technology
Lipha Pharmaceuticals, Inc.
New York, New York 10019-2701

Bruce Goddard, RAC
Senior Director, Regulatory Affairs & Compliance
Lipha Pharmaceuticals, Inc.
New York, New York 10019-2701

Ranga R. Velagaleti, Ph.D.
Vice President, Environmental Assessment
ABC Laboratories, Inc.
7200 E. ABC Lane
Columbia, Missouri 65205

Curricula Vitae of the principal preparers are provided in **Appendix 6.**

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

13. **Certification**

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Date: November 8, 1994

Signature: Bruce Goddard
Bruce Goddard, RAC

Title: Senior Director of Compliance and Regulatory Affairs

14. References

Bres, J., Bressolle, F., Huguet, M.T., **Importance de la dissociation ionique des médicaments en pharmacocinétique. Méthodes de détermination de leur pKa.** [Importance of ionic dissociation of medicines in relation to pharmacokinetics. Method for determining their pKa.] *Trav. Soc. Pharm. Montpelier, 1976, 36(4):331-361.*

Budavari, S., O'Neil, M.J., Smith, A., Heckelman, P.E., eds., 1989, *The Merck Index.* 11th edition. Merck and Company, Rahway, NJ.

Doornbos, D.A., **The determination of the acid dissociation constants of L-cysteine, D penicillamine, N-acetyl-D-penicillamine, amd some biguanides by an accurate method for pH measurement.** *Pharm. Weekblad, 1967, 192(14):269-287.*

Garrett, E.R., Tsau, J., Hinderling, P.H., **Application of ion-pair methods to drug extraction from biological fluids. II: Quantitative determination of biguanides in biological fluids and comparison of protein binding estimates.** *J. Pharm. Sci., 1972, 61(9):1411-1418.*

Metcalf and Eddy, 1979, *Wastewater Engineering: Treatment, Disposal, Reuse.* McGraw Hill, New York, NY.

Pharmaceutical Manufacturers Association, July, 1991, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements For the FDA.* PMA Publication #47.

U.S. Food and Drug Administration, March, 1987, *Environmental Assessment Technical Assistance Handbook.* NTIS Publication #PB87-175345.

15. **List of Appendices**

Appendix 1. Correspondence *re* Waste Disposal from Rollins Environmental Services (N.J.) Inc., dated 11/2/94

Appendix 2: Prefectoral Orders [*Arrêtés d'Autorisation Prefectoraux*] (Certified English Translations and Original French Language); 8/16/94 Letter from Dr. M.C. Bellevegue; 1/17/92 Letter of Agreement - Lipha Calais Plant and Mayor of Calais; 10/3/94 Letter from Mr. Jean-Jacques Barthe, Mayor of Calais

Appendix 3: Memoranda dated 5/25/94 & 8/12/94 from Dr. Brian Curl, Pharmaceutical Director, Lipha Pharmaceuticals, Ltd., *re* U.K. EA Regulations

Appendix 4: Letter dated 10/14/94 from Dr. Phil Heaton, Her Majesty's Inspectorate of Pollution, U.K., *re* Environmental Assessment Inspection of Hitchin Facilities

Appendix 5: Certificates of Registration - Controlling Waste Disposal (UK)

Appendix 6: *Curricula Vitae* of Principal Preparers

CONFIDENTIAL APPENDICES

Appendix 7: Metformin HCl — Material Safety Data Sheet

Appendix 8: Metformin HCl — Physicochemical Data

Appendix 9: Metformin HCl — Identification and Characterization of Impurities

Appendix 10: Metformin HCl — Chemicals of Synthesis

Appendix 11: Metformin HCl — Drug Product Components

15. **List of Appendices (Continued)**

CONFIDENTIAL APPENDICES (Continued)

Appendix 12: Five-Year Production Proforma – MEEC Calculations

Appendix 13: Metformin HCl — Studies of its Physicochemical Properties

Appendix 14: Chemical Degradation of Metformin HCl under Agressive Conditions

Appendix 15: Environmental Fate Studies of Metformin HCl

Appendix 16: Environmental Effects Studies of Metformin HCl

ITEM 3 -- CHEMISTRY, MANUFACTURING AND CONTROLS

15a. Summary Tables of Environmental Fate and Effects Studies

Table 1.
Metformin HCl - Environmental Fate Testing[1]

TAD #	Study Name	Study Conditions	Results
3.05	UV-Visible Absorption Spectrum	Scan solns. of test cpd. in pH 5, 7 & 9 buffers @ 59.6 & 101.2 μg/mL.	No significant absorbance of any soln. between 290 nm & 800 nm.
3.09	Hydrolysis @ oH 5, 7 and 9	10 ppm ^{14}C-metformin HCl solns. in the 3 aq. buffers maintained @ 50°C for 5 days.	The test cpd. did not hydrolyze in the pH range 5-9 @ 50°C.
3.11	Aerobic Biodegradation in Water	^{14}C-metformin HCl & ^{14}C-glucose (ref. cpd.) @ 19 mg C/L were incubated in the dark @ 21±1°C for 28 days with a microbial inoculum	80.5% of the applied ref. cpd. was mineralized to $^{14}CO_2$ as compared to ~0.6% of the applied test cpd. after 28 days, indicating that ^{14}C-metformin HCl is not significantly biodegraded under the test conditions.
3.10	Indirect Aqueous Photodegradation	10.1 ppm ^{14}C-metformin HCl in reagent H_2O containing 1% acetone as sensitizer was exposed to a xenon arc light source for 5 days. Control samples were kept in the dark. Exposed samples were analyzed by HPLC @ 0, 49.7, 96.0 & 120 hr; nonexposed samples @ 0 & 120 hr.	Based on results of HPLC analysis, the indirect photodegradation first-order rate constant and half-life values are -0.0245 day^{-1} and 28.3 days, respectively. 84.9% Parent cpd. remained @ 120 hr with 3 degradation products. All 3 degradates combined were <12%, of which the largest was 5%. The dark control samples showed no appreciable loss of test cpd. during the test period.

[1]Conducted by ABC Laboratories, Inc., Columbia, MO.

Table 2.

Metformin HCl - Environmental Effects Testing[1]

TAD #	Study Name	Species	Time (Hrs)	Results
4.02	Microbial Growth Inhibition	*Aspergillus, Penicillium, Chaetomium* (fungi): *Pseudomonas, Bacillus* (bacteria)	Variable, as req.	No inhibition @ 1000 ppm (**~10^6 times MEEC = 1.4 ppb**)
		Anabaena (alga)		MIC = 100 ppm (**~7×10^4 times MEEC**)
		Azotobacter (N_2-fixing bacterium)		MIC = 800 ppm (**~5.7×10^5 times MEEC**)
4.08	*Daphnia* Acute Toxicity	*Daphnia magna*	48	NOEC = 78 mg/L (**~5.6×10^4 times MEEC**) EC_{50} (calc.) = 130 mg/L (**~10^5 times MEEC**)
4.11	Freshwater Fish Acute Toxicity	Bluegill (*Lepomis macrochirus*)	96	NOEC = 982 mg/L (**~10^6 times MEEC**)

NOEC = No-observed-effects concentration
MEEC = Maximum emitted environmental concentration
MIC = Minimum inhibitory concentration
EC_{50} = Concentration producing 50% immobilization

[1]Conducted by ABC Laboratories, Inc., Columbia, MO.

Appendix 2.

Documentation of Environmental Assessment Compliance (France)

(In French with Certified English Translations)

1. Prefectoral Orders of Authorization [*Arrêtés d'Autorisation Préfectoraux*]

Order of October 28, 1966:	Classification of the Calais Plant
Order of June 16, 1977:	Storage of Flammable Liquids
Order of March 29, 1979:	Chlorine and Pure DMA Storage
Order of November 12, 1984:	Workshop III
Order of October 25, 1993:	Operation of Two Storage Facilities

2. Letter of Agreement - Lipha Calais Plant and Mayor of Calais of January 17, 1992

3. Letter from Monique Bellevegue, Pharm. D., of August 16, 1994 (In English)

4. Letter from Jean-Jacques Barthe, Mayor of Calais, certifying compliance of Lipha Calais facilities with environmental regulations, dated October 3, 1994

du Pas-de-Calais

VILLE DE CALAIS

ATTESTATION

Je soussigné, Jean-Jacques BARTHE, Maire de la Ville de Calais, certifie qu'au vu des résultats d'analyse que l'entreprise effectue dans le cadre de l'autosurveillance, l'usine LIPHA 5 rue Clément Ader 62100 CALAIS satisfait pleinement aux prescriptions de rejet des eaux résiduaires industrielles, les normes établies dans la convention que la société LIPHA a passée avec la Ville de Calais étant respectées.

En conséquence de quoi, la présente attestation a été rédigée pour servir et valoir ce que de droit.

Fait à Calais, le 3 Octobre 1994.

VILLE DE CALAIS

Toute la correspondance doit être adressée à Monsieur le Maire
Mairie - B.P. 329 - 62107 CALAIS Cédex - Télécopie : 21.46.62.09

Appendix 4.

10/14/94 Letter from Dr. Phil Heaton

Her Najesty's Inspectorate of Pollution, U.K.

***re* EA Inspection of Hitchin Facilities**

HER MAJESTY'S
INSPECTORATE OF POLLUTION
ANGLIAN REGION
Howard House 40-64 St John's Street Bedford MK42 0DL

Telephone 0234 272112
Direct Line 0234
Fax 0234 355163
GTN 3015

Lipha Pharmaceuticals Ltd
Cadwell Lane
Hitchin
Herts SG4 0SF

Your Reference
Our Reference
Date 14th October 1994

Attention of Mr Curl

Dear Sirs,

Environmental Protection Act 1990:
Environmental Protection (Prescribed Processes and Substances) Regulations 1991, Statutory Instrument 1991 No. 472

I visited the premises of Lipha Pharmaceuticals Ltd on 11th October 1994 in the company of H. M. Pollution Inspector R Green and met Mr Curl, Dr Corby and Mr Findley.

Several matters were discussed with regard to the above listed acts and regulations:

1. Total output was declared as 300-400 tonnes per annum with approximately 18 tonnes of special waste.

2. No release into water of any prescribed substance in Schedule 5 of SI472 was declared as occurring.

Interpretation of the law is, of course, a matter for the courts. However it is our opinion that the premises do not require authorisation under the 1990 Environmental Protection Act. Lipha Pharmaceuticals does not apparently meet the criteria (see SI472) for regulation as a pharmaceutical production unit, namely the production of 1000 tonnes or more of special waste in any 12 month period nor the release into water of any prescribed substances.

Inspection of the premises was carried out and scale of manufacture appeared consistent with the declarations by Lipha Pharmaceuticals Ltd. All releases to air were apparently acceptable for prescribed substances (Schedule 4 of SI472) with pollution abatement equipment fitted and operational. Release to sewer was minimal and apparently

ANGLIAN REGIONAL MANAGER - Eur.Ing. D.Munns, B.Tech, C.Eng, F.I.ChemE

free of prescribed substances (Schedule 5 of SI472). There was no release to controlled waters nor any radioactive sources on the premises. Pharmaceutical waste was removed from the site by a registered waste disposal company.

Yours faithfully

P. Heaton

Dr Phil Heaton
H M Inspector of Pollution

TOTAL P.03

Appendix 6.

Curricula Vitae of Principal Preparers

Barbara H. Weil, Ph.D.

Bruce Goddard, RAC

Ranga R. Velagaleti, Ph.D.

CURRICULUM VITAE

BARBARA H. WEIL, Ph.D.

PERSONAL

Born USA
Educated public schools, Marion, Indiana
Married, two children

EDUCATION

Ph.D., University of Illinois, Urbana, 1953. Major: organic chemistry; minors: inorganic chemistry, mathematics.
M.S., University of Illinois, Urbana, 1951, chemistry.
B.A., *Magna cum Laude*, Franklin College, Franklin, IN, 1947. Double major: chemistry and German.

RECENT COURSES

November, 1989 - Drug Product Stability and Shelf-life. Center for Professional Advancement, East Brunswick, NJ.

September, 1987 - DIA Workshop, Practical Implementation of New IND/NDA Regulations. Cosponsored by the Drug Information Association and the FDA, Rockville, MD.

April, 1981 - Basic Pharmacokinetics and Biopharmaceutics Workshop. St. Augustine, FL. Given by Prof. E.R. Garrett, Ph.D., D.Sc., and sponsored by the American Society of Clinical Pharmacology and Therapeutics.

October, 1979 - Preparing Clinical Protocols and Managing Clinical Investigations. Center for Professional Advancement, East Brunswick, NJ.

October, 1979 - The Mechanics of Preparing INDs and NDAs and FDA Regulations. Center for Professional Advancement, East Brunswick, NJ.

1976-1977 - Biostatistics (2-semester course). Cornell University Medical School, New York, NY.

1975-1976 - Cancer Biochemistry and Carcinogenesis Mechanisms (2-semester course). New York University Medical School, New York, NY.

1975, 1977, 1978 - Review courses in clinical chemistry, biochemistry, enzymology and cardiovascular disease pathogenesis. Sponsored by the American Chemical Society at Sloan Kettering Institute, New York, NY.

EMPLOYMENT HISTORY

June, 1979 to present - Lipha Pharmaceuticals, Inc. (previously Lipha Chemicals, Inc.), New York, NY.

1979-1981: Research Scientist/Medical Writer.
September, 1981: Director, Science and Technology.
September, 1993: Senior Director, Science and Technology

Duties: Compiling documentation for and writing FDA submissions, including DMFs, INDs, NDAs, Annual Reports, correspondence, etc. Planning, coordinating and supervising projects by outside contractors in the areas of chemistry, manufacturing, toxicology, pharmacokinetics, preclinical and clinical pharmacology and methods validation. Evaluating incoming data from European and American studies and preparing summary reports on an *ad hoc* basis. Providing scientific input for all office operations as required, in conjunction with expert consultants as necessary.

February, 1971 - June, 1979 - Editorial Management Associate, Council for Tobacco Research, USA, Literature Retrieval Division, New York, NY.

Duties: Recruiting, training and supervising biomedical abstractors/indexers and editing their work. Developing, evaluating and improving a computerized scientific information data base and retrieval system. Monitoring commercially prepared English translations from French and German technical literature for accuracy. Personally writing interpretive critiques of highly technical material of greatest user (attorneys) interest and legal sensitivity, requiring skilled scientific knowledge and judgment. These critiques encompassed evaluation of experimental or clinical data for accuracy and consistency with conclusions; of methodology (population sample validity, control groups, patient compliance, protocol compliance, statistical methods suitability); and statistical significance of findings. Working directly with users to answer immediate scientific questions and providing advice on computer-based searches. Selecting documents for inclusion in the data base.

June, 1969 - November, 1970 - Information Scientist, USV Pharmaceutical Corp. (Division of Revlon, Inc.). Yonkers, NY.

Duties: Designing and using a semi-automated indexing system enabling retrieval of data by chemical structure, properties and biological activity, applied to all internal company documents. Preparing summary reports for the research and regulatory affairs departments from pharmacological and chemical raw data sheets. Establishing a "current awareness" program and performing literature and patent searches. USV representative to the Pharmaceutical Manufacturers Association and member of its steering committee. MEDLARS contact.

1963 - 1969 - Abstractor (part-time), Chemical Abstracts Service, Columbus, OH.

Duties: Abstracting French-, German- and English-language patents and journal articles in the fields of organic, pharmaceutical, medicinal, inorganic and analytical chemistry, metallurgy, polymers and plastics.

1959 - 1963 - Temporary retirement to have a family.

1956 - 1959 - Director of Information Services and Publications Editor, Union Carbide Metals Division, Union Carbide Corp., Niagara Falls, NY.

Duties: Developing and implementing a computer-based system for indexing the metallurgical literature. Supervising indexing staff, reference library staff and technical reports staff. Editing internal reports and manuscripts prepared by technical staff for publication.

1953 - 1956 - Materials and Processes Engineer. Bell Aerosystems, Buffalo, NY.

Duties: Evaluating polymers and writing reports. Interaction with vendors entailing selection of materials and specifications thereof.

1947 - 1950 - Research Chemist, Reilly Tar and Chemical Company, Indianapolis, IN.

Duties: Organic syntheses.

PUBLICATIONS

Marvel CS, Weil BH, *et al.*: Some new copolymers with butadiene for low-temperature applications. *Ind Engg Chem*, 1954.

Weil BH, Clapp EA: "A new computer-based system for indexing the metallurgical literature." Chapter in the book, "New Information Systems." John Wiley, 1957.

Weil, BH, Bacon, F: The Monograph, "Chromium," *The Encyclopedia Britannica*, 1965 Ed.

MEMBERSHIPS

Parenteral Drug Association
Drug Information Association
American Medical Writers Association
American Chemical Society, Division of Chemical Documentation

HONORS

Recipient of US Government Rubber Program Fellowship at the University of Illinois, 1951 - 1953.

Elected to membership in Alpha Honorary Society of Franklin College in junior year. (Membership criteria identical to those of Phi Beta Kappa.)

Recipient of Brodhearst Elsey Prize of Franklin College for two successive years, 1944 and 1945, for highest academic rank in freshman and in sophomore class, respectively. (Award limited to two years to the same recipient.)

Recipient of Kiwanis Award for overall excellence in academic achievement and extracurricular activities, Marion High School, 1943.

LANGUAGE CAPABILITIES

Fluent reading knowledge of scientific French and German; moderately good speaking ability in French.

Reading with some comprehension of scientific Spanish and Italian.

CURRICULUM VITAE

BRUCE E. GODDARD, R.A.C.

PERSONAL
Date of Birth: November 14, 1947, Wash., D.C.
Volunteer Firefighter
Emergency Medical Technician - New York State

PROFESSIONAL EXPERIENCE

1993 to Present
Senior Director of Compliance and Regulatory Affairs
Lipha Pharmaceuticals, Inc., 9 West 57th St.
New York, New York 10019-2701

1981 to 1993
Director of Compliance and Regulatory Affairs
Lipha Pharmaceuticals, Inc., New York, New York

1981 to 1986
Director of Regulatory Affairs
Chempar Products Co., New York, New York

1979 to 1981
Clinical Research Associate,
Lipha Chemicals, Inc., New York, New York

1978 to 1979
Clinical Research Associate
International Chemical & Nuclear Co., Los Angeles, California

1974 to 1977
Case Worker
Georgia Department of Human Resources, Hartwell, Georgia

1969 to 1974
Construction Contractor,
Precision Enterprises of Atlanta, Atlanta, Georgia

1967 to 1969
COSTEP (Commissioned Officer Training Program), USPHS
Washington, D.C.

EDUCATIONAL EXPERIENCE

1991 Regulatory Affairs Certified
1976 One year masters work in Education
University of Georgia
1969 B.S. Psychology, University of Georgia

PROFESSIONAL AFFILIATIONS

Regulatory Affairs Professional Society
Drug Information Association
Chemical Specialties Manufacturers Association
American Association for the Advancement of Science
Society for Clinical Trials

Revised December 1993

PERSONAL QUALIFICATIONS

NAME: Ranga R. Velagaleti, Ph.D.

TITLE: Vice President, Environmental Fate and Assessment

YEARS EXPERIENCE: 26

EDUCATION: Ph.D., Plant Pathology/Soil Microbe-Plant Root Interaction Studies, University of Delhi
M.S., Botany with Specialization in Soil Microbiology, University of Delhi
B.S., Honors, Botany, University of Delhi

QUALIFICATIONS SUMMARY:

As Vice President for Environmental Fate and Assessment at ABC Laboratories, Dr. Velagaleti manages research programs related to pesticides and industrial and pharmaceutical chemicals. He supervises technical teams comprising 40 research scientists working in these programs. Prior to this current assignment, Dr. Velagaleti was the manager for Environmental Fate and Assessment at Battelle. He directly supervised a group of 17 scientists, among whom were four Ph.D.-level scientists. In addition to his managerial duties, he coordinated overall registration programs for agrochemicals and pharmaceuticals globally. Prior to this, he held various project coordination and senior scientist positions. He was the investigator and study director on numerous environmental assessment projects to evaluate the impacts of chemicals, and pathogenic microbial releases into soils, ground water and agricultural crops. He was also a study director on metabolism and environmental fate GLP studies conducted under FDA and EPA guidelines. He published 42 research publications in environmental fate and assessment, physiology, and biochemistry.

EXPERIENCE:

Vice President, Environmental Fate and Assessment, December 1993-present, ABC Laboratories, Inc.

Manages four technical teams comprising 35 research scientists conducting research in environmental fate and assessment of agrochemicals, pharmaceuticals, and industrial chemicals.

Manager, Environmental Fate and Assessment, and Other Affiliated Research Programs at Battelle, Columbus, Ohio, 1987 to November, 1993.

Directed a group that was exclusively dedicated to performing and managing product registration projects (under FDA and EPA guidelines) for a number of industrial clients. In this

managerial capacity he directly supervised a group of 17 scientist, four of whom were Ph.D.-level scientist. In addition to his managerial duties, he coordinated overall registration programs for multinational pharmaceutical and agrochemical companies for global registrations (USA, UK, Ireland).

A typical registration portfolio of studies that Dr. Velagaleti coordinated and managed for clients include the following: environmental assessment studies for IND and NDA applications; environmental fate and animal metabolism studies for registration under FDA guidelines; nature of residue (metabolism studies) and environmental fate studies for registration under EPA guidelines; marine (FDA) and fresh water (FDA and EPA) aquatic toxicology studies.

Senior Research Scientist, Battelle 1983-1987

In this capacity, his experience as a project manager and principal investigator ranged from establishing and coordination international programs; marketing R&D programs on-site and off-site (both U.S. and overseas); managing government, industrial, and international agency sponsored projects.

In addition, Dr. Velagaleti has been a principal investigator in developing biotechnology monitoring guideline documents and a quality assurance document for biotechnology releases for EPA. He has participated in numerous environmental assessment projects as an investigator evaluation impacts of chemical and pathogenic microbial releases on soils, ground water, and agricultural crops.

Coordinator International Cooperative Crop Research Programs, Charles F. Kettering Research Laboratory, Yellowsprings, Ohio, 1981-1983

Initiated and coordinated an international cooperative research program on agrochemicals and agricultural technologies.

Manager, Microbiology Department, International Institute of Tropical Agriculture, Ibaden, Nigeria, 1978-1981

Coordinated programs and approximately 20 scientists on fate of agricultural chemicals and microbes.

Other Previous Experiences

Prior to joining Battelle in 1983, Dr. Velagaleti held postdoctoral positions at Rothamsted Experimental Station in England (1975-76); Charles F. Kettering Research Laboratory in Ohio (1976-77); and Boyce Thompson Institute at Cornell University, Ithaca (1978-79). He held permanent positions at the International Institute at Cornell University, Ithaca (1978-1979). He held permanent positions at the International Institute of Tropical Agriculture (1979-1981), and

the Charles F. Kettering Research Laboratory in Ohio (1982-1983). His main areas of research interests at these places were environmental microbiology, biochemistry, and plant physiology.

Professional Recognition and Affiliations:

Member, Proposal Review Panel, National Research Council, National Academy of Sciences, Board on Science and Technology for International Development (1982-86).

Member, Advisory Boards, International Development Institute and Agricultural Trade Council (1984-86).

Member, Crop Science Society, Soil Science Society, and American Society of Agronomy (1978-present)

PUBLICATIONS AND PRESENTATIONS:

Mukerji, K.G., and R.R. Velagaleti, 1968. Gentamicin as an antibiotic in dilution plates for the isolation of soil fungi. *Plant and Soil* 29: 31-32.

Velagaleti, R.R., and K.G. Mukerji, 1968. Isolation of *Schizophyllum commune* from the paddy rhizosphere. *Trans. Mycol. Soc. Japan* 9: 20-24.

Velagaleti, R.R., and K.G. Mukerji, 1969. Cytology of the ascus in *Chaetomidium*. *Can. J. Botany* 47: 869-873.

Velagaleti, R.R., and K.G. Mukerji, 1971. Cytology of the ascus in *Ascotricha guamensis* *Mycologia* 62: 302-310.

Velagaleti, R.R., and K.G. Mukerji, 1971. Cytology of the ascus in *Chaetomidium bostrychodes*. *Trans. Jap. Mycol. Soc.* 13: 105-112.

Velagaleti, R.R., and K.G. Mukerji, 1971. Cytology of the ascus in *Achaetomium globosum* and *A. luteum*. *J. Gen. App. Microbiol.* 97: 311-318.

Velagaleti, R.R., and K.G. Mukerji, 1971. Cytology of the ascus in *Achaetomium strumarium*. *Botan. Gaz.* 132:179-183.

Velagaleti, R.R., and K.G. Mukerji, 1971. Fungi in the root zone of our cultivars of wheat. *Ann. Inst. Pasteur* 121: 533-545.

Velagaleti, R.R., and K.G. Mukerji, 1972. Fungi in the root zone of four cultivated plants. *Trans. Mycol. Soc. Japan* 13: 35-48.

Velagaleti, R.R., M. Jayakar, K.R. Sharma, and K.G. Mukerji, 1972. Effect of foliar spray of morphactin on fungi in the root zone of *Capsicum annum*. *Plant and Soil* 37: 179-182.

Gupta, N.C., P. Nanda, Velagaleti, R.R., and K.G. Mukerji, 1973. Studies on charcoal rot disease of *Abelmoschus esculentus*. IV. Pycnidiospore germination. *Trans. Jap. Mycol. Soc.* 14: 10-21.

Velagaleti, R.R., and K.G. Mukerji, 1973. Studies on charcoal rot disease of *Abelmoschus esculentus*. III. Role of light, plant tissues and tissue extracts on pycnidial formation *Phytopathol. Z.* 76: 123-127.

Velagaleti, R.R., and K.G. Mukerji, 1973. Studies on charcoal rot disease of *Abelmoschus esculentus*. I. Soil-host-parasite relationships. *Trans. Jap. Mycol. soc.* 14: 1-10.

Keister, D.L. and R.R. Velagaleti. 1976. The physiology of acetylene reduction in pure cultures of rhizobia. In *Recent Developments in Nitrogen Fixation* (Newton, W., J.R. Postgate, and C. Rodrigues-Barrueco, Eds.) Academic Press, London, New York, pp> 419-430.

Velagaleti, R.R. 1976. Nitrogenase activity in *Rhizobium* associated with leguminous and non-leguminous tissue cultures. *Plant Sci. Lett.* 6: 77-83.

Velagaleti, R.R. 1977. Effects of root temperature on the infection process and nodulation in *Lotus* and *Stylosanthes*. *J. Expt. Botany* 28:241-261.

Velagaleti, R.R. 1977. Effects of temperature on the nitrogenase activity of intact and detached nodules in *Lotus* and *Stylosanthes*. *J. Expt. Botany* 28: 262-268.

Velagaleti, R.R. 1977. Nitrogenase activity of *Rhizobium* sp CB 1552 on defined medium. *Plant Sci. Lett.* 8: 363-366.

Velagaleti, R.R., R.A. Darrow and D.L. Keister. 1978. Effects of oxygen tension on nitrogenase and on glutamine synthetase I and II in *Rhizobium japonicum*. *Protoplasma* 97: 311-316.

Velagaleti, R.R., R.A. Darrow and D.L.,Keister. 1978. Effect of oxygen tension on nitrogenase and on glutamine synthetase I and II in *Rhizobium japonicum* 61A76. *Biochem. Biophys. Res. Commun.* 81:224-231.

Velagaleti, R.R., and A. Ayanaba. 1980. Multilocation field testing in six countries in Africa to determine the need for *Rhizobium* inoculation and the effects of inoculation on the nitrogen fixation, growth and yield of soybeans. **MIRCEN** (Nairobi) *News Letter* 5: 3-8.

Velagaleti, R.R., A. Ayanba, A.R.J. Eaglesham and E.A. Kueneman, 1981. Exploting symbiotic nitrogen fixation for increasing soybean yields in Africa. *Proceedings of the Symposium on Global Impacts of Applied Microbiology*, September 1980. Academic Press, London, New York, pp. 153-167.

Velagaleti. R.R., A. Ayanaba, and G. Thottappilly, 1982. Studies on the persistence of introduced strains of *Rhizobium japonicum* in soil during fallow and the effects on soybean growth and yield. Proceedings of the International Workshop on BNF technology for tropical agriculture, Cali, Columbia (CIAT),pp. 309-315.

Velagaleti, R.R., Agarwal, A., and Keister, D.L. 1982. Non-symbiotic nitrogen fixation by *Rhizobium*. *J. Scint. Industr. Res.* 41: 507-513.

Velagaleti, R.R. 1982. Effect of Various Nitrogenous Compounds on Depression of Nitrogenase Activity in Cultured *Rhizobium* sp., *J. Gen. Applied Microbiol.* 18: 359-368.

Eaglesham, A.R.J., Ayanaba, A., Velagaleti, R.R., and Eskew, D.L. 1982. Mineral N effects on cowpea and soybean crops in a Nigerian soil I. Development, nodulation, acetylene reduction and grain yield. *Plant and Soil* 68: 171-181.

Kueneman, E.A., Pulver, E.L. and Velagaleti, R.R. 1985. Identification of promiscuous nodulating soybeans efficient in N_2 fixation. *Crop Science* 25: 660-663.

Asanuma, S., Thottappilly, G., Ayanaba, A. and Velagaleti, R.R. 1985. Use of the enzyme-linked immunosorbent assay (Elisa) in detection of *Rhizobium* broth in culture and from root nodules of soybeans and cowpeas. *Can. J. Microbiol.* 31: 524-528.

Velagaleti, R.R., Ayanaba, A. and Eaglesham, A.R.J. 1985. Effect of *Rhizobium* inoculation on field-grown soybeans in Western Nigeria and assessment of inoculum persistence during a two-year fallow. *Tropical Agriculture* 62: 125-130.

Velagaleti, R.R. and Marsh, S. 1989. Influence of host cultivars and *Rhizobium* strains on the growth and symbiotic nitrogen fixation in soybeans grown under salt stress. *Plant and Soil.* 119: 133-138.

Velagaleti, R.R., Kramer, D., Fleischman, D. and Marsh, S. 1990. Genotypic variation in growth and nitrogen fixation in soybean cultivars under salt stress. *Tropical Agriculture.* 67: 169-177.

Velagaleti, R.R., Kramer, D., Reichenbach, N.G., and Fleischman, D.H. 1990. Some Approaches to rapid and pre-symptom diagnosis of chemical stress in plants. ASTM Publication on Use of Plants for Toxicity Assessment (STP; 1091),pp. 333-345; ASTM, Philadelphia, PA.

Velagaleti, R.R., and McClure, T. 1990. Using waste management products as an alternative to depleting nonrenewable fertilizer sources. *Solid/Liquid Seperation: Waste Management and Productivity Enhancement*, 1989 International Symposium. Battelle Press, Columbus, Ohio, pp. 417-428.

Stamm, J. and Velagaleti, R.R. 1992. Selection of field and laboratory studies for environmental assessment. ACS Special Symposium on "Role of Environmental (Ecological) Assessments in the Management of chemical Pollution" 204th ACS National Meeting, August 26-28, 1992, Washington, D.C., J. *Hazardous Materials Research* (in press).

Velagaleti, R.R., and Schweitzer, Sarah, M. 1992. General Effects of Salt Stress on Growth and Symbiotic Nitrogen Fixation in Soybean. *Handbook of Crop Stress*, Marcel Dekker, New York, pp. 118-128.

Velagaleti, R.R. 1994. Technical and Schedule Impacts of Environmental Assessments on the Drug Development Process. Drug Information Association Journal (in press).

Due, K.M., Cornaby, B.W. and Velagaleti, R.R. 1994. Technology Transfer of Environmental Impact Assessment Methodologies to Developed and Developing Countries. *J. Scient. Industr. Res.* (in press).

Velagaleti, R.R., Arthur, M.F., Wyza,R. 1994. Environmental Assessment Methodologies for Genetically Engineered Microorganisms: *J. Environ. Toxicol. Chem.* (manuscript under review).

Marengo, J.R., Kok, R.A., Velagaleti, R.R. and Stamm, J.M. 1994. Aerobic Biodegradation of ^{14}C-Sarafloxacin Hydrochloride in Soil and Formation of Degradates. *J. Environ. Toxicol. Chem.* (manuscript under review).

Marengo, J.R., Kok, R.A., Velagaleti, R.R. and Stamm, J.M. 1994. Biodegradation of ^{14}C-Sarafloxacin Hydrochloride by *Phanerochaete chrysosporium*. *J. Environ. Toxicol. Chem.* (manuscript under review).

Velagaleti, R.R., Davis, M.J., O'Brien, G.K. and Stamm, J.M. 1994. The Bioavailability of Sarfloxacin Hydrochloride in Three Soils and a Marine Sediment as Determined by Adsorption/Desorption Parameters and Biodegradation. *J. Environ. Toxicol. Chem.* (manuscript under review).

CC: Original NDA 20-357/HFD-510
Division File(s)

FONSI File 20-357/HFD-102
P. Vincent/HFD-102
Docket File 20-357/HFD-102

F/T by GSJ/11.22.94

File: 20357.FON

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 26, 1994 Received 8/19/94 Sub.

FROM: Glen Jon Smith, HFD-647

THROUGH: Phillip G. Vincent, Ph.D.
Environmental Assessment Officer, HFD-102

SUBJECT: Environmental Concerns - NDA 20-357 Glucophage®
(Metformin Hydrochloride) Tablets, 500 mg, 850 mg.

TO: John Short, HFD-510

The Center has reviewed the environmental assessment for the subject NDA.

Action: INADEQUATE

Please transmit the following to the firm and copy HFD-102.

Your environmental assessment has been carefully reviewed. Please address the following deficiencies.

1. Regarding Item 4:

   A. Please submit evidence of contractual agreement with your contract disposal firm, Rollins Environmental Services, Inc. Note that a formal letter from the firm indicating knowledge of the type of waste and a brief description of the disposal methods to demonstrate the adequacy of the methods should be sufficient. Note that since the potential for incineration of PVC's from the blister packaging is possible, the document should clearly demonstrate the adequacy of the incineration process for this type of waste.

   B. Please include a brief description of the disposal methods as discussed above in your EA. Note again the description should demonstrate the adequacy of the process for the potential incineration of PVC's.

2. Item 6: Please place all documents and associated translations regarding compliance with foreign environmental laws and regulations in your EA and not as part of a confidential appendix.

3. Item 11: Please revise this item to include a brief discussion of the alternative of no action.

4. Item 12: Please place the *Curricula Vitae* in your EA and not as part of a confidential appendix.

5. Item 14: Item 14 should be a list of citations for all referenced materials, not Item 15. Please revise and include citations for all references materials, including literature cited in support of Items 7, 8 and 15.

6. Item 15: Item 15 should include all appendices, both public and confidential. Note that a data summary table of testing results for Items 7 and 8 should be included in your EA as Item 15a.

Endorsements:

HFD-6472/GJSmith 10/26/94

HFD-102/PGVincent 10/27/94

CC: Original NDA 20-357
EA File 20357.REV
Division File/HFD-510
Supervisory Chemist/HFD-510

20357E01.LGS/GJSEA#01

F/T by GJS/10.26.94

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-357

Glucophage® Tablets

(Metformin Hydrochloride)

HFD-510 REVIEW DIVISION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED 10/26/94

25.31a Environmental assessment for proposed approvals of FDA-regulated products -- Format 1.

(a) For proposed actions to approve food or color additives, drugs, biological products, animal drugs, and class III medical devices, and to affirm food substances as generally recognized as safe (GRAS), the applicant or petitioner shall prepare an environmental assessment in the following format:

Environmental Assessment

1. *Date:* October 1, 1992, Original Submission
August 19, 1994, Amendment - Response to Review #1, 4/12/94.

2. *Name of applicant/petitioner:*

Lipha Pharmaceuticals, Incorporated

3. *Address:*

Lipha Pharmaceuticals, Incorporated
9 West 57th Street
New York, NY 10019-2701

4. ***Description of the proposed action: Briefly describe the requested approval;***

INADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

1.A. The firm revised the description of the proposed action to include manufacturing, packaging and marketing the drug product.

1.B. The firm submitted the following addresses for facilities involved in the manufacture of the drug product.

<u>Manufacture of Drug Substance</u>

Lipha Calais
5/7 rue Clement Ader
62100 Calais, France

Manufacture of Drug Product

Lipha Pharmaceuticals Limited
Cadwell Lane
Hitchin, Hertfordshire, SG4 0SF
United Kingdom

Packaging of Drug Product

Lipha Pharmaceuticals Limited
Units 2-5 Amor Way
Letchworth, Hertfordshire, SG6 1UG
United Kingdom

The environment at or adjacent to each facility was adequately described.

1.C. Comment 1.C was not included in the request to the firm (typographical error).

1.D. The firm submitted packaging descriptions as part of Item 5 (5.D). **Note that the proposed use of blister packs indicates that the potential for incineration of PVC's should be addressed in the EA.**

1.E. The firm indicated that returned, recalled or expired goods will be disposed of in an appropriate manner by distributors, while all rejected or returned products will be incinerated off site and will include container/closure systems.

1.F. The firm indicated that the contract disposal company shall be Rollins Environmental Services (NJ) Inc., EPA I.D. No. NJD 053 288 239.

1. **The firm failed to supply evidence of contractual agreement with Rollins. A letter from Rollins to the firm indicating knowledge of the type of waste and the adequacy of their disposal methods for the waste should be requested.**

2. **Since incineration may include PVC's from the blister packaging, the firm should include a brief description of the incineration process (e.g. two stage combustion, chloride and particulate scrubbers) to demonstrate the process is appropriate for PVC's.**

low levels, further information regarding the impurities should not be considered necessary at this time.

6. *Introduction of substances into the environment: For the site(s) of production:*

INADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

Drug Substance
The firm submitted a list of the chemicals used in the manufacture of the drug substance along with general descriptions of controls used for air, liquid and solid waste controls. The firm also stated that the drug substance is manufactured in compliance with French Government environmental law and submitted copies (and translations) of applicable permits and regulations.

Formal calculations showing the effects of the proposed actions on compliance were not submitted. In support of their statement that increase in production should not adversely effect the compliance status, a description of the French permit and license requirements was submitted. The description (inspection and permitting prior to opening the facility, followed by regular inspections to ensure continuing compliance) is consistent with current understanding of French environmental law. A letter from Dr. Monique Bellevegue, Corporate Director of Quality Assurance of Lipha indicated that since formal notification is made to a firm if it is out of compliance, the *DRIRE (Direction Régionale de l'Industrie, de la Recherche et de l'Environment)* does not issue letters of compliance.

The above is consistent with current understanding of French environmental law and the information indicates current and continuing compliance with applicable regulations for the manufacture of the drug substance. Note also that the drug substance is already manufactured and distributed in Europe, which confirms that the drug substance is manufactured in compliance with applicable environmental regulations. In view of these facts, additional information should not be considered necessary at this time.

Drug Product
The firm submitted a list of the chemicals used in the manufacture of the drug product along with general

descriptions of controls used for air, liquid and solid waste controls. The firm also stated that the drug product is manufactured in compliance with British government and submitted copies of Certificates of Registration for their contract waste haulers. The Manufacturer's "Specials" License for the facility as well as the product license numbers were also submitted.

Formal calculations showing the effects of the proposed actions on compliance were not submitted. However, as indicated by the firm, the facility is not involved in primary chemicals production and does not use any organic solvents in the manufacturing process. These facts along with the small scale of production results in the facility not being covered by regulations as defined in the Environmental Protection (Prescribed Processes and Substances) Regulations 1991 (S1 1991/472). This was certified by Dr. Brian Curl, Pharmaceutical Director of Lipha Pharmaceuticals, Ltd.

The above description is consistent with current understanding of British environmental law. In view of this and the certification of the contract waste haulers, additional information should not be required at this time.

Note that the documents regarding compliance with foreign regulations must be in the EA as part of the public record and not submitted as confidential appendices.

Introduction Into the Environment

The firm indicated that the drug substance is not metabolized in humans, and that more than 80% of absorbed drug is excreted unchanged in urine within the first 24 hours. As a result, the firm submitted a MEEC value of 1.4×10^{-3} mg/L (1.4 ppb) based on the estimated 5th year production estimate and the assumption that 100% of the drug is eliminated into the environment.

7. ***Fate of emitted substances in the environment: Predict environmental concentrations of and exposures to substances entering the environment as a consequence (direct or indirect) of the use and/or disposal of the products affected by the action for the following environmental compartments, including consideration of the major environmental transport and transformation processes involved:***

ADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

It should be noted that many of the studies conducted to characterize the drug substance were conducted prior to current testing requirements. The firm was allowed to submit applicable studies and literature citations instead of repeating the studies. Note that the acceptance of this data for submission did not guarantee the studies would be considered adequate. However, the studies were accepted if a reasonable scientific methodology was used. A secondary condition was that the results were not "on the line" between determining the characteristics of the molecule where the testing method could influence the partitioning of the substance in the environment (e.g. K_{ow} = 100).

Air
The firm cited previous studies which indicated that the vapor pressure of the drug substance is nil at normal temperatures, with a melting point of 225°C. These studies also indicate high water solubility (~30% wt/vol in water) and pK_a of 12.4. It is reasonable to assume that the molecule will exist in protonated form in the environment and should not partition into the atmospheric compartment.

Freshwater, estuarine, and marine ecosystems
The firm cited previous studies and literature for solubility, dissociation and octanol/water partition coefficients. Results from studies conducted according to Technical Assistance Documents (TAD's) were submitted for UV/Visible spectra, hydrolysis, aerobic biodegradation and indirect aqueous photodegradation were also submitted.

The water solubility (~30% wt/vol), dissociation constant (pK_a = 12.4), octanol/water partition coefficient (K_{ow} = 0.056) and estimated sorption coefficient (K_{oc} = 4.966, estimated from K_{ow}) indicate that the drug substance will remain in the aquatic compartment, with little opportunity for bioaccumulation or partitioning into the terrestrial compartment.

UV/Visible spectra, hydrolysis and aerobic biodegradation studies did not identify a viable removal mechanism for the drug substance. However, preliminary indirect aqueous photodegradation studies

indicated a $t_{1/2}$ of approximately 28 days. This suggests that the EEC value will be less than half of the MEEC value (less than 1 ppb).

Terrestrial ecosystems
The firm's data, as stated above, indicate that the drug substance will not partition into the terrestrial compartment.

Review of the above facts show that the firm has adequately characterized the substance, correctly identified the environmental compartment impacted by the substance and provided a removal mechanism for the drug substance.

8. *Environmental effects of released substances: Given the information developed on the introduction (item 6) and fate (item 7) of substances which would be released as a consequence of the use and/or disposal of the products affected by the action,*

ADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

Results submitted for Item 7 indicated that the drug substance should partition into the aquatic compartment and not the atmospheric or terrestrial compartments. Therefore, the firm submitted studies conducted according to the appropriate TAD for microbial inhibition, and acute toxicity to daphnia and bluegill to assess the effects on the aquatic compartment.

Review of the results and studies (See Item 15) showed that NOEL values of 1000 mg/L were obtained for all microorganisms tested except *Azotobacter chroococcum* and *Anabaena flos-aquae*, a blue-green algae. MIC and NOEC values of 1000 mg/L and 800 mg/L were reported for *Azotobacter* while values of 100 mg/L and 80 mg/L were reported for *Anabaena*. Note that the smallest MIC/NOEC values are approximately five orders of magnitude ($x10^5$) greater than the MEEC value and approach six orders of magnitude for the EEC value.

Review of the acute toxicity to Daphnia tests showed similar results to those obtained for the blue-green algae studies. In this case a NOEC value of 78 mg/L was obtained as well as an EC_{50} value of 130 mg/L. Again these results are approximately five orders of magnitude greater than the reported MEEC value.

Review of the acute toxicity to bluegill tests showed a NOEC value of 982 mg/L, with no observed sub-lethal effects. These results are approximately six orders of magnitude greater than the reported MEEC value.

In addition to the above studies, the firm referenced mammalian toxicology studies indicating very low local and systemic toxicity in laboratory animals as well as no teratological effects, negative mutagenicity tests and no increase in malignant tumors associated with drug treatment.

Review of all available data indicates that the drug substance should have no adverse effects on the environment at the expected levels of exposure.

9. *Use of resources and energy:*

ADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

The firm indicated that all raw materials used in the manufacture of the drug product are commercially available, and that energy commitments for all processes are nominal and not excessive. Only small increases in energy utilization are anticipated since existing facilities will be used. Effects on endangered or threatened species are not anticipated.

Note that the firm failed to address effects on property. However, since all manufacturing procedures are conducted in foreign countries, discussion should not be considered necessary.

10. *Mitigation measures: Describe measures taken to avoid or mitigate potential adverse environmental impacts associated with the proposed action.*

ADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

The firm's statement that in light of the information presented, no mitigation measures are necessary appears to be supported by the data submitted in the previous sections. No further information should be considered necessary at this time.

11. *Alternatives to the proposed action: If potential adverse environmental impacts have been identified for the proposed action,*

INADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

The firm indicated that since no negative environmental impact is expected, alternatives are not considered.

Note that the firm should include a brief discussion of the alternative of no action.

12. *List of preparers: Those persons preparing the assessment together with their qualifications (expertise, experience, professional disciplines) shall be listed. Persons and agencies consulted shall also be listed.*

INADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

The firm submitted a list of preparers along with Curricula Vitae. **Note that the CV's were submitted in a confidential appendix instead of part of the EA.**

13. *Certification: The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.*

ADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

The firm submitted an adequate certification, signed on 8/19/94 by Bruce Goddard, RAC, Senior Director of Compliance and Regulatory Affairs.

14. *References: List complete citations for all referenced material. Copies of referenced articles not generally available should be attached.*

INADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

While copies of referenced articles were submitted in Item 15, the firm failed to include complete citation in the list of references. Note also that References were shown as Item 15, with Item 14 being a list of appendices.

15. *Appendices:*

INADEQUATE

Refer to Review #1 per G.J. Smith and comments to firm, 4/12/94.

While the firm included tables in Items 7 and 8, data summary tables showing all relevant data were not submitted as Item 15a.

As previously noted, characterization of the drug substance was conducted prior to current requirements. Therefore, in support of Item 15b, the firm submitted summaries and literature citations regarding the characteristics of the drug substance. Review of the information submitted showed that while not conducted strictly in accordance with the TAD's, sound scientific methods were used in the studies. In addition, the test results were sufficiently unambiguous so that any error inherent in the studies due to procedures would have no significant impact on environmental fate. The studies as submitted should be considered adequate at this time.

The firm also submitted the following studies conducted according to TAD's in support of their EA.

Methods Validation
ADEQUATE

The firm submitted a methods validation study conducted by ABC Laboratories for the determination of Metformin HCl in aqueous media. In general, the laboratory followed acceptable procedures, explained all deviations and problems. The study and therefore the analytical method should be considered adequate with the following notations.

1. The linearity studies exhibited curvature at the highest standard concentration (1000 ppm) and therefore recovered values approximately 10% low (990 ppm vs 1000 ppm). Since the

inaccuracy occurred at the extreme linearity standard and was noted in the data, the results should be considered adequate.

2. The report failed to address the precision of the methodology. However, review of the data showed RSD values at all linearity standards of less than 3%. The precision of the method should therefore be considered adequate.

UV/Vis Absorption Spectra
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for the determination of UV/Vis spectra for the drug substance. The study submitted was stated as following TAD 3.05.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate.

Hydrolysis
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for hydrolysis of Metformin HCl as a function of pH. The study submitted was stated as following TAD 3.09.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate.

Aerobic Biodegradation
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for aerobic biodegradation for the drug substance. The study submitted was stated as following TAD 3.11.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate with the following notations.

1. The study employed activated sludge and secondary effluent from a waste treatment

plant not exposed to industrial wastes in place of soil and secondary effluent. Failure to include soil samples may have precluded introduction of a terrestrial organism which would metabolize the drug substance. The results reported therefore would represent a "worst case" scenario, since no biodegradation was observed.

2. The inoculum was not allowed to acclimate prior to initiation of the study. Again, failure to acclimate the organisms would result in a "worst case" scenario. Neither this observation nor the previous should be considered a fatal flaw.

Indirect Aqueous Photodegradation
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for indirect aqueous photodegradation of the drug substance. The study submitted was stated as following TAD 3.10.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate with the following notations.

The firm failed to include a reference compound in their study. Since the study was for indirect photolysis in order to demonstrate that the compound does not persist indefinitely in the environment, and the xenon arc lamp calibration was checked before and after the tests, the failure to include an actinometry study should not be considered fatal.

Microbial Inhibition
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for microbial growth inhibition due to the drug substance. The study submitted was stated as following TAD 4.02.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate.

Acute Toxicity to Daphnia
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for acute toxicity of the drug substance to *Daphnia magna*. The study submitted was stated as following TAD 4.08.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate.

Acute Toxicity to Bluegill
ADEQUATE

The firm submitted a study conducted by ABC Laboratories for acute toxicity of the drug substance to Bluegill (*Lepomis macrochirus*). The study submitted was stated as following TAD 4.11.

In general, the laboratory followed acceptable procedures, explained all deviations and problems and met all reporting requirements. The study should therefore be considered adequate.

Reviewed by: 10/26/94

Glen Jon Smith

Concurrence:

Phillip G. Vincent, Ph.D. PGV 10/27/94

File: 20357E01.RGS/GJSEA#01

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 12, 1994

FROM: Glen Jon Smith, HFD-102

THROUGH: Phillip G. Vincent, Ph.D.,
Environmental Assessment Officer, HFD-102

SUBJECT: Environmental Concerns - NDA 20-357 Glucophage®
(Metformin Hydrochloride) Tablets, 500 mg, 850 mg.

TO: John Short, HFD-510

The Center has reviewed the environmental assessment for the subject NDA.

ACTION: INADEQUATE

Please transmit the following to the firm and copy HFD-102.

Your environmental assessment has been carefully reviewed. Please address the following deficiencies.

1. Regarding Item 4:

   A. Please revise the description of the proposed action to include that the requested approval was to manufacture, package and market the drug product.

   B. Please submit exact addresses for each facility located in a foreign country used for the manufacture of drug substance or drug product.

   D. Please specify the container/closure systems for each dosage level of drug product.

   E. Please specify in detail the method of disposal for each component of the drug product (e.g. incineration of the container/closure system along with the drug product).

   F. Please revise the description of the contract company used for the disposal of drug product to include the method of disposal (e.g. drug product separated from container/closure system prior to incineration), identification of all applicable permits for disposal

by permit number, issuing agent and expiration date along with documentation of contractual agreement with the firm. Do not submit entire copies of each contract or permit.

2. Items 5 & 6: Please submit structures, CAS numbers or other information (e.g. toxicity data, biodegradability data) regarding the impurities and inactive ingredients.

3. Items 6 through 15. Insufficient information was submitted for these items. You have therefore failed to comply with the regulations for these items per 21 CFR 25.31a(a).

You must prepare an Environmental Assessment (EA) for proposed actions to approve a new drug application (NDA) using a format described in 21 CFR 25.31a unless a categorical exclusion applies as described in 21 CFR 25.24. To assist in the preparation of the EA, the Center for Drug Evaluation and Research provides below several suggestions:

1. You should consult FDA to determine the correct format for the EA and to discuss the type of information that may be necessary. It is particularly important that you consult FDA before conducting any environmental tests to make sure that testing is really needed and, if so, that the right tests are done.

2. Use FDA's Environmental Assessment Technical Handbook. Note the chapter entitled, "Step-by-Step Guidance for Preparing Environmental Assessments," which describes that environmental review process and encourages the use of existing information in preparing environmental assessments. The remainder of the Handbook has protocols for various tests used to predict the environmental impact of chemicals. Although you are encouraged to follow these protocols if you do environmental testing, you may use other protocols if they are based on scientifically validated methods. Note however, that the Handbook protocols represent the minimum testing and reporting requirements for studies conducted as part of the environmental assessment. If an alternate protocol is used, sufficient information must be submitted to demonstrate that the alternate method is equivalent to or better than the corresponding method in the Handbook. When environmental tests are necessary, the use of test-sequencing procedures, called tiered testing, is recommended.

3. Address fully all the items in the applicable EA format. To "address fully" means:

   a. Do not leave any items blank. If you think a particular item is not applicable, provide a

statement to that effect and explain why it is not applicable.

b. Provide a level of analysis commensurate with the potential for environmental impact. Use the Step-by-Step for guidance.

c. Support the claims and conclusions in your EA by providing relevant data from sources such as the open scientific literature, databases, or company files. Do not make claims that are not supported, or that are practically impossible to support. Publicly-available documents may be incorporated by reference in the EA, provided that the pages or paragraphs of the reference are specified in the EA so that the reader can easily find the referenced material. FDA recommends that you summarize the referenced information in the EA to help the reader understand the nature and significance of the referenced material. If extensive cross-referencing would be required, FDA suggests that you instead incorporate the environmental information directly into the EA, either in the text of the EA or as an appendix to it. An EA in which relevant information is directly incorporated may be easier to prepare and is likely to be easier to read.

d. The submission of raw or unprocessed data (e.g. copies of laboratory notebooks, chromatograms for quantitative analysis, printouts from dataloggers) in support of testing results is usually not necessary. If a protocol or test requires determining the average of a set of values, each individual value as well as the mean must be included in the test report. Please refrain from submitting unnecessary raw or unprocessed data unless specifically requested.

e. If your analysis indicates that there are uncertainties as to whether approval of your application will have environmental effects or whether potential environmental effects could be significant, state this and identify the uncertainties. Contact FDA for guidance as to how to proceed in light of these uncertainties.

4. Address the environmental impact at the production site(s) whether the product is manufactured in the United States or in a foreign country. FDA's environmental regulations require the Agency to consider the effects of its actions abroad, 21 CFR 25.50.

Note that when submitting information for production in foreign countries, you may find that it is more convenient to obtain a letter or letters from the appropriate officer(s) of the foreign government stating that the manufacture of the product(s) that is the subject of the application has been evaluated by that government and that it meets their requirements for emissions and occupational controls. Provided that the letter(s) has some specificity about the drug substance and/or the drug product that would be manufactured under the NDA and the government's requirements, such a letter can be used in lieu of the information requested in section [illegible] of the EA format. Note that the letters must include the names and signatures of the appropriate officials, dates of signing and confirmatory seals or insignia where applicable. Letters written in a language other than English must be accompanied by a certified English translation. All documents submitted must be clear and legible.

5. Do not include confidential information in the EA, since the EA is publicly available, 21 CFR 25.20. Instead, submit confidential information pertinent to the environmental review in a separate section of your application (as an appendix). However, you should summarize confidential information to the extent possible in the EA.

6. Keep in mind that the EA must be a complete and independent document that will enable the Agency to decide whether an environmental impact statement (EIS) is necessary and that will permit the public to understand the basis for the Agency's decision.

7. Finally, note that FDA is required to ensure that the information contained in an EA is complete and accurate (21 CFR 25.41(c)) and to take responsibility for the scope and content of the EA once it is accepted (40 CFR 1506.5(b)). FDA therefore will carefully review your EA if it is not adequate for approval. An EA adequate for approval is one that contains sufficient information so that the Agency can determine whether the proposed action may significantly affect the quality of the human environment, 21 CFR 25.22(b).

Endorsements:

HFD-102/GJSmith

HFD-102/PGVincent

cc: Original NDA 20-357
EA File 20357.REV
Division File/HFD-510
Supervisory Chemist/HFD-510

20357E00.LGS/GJSEA#01

F/T by GJS/[illegible].

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-357

Glucophage® Tablets

(Metformin Hydrochloride)

HFD-510 REVIEW DIVISION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED 4/11/94

25.31a Environmental assessment for proposed approvals of FDA-regulated products -- Format 1.

(a) For proposed actions to approve food or color additives, drugs, biological products, animal drugs, and class III medical devices, and to affirm food substances as generally recognized as safe (GRAS), the applicant or petitioner shall prepare an environmental assessment in the following format:

Environmental Assessment

1. *Date:* October 1, 1992

2. *Name of applicant/petitioner:*

Lipha Pharmaceuticals, Incorporated

3. *Address:*

Lipha Pharmaceuticals, Incorporated
9 West 57th Street
New York, NY 10019-2701

4. ***Description of the proposed action: Briefly describe the requested approval;***

INADEQUATE

The firm indicated that the NDA requests approval of the use of the drug as monotherapy, in conjunction with diet, in patients with non-insulin dependent diabetes mellitus (NIDDM) when hyperglycemia cannot be managed with dietary measures and exercise alone, and in conjunction with continued oral sulfonylurea therapy , diet and exercise, in NIDDM patients whose hyperglycemia is not or is no longer adequately controlled with sulfonylurea therapy, diet and exercise.

Note: The firm should revise the request to include the manufacture, packaging and distribution of the drug product for the above indications.

The drug substance will be manufactured at the firm's facility in Calais, France. A general description of the location of the facility was submitted along with

the environmental settings (Industrial park - Zone Industrielle de Beau Marais - maritime plane/sandy soil).

The drug product will be manufactured at the firm's facility in Hitchin, Hertfordshire, U.K. A general description of the location of the facility was submitted along with the environmental settings (sports facilities, light industry, retail business and private residence - chalk based soil).

The drug product will be packaged at the firm's two facilities in Letchworth, Hertfordshire, U.K. General descriptions of the locations were submitted along with the environmental settings (same as Hitchin facility).

The firm should submit exact addresses for each facility located in a foreign country.

The drug product is intended for use throughout the US. All rejected or returned products are to be incinerated off-site by:

Rollins Environmental Services (N.J.) Inc.
Route 322 Bridgeport, NJ 08014
EPA ID No. NJD 053 288 239

1. **Since the rejected or returned materials are final drug product, the firm should specify the container/closure system.**

2. **The method of disposal for the container/closure system and the actual drug product should be defined for the specific component.**

3. **Evidence of a contractual agreement, along with any restrictions or expiration dating should be submitted in support of the use of the outside company.**

5. *Identification of chemical substances that are the subject of the proposed action:*

INADEQUATE

Name: Metformin Hydrochloride

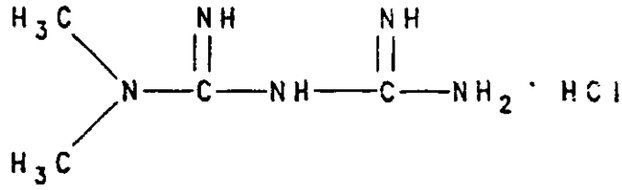
Chemical Name: Imidodicarbonimidic diamide, N,N-dimethyl-, hydrochloride

CAS Registration Number: 657-24-9 (base)

Molecular Weight: 165.63

Molecular Formula: $C_4H_{12}ClN_5$

Structural Formula:



Physical Description: Small white crystals, odorless or with a faint amine odor.

Additives: None listed.

Impurities: None listed.

The firm should submit a list of all potential impurities and associated data where available.

A MSDS for the drug substance was submitted in Appendix 6.

6. ***Introduction of substances into the environment: For the site(s) of production:***

INADEQUATE

The firm submitted lists of chemicals used in the manufacture of the drug substance (Appendix 2) and the drug product (Appendix 3). **CAS Registration Numbers for each chemical were not included in the lists.**

The firm submitted general descriptions of air, liquid and solid controls for each of the manufacturing facilities. The descriptions failed to contain sufficient detail to determine the adequacy of the controls. Note, however, that all manufacturing takes place in either the United Kingdom or in France. Adequate certification of compliance may take the place of detailed environmental controls descriptions.

The firm submitted a copy of the agreement the Lord Mayor of Calais, France, to resolve any problems associated with waste disposal at the Calais facility,\

along with copies of applicable environmental and safety regulations (Appendix 4). A draft of guidelines for the UK was submitted in Appendix 5.

The firm must submit formal statements of compliance from the foreign governments involved. Note that the citations; must be product specific where possible, must clearly exhibit the name, title and signature of the authority, must indicate the effects (or lack of) of production on the state of compliance and include English translations where applicable.

The firm submitted MEEC calculations assuming the use of 240 grams of drug substance per day (0.05% of the population, 2000 mg per day) at the end of five years in the U.S. Note that this results in a total amount of 87,600 kg per year in the U.S. The calculation is in general acceptable, although the value may be high since 100 gallons waste water per day (2.5×10^{-3} ppm) was assumed instead of the standard 150 gallons (1.7×10^{-3} ppm).

EEC values and potential emissions due to disposal were not included in the calculations.

7. *Fate of emitted substances in the environment: Predict environmental concentrations of and exposures to substances entering the environment as a consequence (direct or indirect) of the use and/or disposal of the products affected by the action for the following environmental compartments, including consideration of the major environmental transport and transformation processes involved:*

INADEQUATE

The firm indicated that the drug substance is essentially non-biodegradable and that over 80% is excreted unchanged in the urine within the first 24 hours. **No other information or supporting data was submitted.**

8. *Environmental effects of released substances: Given the information developed on the introduction (item 6) and fate (item 7) of substances which would be released as a consequence of the use and/or disposal of the products affected by the action,*

INADEQUATE

The firm submitted results of toxicity studies (LD_{50}) for mice, rats rabbits and dogs (p. 03 000779) and a summary of chronic toxicity studies (Appendix 7).

The firm failed to submit any environmental effects testing results for the drug substance or product.

9. *Use of resources and energy:*

INADEQUATE

The firm indicated that anticipated energy commitment for the production of additional bulk drug substance in France and the drug product in the U.K. will be nominal since production will occur at existing facilities. The additional drug product volume manufacture will not utilize resources and energy in the U.S.

The firm should supply calculated/estimated values showing the increase in energy use resulting from the increase in production due to the U.S. market.

10. *Mitigation measures: Describe measures taken to avoid or mitigate potential adverse environmental impacts associated with the proposed action.*

The firm indicated that both drug substance and drug product are manufactured under highly regulated and controlled conditions, and that mitigation measures for limiting and containing waste are employed to the greatest possible extent. The firm also stated that there are no known technologies that would further reduce or control waste.

Final disposition on mitigating measures will depend on adequate submission of information for Items 6 - 8. Note that the firm does not appear to understand that mitigation in the EA is for products/processes which may have significant emission/fate/effect conditions associated with them which can be "mitigated."

11. ***Alternatives to the proposed action: If potential adverse environmental impacts have been identified for the proposed action,***

The firm indicated that there are no alternative synthesis, manufacturing or control measures applicable to the drug substance or product.

The firm does not appear to understand that the alternatives to be presented are dependent upon potential adverse environmental impacts. Final disposition will depend upon the demonstrated need for mitigation and/or alternatives.

12. *List of preparers: Those persons preparing the assessment together with their qualifications (expertise, experience, professional disciplines) shall be listed. Persons and agencies consulted shall also be listed.*

INADEQUATE

The firm submitted two names for the preparers without any information regarding their qualifications, titles or positions with the firm. Note that the titles and positions with the firm are shown on the following Certification sheet.

13. *Certification: The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.*

The certification statement was consistent with regulations and was signed on:

June 17, 1993

by:

Bruce Goddard, Director, Regulatory and Compliance, and

Barbara H. Weil, Ph.D., Director, Science and Technology.

14. *References: List complete citations for all referenced material. Copies of referenced articles not generally available should be attached.*

INADEQUATE

The firm failed to submit a complete list of citations for all reference materials.

15. *Appendices:*

INADEQUATE

No data summary charts or test protocols were submitted.

Comments

1. **The firm submitted the environmental assessment as a subsection of the NDA and failed to submit it as a stand-alone document.**

2. **The firm failed to supply a public copy of the assessment.**

3. **The firm failed to indicate what information in the submission was confidential.**

Reviewed by:

Glen Jon Smith

Concurrence:

Phillip G. Vincent, Ph.D.

File: 20357E00.RGS/GJSEA#01

MICROBIOLOGY REVIEW

Not Applicable Because This Is

A Tablet Formulation

CORRESPONDENCE

Attachment 1

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3925 • NEW YORK, NEW YORK 10019-2601
TEL 212-223-1280 • FAX 212-223-1288

Aug. 31, 1994
#29-94

VIA FEDERAL EXPRESS, #2229359521
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #29
Part A. Draft Proposal for a Phase IV Safety Study;
Part B. Overview of Proposed Education Program

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In response to your letter to us, dated June 29, 1994, the current amendment consists of two parts, as follows: (Part A) a DRAFT proposal for a Phase IV Safety Study for Glucophage® (metformin hydrochloride) and (Part B) an overview of a proposed education program for Glucophage, to be initiated post-approval.

In developing the DRAFT proposal for a Phase IV Safety Study, we have given serious thought to the issues raised in your letter and believe that the proposal for a prospective, randomized, controlled (metformin vs. "usual care") simplified clinical trial involving 10,000 patients with NIDDM is the most appropriate approach to resolving the potential public health issues. As noted herein, the proposed trial will particularly focus on detection, confirmation, and evaluation of the incidence of lactic acidosis. The key outcome will be hospitalizations and deaths due to lactic acidosis, although all cause mortality and hospitalization rates will also be examined.

Each of the five study design issues that were raised in your letter of June 29, 1994 (representativeness, confounding, power, validation and timeliness) have been carefully considered and are addressed in the proposal (*see* ***Part A, Pages 13-18, III. Discussion of Draft Proposal***).

As suggested in your letter, this proposal is being submitted for your initial review and response, prior to developing an actual detailed protocol. We would like to accept the Division's offer to meet with us, along with our colleagues from Bristol-Myers Squibb, to discuss this design further, prior to the official submission of a final protocol.

In addition to the Phase IV Safety Study proposal, this amendment provides an overview of the type of medical education program envisioned by Bristol-Myers Squibb (BMS), relative to Glucophage (Part B). As indicated, this multi-faceted program, directed toward physicians, pharmacists, diabetes educators and other health professionals, will include an emphasis on lactic acidosis, primarily from the perspective of preventing its occurrence through education about the appropriate use of Glucophage. This program and the nature of the communications will be developed, in part, through collaboration with various professional organizations, such as the American Diabetes Association and the American Association of Diabetes Educators.

We look forward to your response on both parts of this amendment. I will follow up with Capt. John Short to determine a mutually convenient time for the meeting to discuss this Phase IV program.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gérard L. Dallei, M.D.
Chairman, President &
Chief Executive Officer

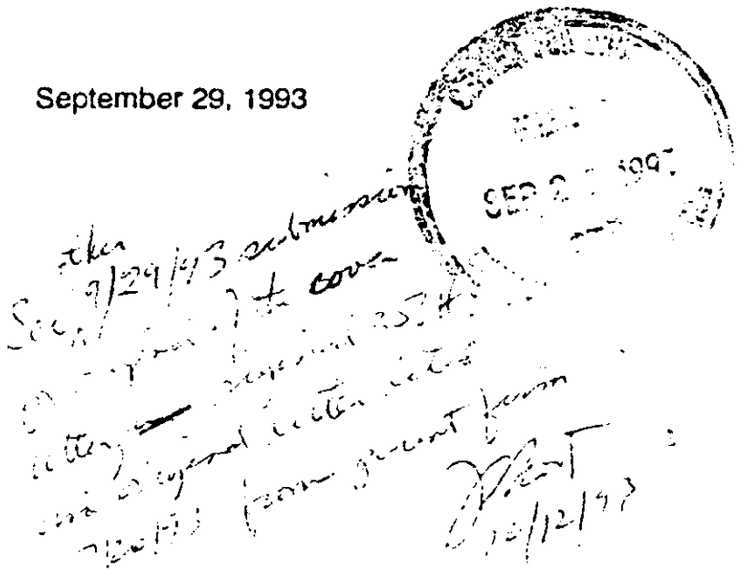
(1 Archival Copy, 2 Clinical Copies)

GLD/AMG

N 20-357

LIPHA

September 29, 1993



HAND CARRIED

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: **IND Metformin HCl Oral**
NEW DRUG APPLICATION
NDA #20-357 (Preassigned Number)

Gentlemen:

Reference is made to our Notice of Claimed Investigational Exemption for a New Drug for Metformin, IND Submitted herewith is the New Drug Application for this drug. The preassigned NDA number is **20-357**. Request is hereby submitted for an expeditious review and approval.

For ease of review, we have placed a listing of the volumes contained in the ARCHIVAL and REVIEWER copies under Attachment I. Please note that the clinical report volumes contained in Item 8 are provided in full and intact, as presented in Item 8, in Item 10 for the STATISTICAL review copy. By prior agreement with Captain John Short, however, the Final Study Reports in Item 8 are referenced in Item 10 of the ARCHIVAL copy.

Note that Items 7 (Microbiology) and 14 (Patent Certification) are not applicable to this NDA. Item 13 (Patent Information) is attached to the application form in Volume 1.1.

Lipha Pharmaceuticals, Inc. hereby requests for Metformin the five-year post-approval exclusivity period provided for under sections 505 (c) (3) (D) (ii) and 505 (j) (4) J(D) (ii) of the Federal Food, Drug, and Cosmetic Act on the ground that neither Metformin's active ingredient, nor any ester or salt of that active ingredient, has been approved in any other application submitted under section 505 (b) of the Act.

Lipha Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under section 306 of the Act in connection with this application.

Debarment Certification

For your information, a check in the amount of . representing of the application fee for the Metformin NDA (including clinical data) has already been submitted with our letter #082 dated September 23, 1993 (see Attachment II).

A letter of authorization from our parent company, Lyonnaise Industrielle Pharmaceutique (LIPHA, S.A.), appears as Attachment III. The contact person at Lipha Pharmaceuticals, Inc. is the undersigned. Should there be any questions, please call me at (212) 223-1332.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/eg

Letter and Attachments in Triplicate

NOV 29 1994

Memorandum
November 29,1994
To:the File NDA # 20-357 Metformin Tablets (Glucophage)
From: Solomon Sobel M.D. Director of Division of Metabolism and Endocrine Drug Products 11-29-94
Subject: Approval of NDA

The NDA rests on 2 clinical studies:
1. Study No. 87-1D-6023: A double-blind, placebo controlled, randomized parallel group, multi-center study in obese, type II NIDDM patients who are not adequately controlled with diet alone.
2.Study No. 87-2D-6023: A double -blind, placebo-controlled randomized parallel group multi-center study to compare metformin alone to metformin in combination with glyburide and to glyburide alone in the control of obese type II NIDDM patients who are not well controlled at the maximum dose of a first or second generation sulfonylurea.
In the first study (1D) 289 patients were randomized and 217 patients completed the study which had a 6 month pericd of treatment (after a prebaseline phase of 2 months and a dose titration phase of 5 weeks)
Metformin therapy was associated with a clinically significant drop in fasting plasma glucose (53 mg/dL) and of HbA1c (1.4%). There were small favorable effects on blood lipids (total cholesterol,LDL and triglycerides;there was no significant effect on HDL).
Fasting insulin levels were not decreased by metformin; the 2 hour post glucose load insulin response increased significantly with metformin.
GI symptoms (nausea and diarrhea) were significantly greater in the metformin group.
No cases of lactic acidosis were seen. Serum lactate levels did not change in the metformin group compared to the placebo group,. A significant decrease in serum vitamin B12 levels was noted. No cases of megaloblastic anemia developed.
In the second study (2D), 632 patients were randomized:
210 to metformin
209 to glyburide
213 to the combination metformin/glyburide.
157,174and 192 patients in the respective groups completed the study which had a six month treatment phase (there was a 1 month pre-enrollment phase and a five week titration phase)
The changes in the fasting plasma glucose in the respective groups in mg/dL were -0.9,+13.7 and -63.5.
HbA1c similarly showed the best effects in the combination group (-0.4 +0,2 and -1.7 %)
Again the very modest beneficial effect on blood lipids was noted.

In this study a decrease in fasting insulin levels was noted (-5.0, -0.2 and -1.1 micro IU/ml) reflecting a putatively beneficial effect on insulin sensitivity.
The 2 hour post-glucose load insulin levels were -4.5,+1.1 and +4.8 micro IU/ml
This may be interpreted as showing a persistent effect of the sulfonylurea in inducing insulin secretion and perhaps an increase insulin sensitivity in patients who are at their maximal insulin secretion capacity (after secondary failure on sulfonylurea). These results are at variance with those seen in study 1D.
The most prominent side effects were gastrointestinal adverse reactions to metformin. Adverse effects on serum vitamin B12 levels were again noted.
There were no instances of lactic acidosis. A slight non significant trend in increasing serum lactate levels was noted in the the metformin containing groups.
On the basis of the above described studies a treatment IND was granted in April of 1993 under (87-2D -6023)

Current issues surrounding the NDA approval:

<u>1. Lactic acidosis and other safety considerations.</u>

There are a number of reasons to believe that metformin is different from phenformin in its propensity to cause lactic acidosis.
Pharmacokinetic, metabolic and epidemiologic distinguishing characteristics have been presented to support the contention that metformin is a safer drug than phenformin.
Phenformin is metabolized by the liver; metformin is excreted unchanged in the urine.
There are differences of effect on pyruvate dehydrogenase.
The reported incidence of lactic acidosis is one eighth that of phenformin.
The adverse reaction profile of metformin shows a high incidence of gastrointestinal intolerance. However, pateints have continued in the face of some GI intolerance without evident serious consequences.
There is a definite adverse effect on the level of vitamin B12 in the serum. However,the degree of decrease is mot enough to cause megaloblastic anemia or neuropathy..

<u>2. The issue of proper dose ranging was addressed at the advisory committee.</u>

There was no clear dose ranging performed during the clinical studies. However, the mode of administration of this drug will be by titration starting from low doses. Response in fasting blood glucose will guide the titration. The low dose starting approach is also dictated by the need to avoid gastrointestinal complaints. There is amelioration of the frequency of this adverse effect by slow increase in dose.
The advisory committee recommended a phase 4 study to establish dose response based on appropriate time periods to allow for the

stabilization of blood glucose response. This will be one of the conditions of approval.

3. A phase 4 sudy will be performed to further define the safety of the drug.

A protocol has been submitted. This will require further discussion. The Division believes a one year rather than the proposed 6 month duration is preferable. The study will include 10,000 patients; 8000 will be on metformin and 2000 will be on other forms of therapy for type 2 diabetes.

4. Deaths in the metformin studies were analyzed by the medical officer, Dr. Innerfield who concluded that there were significantly more deaths in those patients treated with metformin.

Subsequently,this issue was reanalyzed by Dr. Bruce Stadel (epidemiologist) with the assistance of Mr. Dan Marticello (statistitian) and myself.

I concluded that the analysis of deaths that Dr. Innerfield performed is problematic.

During the 6 mos of controlled study (2D) there was one death in the metformin group.

In the open extension (1C) during which all patients receive M or M/G there were six deaths; 2 were in the original metformin group and 4 in the original M/G group .

The open extension also included patients from the 1D study. These were relatively healthy patients who were not sulfonylurea failures. No deaths occurred in the M patients from this cohort.

It is incorrect to use an intention to treat analysis(based on the 2D randomization) in the open extension. The blind had been broken and patients from various sources had been merged.

1C is a separate study with all patients receiving M or M/G.

Even if one were to permit the intention to treat approach using 2D randomiztion with each group maintaining its original assignment through the extension period we have the following result:

M group had 3 deaths

M/G had 4 deaths

G group had 0 deaths.

It is incorrect to combine M and M/G . To do so would be to give the presence of metformin in any regimen a greater risk potential(a priori). Each group must be handled separately . With 7 deaths (assuming equality of exposure)* each group would have the following expected and observed deaths.

original assignment	expected deaths	observed deaths
metformim	2.3	3
metformin/glyburide	2.3	4
glyburide	2.3	0

*adjustment for exposure would yield more expected deaths in the M and M/G groups. We can consider the chance for death as

dependent on the time the patient is observed. It could be argued that had the patients remained on glyburide during the period of open extension the result for that group would have been worse than that which occurred on switching to M or M/G. We have no way of knowing how may deaths would have occurred in the original G group if that group had remained on G.

original assignment	randomized	completed 6 months	entered open extension
Metformin	210	157	132
Metformin/Glyburide	209	192	168
Glyburide	213	174	142

original assignment	treatment during blinded study for 6 months	treatment during open extension
Metformin	Metformin	metformin or metformin/glyburide
Metformin/Glyburide	metformin/glyburide	metformin or metformin/glyburide
Glyburide	glyburide	metformin or metformin/glyburide

The above exposure periods gives metformin and even more so metformin/glyburide a greater chance of "causing" deaths; glyburide (given as sole therapy) is "protected from" causing deaths by not having been given for the time period of the open extension.
Dr. Stadel 's memorandum appears elsewhere in the NDA approval volumes.
We differ from the conclusion of Dr. Innerfield.
We believe that there is little or no evidence for more deaths in the metformin treated patients.

Conclusions:
1.The Division recommends approval of the NDA for metformin.
2.There are clear reasons for distinguishing this drug from phenformin in regard to the propensity for producing lactic acidosis.
3.The drug appears to be sufficiently safe to warrant approval: The benefits of improved glucose control especially in patients who have failed on sulfonylurea therapy outweigh the demonstrated risks.
3. Phase 4 commitments include a large study to further define safety and also a dose ranging study.

LIPHA PHARMACEUTICALS

9 WEST 57TH STREET • SUITE 3875 • NEW YORK NEW YORK 10019-2701
TEL 212-223-1280 • FAX 212-223-1398

VIA FAX and FEDERAL EXPRESS
ACKNOWLEDGMENT OF DELIVERY REQUESTED

December 16, 1994
#36-94

Food and Drug Administration
Center for Drugs and Biologics, HFD-510
Attention: Document Control Room #14B-03
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Amendment #36/USAN Listing

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In accordance with a telephone conversation between Dr. Xavier Ysern and Mr. Bruce Goddard on December 16, 1994, we will submit a formal request to include "metformin hydrochloride" as a separate name in the USP Dictionary of USAN and International Drug Names.

Should you have any questions regarding this submission or if additional information is required, please advise.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

1 Archival Copy, 2 Chemistry copies

15/15

Attachment 2

NDA 20-357

Lipha Pharmaceuticals Inc.
Attention: Gerard L. Daniel, M.D.
Chairman, President & Chief Executive Officer
9 West 57th Street, Suite 3825
New York, NY 10019-2701

JUN 29 1994

Dear Dr. Daniel:

Please refer to your pending September 29, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage (metformin hydrochloride) 500 and 850 mg Tablets.

We have not yet completed the review of this application, but we do have comments regarding Phase 4 commitments. We note that your communication dated May 27, 1994, contains a draft Phase 4 dose-ranging study for our consideration. We have reviewed that proposal and find it acceptable. The following comments relate to an additional Phase 4 study commitment, which should be a condition of approval of this NDA.

It is important that a Phase 4 study be conducted to define better the safety of metformin therapy in the treatment of Type II Diabetes Mellitus under the conditions of medical care that are generally prevalent in the United States. Lipha may wish to include other outcomes in the study, but total mortality risk is the endpoint which would appear to be most amenable to analysis.

Accordingly, the Division requests that you submit a written proposal for a study designed to meet the above requirement. Upon receipt of such a proposal, the Division intends to:

1) solicit written review of the proposal by an ad hoc panel of experts;

2) provide the written reviews to Lipha, requesting that you respond with clarification or revision of the proposal;

3) solicit written review of the clarifications and/or revisions of the proposal, by the ad hoc panel referred to above; and

4) make a final determination that the proposal is either "satisfactory" or "unsatisfactory" to meet the Division's requirement that the study be designed adequately to examine one or more clinically meaningful outcomes.

It is not the intent of the Division, prior to receipt and review of your proposal, to specify the design, data resources, data collection procedures, or methods of analysis for a study that will be "satisfactory" to meet the requirement for risk evaluation of metformin. However, the Division does anticipate that a "satisfactory" protocol will address the following issues:

1) Representativeness. The study population should be representative, to the extent feasible, of Type II diabetics in the U.S. who are candidates for metformin treatment.

2) Confounding. The study should be designed to prevent possible confounding by factors, such as disease severity, which may be related to both the likelihood that metformin is considered to be the "drug of choice" and to the risk of dying or some other outcome during the study.

3) Power. The study should have adequate power to detect small differences in the relative risk of death or other relevant outcome(s), for metformin compared to the other concurrently-available treatments for Type II Diabetes Mellitus.

4) Validation. The study should incorporate explicit and thorough procedures for verifying both the eligibility of participating patients and the data collected.

5) Timeliness. The study should be designed and conducted in a timely manner.

If you wish, we would be pleased to discuss the design of such a protocol prior to the official submission of a final protocol to your IND.

Please refer to the following documents as they pertain to the above discussion:

1) Proceedings of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held March 18, 1994.

2) Interoffice memorandum dated January 27, 1994, from Dr. Bruce Stadel (enclosed), which was sent to the E & M Advisory Committee prior to the meeting of March 18, 1994.

It is advisable that you submit a preliminary protocol outline as soon as possible in order to achieve a clear and mutual understanding of the commitment on which an approval of this application will be contingent.

We also request that you consider measures which would minimize the occurrence of lactic acidosis and enhance the early diagnosis and prompt reporting of this condition in metformin-treated patients. Such measures might include targeted physician education programs, hospital emergency department advertisements, collaboration with various professional organizations (e.g., American Diabetes Association, American College of Physicians, American College of Emergency Physicians), patient information, and highlighted messages in all promotional material. Because NDA approval may also be conditioned on the use of one or more such measures during metformin's marketing, we urge you to submit a proposal which tentatively could be accepted prior to final regulatory action.

If you have any questions, please contact:

Mr. John Short
Consumer Safety Officer
301-443-3510

Sincerely yours,

6-29-94

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

Enclosure:
Interoffice Memorandum from Dr. Bruce Stadel Dated January 27, 1994

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-80
HFD-240
HFD-510/BStadel, JGueriguian, RInnerfield, AFleming
HFD-511/JShort 6/1/94/ft/js/6/29/94 \N20357IR.3JS
Concurrence: BStadel 6/1, AFleming 6/16/94
Revised as per Dr. Fleming's comments – 6/16/94
Revised as per Dr. Sobel's comments – 6/27/94
Concurrence: BStadel, AFleming 6/28/94

INFORMATION REQUEST

6/29/94

NDA 20-357

Lipha Pharmaceuticals Inc.
Attention: Gerard L. Daniel, M.D.
Chairman, President & Chief Executive Officer
9 West 57th Street, Suite 3825
New York, NY 10019-2701

JUN 29 1994

Dear Dr. Daniel:

Please refer to your pending September 29, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage (metformin hydrochloride) 500 and 850 mg Tablets.

We have not yet completed the review of this application, but we do have comments regarding Phase 4 commitments. We note that your communication dated May 27, 1994, contains a draft Phase 4 dose-ranging study for our consideration. We have reviewed that proposal and find it acceptable. The following comments relate to an additional Phase 4 study commitment, which should be a condition of approval of this NDA.

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Accordingly, the Division requests that you submit a written proposal for a study designed to meet the above requirement. Upon receipt of such a proposal, the Division intends to:

1) solicit written review of the proposal by an ad hoc panel of experts;

2) provide the written reviews to Lipha, requesting that you respond with clarification or revision of the proposal;

3) solicit written review of the clarifications and/or revisions of the proposal, by the ad hoc panel referred to above; and

4) make a final determination that the proposal is either "satisfactory" or "unsatisfactory" to meet the Division's requirement that the study be designed adequately to examine one or more clinically meaningful outcomes.

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1) Representativeness. The study population should be representative, to the extent feasible, of Type II diabetics in the U.S. who are candidates for metformin treatment.

2) Confounding. The study should be designed to prevent possible confounding by factors, such as disease severity, which may be related to both the likelihood that metformin is considered to be the "drug of choice" and to the risk of dying or some other outcome during the study.

3) Power. The study should have adequate power to detect small differences in the relative risk of death or other relevant outcome(s), for metformin compared to the other concurrently-available treatments for Type II Diabetes Mellitus.

4) Validation. The study should incorporate explicit and thorough procedures for verifying both the eligibility of participating patients and the data collected.

5) Timeliness. The study should be designed and conducted in a timely manner.

If you wish, we would be pleased to discuss the design of such a protocol prior to the official submission of a final protocol to your IND.

Please refer to the following documents as they pertain to the above discussion:

1) Proceedings of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held March 18, 1994.

2) Interoffice memorandum dated January 27, 1994, from Dr. Bruce Stadel (enclosed), which was sent to the E & M Advisory Committee prior to the meeting of March 18, 1994.

It is advisable that you submit a preliminary protocol outline as soon as possible in order to achieve a clear and mutual understanding of the commitment on which an approval of this application will be contingent.

We also request that you consider measures which would minimize the occurrence of lactic acidosis and enhance the early diagnosis and prompt reporting of this condition in metformin-treated patients. Such measures might include targeted physician education programs, hospital emergency department advertisements, collaboration with various professional organizations (e.g., American Diabetes Association, American College of Physicians, American College of Emergency Physicians), patient information and highlighted messages in all promotional material. Because NDA approval may also be conditioned on the use of one or more such measures during metformin's marketing, we urge you to submit a proposal which tentatively could be accepted prior to final regulatory action.

If you have any questions, please contact:

Mr. John Short
Consumer Safety Officer
301-443-3510

Sincerely yours,

6-29-94

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

Enclosure:
Interoffice Memorandum from Dr. Bruce Stadel Dated January 27, 1994

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-80
HFD-240
HFD-510/BStadel, JGueriguian, RInnerfield, AFleming
HFD-511/JShort 6/1/94/ft/js/6/29/94 \N20357IR.3JS
Concurrence: BStadel 6/1, AFleming 6/16/94
Revised as per Dr. Fleming's comments - 6/16/94
Revised as per Dr. Sobel's comments - 6/27/94
Concurrence: BStadel, AFleming 6/28/94

INFORMATION REQUEST 6/29/94

NDA 20-357

MAR 2 4 1994

Lipha Pharmaceuticals Inc.
Attention: Gerard L. Daniel, M.D.
Chairman, President & Chief Executive Officer
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Dr. Daniel:

Please refer to your pending September 29, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage (metformin hydrochloride) 500 and 850 mg Tablets.

We have completed the review of the Chemistry section of your submission and have the following recommendations and requests:

Drug Substance:

1) Please provide the limits for the total amount of impurities. This limit should be incorporated as part of the drug substance specifications. Please provide the actual values of the total amount of impurities for representative drug substance batches.

2) Total amount of impurities should be monitored in the stability studies and they should be within the limit specified. Please provide the actual values determined from the ongoing stability studies.

Drug Product:

1) Please provide a specification for the total amount of impurities as part of the dosage form specifications. Also, provide the corresponding values for the total amount of impurities for lots 109448 and 110179.

2) Monitoring the total amount of impurities should be part of the drug product stability study. Please provide data on the total amount of impurities determined from the ongoing stability study.

3) The actual dissolution data (lots 109448 and 110179, representatives of 500 and 850 mg dosage strength, respectively) seem to indicate that the tablets are fully dissolved before 45 minutes. Please provide the actual dissolution profiles for these and other representative lots. A dissolution specification that mimics the dissolution behavior should also be provided.

Labeling:

Please provide copies of the draft package (carton) labels.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Mr. John Short
Consumer Safety Officer
301-443-3510

Sincerely yours,

SS 3-23-94

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

RH 3/23/94

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-80/DDIR
HFD-510/XYsern, YYChiu
HFD-511/JShort 3/22/94/ft/dj/3.23.94/ft/lp/3/23/94/N20357IR.JRS
Concurrence: Galliers3.22.94/Ysern/Chiu3.23.94

INFORMATION REQUEST

SHORT

NDA 20-357

OCT 7 1993

Lipha Pharmaceuticals
Attention: Gerard L. Daniel, M.D.
Chairman and President
9 West 57th Street (Suite 3825)
New York, NY 10019-2701

Dear Dr. Daniel:

We have received your new drug application submitted pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Glucophage (metformin hydrochloride) Tablets

Date of Application: September 29, 1993

Date of Receipt: September 29, 1993

Our Reference Number: NDA 20-357

Unless we find the application not acceptable for filing, the filing date will be November 28, 1993.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning this NDA, please contact Mr. John Short at (301) 443-3510.

Sincerely yours,

10/6/93

Enid M. Galliers
Supervisory Consumer Safety Officer
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-510
HFD-511/JShort 10/6/93 \N20357AC.JRS
Concurrence: EGalliers 10/6/93

ACKNOWLEDGEMENT

10/6/93

LIPHA PHARMACEUTICALS INC.
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

Dec. 29, 1994

VIA FAX AND FEDERAL EXPRESS
ACKNOWLEDGMENT OF RECEIPT REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #38

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In accord with our telephone conference of December 29, 1994 with Capt. John Short, we agree that Glucophage® will not be marketed in the United States without an accompanying Patient Package Insert (PPI). The language of this PPI will be mutually agreed upon by FDA and Lipha Pharmaceuticals, Inc. in the immediate future. This PPI will accompany the trade package of 100 tablets. If a larger bulk package is provided for in the NDA, a mechanism will be mutually agreed upon and implemented so that each patient will be provided with a copy of the PPI.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

LIPHA PHARMACEUTICALS, INC.
Lipha
17 WEST 57TH STREET • SUITE 3875 • NEW YORK NEW YORK 10019-2211
TEL 212 223 1280 • FAX 212 223 1398

Dec. 29, 1994
#38-94

VIA FAX AND FEDERAL EXPRESS, #2494063541
ACKNOWLEDGMENT OF RECEIPT REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #38
Revised Package Insert (Dec. 29, 1994)

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

The current amendment is the Revised Package Insert and is in response to the Division's critique of the November 28 Proposed Package Insert, received by us via FAX on December 28, 1994.

All recommended changes have been incorporated with the following exceptions, both of which are by mutual agreement with Capt. John Short, as per our teleconferences of Dec. 29, 1994: (1) we have not included the MedWatch contact information in this Package Insert; (2) the frequency of "..reported incidence of lactic acidosis.." has been changed to "very low" from "low".

One ARCHIVAL and two CLINICAL copies of this letter and the amendment are provided. An additional DESK copy is enclosed, which is to be directed to Capt. John Short.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 2 Clinical Copies, 1 Desk Copy)
GLD/AMG

LIPHA PHARMACEUTICALS
[illegible] 5TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019 [illegible]
TEL [illegible] • FAX [illegible]

Dec. 28, 1994
#37-94

VIA FAX AND FEDERAL EXPRESS, #2494063585
ACKNOWLEDGMENT OF RECEIPT REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #37
Revised Patient Package Insert (Dec. 28, 1994)

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

At the request of Capt. John Short and in response to the Division's recommendation that a Patient Package Insert be developed for Glucophage® brand of metformin hydrochloride, the current amendment is a revision of the Proposed Patient Package Insert sent to us via FAX by the Division on December 23, 1994. This revised version of the Patient Package Insert is dated December 28, 1994.

The revisions of the Proposed Patient Package Insert (Proposed PPI) are primarily in the nature of somewhat greater clarification or elaboration on certain points. However, more importantly, the modifications correct two notable errors in the document of December 23, 1994, as follows:

1. *(on Page 2 of the Dec. 23, 1994 Proposed PPI)*

   The estimated incidence rate of lactic acidosis in patient's treated with metformin should read "...about 3 people in **100,000** who take this drug for a full year..." as opposed to "...3 people in **10,000** who take this drug for a full year...".

2. *(on Page 3 of the Dec. 23, 1994 Proposed PPI)*

   The caution concerning the interference of Glucophage with "...'contrast agents' **that people drink before X-ray examinations**..." is incorrect, since the caution involves parenteral (intravascular) administration of contrast agents. The statement has been amended to read "...'contrast agents' **that are given by injection (into a blood vessel) either before or during certain special X-ray examinations**...".

In addition, in accordance with today's teleconference, a paragraph has been added which recommends that patient's taking Glucophage consult their physician whenever an illness associated with reduced food or fluid intake or risk of dehydration occurs.

To facilitate your review of the revised Patient Package Insert as well as to provide the rationale for or commentary on certain changes that have been made to the Proposed PPI of December 23, 1994, an attachment is included (**Attachment 1**), which is a side-by-side presentation, consisting of three columns, as follows:

1) in **Column 1**, the Dec. 23, 1994 Proposed Patient Package Insert, prepared by the Division, is provided;

2) in **Column 2**, the proposed changes to the Dec. 23 document are provided *(all these changes have been incorporated into the revised Patient Package Insert, Dec. 28, 1994);*

3) in **Column 3**, the Comments/Rationale for each proposed change are provided.

The following conventions were used to indicate the nature of the changes in Columns 1 and 2:

1) Strikeouts (~~strikeouts~~) for word or text deletions in Column 1. (*The rationale for such strikeouts is provided in Column 3, when not self-evident*);

2) Italics (*italics*) for word or text additions. (*The placement of such new words or text is indicated by arrows going from Column 2 to the appropriate location in Column 1 and the rationale for the new word/text is provided in Column 3*).

Finally, it should be noted that the current revisions were made without the benefit of our having the opportunity to review recent Division-generated changes in the Physician's Package Insert that have been previously alluded to by the Division but which we have not yet received. Thus, it is possible that further revision of this Patient Package Insert will be required.

One ARCHIVAL and two CLINICAL copies of this letter and the amendment are provided. An additional DESK copy is enclosed, which is to be directed to Capt. John Short.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 2 Clinical Copies, 1 Desk Copy)
GLD/AMG

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223-7280 • FAX 212-223-1358

Nov. 29, 1994
#35-94

VIA FAX AND FEDERAL EXPRESS, #3776899405
ACKNOWLEDGMENT OF RECEIPT REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention. Document Control Room #14B 04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #35
Revised Package Insert, Nov. 28, 1994

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

The current amendment is a revision of the Proposed Package Insert, submitted to the Division on October 20, 1994 (Amendment #30) and is in response to the FAX sent to us by the Division on November 28, 1994.

This Revised Package Insert (dated Nov. 28, 1994) incorporates all recommended changes made in the above-referenced FAX and is submitted as a complete document.

One ARCHIVAL and two CLINICAL copies of this letter and the amendment are provided.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D./gp

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 2 Clinical Copies)
GLD/AMG

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212 223 1280 • FAX 212 223 1398

Nov. 21, 1994
#34-94

VIA FEDERAL EXPRESS, #2494063666
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #30
Amendment #34, Metformin Safety Update

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

The current amendment, the contents of which are described below, represents the third safety update to NDA #20-357. Two prior safety updates have been submitted to this NDA. **Amendment #17** (dated February 23, 1994) presented tabular listings of adverse experiences and key safety laboratory parameters from U.S. Study No. 89-1C-6023, a long-term open label safety study of metformin. **Amendment #24** (dated May 19, 1994) presented all worldwide adverse experiences reported to our parent company, Lipha S.A., Lyon, France, through Dec. 31, 1993.

The present safety update is divided into four major items and is presented in two volumes. Following is a brief description of the content of each item, as well as the organization of each item:

Item 1. Worldwide Pharmacovigilance (Volume 1)

This item provides all safety information on Glucophage reported to Lipha S.A. by its subsidiaries and licensees, through October 31, 1994.

It is organized by country, as follows: **France, Belgium, The Netherlands, Sweden, Germany, Australia, and New Zealand.**

The major emphasis and the greatest detail is available on those adverse events which have occurred in France. Therefore, the section devoted to France is divided into **Part A**, which provides an overview and analysis of the reported

adverse experiences, and **Part B**, which provides individual patient summaries and, when available, reports to be sent to the World Health Organization (CIOMS forms). (**Part B** is organized numerically, by adverse event [AE] patient identification number).

For countries other than France (which, for the most part have only single AE reports), separate subsections are provided for each individual patient, arranged according to the patient AE identification number, followed by the available information.

Item 2. Safety Update, U.S. Studies (Volume 1 and Volume 2)

This item consists of **Part A** (safety-related information on **U.S. Phase II and III-B Studies** [Clinical Pharmacology studies]) and **Part B** (safety-related information relative to the **Treatment IND**).

In **Part A** (*presented in Volume 1*), eight Clinical Pharmacology studies, involving a total of 181 patients, are individually presented. In addition to a Protocol Information sheet for each study (which provides basic information regarding the study status and objectives), a List of Study Patients is provided, which gives a study census and individual patient completion/termination status.

For all patients who have been terminated from these studies for an adverse experience or intercurrent medical event (AE/IME), narrative summaries are provided and, when available, complete Case Report Forms are also provided. (These immediately follow the study summary sheets, described above). Of the 181 patients, six have been terminated because of an AE/IME. A seventh patient was hospitalized for a serious AE/IME (pneumonia), but continued in the study and a narrative summary is also provided on this patient.

Part B (*presented in Volume 2*) provides information similar to the above on the **Treatment IND**. To date, 135 patients have been enrolled in this study and there have been five terminations. In addition to the Protocol Information sheet and List of Study Patients (terminated patients only), narrative summaries and Case Report Forms (unedited FAX copies) are provided, arranged numerically by patient Identification Number.

Item 3. Long-Term Safety Update, Study No. 89-1C-6023 (Volume 2)

This item provides a synopsis of previously unsubmitted safety-related information (further analysis of adverse events and safety-related laboratory parameters) from U.S. Study No. 89-1C-6023, a long-term open-label extension study of the previous Phase III double-blind pivotal U.S. studies. In addition to the synopsis, a tabular listing of patients who had "serious" AE/IMEs during the study is

provided (**Table 20.1**). (*It should be noted that long-term treatment with either metformin alone or metformin plus glyburide did not result in any unusual safety findings or issues, and data are consistent with results of the previous double-blind studies*).

Item 4. Literature Safety Update (Volume 2)

Worldwide English-language publications, relevant to metformin, and received/identified by Lipha since July, 1993 through October, 1994 were reviewed for safety-related information. Fifteen articles (13 clinical publications and two pre-clinical publications) were considered to be of interest.

Following an **Overview** of these 15 articles, **Part A** of this Item provides a listing (numerical, by Lipha BCA number) of the 13 clinical publications, followed by each article (or abstract), in full. **Part B** provides a listing (again, numerical, by Lipha BCA number) of the pre-clinical publications and these publications then follow, in full. (*It should be noted that these 15 articles--from 11 different countries--did not contain any new or unexpected safety information).*

In conclusion, the current amendment and the data therein--including worldwide pharmacovigilance information--do not raise any new or unexpected safety issues and are consistent with previous reporting, both in terms of nature and incidence of adverse events.

One ARCHIVAL and two CLINICAL copies of this letter and the amendment (in two volumes) are provided.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel /gl

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 2 Clinical Copies)
GLD/AMG

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 4820 • NEW YORK NEW YORK 10019-2701
TEL 212 223 0981 • FAX 212 223 1490

VIA FAX & FEDERAL EXPRESS
ACKNOWLEDGMENT OF DELIVERY REQUESTED

November 20, 1994

Food and Drug Administration
Center for Drug Evaluation and Research, HFD-510
Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Environmental Assessment

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), and, in particular, to the revised Metformin Environmental Assessment submitted to the FDA on November 8, 1994.

Please be advised that you are hereby authorized to remove the metformin MSDS form from the confidential section of the appendices and place it into the non-confidential section of the Metformion Environmental Assessment. If there are any questions, please do not hesitate to contact this office.

Sincerely,
LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/BG
In triplicate

LIPHA
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VIA FEDERAL EXPRESS
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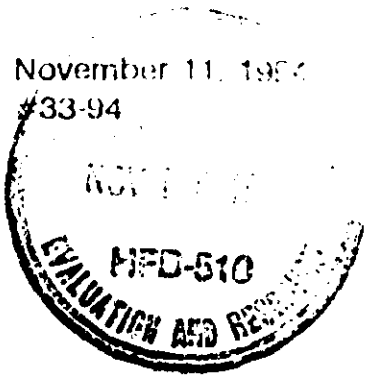
November 11, 1994
#33-94



Food and Drug Administration
Center for Drug Evaluation and Research, HFD-510
Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Amendment #33/Blister Packs

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) and, in particular, to your FAX sent to us on September 8, 1994, citing deficiencies in the metformin blister pack information submitted June 22, 1994 as Amendment #26.

In accordance with your request we are hereby submitting in triplicate, as Amendment #33, additional metformin blister pack information as follows:

ITEM 1: A diagram of the blister package.

ITEM 2: A diagram of the aluminum foil.

ITEM 3: A copy of the blister pack draft labeling for the foil backing and the outer carton

ITEM 4: Specifications for the foil and film.

NOTE: Item 4 was previously submitted as part of Amendment #26
It is repeated here for convenient reference.

Should you have any questions regarding this submission please don't hesitate to call me (212) 223-1280.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel

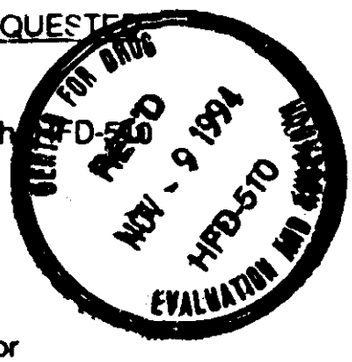
Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

Attachments: as above
1 Archival copy, 2 Chemistry copies

LIPHA PHARMACEUTICALS
[illegible] EAST 57TH STREET • SUITE 3805 • NEW YORK, NEW YORK 10019-2701
TEL: [illegible] 223-1300 • FAX: 212-223-1398

VIA CERTIFIED MAIL
ACKNOWLEDGMENT OF DELIVERY REQUESTED

November 8, 1994
#32-94



Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Room #14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Amendment #32
Metformin Environmental Assessment

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) and, in particular, to your FAX sent to us on November 1, 1994, citing deficiencies in the Metformin Environmental Assessment (EA) submitted August 19, 1994 as Amendment #27.

In accordance with the six recommendations made, and subsequent discussions with Mr. Glen Smith, we are hereby submitting in triplicate, as Amendment #32, a revision of the Metformin Environmental Assessment.

In response to part A of **recommendation #1**, we have provided letters from Rollins Environmental Services detailing the information requested (see Appendix 1). Part B requested inclusion of a brief description of the disposal methods in the EA with particular attention to PVC's. This information has been added to pages 10 to 11 of the EA.

Regarding **recommendations #2 and #4**, after further explanation from Mr. Smith, we have moved the foreign environmental compliance statements and the *Curricula Vitae* into non-confidential appendices 2 to 6. Item 6.C., pages 21 - 24, has been revised to reflect these changes. All confidential appendices (7 - 16) are now placed at the rear of the document for easy removal, and all appendices have been renumbered.

As requested in **recommendation #3**, we have revised Item 11 to include a brief discussuion of the alternative of no action (see page 42).

As per **recommedation #5**, Item 14 now consists of the list of published references. These include publications cited in support of Items 7, 8 and 15.

RE: **NDA #20-357 - AMENDMENT #32, METFORMIN ENVIRONMENTAL ASSESSMENT**

Item 15 is now the location of all appendices. Item 15a contains summary tables of testing results presented in detail in Item 7 (see page 48, Table 1) and Item 8 (see page 49, Table 2). (See **recommendation #6**).

Should you have any questions regarding this submission please don't hesitate to call me at (212) 223-1392.

Sincerely,
LIPHA PHARMACEUTICALS, INC.

Gerald L. Daniel/gg

Gerard L. Daniel, M.D.
Chairman and President

Enclosure
1 Archival Copy, 2 Chemistry copies

LIPHA PHARMACEUTICALS
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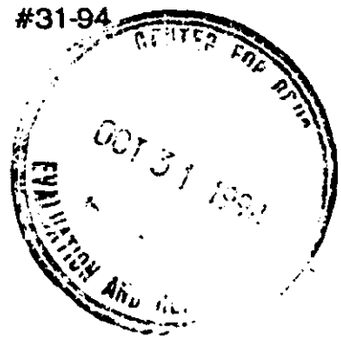
ACKNOWLEDGMENT OF DELIVERY REQUESTED

October 28, 1994
#31-94



Food and Drug Administration
Center for Drugs and Biologics, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Amendment #31
Metformin Environmental Assessment -
Additional Documentation

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) submitted to FDA on September 29, 1993.

As agreed to in a telephone conversation with Ms. Christina Good on today's date, we are providing, as additional documentation to the Environmental Assessment, the following:

ITEM 1. Certificate of compliance with local environmental standards signed by the Mayor of Calais, dated October 3, 1994 (translation with certification of accuracy also provided). This pertains to the metformin substance manufacturing site located in Calais, France.

ITEM 2. Letter from Her Majesty's Inspectorate of Pollution dated October 14, 1994. The letter provides inspection results including a statement of acceptability for the product manufacturing site lacated in Hitchin, Hertfordshire, UK.

We trust that this amendment completes the metformin Environmental Assessment file. Should you have any questions, please don't hesitate to call me at (212) 223-1392.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman and President

Enclosure
1 Archival copy, 2 Chemistry copies

LIPHA
PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

Oct. 19, 1994
#30-94

VIA FEDERAL EXPRESS, #2494063762
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fisher's Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #30
Proposed Package Insert, Oct. 18, 1994

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

The current amendment is a revision of the Proposed Package Insert (dated Oct. 18, 1994) for Glucophage® (metformin hydrochloride), based on comments and inputs from the Division of Metabolism and Endocrine Drug Products as well as the Biopharmaceutics Division on the Proposed Package Insert of Aug. 30, 1994 (submitted on Aug. 30, 1994 as Amendment #28 to NDA #20-357).

In addition to the Proposed Package Insert, two additional documents and two appendices are included as attachments to the amendment, to both facilitate your review and provide the rationale for or commentary on certain changes.

Attachment 1 consists of the Aug. 30, 1994 Proposed Package Insert with handwritten comments from the Division, as well as several pages of commentary from the Biopharmaceutics Division. These served as the basis for the majority of the changes in the current revision of the Proposed Package Insert.

Attachment 2 is a side-by-side presentation, consisting of three columns:

1) in **Column 1**, the Aug. 30, 1994 Proposed Package Insert *(without the Division's handwritten edits)*;

2) in **Column 2**, the proposed changes to the Aug. 30 document are provided *(all changes have been incorporated into the Oct. 18, 1994 Proposed Package Insert)*.

3) in **Column 3**, the Comments/Rationale for each proposed change and acknowledgment of whether the change was suggested by the Division of Metabolism and Endocrine Drug Products (referred to as "FDA"), by the Biopharmaceutics Division (referred to as "Biopharm") or is being suggested by Lipha/BMS.

Appendix 1 to Attachment 2 provides a complete table of mean metformin pharmacokinetic parameters following single or multiple oral doses of Glucophage and is the basis for Table 4 in the revised Proposed Package Insert.

Appendix 2 to Attachment 2 provides a list of literature references to the use of metformin with various sulfonylureas, as was requested by the Division.

In **Attachment 2**, the following conventions were used to indicate the nature of the changes in Columns 1 and 2:

1) Strikeouts (~~strikeouts~~) for word or text deletions in Column 1.

   The rationale for such strikeouts is provided in Column 3;

2) Italics (*italics*) for word or text additions (including tables).

   The placement of such new words or text is indicated by arrows going from Column 2 to the appropriate location in Column 1 and the rationale for the new word/text is provided in Column 3;

3) Shading (shading) for text which has been retained but which has been moved.

   Text is shaded in Column 1, in its original location, with an arrow indicating that it is being moved out (Column 2 indicates **to** where it is being moved within the side-by-side document); the same text is shaded in Column 2 next to its new location (and with an indication **from** where it came in the side-by-side document), with an arrow going from Column 2 to the appropriate new location in Column 1. The rationale for the text move is provided in Column 3;

We trust that the enclosed document adequately responds to the critique of the Aug. 30 Proposed Package Insert by both the Division and Biopharmaceutics.

One ARCHIVAL and one CLINICAL copy of this letter and the amendment, with attachments and appendices, are provided. Three additional complete DESK copies are also enclosed, for your convenience, to be directed to Capt. John Short. The documents are also available on diskette, using Word Perfect 5.1, and we would be happy to send such a diskette to you, if that would be helpful.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel /gp

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 1 Clinical Copy;
3 Desk Copies for Capt. John Short)

GLD/AMG

LIPHA PHARMACEUTICALS
Lipha
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019
TEL 212 223 1280 • FAX 212 223 1398

Aug. 31, 1994
#29-94

ORIGINAL

VIA FEDERAL EXPRESS, #2229359521
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #29
Part A. Draft Proposal for a Phase IV Safety Study;
Part B. Overview of Proposed Education Program

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In response to your letter to us, dated June 29, 1994, the current amendment consists of two parts, as follows: (**Part A**) a DRAFT proposal for a Phase IV Safety Study for Glucophage® (metformin hydrochloride) and (**Part B**) an overview of a proposed education program for Glucophage, to be initiated post-approval.

In developing the DRAFT proposal for a Phase IV Safety Study, we have given serious thought to the issues raised in your letter and believe that the proposal for a prospective, randomized, controlled (metformin vs. "usual care") simplified clinical trial involving 10,000 patients with NIDDM is the most appropriate approach to resolving the potential public health issues. As noted herein, the proposed trial will particularly focus on detection, confirmation, and evaluation of the incidence of lactic acidosis. The key outcome will be hospitalizations and deaths due to lactic acidosis, although all cause mortality and hospitalization rates will also be examined.

Each of the five study design issues that were raised in your letter of June 29, 1994 (representativeness, confounding, power, validation and timeliness) have been carefully considered and are addressed in the proposal (*see **Part A**, Pages 13-18, III. Discussion of Draft Proposal*).

As suggested in your letter, this proposal is being submitted for your initial review and response, prior to developing an actual detailed protocol. We would like to accept the Division's offer to meet with us, along with our colleagues from Bristol-Myers Squibb, to discuss this design further, prior to the official submission of a final protocol.

In addition to the Phase IV Safety Study proposal, this amendment provides an overview of the type of medical education program envisioned by Bristol-Myers Squibb (BMS), relative to Glucophage (**Part B**). As indicated, this multi-faceted program, directed toward physicians, pharmacists, diabetes educators and other health professionals, will include an emphasis on lactic acidosis, primarily from the perspective of preventing its occurrence through education about the appropriate use of Glucophage. This program and the nature of the communications will be developed, in part, through collaboration with various professional organizations, such as the American Diabetes Association and the American Association of Diabetes Educators.

We look forward to your response on both parts of this amendment. I will follow up with Capt. John Short to determine a mutually convenient time for the meeting to discuss this Phase IV program.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 2 Clinical Copies)

GLD/AMG

LIPHA PHARMACEUTICALS
[illegible] SUITE 3825 • NEW YORK, NEW [illegible]
[illegible] • FAX 212 [illegible]

Aug. 30, 1994
#28-94

VIA FEDERAL EXPRESS, #2229359495
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #28
Proposed Package Insert, Aug. 30, 1994

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

The current amendment is the formally submitted Proposed Package Insert (dated Aug. 30, 1994) for Glucophage® (metformin hydrochloride), based on comments and inputs from the Division on an earlier DRAFT proposal for a Package Insert received with a cover FAX dated May 24, 1994 (hereafter referred to as the "May 24 Package Insert"). This Package Insert also supersedes a DRAFT Package Insert faxed to the Division on July 11, 1994, which lacks annotation.

In addition to the Proposed Package Insert, two additional documents are included as attachments to the amendment, to both facilitate your review and provide the rationale for or commentary on certain changes.

Attachment 1 consists of the May 24 Package Insert with handwritten comments from the Division. These served as the basis for the majority of the changes in the current Proposed Package Insert (Aug. 30, 1994).

Attachment 2 is a side-by-side presentation, consisting of three columns:

1) in **Column 1**, the May 24 Package Insert *(without the Division's handwritten edits)*,

2) in **Column 2**, the proposed changes to the May 24 document, based [illegible]ly on the Division's comments, but also on the mutual review and discussion of this document by Lipha and our licensing partner, Bristol-Myers Squibb (BMS); *(all changes have been incorporated into the Aug. 30, 1994 Proposed Package Insert).*

3) in **Column 3**, the Comments/Rationale for each proposed change and acknowledgment of whether the change was suggested by the FDA or is being suggested by Lipha/BMS.

In **Attachment 2**, the following conventions were used to indicate the nature of the changes in Columns 1 and 2:

1) Strikeouts (~~strikeouts~~) for word or text deletions in Column 1.

The rationale for such strikeouts is provided in Column 3;

2) Italics (*italics*) for word or text additions (including tables).

The placement of such new words or text is indicated by arrows going from Column 2 to the appropriate location in Column 1 and the rationale for the new word/text is provided in Column 3;

3) Shading (shading) for text which has been retained but which has been moved.

Text is shaded in Column 1, in its original location, with an arrow indicating that it is being moved out (Column 2 indicates **to** where it is being moved within the side-by-side document); the same text is shaded in Column 2 next to its new location (and with an indication **from** where it came in the side-by-side document), with an arrow going from Column 2 to the appropriate new location in Column 1. The rationale for the text move is provided in Column 3;

4) Bolding (**bolding**) is used in Column 2, when appropriate, with the rationale for the bolding being provided in Column 3.

As you will note in the WARNINGS section, we have incorporated the Division's request for a boxed and bolded warning on lactic acidosis. However, we request that the necessity for this be reevaluated for the Glucophage Package Insert, since adverse events of a similarly serious nature have not been boxed or bolded in either oral sulfonylurea or parenteral insulin labelling. Specifically, severe and even fatal hypoglycemia can occur with both of these classes of compounds and neither have requirements for related bolded or boxed warnings.

In addition, as recommended by the Division, we have included a bolded Special Warning on Increased Risk of Cardiovascular Mortality, comparable to that in current sulfonylurea labeling but based on phenformin data from the University Group Diabetes Program. As noted in the side-by-side document, we consider the applicability of this warning to Glucophage to be questionable. As described in detail in the NDA, there are considerable differences between Glucophage and phenformin, which, we believe, translate into perceptible clinical safety differences. Furthermore, the ongoing United Kingdom Prospective Diabetes Study (UKPDS), which involves 341 NIDDM

patients on Glucophage monotherapy and 227 NIDDM patients on combined Glucophage + sulfonylurea therapy (as well 4,534 patients on other pharmacologic therapy for diabetes, or on dietary management alone), currently has a median follow-up of 7 years, without any Safety Committee intervention due to disparate incidence of adverse events in any treatment arm, including Glucophage.

We trust that the current Proposed Package Insert meets with your expectations on a timely basis. However, as mentioned herein, we would appreciate an opportunity for further dialogue on some of the issues and we, along with Bristol-Myers Squibb, would be pleased to meet with you and other members of the Division toward this end.

One ARCHIVAL and one CLINICAL copy of this letter and the amendment, with attachments, are provided. Three additional complete DESK copies are also enclosed, for your convenience, to be directed to Capt. John Short. The documents are also available on diskette, using Word Perfect 5.1, and we would be happy to send such a diskette to you, if that would be helpful.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

(1 Archival Copy, 1 Clinical Copy;
3 Desk Copies for Capt. John Short)

GLD/AMG

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9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212 223 1280 • FAX 212 223 1398

VIA FEDERAL EXPRESS
ACKNOWLEDGMENT OF DELIVERY REQUESTED

August 19, 1994

Food and Drug Administration
Center for Drugs and Biologics, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Amendment #27
Metformin Environmental Assessment

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) submitted to FDA on September 29, 1993.

In accordance with recommendations made by the FDA Environmental Assessment Staff at a meeting held on May 26, 1994 and subsequent follow up discussions, we have completed a program of both fate and effects testing for Metformin HCl. We are pleased to note that the findings demonstrate a major pathway of degradation and a very low toxicity profile. The data contained herein indicate that the manufacture and use of Metformin HCl will have no significant effects on the environment.

Submitted in triplicate, as Amendment #27, is the fully revised Metformin Environmental Assessment (Item 3.5). In addition, we are sending a desk copy under separate cover for the reviewer. Please consider the appendices to this document as confidential and not for release through the Freedom of Information Act.

Should you have any questions, please don't hesitate to call me at (212) 223-1392.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman and President

Enclosure
1 Archival copy, 2 Chemistry copies

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ACKNOWLEDGMENT OF DELIVERY REQUESTED

June 22, 1994

ORIGINAL

Food and Drug Administration
Center for Drugs and Biologics, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 - Metformin HCl Oral/Amendment #26
Blister Packs

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) submitted to FDA on September 29, 1993.

GLUCOPHAGE® Tablets, 500 mg and 850 mg, have been previously filed to be marketed in containers known as "SNAP SECURE" (supplier: McKenzie PBC Ltd.), "Securitainers" or "TraCer PACKS" (child-resistant; supplier: Jaycare Ltd.), comprising a polypropylene body and polyethylene cap.

We now wish to amend our pending application to include a blister pack presentation for both the 500 mg and 850 mg potencies. Included in this submission are the following items:

Item 1: Stability data for both potencies packaged in blisters

Item 2: Specifications for the foil and film used in the blister packs

Item 3: Names and addresses of the suppliers

Item 4: Quality Assurance Procedure 2026/02 (for identify of lacquer on foil)

Item 5: DMF authorization letters

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 - Metformin HCl Oral/Amendment #26
Blister Packs

The packaging site listed in the NDA for polypropylene container packaging will also be used for the blister packaging.

Please do not hesitate to contact us should there be any questions regarding this amendment.

Sincerely,

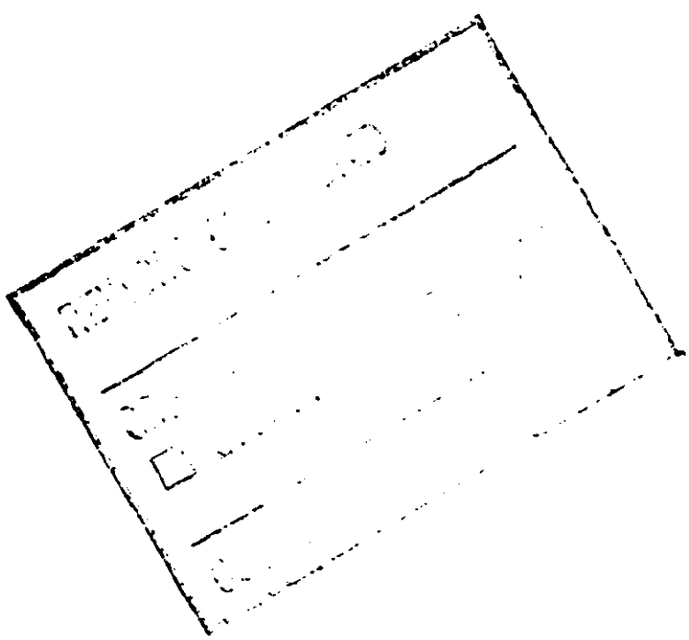
LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman and President

GLD/ski

Attachments: as above

1 Archival copy; 2 Chemistry copies



LIPHA PHARMACEUTICALS
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TEL 212 223 1280 • FAX 212 223 1198

June 15, 1994
#25-94

VIA FEDERAL EXPRESS #2064180742
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Food and Drug Administration
CDER, HFD-510
Attn: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism & Endocrine Drug Products

Reference: NDA #20-357 - Metformin HCl Oral/Amendment #25 5/23/94 Faxed Response to Telephoned Questions from Mr. John Hunt to Lipha *re* Dissolution Testing

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) and, in particular, to questions relative to dissolution testing of metformin hydrochloride tablets posed by Mr. John Hunt during a telephone call on May 20, 1994 in connection with his review of the biopharmaceutics section of the NDA.

A written response was sent to him by fax dated May 23, 1994, a copy of which was also faxed to you on that date. He subsequently requested that our response be submitted as a formal amendment to the NDA. This response is now being submitted herewith as Amendment #25.

Part of the information he requested was previously provided in our Amendment #23, submitted May 13, 1994, in response to your letter dated March 24, 1994 with recommendations and requests resulting after completion of the review of the Chemistry Section of the NDA, which Mr. Hunt had not seen. His questions, in italics, and our responses are as follows:

1. *Can you clarify the methods used for in-vitro dissolution testing, explaining both methods and specifications?*

Methods: The method used for dissolution testing in pH 6.8 buffer solution is that of the British Pharmacopoeia 1988, Vol. II, pp. A143-A144, Appendix XIID, Method 2, Rotating basket, in pH 6.8 buffer solution at 37 ± 0.5°C, at a rotation speed of 100 ± 5 rpm. The assay of metformin hydrochloride was carried out spectrophotometrically at 232 nm. This method is identical to that of USP XXII, 711, pp. 1578-1579, Apparatus 1, Rotating basket, except that 5 tablets (rather than 6) are used in each test. The method was validated by the Apparatus Suitability Test using *USP Dissolution Calibrator, Disintegrating Type* and *USP Dissolution Calibrator, Nondisintegrating Type*.

RE: NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #25

The method used to obtain the dissolution profile in 0.1 N HCl was that of USP XIX, Rotating basket, in 0.1 N HCl at 37 ± 0.5°C at a rotation speed of 100 ± 5 rpm. Spectrophotometric assay of metformin HCl was carried out at 232 nm.

Dissolution Specification: The dissolution specification of "not less than 70% released in 45 minutes (single point determination)", contained in the monograph for Metformin Tablets in the British Pharmacopoeia, was imposed unilaterally by the British Pharmacopoeia Commission. This dissolution specification replaced the disintegration test previously required. The BP Commission did not agree with the argument that, for a highly soluble compound such as metformin hydrochloride, the dissolution test proposed had little scientific relevance for a standard, *i.e.*, non-delayed release, formulation which previously had to comply with the disintegration test (Limit: disintegration within 15 minutes under the specified test conditions). The limit as stated was reaffirmed by the BP Commission and it was adopted by Lipha UK.

In response to your 3/24/94 letter, Item 3 under Drug Product, recommending that "a dissolution specification that mimics the dissolution behavior should be provided", we proposed, as part of Amendment #23, an alternative single point dissolution specification as "not less than 90% released in 30 minutes."

2. *Do you have a pH-dependent drug solubility profile?*

Solubility data obtained on metformin HCl drug substance in a number of solvents showed that it is freely soluble in water and acid pH solutions. It is unstable in 0.1 N NaOH. Exposure to strong alkali is contraindicated in the monograph.

3. *Do you have dissolution testing profiles on the two tablet strengths for the following media?*
   simulated gastric fluid
   simulated intestinal fluid
   water

Dissolution profiles have been conducted on metformin hydrochloride 500-mg and 850-mg tablets in pH 6.8 phosphate buffer solution, the test medium specified in the BP Metformin Tablets monograph for routine dissolution testing, and on 500-mg tablets in 0.1 N hydrochloric acid (HCl) for comparison. The results are presented in the tables in **Appendix 1**. (These tables were also submitted as Appendix 8 of Amendment #23, dated May 13, 1994. It was subsequently found that the bibliographic reference to the BP Dissolution Testing method contained in Amendment #23 is erroneous. It is corrected herein.) The dissolution media were prepared as follows:

(a) pH 6.8 phosphate buffer: Weigh 408 g of potassium dihydrogen phosphate (KH_2PO_4) and 52 g of sodium hydroxide (NaOH) pellets into a 5-L plastic beaker. Add 4 L of ice-cold water. Cover and stir with a magnetic stirrer or ultrasonicate until completely

RE: NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #25

dissolved. Transfer to a suitable plastic container, dilute to 60 L with ice-cold water and stir with a plastic rod. Check the pH and, if necessary, adjust to pH 6.8 with 1 N NaOH or phosphoric acid solution.

(b) 0.1 N HCl: Use reagent-grade 0.1 N HCl solution.

Although no dissolution studies of metformin HCl tablets were conducted in simulated gastric fluid *per se*, one would expect the dissolution profile to be similar to that in 0.1 N HCl, since the pH is similar for each, *i.e.*, 1.1 for 0.1 N HCl and 1.2 for USP simulated gastric fluid. Similarly, because metformin HCl is freely soluble in water, one would expect the dissolution profile in water to be similar to that in pH 6.8 phosphate buffer. Furthermore, disintegration testing, formerly required until it was replaced by order of the British Pharmacopoeia Commission with dissolution testing, was carried out in water with a specification of complete disintegration within 15 minutes, with which metformin hydrochloride tablets complied. No studies have been done using simulated intestinal fluid (pH 7.5).

Should there be any further questions regarding this submission, please contact us.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Bariel, M.D.
Chairman, President &
Chief Executive Officer

GLD/BHW

Enc.

1 Archival Copy, 2 Human Pharmacokinetics/Bioavailability Copies

ORIGINAL

NDA ORIG AMENDMENT

LIPHA

May 27, 1994

MAY 31 1994

VIA FAX 301-443-9282

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B03
5600 Fishers Lane
Rockville, MD 20857-1706

Attention: Captain John Short, C.S.O.
Division of Metabolism and Endocrine Drug Products

Reference: **NDA #20-357 Metformin HCl Oral**
Draft Proposal of a Phase IV
Dose-Ranging Protocol

Dear Capt. Short:

Pursuant to Dr. Gueriguian's Fax request dated May 17, 1994, enclosed is a DRAFT Phase IV dose-ranging study for your consideration.

It should be looked upon as a preliminary, unedited draft and lacking certain data, such as a study-schema, but will provide a good insight as to what is being contemplated as a dose-ranging study. For your evaluation and further discussion.

I look forward to an early reply.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/eg

Letter and Attachments in Triplicate

cc: John Gueriguian, M.D. Via Fax

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
DATE
CSO INITIALS

Mailed
5/24/94

LIPHA
PHARMACEUTICALS

5/25/94

VIA FEDERAL EXPRESS
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

May 20, 1994

Food and Drug Administration
Center for Drugs and Biologics, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Captain John Short, CSO
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357, Metformin HCl Oral
ENVIRONMENTAL ASSESSMENT

Dear Capt. Short:

As per our telephone conversation on Monday, May 16, 1994, enclosed please find three copies of the newly revised Environmental Assessment for metformin. I have also sent two copies to Mr. Glen J. Smith under separate cover.

We appreciate your offer to meet with us next week and we confirm our appointment at 2:00 pm on Thursday, May 26, 1994. Attached as Item 1 please find a list of our attendees. Item 2 is a proposed agenda for the meeting. We would appreciate it very much if you could let us know in advance of the meeting who will be attending from FDA.

Also, we are awaiting copies of the licenses from the Medicines Control Agency in the United Kingdom for the manufacturing plant and the two product strengths of metformin. We will hand carry these copies for the meeting.

Should you need anything further, please don't hesitate to call me at (212) 223-1399.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Bruce Goddard
Senior Director of Compliance &
Regulatory Affairs

cc: Solomon Sobel, M.D. FDA - cover letter
Glen J. Smith, EA Reviewer - 2 copies
Gerard L. Daniel, M.D.
Anita M. Goodman, M.D.

6/23/94

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL. 212-223 1280 • FAX 212-223 1398

May 19, 1994
#24-94

VIA FEDERAL EXPRESS, #2032536726
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Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #24
Update on Safety Information (Adverse Events Reported to/by Lipha S.A. during 1993)

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

The current amendment provides additional safety information on metformin, and consists of all adverse events reported to our parent company, Lipha S.A. during 1993, which involved patients taking Glucophage® brand of metformin hydrochloride[1].

Incorporated in the amendment are all adverse events occurring in France with Glucophage, which were reported to Lipha S.A. and which, in turn, were reported by Lipha S.A. to the French National Commision of Pharmacovigilance, as required by French law (Art. R. 5144-9 du code de la santé publique). For the non-U.S. subsidiaries of Lipha S.A. and Lipha's principal licensees of Glucophage, this consists of all events reported by them to Lipha S.A.

Item 1, Part A consists of a tabular summary, arranged by body system, of all adverse events (AEs) occurring in France, which summarizes the causality (imputability) assessment attributed to Glucophage.

Item 1, Part B provides further detail regarding these cases and includes the following information: the AE case number, the patient's sex and age, the number of the French departmental code (geographic region) from which the report originated, the month and year of occurrence of the AE, the nature of the AE, the outcome, and, finally, the causality assessment

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[1] - The exception to this is Australia, where the brand name of metformin hydrochloride is Diabex.

for both Glucophage and concomitantly administered medications. (***NOTE:*** *The information is almost exclusively related to administration of the 850 mg dosage strength of Glucophage, the most widely used dosage strength of Glucophage in France, with only one case having been reported with the 500 mg dosage strength of Glucophage. This case is also included in this table*).

Item 1, Part C consists of narrative summaries of the majority of cases listed in the Part B table, arranged in order of the AE case number and according to their order of presentation in the table.

Item 1, Part D consists of a general discussion of the reported cases, particularly with reference to the cases of lactic acidosis and the concomitant ailments and attendant circumstances of these cases. In addition, an analysis of the incidence of lactic acidosis in France during this reporting period (1993) is provided. As noted in this section, the calculated incidence of lactic acidosis in France (the country with the greatest usage of Glucophage), based on considerations of total tablet sales in 1993 and usual daily dose, continues to be very stable, at approximately 0.03 cases of lactic acidosis per 1,000 patient years.

Item 2 consists of reports received by Lipha S.A. of adverse events occurring in patients taking either dosage strength of Glucophage, from Lipha's subsidiaries and key licensees, arranged according to country, as follows:

- Germany
- Sweden
- Switzerland
- Belgium
- England
- Australia
- Canada

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided. If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel /gg

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

BC

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

May 13, 1994
#23-94

ORIG AMENDMENT

VIA FEDERAL EXPRESS #1710339083
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

ORIGINAL

Food and Drug Administration
CDER, HFD-510
Attn: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism & Endocrine Drug Products

Reference: NDA #20-357 - Metformin HCl Oral/Amendment #23
Response to 3/24/94 Letter re Chemistry Section

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) and, in particular, to your letter dated March 24, 1994 with recommendations and requests resulting after completion of the review of the Chemistry Section of the NDA.

Your comments (printed in italics) are addressed as posed in your letter, as follows:

Drug Substance:

1) *Please provide the limits for the total amount of impurities. This limit should be incorporated as part of the drug substance specifications. Please provide the actual values of the total amount of impurities for representative drug substance batches.*

The current limits for impurities are those specified in the published monographs for metformin hydrochloride of the British Pharmacopoeia (BP), the French Pharmacopeia (FP) and the European Pharmacopeia (EP). Using the HPLC method described (for which the operating conditions vary slightly among the monographs), all three monographs specify, for "Related substances," to include the major impurity, cyanoguanidine, that the test chromatogram must show that the area of any peak corresponding to cyanoguanidine (dicyandiamide) is not greater than the area of the peak obtained with a 0.02% aqueous solution of cyanoguanidine reference standard (relative to the aqueous metformin hydrochloride solution). Similarly, the peak area of any secondary impurity (or "other related substance") is not greater than that of a 0.1% secondary impurity reference standard solution (relative to the metformin hydrochloride solution).

RE: **NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #23**

Copies of each of these monographs (with English translations of the FP and EP) are provided in **Appendix 1.** (A copy of the BP monograph was submitted in the NDA, Vol. 1.3, p. 03 000439.)

A comparison of these monographs shows that the specifications for metformin hydrochloride are the same in all three.

Quantitative determination of each impurity at release for finished lots of metformin hydrochloride drug substance is, in fact, carried out. The values of impurities obtained for six recent lots, as percentages of the metformin peak area, are shown in the table in **Appendix 2.** (The section of the table related to impurities is highlighted for quick reference.)

We will revise the specification to incorporate a total limit value. We propose the specification for the total amount of impurities to be ≤ 0.5%, of which the amount of cyanoguanidine must be ≤ 0.02% and that of other impurities, none more than 0.1%, relative to the metformin hydrochloride content. Such a revision provides a realistic value which is also consistent with the existing international monographs.

2) ***Total amount of impurities should be monitored in the stability studies and they should be within the limit specified. Please provide the actual values determined from the ongoing stability studies.***

Appendix 3 provides tables listing the quantitative results obtained at each test interval for the six lots of metformin hydrochloride drug substance currently in long-term ambient stability testing (Lot Nos. 3184, 3487, 3787, 4106, 4450 and 4866, at one lot per year placed on test). These data, except those for the last lot, #4866, manufactured in 1993, were submitted in the NDA, Vol. 1.2, pp. 03 000087 - 03 000092, but have been revised to provide all of the impurity values in percentages of metformin HCl content for ease of comparison, rather than showing some values as percentages and others as parts per million (ppm) as are given in the NDA tables. The lots were tested in accordance with a protocol complying with the FDA's February 1987 guideline for stability testing of drug substances, except that samples are kept on stability for 7 years instead of 5 years (Lipha internal requirement). Values at release (0 time) are included for each lot, and the section of each table listing impurities is highlighted for your convenience.

It is clear that metformin hydrochloride is a stable compound and that the values for impurities remain low throughout the stability testing period. Also, values for individual impurities remain remarkably constant, within experimental error, for individual lots.

The values obtained comply with release specifications as listed in the official monographs. They also meet the proposed revised specification for total amount of impurities of ≤ 0.5%.

RE: **NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #23**

Drug Product:

1) *Please provide a specification for the total amount of impurities as part of the dosage form specifications. Also, provide the corresponding values for the total amount of impurities for lots 109448 and 110179.*

A copy of the official monograph for metformin tablets from the 1988 Edition of the British Pharmacopoeia and its 1990 Addendum is provided as **Appendix 4.** (These monographs were submitted in the NDA, Vol. 1.3, p. 03 000582.)

The HPLC analytical method specified in the 1992 Addendum for the drug substance (see Appendix 1), as stipulated in the BP metformin tablets monograph, is that required by the UK regulatory authorities and is used for control of all lots of tablets manufactured by Lipha UK. This method is not feasible for routine use to quantify small amounts of secondary impurities more accurately than in the 0.1% range. This is especially difficult in view of the small amount of total impurities generally contained in the raw material drug substance as received from Lipha Calais. (See Appendix 2.)

The lot numbers referred to in your March 24, 1994 letter, under Drug Product item 1 are actually Lot Nos. CMC (500-mg tablets) and ACE (850-mg tablets), respectively. The numbers 109448 and 110179 are the respective control numbers of these lots, not the lot numbers. The values obtained for dicyandiamide (cyanoguanidine) are listed on the certificates of analysis for these lots (submitted in the NDA, Vol. 1.3, pp. 03 000569 and 03 000581, respectively), copies of which are provided in **Appendix 5.**

Samples of these lots of drug product are currently being analyzed for impurities using the Lipha Suresnes HPLC method for quantifying impurities in the drug substance and will be submitted as soon as available. However, as stated in the previous paragraph, the levels of secondary impurities may be so small as to be near or below the sensitivity limits (0.0005% to 0.0020%, which vary depending on the HPLC instrumentation used and on the individual impurity).

The chromatograms obtained from accelerated testing of the three lots of 500-mg and three lots of 850-mg Glucophage Tablets in US packaging which were submitted in the NDA (Vol. 1.4, pp. 03 000675 - 03 000728) have been re-examined. Because the Lipha Suresnes HPLC method has not been validated for the UK HPLC equipment, the peak areas of the secondary impurities were calculated by computer to obtain "ball park" values for each impurity. Thus, considering the experimental error, the accuracy of the values obtained can only be approximate until the results from the samples being done at Lipha Suresnes are available.

The levels of impurities from the above-mentioned accelerated stability studies of the six lots are provided as **Appendix 6.**

RE: **NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #23**

The results show that only Lot No. 301CWC (500-mg tablets) had detectable amounts of secondary impurities at release (0 time). Dicyandiamide, quantified using a 0.02% reference standard solution, was 0.0048%. The values calculated for related substances (secondary impurities) yielded one impurity eluting at 3.4 min ≈ 0.0050% and one at 3.7 min ≈ 0.0080%, a total amount of impurities of approximately 0.0180%. The peaks for secondary impurities were not detectable at the subsequent 1-, 2- and 3-month test intervals. Neither of the other two lots of 500-mg tablets nor the three lots of 850-mg tablets showed detectable levels of secondary impurities at any test interval in any of the packaging configurations used. Cyanoguanidine ranged from 0.0014% to 0.0058% (500-mg tablets) and 0.0014% to 0.0019% (850-mg tablets).

We propose that the specification for total impurities in the drug product be revised to be the same as for the drug substance, *i.e.*, total amount of impurities ≤ 0.5%, with dicyandiamide, ≤ 0.02% and secondary impurities, none more than 0.1%.

2) *Monitoring the total amount of impurities should be part of the drug product stability study. Please provide data on the total amount of impurities determined from the ongoing stability study.*

The same comments relative to quantification of secondary impurities as discussed above under Drug Product item 1 apply. The level of dicyandiamide is quantified at each test interval, but the level of other impurities is given as "none more than 0.1%", because of the limits of the control HPLC analytical method stipulated in the BP monograph. Data on ongoing stability studies under ambient conditions for three recent lots of each dosage strength (Lot Nos. DFD, DFL and DFM, 500-mg tablets, ADS, ADV and ADW, 850-mg tablets) in packaging intended for US marketing are provided through the 9-month test interval in the tables in **Appendix 7**.

Based on the calculations presented in Appendix 6, we believe that it is safe to conclude that lots of Glucophage in both tablet strengths do comply with a revised specification for total amount of impurities of ≤ 0.5%.

3) *The actual dissolution data (lots 109448 [CMC] and 110179 [ACE], representative of 500 and 850 mg dosage strength, respectively) seem to indicate that the tablets are fully dissolved before 45 minutes. Please provide the actual dissolution profiles for these and other representative lots. A dissolution specification that mimics the dissolution behavior should also be provided.*

Appendix 8 provides, in tabular form, the dissolution profiles, in pH 6.8 buffer medium, for Lot Nos. CMC and ACE (Control Nos. 109448 and 110179) 500-mg and 850-mg tablets, respectively, as requested. Tables are also presented for results obtained earlier on three lots of 500-mg tablets used in clinical studies (Lot Nos. 123, 137 and 148) in the same pH 6.8 buffer medium, and for one lot (number unspecified) of 500-mg tablets, all of which are the current formulation, in 0.1N HCl medium. The data for the results on Lot Nos. 123, 137 and 148 and the unspecified

RE: **NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #23**

lot of 500-mg tablets were extracted from Item 6.7 of the NDA, Vol. 1.41, p. 06 000131, intext Tables 27 and 28, reformatted to conform with the data in the tables for Lot Nos. CMC and ACE.

The dissolution specification of "not less than 70% released in 45 minutes (single point determination)", contained in the monograph for Metformin Tablets in the British Pharmacopoeia, was imposed unilaterally by the British Pharmacopoeia Commission. This dissolution specification replaced the disintegration test previously required. The BP Commission did not agree with the argument that, for a highly soluble compound such as metformin hydrochloride, the dissolution test proposed had little scientific relevance for a standard, *i.e.*, non-delayed release, formulation which previously had to comply with the disintegration test (Limit: disintegration within 15 minutes under the specified test conditions). The limit as stated was reaffirmed by the BP Commission and it was adopted by Lipha.

We propose a revised single point dissolution specification which is more consistent with actual behavior, as "not less than 90% released in 30 minutes," with which Glucophage Tablets comply, as demonstrated in the tables in Appendix 8.

Labeling

Please provide copies of the draft package (carton) labels.

Currently, there are no plans to package the bottles of GLUCOPHAGE® Tablets in cartons. Copies of the draft bottle labels were submitted in Item 4.3.1 of the NDA, Vol 1.5, pp. 04 000015 - 04 000016. They are reproduced in **Appendix 9** herewith.

Summary

In summary, we trust that our responses to the various items are to your satisfaction. The revisions being proposed for certain specifications, i.e., a limit for total amount of impurities for the drug substance and for the drug product of "≤ 0.5%, of which that for cyanoguanidine must be ≤ 0.02% and for secondary impurities, none greater than 0.1%", and a single point dissolution specification for metformin hydrochloride tablets of "not less than 90% released in 30 minutes", may be better suited for U.S. requirements. In any case, it should be noted that past as well as current results are within the limits of the proposed revised specifications as well as those of the previously established specifications in the BP, FP and EP monographs.

It should also be noted that the intent for this drug is to have the finished product manufactured in the U.S. rather than in the U.K. and, thus, specifications will be more consistent with our U.S. requirements.

RE: **NDA #20-357 - METFORMIN HYDROCHLORIDE ORAL/AMENDMENT #23**

Should there be any further questions relative to this response, please contact us.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/BHW/eg

Enc.

1 Archival Copy, 2 Clinical Copies

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX 212-223 1398

May 12, 1994
#22-94

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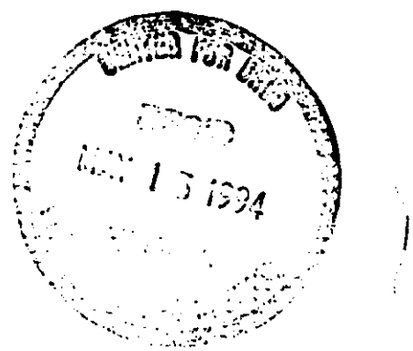


Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #22
Request of Dr. Ronald Innerfield: Re-Analysis of ECG Changes/Cardiovascular Events in Controlled Clinical Trials

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

Pursuant to a request from Dr. Ronald Innerfield, received subsequent to the March 18, 1994 meeting of the Endocrine and Metabolism Drugs Advisory Committee, enclosed is further analysis and information on electrocardiographic (ECG) findings and cardiovascular events occurring during controlled clinical trials of metformin. The submission is organized according to the sequence of requested information listed in an internal memo from Dr. Innerfield to Dr. Alexander Fleming, dated March 22, 1994 (*See attached, following this letter*). A description of what has been done and what is being submitted relative to each point in the memo (*listed in italicized print, below*) is provided in the following paragraphs:

Item 1. ***(Points 1 & 2): All "significantly changed" ECGs from Category I trials (U.S. controlled clinical trials), with available follow-up information.***

As background information, in the double-blind U.S. studies (U.S. Study Nos. 87-1D-6023 and 87-2D-6023), patients had an electrocardiogram performed at Baseline and at their Final Visit. Investigators were at liberty to perform and interpret these ECGs, according to their usual convention. No effort was made to either standardize the ECG interpretations or to have them

read by an "official" person/group. As shown, by way of example, in **Part A of Item 1** (*Page 30 from Study No. 87-1D-6023 case report form*), investigators were asked if the Baseline ECG was "normal", "abnormal, but acceptable for the study", or "abnormal". With regard to the Final Visit ECG, as shown in **Part A** (*Page 98 from Study No. 87-1D-6023 case report form*), investigators were again asked if the ECG was normal or abnormal, but also had to indicate if there had been any significant changes in the ECG since the previous tracing and were asked to specify the nature of such changes, if present. (All ECGs were, of course, also submitted along with this "global" assessment).

The responses to these latter questions were the basis for the creation of Appendix 7 of the individual Final Study Reports: namely, patients were listed whose ECGs had been "normal" at Baseline but "abnormal" at Final Visit--or--"abnormal" at Baseline but not considered to be "abnormal" at Final Visit--or--"abnormal" at both Baseline and Final Visit but with "significant" changes from Baseline. Listing in this Appendix was strictly based on the **investigator** interpretation of the ECGs. These electrocardiograms were then reviewed by an "unblinded" Lipha medical monitor (M.D.) and resulted in creation of the "Comments" field of the respective Appendix 7 listing. (*The original Appendix 7 of Study No. 87-1D-6023 is located in Vol. 1.119, beginning on Page 08B-05345 and the original Appendix 7 of Study No. 87-2D-6023 is located in Vol. 1.156, beginning on Page 08B-18582 of the Metformin NDA #20-357*).

As discussed in the text of the Final Reports of these studies (*Vol. 1.104, Pages 08B-00153 to 08B-00155 for Study No. 87-1D-6023 and Vol. 1.120, Page 08B-05543 for Study No. 87-2D-6023*), upon our **internal** review, many of the "abnormalities" at Final Visit, in fact, were present at Baseline or had shown improvement. In our opinion, no consistent pattern, relative to randomly assigned treatment group, was observed, based on this review.

However, since the issue of a **potentially** greater number of ECG abnormalities in the metformin treatment groups has been raised by Dr. Innerfield, we have taken the following actions: ECGs from all patients listed in the original Appendix 7 of each of the two U.S. studies were submitted to an expert cardiologist and electrocardiographer (*Dr. William Proudfit, Cleveland Clinic Foundation, Cleveland, Ohio: see **Item 1, Part F** for Dr. Proudfit's curriculum vitae and list of publications, exclusive of book reviews and patient education materials*), for his interpretation, "blinded" for treatment group. Additionally, he was provided ECGs from the Final Visit of the subsequent open-label metformin (or metformin + glyburide) study (U.S. Study No. 89-1C-6023), when patients had been enrolled in that study.

This has resulted in a **revised Appendix 7** for each of the two double-blind studies, entitled "Expert Reading of Appendix 7 (ECG Abnormalities) from Double-Blind Study (Study No. 87-1D-6023 or Study No. 87-2D-6023) with Open-Label (Study No. 89-1C-6023) Follow-Up When Applicable".

The revised Appendix 7 for U.S. Study No. 87-1D-6023 is presented as **Part B of Item 1**. The revised Appendix 7 for U.S. Study No. 87-2D-6023 is presented as **Part D of Item 1**.

As can be seen and as described below, based on this expert review, there has been considerable modification in each of these Appendices, relative to the original interpretations (the original Appendix 7 of Study No. 87-1D-6023 is provided as **Part C of Item 1** and the original Appendix 7 of Study No. 87-2D-6023 is provided as **Part E of Item 1**, for ease of review).

With regard to **U.S. Study No. 87-1D-6023** *(metformin vs. placebo), in the metformin-treatment* group, as indicated in the original Appendix 7 of that study, according to **investigator** interpretation, **18** of the 143 metformin-treated patients were thought to have had "normal" ECGs at Baseline and "abnormal" ECGs at Final Visit. Based on Dr. Proudfit's review, this has now been changed to only **four** metformin-treated patients. Whereas, according to **investigator** interpretation, **three** metformin-treated patients were thought to have had initially "abnormal" ECGs which became "normal" or "less abnormal" at Final Visit, this has now been revised to **eight** metformin-treated patients, with this direction of change. No change in categorization occurred for nine metformin-treated patients. Three patients had ECG evidence of remote myocardial infarction at Baseline.

Among the four metformin-treated patients whose ECGs were interpreted as abnormal at their final visit, Patient 04008 had T-wave changes without clinical abnormalities; Patient 11013 had ECG evidence of an old inferior myocardial infarction (and had experienced a clinical infarction at Visit 7 [*see Item 3 for further details*]); Patient 13001 had ECG evidence of a probable early acute myocardial infarction (and had a clinical infarction at Visit 6.1 [*see Item 3 for further details*]); Patient 12010 had increased T-wave changes at Final Visit (and had clinical symptomatology of coronary artery disease and a positive stress and thallium test [*see below for further details*]). An additional patient (Patient 10021) had an initially normal ECG which was questionably abnormal at Final Visit (? old inferior myocardial infarction). This patient had sustained a myocardial infarction post-Visit 4 but completed the study [*see Item 3 for further details*]).

With regard to the placebo group, according to **investigator** interpretation, **10** of the 146 placebo-treated patients were thought to have had initially "normal" ECGs at Baseline and "abnormal" ECGs at Final Visit. Based on Dr. Proudfit's review, this has now been changed to **three** placebo-treated patients (Patients 03011, 04022 and 10009: all with T-wave changes, without any apparent clinical correlations). No placebo patients were originally thought to have had "abnormal" ECGs which became "normal" at Final Visit. This has now been revised to **five** placebo-treated patients, with this direction of change. No patients in the placebo group had Baseline evidence of prior myocardial infarction.

According to Dr. Proudfit, **six** of the metformin-treated patients and **three** of the placebo-treated patient in the original Appendix had ECGs which were **normal** at **both** Baseline and Final Visit.

Thus, classifications were changed, based on the expert review, for **17 of the 26 metformin-treated patients** listed in the original Appendix 7 of Study No. 87-1D-6023 and **11 of the 14 placebo-treated patients** listed in the Appendix.

As indicated in the original Appendix 7 of **U.S. Study No. 87-2D-6023** (metformin monotherapy vs. glyburide monotherapy vs. metformin + glyburide), according to **investigator** interpretation, **18** of the 210 metformin-treated patients were thought to have had "normal" ECGs at Baseline and "abnormal" ECGs at Final Visit. Based on Dr. Proudfit's review, this has now been changed to **three** metformin-treated patients. According to Dr. Proudfit, **15** of the metformin-treated patients in the original Appendix had ECGs which were **normal** at **both** Baseline and Final Visit. There were no metformin-treated patients in this Appendix who had an initially "abnormal" ECG which then became "normal" at Final Visit, based on both the original **investigator** interpretation and the current expert's review.

Among the three metformin-treated patients whose ECGs were interpreted as abnormal at Final Visit, Patient 10013 had ECG changes consistent with a recent inferior myocardial infarction, without any clinical correlation (this patient had been prematurely terminated because of an urticarial reaction secondary to gastritis. He also had post-study coronary arteriography which showed minimal coronary disease [*See Narrative, Vol. 1.80, Page 08A-03008*]); Patient 18019 had Final Visit ECG changes consistent with an inferior infarct of questionable age, but without any clinical correlations and went on to complete the open-label study and had a normal ECG at the Final Visit of that study; Patient 19017 had T-wave changes, without clinical correlations and also completed the open-label study with a normal ECG at Final Visit.

With regard to the glyburide group, according to **investigator** interpretation, **17** of the 209 glyburide-treated patients were thought to have had initially "normal" ECGs at Baseline and "abnormal" ECGs at Final Visit. Based on Dr. Proudfit's review, this has now been changed to **two** glyburide-treated patients. No glyburide patients were originally thought to have had "abnormal" ECGs which became "normal" at Final Visit. This has now been revised to **one** glyburide-treated patient, with this direction of change. **Twelve** glyburide-treated patients, were considered by the expert reviewer to have had normal ECGs at both Baseline and Final Visit.

Of the two glyburide-treated patients whose ECGs had become abnormal, Patient 03019 (hypertensive, on treatment) had changes of hypokalemia and possible incomplete RBBB (see *below for further details*) and Patient 18004 had progression of T-wave changes without any clinical correlations.

With regard to the metformin + glyburide group, according to **investigator** interpretation, **23** of the 213 patients in this group were thought to have had initially "normal" ECGs at Baseline and "abnormal" ECGs at Final Visit. Based on Dr. Proudfit's review, this has now been changed to **four** patients in the metformin + glyburide group. There were no metformin-treated patients in this Appendix who had an initially "abnormal" ECG which then became "normal" at Final Visit, based on both the original **investigator** interpretation and the current expert's review. According to Dr. Proudfit, **13** patients in the original Appendix in the metformin + glyburide group had ECGs which were **normal** at **both** Baseline and Final Visit.

Among the four patients on metformin + glyburide whose ECGs had become abnormal, three patients had increased T-wave changes, without any clinical correlations (Patients 11013, 11015 and 18031). Patient 17001 had ECG changes consistent with an inferior myocardial infarction, without any clinical correlations. This patient went on to participate in the open-label study and had the same ECG changes at the end of that study (without, again, any clinical symptomatology) and was, accordingly, going to be evaluated by a cardiologist.

Thus, classifications were changed, based on the expert review of these ECGs from Study No. 87-2D-6023, for **18 of the 22 metformin-treated patients**, for **16 of the 25 glyburide-treated patients** and for **22 of the 30 metformin + glyburide-treated patients** listed in the original Appendix 7.

To summarize, based on an expert reading of the ECGs, "blinded" for treatment group, from subjects originally listed in Appendix 7 of the reports of the two pivotal U.S. studies, we can conclude that there is no increased incidence of ECG abnormalities in metformin-treated patients and, additionally, there were no consistent treatment-related ECG effects seen in these studies. In U.S. Study No. 87-1D-6023, four of 143 metformin-treated patients compared to three of 146 placebo-treated patients had normal ECGs at Baseline, which later became abnormal. Although two of the four metformin-treated patients in this study had clinical and ECG evidence of myocardial infarction, both also had the recognized risk factors of male sex, obesity, diabetes, known hypertension and smoking (one of the two). In U.S. Study No. 87-2D-6023, we can conclude that three of 210 metformin-treated patients, two of 211 glyburide-treated patients and four of 213 metformin + glyburide-treated patients, had normal ECGs at Baseline which later became abnormal. In this study, two metformin-treated patients had ECG changes consistent with infarction, but without clinical correlations, and one of these patients had coronary angiography which failed to confirm significant coronary artery disease, while the other patient had a subsequent normalization of the ECG. One patient in the metformin + glyburide group had ECG changes consistent with infarction, which persisted, but he was totally asymptomatic for more than one year, subsequent to the initial identification of these changes.

As requested, when applicable, Dr. Proudfit has also interpreted the Final Visit ECGs for all patients originally listed in Appendix 7 of each study report, who participated in the open-label study.

***(NOTE:** Copies of the ECGs for Study No. 87-1D-6023, comprising the subject matter of the original and revised Appendix 7 are included in Volume 2 of this Amendment, arranged according to treatment group, and for Study No. 87-2D-6023 as Volume 3, again arranged according to treatment group).*

Item 2. ***(Points 3 & 4): A pooled listing and all ECGs available for patients who died in controlled trials sorted by study and by exposure (±) to metformin.***

The pooled listing of patients who died during controlled U.S. and non-U.S. clinical trials are presented in Tables A1 and A2, respectively, located in **Item 2, Part A.** Brief narrative summaries of these patients (all of which were presented in the NDA) are given in the following paragraphs:

U.S. Controlled Clinical Trials:

In the U.S. controlled clinical trials, there was only one death among randomized patients. This patients: **Patient #20/06**, enrolled in **U.S. Study No. 87-2D-6023**, had been randomized to treatment with **metformin and Placebo G.** This 52 year old obese male smoker, with a 12 year history of NIDDM, died of an apparent myocardial infarction, after approximately 15 weeks on study. At the time of his death, he was taking 2.5 g/day of metformin and 4 tabs/day of Placebo G. His complete case report form, including available ECGs, has been previously submitted with the NDA (*see Vol. 1.394, Pages 12/009864 through 12/010016*) and a narrative summary of his case has also been submitted (*see Vol. 1.80, Pages 08A-02293 and 02294*). These ECGs are now resubmitted as **Item 2, Part B.**

There was an additional death, previously reported in the context of the Metformin Annual Progress Report to IND #27,966 (*Serial No. 048, submitted April 26, 1991*). This death occurred during the Pre-Enrollment (pre-randomization) Phase of **U.S. Study No. 87-1D-6023**, during the two month dietary run-in period, when NIDDM subjects were managed with weight-reduction **diet alone.** The patient[1], a 68 year old obese male, nonsmoker, with a three year history of diabetes mellitus, occasional aspirin user and without a history of prior cardiovascular disease, entered the Pre-Enrollment phase on Aug. 3, 1990. When the patient did not appear for his penultimate pre-randomization visit, his family was contacted and the site was informed that the patient had died while on vacation, following an apparent myocardial infarction accompanied by ventricular tachycardia, sustained on August 19, 1990. Heart failure ensued, despite thrombolytic therapy and, following coronary arteriography, balloon angioplasty was attempted. However, heart failure persisted and he expired on Aug. 24, 1990. No ECGs are available on this patient. Records for this patient are submitted as **Item 2, Part C.**

Non-U.S. Controlled Clinical Trials:

There were two deaths occurring during the course of the non-U.S. controlled clinical trials, reported in the NDA.

---

[1] This patient (JJA: DOB 03/18/22), has no Study ID number, since he never was randomized.

Patient #037, enrolled in **non-U.S. Study No. MET/GB/86/CAMP1**, was a 61 year old female smoker with NIDDM, with a past history of squamous cell carcinoma of the uterine cervix, treated with radiotherapy. She entered the study and was randomized to **glipizide** therapy. During the study, she was noted to have abnormal liver function tests (12/85). In July, 1986, she had biopsy of a breast mass which revealed squamous cell carcinoma, considered to be either of cervix or pulmonary origin. She subsequently developed acute abdominal symptoms and exploratory laparotomy revealed disseminated carcinomatosis with intestinal perforation. The patient was discontinued from study participation on July 2, 1986, after 306 days of glipizide therapy and died four days later. The complete case report form for this patient, has been previously submitted with the NDA (*see Vol. 1.398, Pages 12/011673 through 12/011678*) and a narrative summary of her case has also been submitted (*see Vol. 1.81, Page 08A-03270*). No ECGs are available on this patient.

Patient #209, enrolled in **non-U.S. Study No. MET/S/86/HERMA**, was a 63 year old male, with NIDDM, previously managed with diet alone who, at study entry, had a history of a prior myocardial infarction, persistent angina pectoris and atrial fibrillation. He was on multiple medications for his cardiac problems (digitalis preparation, calcium-channel blocker, diuretics, coronary vasodilators). Following the run-in period, he was initially randomized to **glibenclamide** monotherapy (started on Dec. 16, 1986) but active **metformin** therapy was added on Feb. 10, 1987, because of inadequate glycemic control with glibenclamide monotherapy. The patient reported symptoms of angina pectoris at almost all visits. On April 19-20, 1987, the patient apparently had a fatal myocardial infarction. No autopsy was performed. At the time of the patient's death, he was on 10.5 mg/day of micronized glibenclamide and 1 g/day of metformin (Dose level 4). The complete case report form for this patient, has been previously submitted with the NDA (*see Vol. 1.396, Pages 12/010577 through 12/010652*) and a narrative summary of his case has also been submitted (*see Vol. 1.81, Pages 08A-03179 and 03180*). No ECGs are available on this patient, although his Baseline ECG was interpreted as being "abnormal", with the following commentary: "Atrial fibrillation, status post infarct").

Item 3. ***(Points 5, 6 & 7): A pooled listing, from all controlled clinical trials, sorted by study and by exposure (±) to metformin, of all patients with any terms associated with:***

Coronary artery disease

Arrhythmia

Cardiovascular disease

The requested pooled listings are presented in Item 3. Within the tabular listings for U.S. controlled trials, organized by protocol and treatment group, the following information is provided: total treatment duration, investigator number, patient number, days to first occurrence of the event, the dose of metformin at the time of first occurrence of the event and the event as coded

by COSTART. The tabular listings for the non-U.S. controlled trials are organized by protocol and treatment group, total treatment duration (when available), investigator number, patient number, metformin dose at time of first occurrence of the event and the event as coded by COSTART terminology. The days to first occurrence for events could not be calculated for the non-U.S. studies, since "start dates" for adverse events were not provided in any CRF for any of the studies.

In addition to the listings, brief narratives for each patient are provided and location of corresponding information in the NDA is indicated, whenever applicable. Creation of these brief narratives was deemed necessary in order to provide background information on patients (e.g., presence or absence of preexistent cardiovascular disease) and to qualify some terms which, although listed among Cardiovascular System terms, in fact, did not connote cardiovascular disease (e.g., chest discomfort of a neuromuscular nature, palpitations, etc.). Furthermore, the narratives provide information indicating that a number of the "adverse events" in this System category, particularly for the non-U.S. studies, were not treatment-emergent.

Specifically, the following pooled listings are provided:

> A pooled listing of patients with experiences/intercurrent medical events, the coding of which suggested a potential association with **coronary disease**, is presented in **Item 3, Part A, Table B1 (controlled U.S. studies) and Table B2 (controlled non-U.S. studies)**. Brief narratives on each such patient are provided in **Item 3, Part B**, following the tables.
>
> A pooled listing of patients with treatment-emergent adverse experiences/intercurrent medical events, the coding of which suggested a potential association with **arrhythmias**, is presented in **Item 3, Part C, Table C1 (controlled U.S. studies) and Table C2 (controlled non-U.S. studies)**. Brief narratives on each such patient are provided in **Item 3, Part D**, following the tables.
>
> A pooled listing of patients with treatment-emergent adverse experiences/intercurrent medical events, the coding of which suggested a potential association with **cardiovascular disease** is presented in **Item 3, Part E, Table D1 (controlled U.S. studies) and Table D2 (controlled non-U.S. studies)**. Brief narratives on each such patient are provided in **Item 3, Part F**, following the tables.

As with the ECGs, these listings, and the accompanying narratives, support the lack of any consistent treatment-related effects on cardiovascular-related disease. They also support the generally high incidence of preexistent cardiovascular disease in these high-risk, diabetic patient groups.

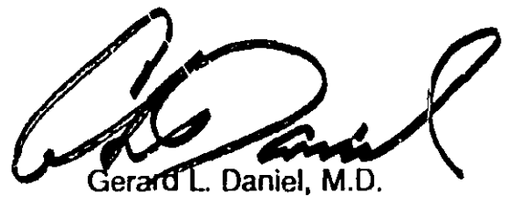
In conclusion, we are confident you will agree with our interpretation that there is no evidence from these data that the use of metformin predisposes to either cardiovascular or electrocardiographic disorders.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided. Please provide one CLINICAL copy to Dr. Ronald Innerfield.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.



Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

BB

ORIG AMENDMENT

LIPHA PHARMACEUTICALS INC

9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
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March 12, 1994
#20-94

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Food and Drug Administration
CDER, HFD-510
Attn: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: *Solomon Sobel, M.D., Director*
Division of Metabolism & Endocrine Drug Products

Reference: NDA #20-357 - Metformin HCl Oral/Amendment #20
Internal Report - Optical Activity of Metformin HCl
Request of Mr. John Hunt

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357). Reference is also made to our faxed response dated 3/2/94 to Mr. John Hunt relative to whether or not metformin hydrochloride possesses any chiral sites which could give rise to enantiomers.

In our response we stated that measurement of the optical rotation of metformin hydrochloride in two solvents showed no optical activity, thus confirming the absence of chiral sites and enantiomers.

Enclosed herewith as Amendment #20, in triplicate, for your review, is a copy of our Internal Report, METFORMIN HYDROCHLORIDE, BATCH #21889 - DETERMINATION OF THE OPTICAL ACTIVITY, by D. Descours and P. Briet, dated February 28, 1994, which was done at the Lipha Research and Development Center in Lyon, France.

If there are questions relative to the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President & Chief Executive Officer

GLD/BHW

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March 12, 1994
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Food and Drug Administration
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Attn: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attn: Solomon Sobel, M.D., Director
Division of Metabolism & Endocrine Drug Products

Reference:NDA #20-357 - Metformin HCl Oral/
Amendment #21/Lactate Turnover

3/23/94

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357).

Enclosed is Amendment #21/94 which contains a preliminary report on the recently completed study on the effects of Metformin on lactate turnover. These data show that there is no effect of metformin on lactate turnover in Type II diabetics when metformin is used in therapeutic doses.

If there are questions relative to the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

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March 11, 1994
#19-94

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Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #19
Safety Update: UK Prospective Diabetes Study (Manuscript); Corrected and Updated Information on Published Cases of Lactic Acidosis

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In an earlier conversation with Dr. Ronald Innerfield and this office, Dr. Innerfield pointed out some minor discrepancies in a table contained within the NDA (*Item 8, Section 8.8.13.1.5.6, "Tabular Summary of the Major Accompanying Biochemical and Clinical Signs and Clinical Outcome of 95 Cases of Metformin-Associated Lactic Acidosis [308]", Vol. 1.76, Pages 08A-02031 through 08A-02039).* Although some of the errors were transcriptional, it appears that one of the reasons for some of the discrepancies may be related to the fact that the original preparation of the chart was based, in part, on **secondary references** to the cases, rather than both the **primary and secondary references.** In some cases we have found that the primary and secondary references, or even publications by the same author of the same cases, contain minor inconsistencies.

As examples of some of the changes made, are the following: the pH for Case 6 was originally given as 7.4 instead of the correct value of 7.2; similarly, for Case 10, the pH was given as 7.3 instead of the correct value of 7.2; for Case 11, the metformin plasma level was given as 11,000 ng/ml instead of the correct value of 110,000 ng/ml; for Case 27, the metformin plasma level was given as 11,900 instead of 14,900 ng/ml; information on Cases 87 and 88 had been transposed, in part, etc.

We have now carefully re-analyzed and updated the table, to include published cases through 1992 and 1993, bringing the total number of cases reported to 110, from the original of 95. This increase results largely from incorporation of cases from the **retrospective** Swedish report of Wiholm and Myrhed, published in 1993 (BCA-2271), which added 11 new cases (Cases 96 through 106). Cases 17 through 23, which are also part of the Wiholm and Myrhed review, were previously reported in the table since they were originally reported by other authors, in the late 1970s. Based on the Wiholm and Myrhed review, further detail on Cases 19 through 23 is now available and has been incorporated into the updated table (Pages 28 and 29).

Cases 107 through 110 have been recently reported in the literature (respective BCA numbers of 2315, 2124, 2166 and 2333). Two of these articles (BCA 2124 [Item 8, reference 346] and BCA 2166 [Item 8, reference 345]) were previously referred to in Item 8 but the two cases had not been incorporated into the above-mentioned table, since the table had been prepared prior to their publication.

In addition to the case update, the information contained in the table has been expanded to include, where available, the following:

- pCO_2 and/or HCO_3 levels;
- for all laboratory analytes, both the originally reported units as well as the conversion to international units for purposes of uniformity;
- a category of "Other", in the column of Associated Clinical Conditions,
- concomitant Medications;
- use of alcohol (yes or no);
- both primary and secondary references (sometimes multiple), which are presented by Lipha's BCA number and, in brackets, the reference number in Item 8, if already cited;
- the year of the primary reference publication.

In addition, commentaries are provided on each case which either explain prior discrepancies or give further information on the case, including information on associated illnesses.

Following the table, there is also a compilation of the statistical analysis of the table content, performed by Lipha S.A., providing means, standard errors and ranges for a variety of the parameters and an analysis of frequencies of coexistent illnesses, outcome, use of dialysis, etc.

We are also now providing translations of all articles previously referred to in the table, for which translations had **not** been available at the time of the original NDA submission. In addition, all new primary and secondary references have been provided, and translated, as appropriate. Also provided is a section with unpublished communications relative to Cases 2, 3, 11-15 and 17.

It should be noted that at least three of the **published cases** (Cases 87, 88 and 110) were included among the **cases reported to the French National Adverse Effect Surveillance Commission** (Cases 336 [1985], 302 [1984] and 743 [1991]), respectively. These cases are included in listings appearing in Item 8, Section 8.8.7.4.2.1 (Vol. 1.75, beginning on Page 08A-01716) and in Section 8.8.13.1.5.5 (Vol. 1.76, beginning on Page 08A-02013). *(**NOTE:** There may be further duplicate reporting, of which we are currently unaware, just as there have been multiple reports of the same case appearing in the published literature, as noted in the enclosed table).*

In addition to the above, we are providing a small supplemental table of seven published cases of "acidosis", which, however, were not included in the original review of Professor Cesare Sirtori because of the poor quality of the information, primarily, the lack of important biochemical data. Case 1, however, in this table, reported by Assan et al ***(Coma métaboliques non acido-cétosiques chez des diabétiques: Presse Med.,1969,77.21:787-789 [BCA-1773])***, is considered by some authors to represent the first reported case of lactic acidosis associated with metformin use. However, the only biochemical parameter available is the pH of 7 and there is no measurement of either lactic acid levels or metformin levels in blood. For Cases 2, 3 and 5 in this table, no lactate levels are available. For Case 4 in the table, there is a very minor increase in lactate level and the patient had just been switched from phenformin to metformin. Finally, for Cases 6 and 7 in this table, there is neither a lactate value nor a value for pH and thus, even the diagnosis of acidosis cannot be firmly established. However, we are submitting these cases for completeness.

With reference to this latter supplemental table, we are also submitting BCA-1773, previously not included among the Item 8 references (but listed in Item 15 and submitted in abstract form in that item) and the translation of BCA 534 (Item 8, reference 378) and BCA 490 (Item 8, reference 374). The remainder of the citations for this supplemental table (which had been previously cited in Item 8 but submitted only in their original language), are currently being translated and will be submitted as soon as available.

Finally, of considerable interest and related to further long-term safety and efficacy information of metformin, is the manuscript submitted to the British Medical Journal, on three-year follow-up on all patient groups in the UK Prospective Diabetes Study (UKPDS). Since metformin is one of the treatment arms in this group, it is interesting to note its continued efficacy during that follow-up period as well as the absence of either lactic acidosis or other important events of safety concern. *(**NOTE:** The manuscript, authored by the UK Prospective Diabetes Study Group, immediately follows this letter).*

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter, the manuscript and the full amendment are provided. Please provide one CLINICAL copy to Dr. Innerfield.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

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March 7, 1994

Food and Drug Administration
Center for Drugs and Biologics, HFN-810
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral
Briefing Book

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) submitted to FDA on September 29, 1993.

We have enclosed for your consideration a copy of the Metformin Briefing Book for the Endocrinologic and Metabolic Drugs Advisory Committee meeting scheduled for March 18, 1994. We are also sending a copy (via Federal Express) to Dr. Igor Cerny, Executive Secretary to the Committee.

Unless we from you to the contrary, an additional twenty-five copies of this book will be sent tomorrow afternoon, via overnight delivery, to Dr. Cerny for distribution to the Division as well as the Advisory Committee.

Should you have any comments or questions, please don't hesitate to call me at (212) 223-1392.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Gerard J. Daniel, M.D.
Chairman and President

cc: Igor Cerny, Pharm D., FDA

LIPHA PHARMACEUTICALS

March 4, 1994
#18-94

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Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #18
Corrected Pharmacokinetic Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

Based on earlier conversations with Mr. John Hunt, Division of Biopharmaceutics, and Lipha personnel (Mr. Bruce Goddard, Dr. Anita Goodman), we have sent today, via FAX, some corrections in tables related to data from U.S. Study 89-11-6023 (Food/Fasting/Bioequivalence study) and some other minor corrections. (***NOTE:*** *All corrections are indicated by shading*).

In the NDA submission of the Final Report of this study, located in Volumes 1.42 and 1.43, metformin plasma clearance had been incorrectly given. The four corrected pages of the Final Report (one page per treatment phase) are now provided as well as the related corrections in summary tables of *in vivo* human pharmacokinetic data (simultaneously presented in Items 2, 6 and 8) and, where applicable, text pages of Items 6 and 8. (***NOTE:*** *In the in vivo human pharmacokinetic summary tables, in some instances conversions of units from those provided in original Final Reports [e.g., liters to milliliters and hours to minutes] have been made by Lipha, so that all data can be compared).*

In addition, a transcription error was noted in summary table data for U.S. Study 91-06-6023 (metformin/ibuprofen), such that values for metformin plasma clearance and renal clearance for the co-administration period and the metformin alone period, respectively, were transposed. This has also been corrected. Again, these corrections have been made in the relevant summary table for Items 2, 6 and 8.

Finally, in an intext table, presenting data from U.S. Study 89-12-6023 (Single and Multiple Dose PK/PD Study in Diabetics and Non-Diabetics), values given for AUCX were actually values for AUC and this has been so-indicated.

Mr. Hunt had also questioned whether metformin might have a chiral center. Clearly, metformin does not have any chiral sites which would give rise to enantiomers. This information was sent to Mr. Hunt via FAX on March 2, 1994 (FAX copy enclosed) and has been sent to him again via FAX today.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided. Please provide one CLINICAL copy to Mr. John Hunt.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies

ALPHA PHARMACEUTICAL

February 23, 1994
#17-94

VIA FEDERAL EXPRESS, #1297777725
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #17
Update on Safety Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

Enclosed is an update on safety information, subsequent to our NDA submission on September 29, 1993. These data are derived from our long-term, open-label safety study, identified as U.S. Study No. 89-1C-6023 (***"The Safety and Effectiveness of Long-Term, Open-Labeled Metformin Treatment in Obese, Non-Insulin Dependent, Diabetes Mellitus (NIDDM) Patients--An Extension Study of Protocols #87-1D-6023 and #87-2D-6023"***).

This study, which continues to be under analysis, was described, in general, in Item 8, Section 8.5.3.1.1 (*Volume 1.81, Pages 08A-00604 through 08A-00610*) of the NDA. Also included were narrative summaries on all patients prematurely terminated for either an adverse experience/intercurrent medical event or significantly abnormal laboratory result and for all patients who had died (*Item 8, Section 8.16.1, Volume 1.189, beginning on Page 08B-29753*).

The current submission consists of the following:

PART 1.A

Table I.a. A listing of **all** adverse experiences/side-effects reported during the study (including those present at "Baseline"), by both COSTART Body System and specific events, according to **severity** of event.

The numbers of patients reporting events in any COSTART Body System and the numbers of events within that Body System are provided, as well as the numbers of individual events.

As noted on the page preceding this table, multiple episodes of the same event have been counted only once, listed according to the **worst** reported severity. (It should be noted that severity was judged *by the individual investigator* and no standard severity scale guidelines were provided for any event).

Table I.b. This table lists those events, according to severity, which were thought, *by the individual investigator*, to have **any** relationship (possible, probable or definite) to study drug administration.

The numbers of such patients reporting events, according to COSTART Body System, and the numbers of events within that Body System are provided, as well as the numbers of individual events and their severity (listed according to **worst** severity, if occurring more than once).

Table I.c. This table lists those events which, according to the investigator, were thought to have any relationship to study drug administration by event and **by suspected relationship**. As with "severity", the highest degree of causality was used, when an event occurred more than once with different investigator-assessed causality relationships.

PART 1.B

Appendix 5.9, Part 3 of 13, Electrolytes/Lactate
(for Final Report of Study No. 89-1C-6023)

This listing provides individual patient electrolye and lactate values, as well as the calculated anion gap (one page per patient), for all enrolled patients in Study No. 89-1C-6023, alphabetically by investigator and according to *prior treatment group* (i.e., *treatment group during the prior double-blind* studies).

It should be noted that values given for Visit 1.00 may represent the Final Visit value from the prior double-blind study (Study No. 87-1D-6023 or Study No. 87-2D-6023) or may be a true "Baseline" value (i.e., blood sampling while on no anti-diabetic medication or while on other anti-diabetic treatment [e.g., open-label sulfonylurea], prior to enrollment in Study No. 89-1C-6023, if a hiatus occurred between the two studies of more than two weeks). Thus, patients may have been on any of the following regimens at the time of that visit: metformin alone, metformin + glyburide, glyburide alone, placebo, diet only, other commercially available sulfonylurea, or even insulin. At the present stage of our analysis of the data, the precise information, relative to this visit, is not available on the listing.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided. Please provide one CLINICAL copy to Dr. Ronald Innerfield.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies

15 February 1994
#16-94

VIA AIRBORNE, #6242547533
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #16
Request of Dr. Ronald Innerfield

Dear Dr. Sobel:

On behalf of LIPHA PHARMACEUTICALS, INC., reference is made to their New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In continued follow-up to the request of Dr. Ronald Innerfield for reformatting of the U.S. and non-U.S. databases for safety and efficacy, enclosed are two diskettes in the Q&A format, relative to these databases.

These diskettes contain the data files, reformatted into Q&A, for the non-U.S. uncontrolled Phase IV Study MET/AM/87/PHASE (TMPL_NN3, storage space of 20 Meg required).

In addition to the diskettes, attached **Item 1** consists of a 22-page document describing the content of the entire Q&A database in detail, to date, and indicates all data fields which have or have not been sent.

Quintiles Inc
Post Office Box 13979
Research Triangle Park, NC
27709-3979
919 941 2888 Fax 919 941 6050

In addition, there remain a few outstanding data fields recently requested in the Q&A format for the U.S. studies, including concomitant medication, placebo dose and reasons for dropout. These remaining reformatted fields will be forwarded to the Division as soon as the reformatting process and related procedures have been completed.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the attached item are provided. These diskettes and Item 1 should be directed to Dr. Ronald Innerfield, as in the past.

If there are questions relative to any of the above, please do not hesitate to contact this office or LIPHA PHARMACEUTICALS, INC.

Sincerely yours,

Quintiles, Inc. for
LIPHA PHARMACEUTICALS, INC.

Paula B. Stafford, M.P.H.
Associate Director, Project Administration
Project Management and Planning

cc: Gerard L. Daniel, M.D.
Lipha Pharmaceuticals, Inc.

1 Archival Copy, 2 Clinical Copies; 2 mailing folders with 1 diskette each
(for Dr. Ronald Innerfield)

QUINTILES

11 February 1994
#15-94

VIA AIRBORNE, #6242547636
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #15
Request of Dr. Ronald Innerfield

Dear Dr. Sobel:

On behalf of LIPHA PHARMACEUTICALS, INC., reference is made to their New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In continued follow-up to the request of Dr. Ronald Innerfield for reformatting of the U.S. and non-U.S. databases for safety and efficacy, enclosed is one diskette in the Q&A format, relative to these databases.

This diskette contains the data files, reformatted into Q&A, for the controlled, Category II, non-U.S. Studies MET/GB/86/CAMPI, MET/AM/88/DUCHI, MET/S/87/HERMA (TMPL_NN2 and CORR_NON).

The non-U.S. uncontrolled Phase IV Study MET/AM/87/PHASE remains outstanding (storage space of 20 Meg required).

In addition to the diskette, attached **Item 1** consists of a 22-page document describing the content of the entire Q&A database in detail, to date, and indicates all data fields which have or have not been sent.

Quintiles Inc.
Post Office Box 13979
Research Triangle Park, NC
27709-3979
919 941 2368 Fax 919 941 0250

In addition, there remain a few outstanding data fields recently requested in the Q&A format for the U.S. studies, including concomitant medication, placebo dose and reasons for dropout. These remaining reformatted fields will be forwarded to the Division as soon as the reformatting process and related procedures have been completed.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the attached item are provided. These diskettes and Item 1 should be directed to Dr. Ronald Innerfield, as in the past.

If there are questions relative to any of the above, please do not hesitate to contact this office or LIPHA PHARMACEUTICALS, INC.

Sincerely yours,

Quintiles, Inc. for
LIPHA PHARMACEUTICALS, INC.

Paula B. Stafford

Paula B. Stafford, M.P.H.
Associate Director, Project Administration
Project Management and Planning

cc: Gerard L. Daniel, M.D.
Lipha Pharmaceuticals, Inc.

1 Archival Copy, 2 Clinical Copies; 1 mailing folder with 3 diskettes (for Dr. Ronald Innerfield)

LIPHA PHARMACEUTICALS INC
Lipha
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

February 7, 1994
#1494

Received & Noted (Bm)

VIA FEDERAL EXPRESS, #1439367720
ACKNOWLEDGMENT OF DELIVERY REQUESTED

3/10/94

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #14
Additional Dose/Response Assessment:
Request of John L. Guerigulan, M.D.

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

As you know, a formal dose-response study with metformin has never been done, largely because historical precedent had established an overall approach to the use of metformin in NIDDM (both dose and administration schedule), which has been verified as being both effective and safe, on an empirical basis, as well as in the context of controlled clinical trials. In most western countries, where metformin is regularly used for the treatment of NIDDM, either alone or in combination with sulfonylurea therapy, the average daily dose is between 1500 and 2550 mg daily. However, understandably, there is interest in what might be considered the minimum effective dose.

Within the metformin NDA, as submitted, there is a review of the historical basis for the conventional clinical dosing and dose-scheduling of metformin as well as a presentation of data generated during the course of the U.S. Phase III prospective, randomized, controlled, parallel arm, multicenter trials (U.S. Study No. 87-1D-6023 and U.S. Study No. 87-2D-6023). Because these two studies involved an initial metformin dose Titration Phase, during which time metformin dosage was increased in stepwise fashion, based on considerations of efficacy and tolerability, an analysis was presented in the NDA of the fasting plasma glucose response at various metformin dose levels.

Based on subsequent communications with Dr. John L. Gueriguian and in an effort to satisfy the Division's concerns regarding dose-response, the current amendment to the NDA is being made.

This enclosed amendment consists of a further, in-depth analysis of the Titration Phases of the two U.S. pivotal Phase III studies, noted above, with related Tables, Figures and Appendices. Appendices 1 and 2 provide the statistical basis for the numbered tables and for statements contained within the text. Appendices 3 through 5 consist of relevant portions of the NDA, as already submitted, for ease of reference. These summarize, respectively, the historical background on metformin dose selection and dose scheduling, the analysis of dose-response during the titration phase of U.S. Phase III studies, as originally provided in the NDA, and narrative overviews of the two Phase III studies.

Because the Titration Phase of these two U.S. studies was analogous to a within-patient dose-escalation study, with the majority of patients on metformin-containing treatment arms undergoing all potential dose-escalation steps, this is the portion of the study which has been subjected to further analysis. Emphasis has been placed, in the analysis, on the metformin treatment group from U.S. Study No. 87-1D-6023 and on the metformin + glyburide treatment group from U.S. Study No. 87-2D-6023. The analysis provides information on fasting plasma glucose response over the dosage range of 500 mg/day through 2,550 mg/day, with patients remaining at each dose level for one (2-D) or two (1-D) weeks.

Although it was suggestive from the original analysis of our overall results, presented in the NDA, that the magnitude of the plasma glucose-lowering effect of metformin was related to the severity of the initial hyperglycemia, one aspect of the re-analysis has been to look at the magnitude of the incremental response in fasting plasma glucose (FPG) with step-wise metformin dose escalation, according to baseline FPG subgroups, ranging from $\leq$180 mg/dL to >300 mg/dL. Additionally, we have looked at the incremental dose-response in FPG during the Titration Phase as a function of gender and as a function of body weight subgroups.

The more in-depth analysis has provided some interesting information and substantiates earlier perceptions based on the more general analysis of dose-response as well as the analysis of the degree of glycemic control at final visit, as presented in the NDA. It is clear that with each incremental increase in metformin dose, an additional effect on decreasing FPG is seen and, in fact, there is no indication that, overall, this effect has plateaued at the **maximum** dose that we considered using in these studies (i.e., 2500 to 2550 mg/day of metformin). Conversely, the **lowest** daily doses of metformin during this period (i.e., 500 mg or 850 mg/day of metformin) were not "no-effect" doses. With <u>all</u> incremental increases in metformin dose, for both dosage strengths, the resultant magnitude of the decrease in FPG was clearly related to the severity of initial hyperglycemia.

Based on this supplemental analysis (and corroborated by other data in the NDA) and considering the metabolic heterogeneity of NIDDM patients--we continue to conclude (as recommended in the proposed Package Insert) that the dose of metformin used clinically must be **individualized**, starting with the **lowest** dose and gradually increasing the dose until the

optimal anti-hyperglycemic effect is obtained, obviously, keeping all other risk-benefit considerations in mind. (In essence, performing an individualized dose-ranging assessment in each patient).

By virtue of the disease and the characteristics of metformin (i.e., an **anti-hyperglycemic** agent as opposed to a **hypoglycemic** agent), there is **not** one minimum effective dose that can be identified, globally, for all Type II diabetics. The minimum effective dose must be based on the needs of the individual for good glycemic control, with consideration given to the type and severity of his/her diabetes as well as to other metabolic parameters and medical conditions. In fact, for some patients, the maximum recommended dose (as per the proposed Package Insert) may not even be a minimum effective dose, since there was no evidence of a plateauing of the glucose-lowering effect, even at these doses.

Although this retrospective analysis does not (and cannot) provide all the end-points resembling an ideal dose-response curve, we hope you concur that there is reason to support the view that a classical dose-ranging study is unlikely to produce evidence that would change the proposed prescribing recommendations for metformin.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the amendment are provided.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

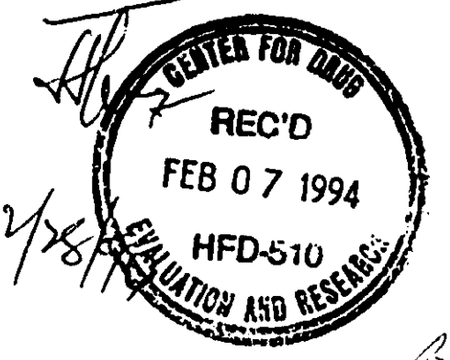
GLD/AMG

1 Archival Copy, 2 Clinical Copies

ORIG AMENDMENT

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3875 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX 212-223 1398

February 4, 1994
#13-94



VIA FEDERAL EXPRESS, #1439367716
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #13
Final Report: U.S. Study No. 90-13-6023

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In the NDA, an Interim Report on U.S. Pharmacokinetic Study No. 90-13-6023 (*"Single Dose Study of Metformin in Patients with Renal Impairment and in Healthy Elderly and Young Individuals"*), conducted at the University of California-San Francisco Drug Studies Unit, was submitted. This Interim Report consisted of a comparative analysis of single-dose pharmacokinetics of metformin in the healthy elderly vs. the healthy young group. That analysis demonstrated that both total oral clearance and renal clearance of metformin were approximately 35% lower in healthy elderly subjects, compared to healthy young subjects, resulting in increases in concentration-related pharmacokinetic parameters (C_{max} and AUC in both plasma and blood) and a smaller elimination constant (k_{el})(and longer t½) in both plasma and blood. There were no differences in volume of distribution/bioavailability between the groups.

The Interim Report of this study was summarized in the NDA in Item 6, Vol. 1.41, Pages 06 000056 through 06 000060 and was submitted as Item 6.12.3, Vols. 1.49-1.50 (Pages 06 002073 through 06 002564).

The current amendment (Amendment #13) to the NDA consists of the Final Report on this same study, which now includes an analysis and comparison of the single-dose pharmacokinetics of metformin in three subgroups of subjects with chronic renal impairment (CRI), classified according to measured creatinine clearance (corrected for body surface area) as mild (5

subjects), moderate (4 subjects) and severe (6 subjects). In addition, four healthy middle-aged subjects are included in the overall comparison.

As can be seen in Tables 5-7 (Pages 0054-0056) of the Final Report (appended to this letter as **Item 1, for ease of review**), for essentially all of the evaluable parameters, subjects with moderate and severe CRI differed significantly from the healthy young/middle-aged, healthy elderly and mild CRI groups, but did not differ from each other. In the moderate and severe CRI groups, total oral clearance was about 75% less than in the healthy young group.

Pharmacokinetic parameters of metformin in the mild CRI group were statistically comparable to those from the healthy elderly group.

Multivariate regression analysis revealed that both renal function (as measured by corrected creatinine clearance) and age are predictors of metformin clearance (both total and renal). Whereas creatinine clearance as a single covariate was significant, age was only significant when creatinine clearance was considered and was not significant as a single covariate.

A model describing these relationships was developed, which indicates that, for individuals of the same age, metformin clearance decreases linearly as a function of (corrected) creatinine clearance. For older individuals, the slope of the linear function is smaller, since they are already starting out at a lower clearance because their creatinine clearance is lower. Thus, for individuals having the same creatinine clearance, the older someone is, the lower the metformin clearance will be. However, for individuals with more severe degrees of renal impairment, the change in metformin clearance due to age is dampened. These model-based relationships are shown graphically in Figures 4a, 4b, 5a, 5b, 6a, 6b, 7a and 7b of the report (Pages 0064 through 0071, appended to this letter, for ease of review, as **Item 2**) and in tabular form in Tables 8 through 11 (Pages 0057 through 0060, appended to this letter, for ease of review, as **Item 3**).

For example, according to the model, it is predicted that for a typical individual of ***30 years of age*** with a ***corrected creatinine clearance of 80 ml/min***, metformin total oral plasma clearance (CL/F) will be 834 ml/min. In such an individual, according to the model, CL/F is expected to decrease (increase) about 92 ml/min for every 10 ml/min decrease (increase) in corrected creatinine clearance. In contrast, according to the model, for a typical individual **70 years of age** and with the same corrected creatinine clearance (i.e., 80 ml/min), CL/F is predicted to be about 665 ml/min and is expected to decrease (increase) about 71 ml/min for every 10 ml/min decrease (increase) in corrected creatinine clearance.

For your convenience, four copies (one ARCHIVAL, two CLINICAL and one PHARMACOKINETIC) of this letter and its attached items, as well as the enclosed Final Report, are provided. Please direct the latter copy to Dr. Daniel Gordon, if appropriate.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies, 1 Pharmacokinetic Copy

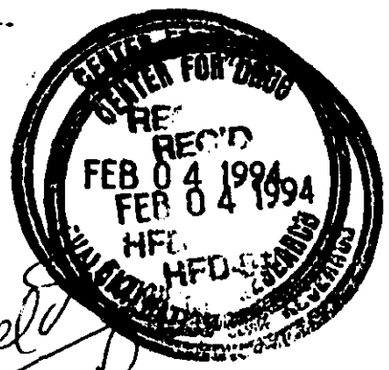
BM

DRUG AMENDMENT

LIPHA PHARMACEUTICALS INC
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

February 3, 1994
#12-94

ORIGINAL



VIA FEDERAL EXPRESS, #1439367705
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment #12
Request of Dr. Ronald Innerfield

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In continued follow-up to the request of Dr. Ronald Innerfield for reformatting of the U.S. and non-U.S. databases for safety and efficacy, enclosed are three diskettes in the Q&A format, relative to these databases.

One diskette contains a revision to the Q&A file for U.S. Study 87-1D-6023 and U.S. Study 87-2D-6023, submitted to the Division as an Amendment on January 9, 1994. Specifically, TMPL_USB replaces TMPL_USA.

Two diskettes contain the data files, reformatted into Q&A, for the controlled, Category II, non-U.S. Studies MET/AM/87/DORF1, MET/AM/86/DORF2, MET/GB/85/DORNA, MET/D/86/BERGI and non-U.S. uncontrolled Phase IV Study, MET/D/86/HAUPT (TMPL_NON and CORR_NON).

In addition to the three diskettes, attached **Item 1** consists of a 22-page document, prepared by Quintiles, Inc., describing the content of the entire Q&A database in detail, to date, and indicates all files which have or have not been sent.

Four more non-U.S. Category II reformatted data files remain to be submitted (controlled, Category II non-U.S. Studies MET/GB/86/CAMP1, MET/AM/88/DUCHI, MET/S/87/HERMA and non-U.S. uncontrolled Phase IV Study MET/AM/87/PHASE).

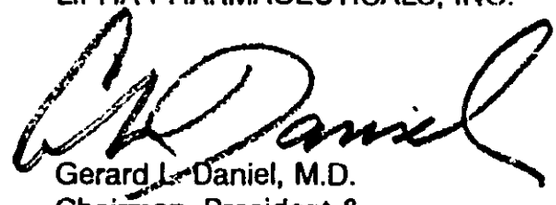
In addition, there remain some outstanding additional recent requests for Q&A files for the U.S. studies for concomitant medications, placebo dose and reasons for dropout. These remaining reformatted files and additions to already reformatted files will be forwarded to the Division as soon as Quintiles, Inc. has completed the reformatting process and related procedures.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and the attached item is provided. The diskettes should be directed to Dr. Ronald Innerfield, as in the past.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.



Gerard J. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies; 1 mailing folder with 3 diskettes (for Dr. Ronald Innerfield)

BS

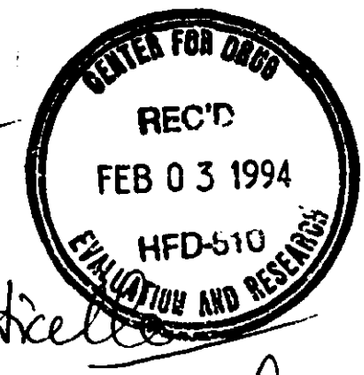
LIPHA PHARMACEUTICALS INC
Lipha
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

February 2, 1994
#11-94

ORIG AMENDMENT

ORIGINAL

VIA FEDERAL EXPRESS, #1439367742
ACKNOWLEDGMENT OF DELIVERY REQUESTED



Voted
Send to
Dr Marticello

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment
Request of Dr. Daniel Marticello

1/28/94

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In follow-up to telephone conversations between Dr. Daniel Marticello, Division of Biometrics, and Lipha and, subsequently, Quintiles, Inc. on Jan. 19 and 21, 1994 and, in response to his request, supplemental tables are enclosed, relative to U.S. Phase III studies, Study No. 87-1D-6023 (metformin vs. placebo) and Study No. 87-2D-6023 (metformin vs. glyburide vs. metformin/glyburide). Final reports of these two studies (including appended tables, figures and data listings) are located, respectively, in Volumes 1.104 through 1.119 and Volumes 1.120 through 1.156 of Item 8, as well as in Volumes 1.221 through 1.236 and Volumes 1.237 through 1.273 of Item 10.

Specifically, Dr. Marticello requested a comparison between treatment groups of the baseline values for the efficacy parameters of FPG, HbA_{1c} and lipids for subjects having both a Baseline as well as a Post-Baseline (one or more) measurement for the specific parameter in question.

Item 1.a is comprised of **Supplemental Table A for U.S. Study No. 87-1D-6023** (*"Summary of Mean Changes from Baseline in Fasting Plasma Glucose and HbA_{1c} - LOCF Analysis For Patients with both Baseline and Final Visit Values*), dated January 28, 1994.

Supplemental Table A supplements intext Table H of the Final Report (***Vol. 1.104, Page 08B-00087 [Item 8]; Vol. 1.221, Page 08B-00087 [Item 10]***). The "n" (numbers of patients) in Table

H, comprising the Baseline and Visit #9 populations for each treatment group, are derived from Table 9.1 of the Final Report for Fasting Plasma Glucose (***Vol. 1.105, Page 08B-00201 [Item 8]***; *Vol. 1.222, Page 08B-00201 [Item 10]*) and from Table 10.1 of the Final Report for HbA_{1c} (***Vol. 1.105, Page 08B-00204 [Item 8]***; *Vol. 1.222, Page 08B-00204 [Item 10]*). *(For ease of reference, Intext Table H from the Final Report is included as* ***Item 1.b*** *and appended Tables 9.1 and 10.1 from the Final Report are included as* ***Items 1.c and 1.d****, respectively).*

Item 2.a is comprised of **Supplemental Table B for U.S. Study No. 87-1D-6023** (*"Summary of Mean Changes from Baseline in Lipid Parameters - LOCF Analysis For Patients with both Baseline and Final Visit Values*), dated January 28, 1994.

Supplemental Table B supplements intext Table L of the Final Report (***Vol. 1.104, Page 08B-00104 [Item 8]***; *Vol. 1.221; Page 08B-00104 [Item 10]*). *(For ease of reference, Intext Table L from the Final Report is included as* ***Item 2.b***). The "n" (numbers of patients) in Table L, comprising the Baseline and Visit #9 populations for each treatment group, are derived from the following appended tables of the Final Report:

Table 13.1.1 for total cholesterol (***Vol. 1.105, Page 08B-00219 [Item 8]***; *Vol. 1.222, Page 08B-00219 [Item 10]);* (included as ***Item 2.c***).

Table 13.2.1 for triglycerides (***Vol. 1.105, Page 08B-00221 [Item 8]***; *Vol. 1.222, Page 08B-00221 [Item 10]*); (included as ***Item 2.d***).

Table 13.3.1 for LDL (***Vol. 1.105, Page 08B-00223 [Item 8]***; *Vol. 1.222, Page 08B-00223 [Item 10]*); (included as **Item 2.e**).

Table 13.4.1 for HDL (***Vol. 1.105, Page 08B-00225 [Item 8]***; *Vol. 1.222, Page 08B-00225 [Item 10]*); (included as ***Item 2.f***).

Table 13.7.1 for Apolipoprotein A-1 (***Vol. 1.105, Page 08B-00231 [Item 8]***; *Vol. 1.222, Page 08B-00231 [Item 10]*); (included as ***Item 2.g***).

Table 13.8.1 for Apolipoprotein B (***Vol. 1.105, Page 08B-00233 [Item 8]***; *Vol. 1.222, Page 08B-00233 [Item 10]*); (included as ***Item 2.h***).

Table 13.9.1 for Total Cholesterol/HDL Ratio (***Vol. 1.105, Page 08B-00235 [Item 8]***; *Vol. 1.222, Page 08B-00235 [Item 10]*); (included as ***Item 2.i***).

Table 13.10.1 for LDL/HDL Ratio (***Vol. 1.105, Page 08B-00237 [Item 8]***; *Vol. 1.222, Page 08B-00237 [Item 10]*); (included as ***Item 2.j***).

Table 13.11.1 for Apo A-1 to Apo B Ratio (***Vol. 1.105, Page 08B-00239 [Item 8]***; *Vol. 1.222, Page 08B-00239 [Item 10]*); (included as ***Item 2.k***).

Item 3.a is comprised of **Supplemental Table A for U.S. Study No. 87-2D-6023** (*"Summary of Mean Changes from Baseline in Fasting Plasma Glucose and HbA_{1c} - LOCF Analysis For Patients with both Baseline and Final Visit Values*), dated January 28, 1994.

Supplemental Table A supplements intext Table H of the Final Report (***Vol. 1.120, Page 08B-05454 [Item 8]; Vol. 1.237, Page 08B-05454 [Item 10]***). The "n" (numbers of patients) in Table H, comprising the Baseline and Visit #11 populations for each treatment group, are derived from Table 9.1 of the Final Report for Fasting Plasma Glucose (***Vol. 1.121, Page 08B-05605 [Item 8]; Vol. 1.238, Page 08B-05605 [Item 10]***) and from Table 10.1 of the Final Report for HbA_{1c} (***Vol. 1.121, Page 08B-05612 [Item 8]; Vol. 1.238, Page 08B-05612 [Item 10]***). *(For ease of reference, Intext Table H is included as **Item 3.b** and appended Tables 9.1 and 10.1 from the Final Report are included as **Items 3.c and 3.d**, respectively).*

Item 4.a is comprised of **Supplemental Table B for U.S. Study No. 87-2D-6023** (*"Summary of Mean Changes from Baseline in Lipid Parameters - LOCF Analysis For Patients with both Baseline and Final Visit Values*), dated January 28, 1994.

Supplemental Table B supplements intext Table L of the Final Report (***Vol. 1.120, Page 08B-05477 [Item 8]; Vol. 1.237; Page 08B-05477 [Item 10]***). *(For ease of reference, Intext Table L is included as **Item 4.b**).* The "n" (numbers of patients) in Table L, comprising the Baseline and Visit #11 populations for each treatment group, are derived from the following appended tables of the Final Report:

Table 13.1.1 for total cholesterol (***Vol. 1.121, Page 08B-05641 [Item 8]; Vol. 1.238, Page 08B-05641 [Item 10]);*** (included as **Item 4.c**).

Table 13.2.1 for triglycerides (***Vol. 1.121, Page 08B-05645 [Item 8]; Vol. 1.238, Page 08B-05645 [Item 10]***); (included as **Item 4.d**).

Table 13.3.1 for LDL (***Vol. 1.121, Page 08B-05649 [Item 8]; Vol. 1.238, Page 08B-05649 [Item 10]***); (included as **Item 4.e**).

Table 13.4.1 for HDL (***Vol. 1.121, Page 08B-05653 [Item 8]; Vol. 1.238, Page 08B-05653 [Item 10]***); (included as **Item 4.f**).

Table 13.7.1 for Apolipoprotein A-1 (***Vol. 1.121, Page 08B-05665 [Item 8]; Vol. 1.238, Page 08B-05665 [Item 10]***); (included as **Item 4.g**).

Table 13.8.1 for Apolipoprotein B (***Vol. 1.121, Page 08B-05669 [Item 8]; Vol. 1.238, Page 08B-05669 [Item 10]***); (included as **Item 4.h**).

Table 13.9.1 for Total Cholesterol/HDL Ratio (***Vol. 1.121, Page 08B-05673 [Item 8]; Vol. 1.238, Page 08B-05673 [Item 10]***); (included as **Item 4.i**).

Table 13.10.1 for LDL/HDL Ratio (***Vol. 1.121, Page 08B-05677 [Item 8]***; *Vol. 1.238, Page 08B-05677 [Item 10]*); (included as ***item 4.j***).

Table 13.11.1 for Apo A-1 to Apo B Ratio (***Vol. 1.121, Page 08B-05681 [Item 8]***; *Vol. 1.238, Page 08B-05681 [Item 10]*); (included as ***Item 4.k***).

For your convenience, four copies (one ARCHIVAL, two CLINICAL and one DESK COPY for the Division of Biometrics) of this letter and attached items are provided. Please direct the DESK COPY to Dr. Marticello.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies, 1 Desk Copy for Biometrics

BM

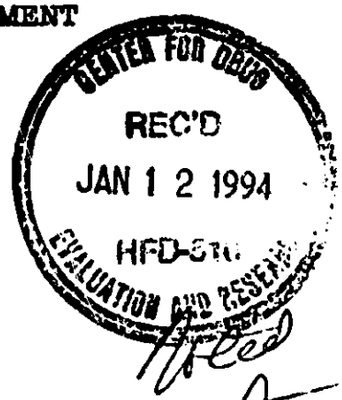
LIPHA PHARMACEUTICALS INC
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX 212-223 1398

January 11, 1994
#09-94

ORIGINAL

VIA FEDERAL EXPRESS, #1297778005
ACKNOWLEDGMENT OF DELIVERY REQUESTED

ORIG AMENDMENT



Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment
Request of Dr. Ronald Innerfield

1/14/94

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In follow-up to our letter to the Division of December 15, 1993 (Lipha reference #08-93), which accompanied four diskettes of reformatted safety and efficacy data from Lipha's pivotal metformin studies (U.S. Study Nos. 87-1D-6023 and 87-2D-6023, Category I), enclosed is an additional 3.5" diskette containing the Q&A supplementary TEMPLATE file for these two studies, as requested by Dr. Ronald Innerfield during the course of telephone conversations with Quintiles, Inc. on December 17 and 20, 1993 *(see Item 1, for a memorandum referable to those telephone calls)*.

Accompanying this diskette is a four page document, prepared by Quintiles, Inc., describing, in detail, the contents of this file *(see Item 2, attached)*.

Currently, Quintiles, Inc. is in the process of reformatting the safety and efficacy data into the Q&A software program for the supportive non-U.S. studies (Category II), as per Dr. Innerfield's initial request. It is anticipated that the reformatted data base for these studies will be available before the end of January, 1994.

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and attached items are provided.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies; 1 mailing folder with 1 diskette (for Dr. Ronald Innerfield)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS - DATE

BB

LIPHA PHARMACEUTICALS INC
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

January 11, 1994
#10-94

ORIG AMENDMENT

VIA FEDERAL EXPRESS, #1297777994
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment
Request of Dr. Daniel Gordon

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In follow-up to several telephone conversations between Dr. Daniel Gordon, Division of Biopharmaceutics, and Lipha (Teleconferences of November 4, 1993 and December 22, 1993) and, in response to his request, a gender analysis has been performed on pharmacokinetic parameters following administration of a single dose of metformin hydrochloride (an 850 mg tablet), in two Lipha studies which involved a population comprised of both sexes (U.S. Study No. 89-12-6023 and U.S. Study No. 91-06-6023). This analysis did not reveal any significant differences in pharmacokinetic disposition of metformin between male and female subjects (diabetic and non-diabetic). *(The gender analysis of U.S. Study No. 89-12-6023 is attached as Item 1 and that of U.S. Study No. 91-06-6023 as Item 2).*

We would also like to refer Dr. Gordon to the gender analysis involving the U.S. Category I and non-U.S. Category II clinical trials included within Item 8 of the NDA, as part of the Drug-Demographics analysis in both the Integrated Summary of Efficacy *(Item 8.7.5, Volume 1.70, Pages 08A-00836 through 08A-00880 and Pages 08A-00971 through 08A-00989)* and the Integrated Summary of Safety *(Item 8.8.11, Volume 1.76, Pages 08A-01946 to 08A-01957). (Copies of these sections of the NDA are attached, for convenience of review, as Items 3 and 4, respectively).*

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and attached items are provided. Please direct one CLINICAL copy to Dr. Gordon.

If there are questions relative to any of the above, please do not hesitate to contact this office.

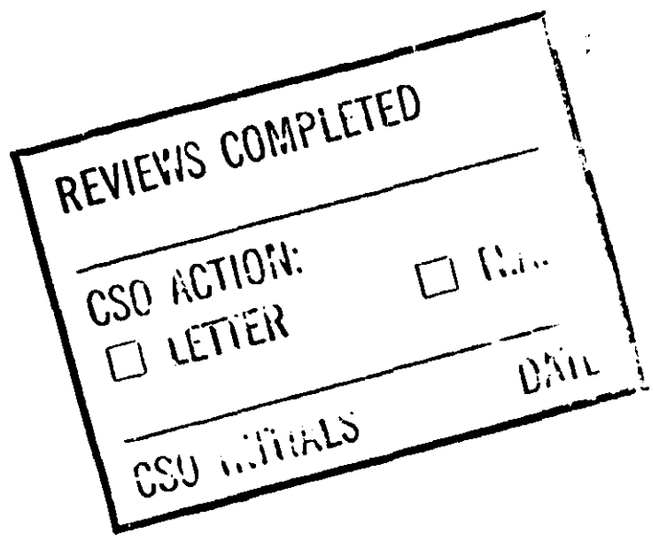
Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG

1 Archival Copy, 2 Clinical Copies



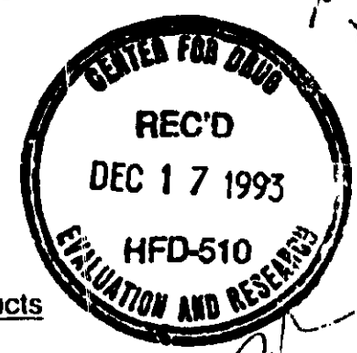
BM

LIPHA PHARMACEUTICALS INC
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

December 15, 1993
#08-93

VIA FEDERAL EXPRESS, #1092660564
ACKNOWLEDGMENT OF DELIVERY REQUESTED

ORIG NDA



Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30 ORIG AMENDMENT
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral/Amendment

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In early to mid-October, 1993, several discussions were held with Dr. Ronald Innerfield and this office regarding his interest in having all safety and efficacy data from Lipha's pivotal studies (U.S. Studies 87-1D-6023 and 87-2D-6023, Category I) and supportive non-U.S. studies (Category II) reformatted into a software program he prefers using, namely Q&A, version 4.0 for DOS. At the time, Dr. Innerfield explained that he was very familiar with this program and that it permitted storage of considerable numbers of files, allowing him to perform many data manipulations.

In response to this request, an initial teleconference was held with Dr. Innerfield and personnel from Lipha and Quintiles, Inc. (the company performing all of Lipha's statistical analyses relative to the clinical trial data base) on October 19, 1993, in order to further clarify the specifics of the request as well as obtain further information about the Q&A software program.

Since we were interested in facilitating Dr. Innerfield's review and, obviously, the re-formatting would require prompt and intensive effort, we agreed to the mobilization and re-assignment of key statistical and data management personnel by Quintiles, in order to fulfill his request in a timely fashion.

This was followed by a second "working" teleconference with Dr. Innerfield and Quintiles, Inc. personnel on November 8, 1993 (*see Item 1, attached, for a memorandum referrable to that teleconference*) at which time, he also requested that we obtain from the central laboratory, SciCor, values for one standard deviation from the reference range for all analytes involved in these studies.

Because of the rather unusual nature of this latter request (*see Item 2, a letter from Marietta M. Henry, M.D., Vice President, Medical Affairs and Laboratory Director of SciCor, regarding her perception and reservations about these values*), a delay in the originally projected timetable of several weeks occurred until these values could be transmitted to Quintiles by SciCor.

Overall, the process involved restructuring existing safety and efficacy information to match an existing Q&A file structure and converting the restructured SAS datasets into Q&A. Quality control checks were performed at a number of stages during this process.

At this time, enclosed are four diskettes (Q&A file: TEMPLATE [3 diskettes]; Q&A file: CORRLATE [1 diskette]) which are to be given to Dr. Innerfield for his use and which contain the majority of the reformatted data for U.S. Studies 87-1D-6023 and 87-2D-6023. In addition, enclosed is a 12-page document, prepared by Quintiles, describing the content of these files in detail (*see Item 3*). Since some of the information requested by Dr. Innerfield required considerable reformatting, certain fields on these diskettes currently have missing data, as indicated in the accompanying document. These additional data fields, as well as the reformatted data for the non-U.S. Category II studies, will be sent to the Division (and Dr. Innerfield), during the first week of January, 1994, according to Quintiles personnel.

Finally, since neither Lipha nor Quintiles has had past experience with the Q&A system, it should be noted that these reformatted data have not been (and can not be) analyzed/validated by us in this form. Therefore, we request that we be promptly sent any statistical results or reports generated by Dr. Innerfield through this sytem. In addition, since the single standard deviation information was not used in the data evaluation contained in Lipha's NDA #20-357, we request being informed also of any statements made or conclusions reached based on this approach of Dr. Innerfield's (*see again, Item 2, for further discussion on this topic*).

For your convenience, three copies (one ARCHIVAL and two CLINICAL) of this letter and attached items are provided.

If there are questions relative to any of the above, please do not hesitate to contact this office.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG
1 Archival Copy, 2 Clinical Copies; 2 mailing folders with 4 diskettes (for Dr. Ronald Innerfield)

BM

ORIGINAL

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

December 13, 1993
#07-93

VIA FEDERAL EXPRESS, #9633889591
ACKNOWLEDGMENT OF DELIVERY REQUESTED

ORIG AMENDMENT

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

Dr. Ronald Innerfield called this office on November 22, 1993, to discuss obtaining additional information on Patient #20-006, a 52 year old obese male with long-standing (10 years) diabetes who had participated in U.S. Study No. 87-2D-6023 and who had died suddenly of an apparent cardiac event (June 6, 1989) while receiving metformin and Placebo G in that double-blind study.

Dr. Innerfield was informed that all available information from the investigational site on this patient had been submitted with the above-noted NDA, consisting of the complete Case Report Form (which included the assessment by the Emergency Medical Service at the time of the patient's demise)(*Vol. 1.394, Pg. 12-009864*). A Patient Narrative concerning this individual was also submitted in the above-noted NDA (*Vol. 1.80, Pg. 08A-02993*).

Dr. Innerfield was also informed that the Principal Investigator, Dr. Louis Vignati, had closed his practice in the Boston suburban area, as of approximately April, 1990.

In addition, information on this patient's death was reported to the Division in the Metformin Annual Progress Report, submitted on May 31, 1990 *(Serial #038 to IND 27,966)*, as follows:

> *This 52 year old white male had NIDDM for greater than 10 years, complicated by both peripheral and autonomic neuropathy as well as peripheral vascular disease (infected foot ulcer). At the time of entry onto the study, despite maximum dose of a sulfonylurea, his fasting glucose was >200 mg/dl. The patient was obese and a cigarette smoker. There was no prior history of cardiovascular disease. On Tuesday morning, June 6, 1989, the*

patient (at work at the time) reported to the nurse at his workplace that he was experiencing chest and abdominal pain. She checked his blood pressure (normal) and wanted to obtain an electrocardiogram, which the patient refused. He was advised to go to an Emergency room for further evaluation but, instead, he went home. Several hours later, he contacted the Principal Investigator's (Louis Vignati, M.D.) office with the same complaints and was again advised to go to the Emergency room. Subsequently, he apparently collapsed at home, emergency medics were contacted by his daughter and he was brought to the local hospital DOA (dead on arrival). The hospital contacted Dr. Vignati's office at approximately 3:00 PM. The family refused permission for an autopsy and the coroner concurred.

The patient had been seen at the study site on June 1, 1989 (week 13 of the study). At that visit, his only complaint was of mild fatigue. Fasting plasma glucose was 222 mg/dl. Serum creatinine, electrolytes, liver function, renal function tests and plasma lactate were all normal.

It was Dr. Vignati's impression that the patient probably had had a myocardial infarction followed by cardiac arrhythmia and cardiac arrest. He did not think this was study drug related and thought that the patient had a number of accepted risk factors for such an event: namely, diabetes, obesity and smoking.

(The study code for this patient was promptly broken: his treated [sic] assignment had been metformin and placebo for glyburide. At the time of his study visit on May 4, 1989 [week 9], metformin plasma level was 629 ngs/ml, which is in the therapeutic range for a daily dose of 2.5 gms metformin).

Although, as stated, all available information on this patient has already been submitted to the Division, for your ease of review, enclosed, in triplicate (one ARCHIVAL copy and two CLINICAL copies), are the following items:

Item 1. Complete Case Report Form on Patient #20-006 (*a copy of this is in Vol. 1.394, Pg. 12-009864 of the NDA*);

Item 2. Narrative Summary on Patient #20-006 (*from Vol. 1.80, Pg. 08A-02993*);

Item 3. Cover letter and submission form for Metformin Annual Progress Report (Serial #038, IND No. , and Pages 076-077 and Page 085 of that report, relevant to Patient #20-006;

Item 4. A copy of the letter to Lipha from Dr. Vignati, dated April 4, 1990, indicating that he was closing his practice.

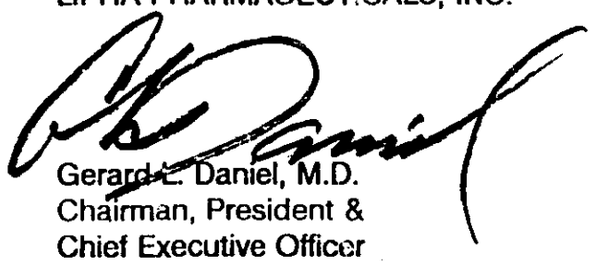
Although Dr. Innerfield had suggested contacting the deceased's family to discuss further the events surronding his death, we do not think that this would provide further insight and think that it would be needlessly upsetting to the family.

Please provide Dr. Innerfield with one of the enclosed clinical copies of this information.

Should you have any questions regarding this submission or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.



Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG
1 Archival Copy, 2 Clinical Copies

LIPHA PHARMACEUTICALS

December 6, 1993

VIA FEDERAL EXPRESS, #1092660715
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Mr. Robert Young
Division of Scientific Investigations
7520 Standish Place, Room 125
Rockville, MD 20855

Reference: NDA #20-357 Metformin HCl Oral

Dear Mr. Young:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In response to your telephone conversation today with Dr. Anita Goodman, attached is the information you requested, related to Lipha's adequate and controlled clinical trials, as submitted in the above-noted NDA:

Item 1. Listing of the adequate and controlled U.S. clinical trials (Study No. 87-1D-6023 and Study No. 87-2D-6023)*(from Vol. 1.69, Pgs. 08A-00450 and 08A-00458)*;

Item 2. A copy of the final protocol for Study No. 87-1D-6023, as well as all amendments *(from Vol. 1.107, Pg. 08B-00468)*;

Item 3. A copy of the final protocol for Study No. 87-2D-6023, as well as all amendments *(from Vol. 1.123, Pg. 08B-06092)*;

Item 4. A list of all investigators (both alphabetical and numerical, by site) for each of the above-noted studies *(from Vol. 1.107, Pg. 08B-00853 [Study No. 87-1D-6023] and Vol. 1.124, Pg. 08B-06597 [Study No. 87-2D-6023)*;

Item 5. A tabular display of enrollment, by site, for each of the above-noted studies *(from Vol. 1.105, Pg. 08B-00165 [Study No. 87-1D-6023] and Vol. 1.121, Pg. 08B-05555A [Study No. 87-2D-6023])*.

We hope this adequately responds to your request. Should you have any questions or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D. /ag

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

cc (letter only):
Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Rockville, MD

GLD/AMG

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

December 1, 1993
#06-93

ORIG AMENDMENT

VIA FEDERAL EXPRESS, #1092660704
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In response to a telephone conversation with Dr. Ronald Innerfield and this office on November 22, 1993, enclosed in triplicate (one ARCHIVAL copy and two CLINICAL copies) is the case report form for Patient #06-006, participant in U.S. Study No. 87-2D-6023 (**Item 1**), and also the case report form reflecting this same patient's participation in the open-label Extension Study, U.S. Study No. 89-1C-6023 (Patient #06-006-2) (**Item 2**). Dr. Innerfield had requested these data on this patient because she had been terminated after approximately five months of participation in Study No. 89-1C-6023, based on a persistently elevated fasting plasma lactate level. ***(NOTE:*** *A preliminary report on Study No. 89-1C-6023, an uncontrolled open-label extension study of the two Phase III double-blind studies, was provided in the metformin NDA. This study will be reported on, in full, in the first safety update to this NDA).*

It should be noted that, on Dec. 30, 1988, at the time of her Baseline evaluation for Study No. 87-2D-6023 (i.e., prior to receiving any study drug, and while on maximum dose glyburide [20 mg/day]), this 70 year-old female patient had an elevated fasting plasma lactate value (2.4 mmol/L), in conjunction with a fasting plasma glucose value of 216 mg/dL. Since, despite the elevated baseline lactate value, the patient was entirely well and had normal renal function, she was enrolled in the study and was randomized to receive metformin and glyburide. On this regimen, her plasma glucose had decreased to 134 mg/dL by study termination, with a fasting plasma lactate level of 0.9 mmol/L at the final visit of this 29 week study (July 7, 1989). During Patient #06-006's participation in Study No. 87-2D-6023, plasma metformin levels were consistently within the expected range, as were plasma glyburide levels. During this same study, her serum bicarbonate level varied from 22.0 to 32.0 mEq/L, with a calculated anion gap varying from 2 to 11 mEq/L, given as $[Na+] - ([Cl] + [HCO^{-3}])$ = anion gap.

Subsequently, there was approximately a ten month hiatus between the end of the double-blind study and this patient's enrollment in the open-label study (Study No. 89-1C-6023), during which time, her diabetes was managed with diet and glyburide, 20 mg/day.

At the time of enrollment into Study No. 89-1C-6023 (Visit 1, May 1, 1990), her fasting plasma glucose on this regimen was 239 mg/dL and her fasting plasma lactate was again elevated at 3.2 mmol/L (on glyburide alone).

Thereafter, the fasting plasma lactate level, while on metformin alone or on metformin plus glyburide, remained high. At Visit 4 (June 20, 1990), while on metformin alone, the lactate was reported as being 3.6 mmol/L. At this time, it was noted that the patient had possibly been inappropriately instructed to take four 850 mg metformin tablets per day, and she was promptly instructed to reduce the metformin dose to two such tablets per day. On this dose, the plasma lactate level at the subsequent visit (Visit 5, July 9, 1990) was 3.9 mmol/L and her plasma glucose was 210 mg/dL. *(**NOTE:** It was decided, with the site, that this patient's "maximum tolerated dose" of metformin should be considered as two 850 mg tablets per day or 1700 mg).*

At this visit, because of persistently elevated plasma glucose levels, glyburide was added to the continued metformin treatment, with gradual improvement in glucose control on the combined regimen, such that at Visit 8 (Sept. 28, 1990), while on 1700 mg/day of metformin and 10 mg/day of glyburide, the patient's fasting plasma glucose was 162 mg/dL. However, at this same visit, the patient's fasting plasma lactate level was 5.3 mmol/L. At the time, the patient was feeling well, although somewhat fatigued following completion of a cross-country trip. Metformin was temporarily discontinued when these laboratory results became available. (No other biochemical parameters except for the fasting plasma glucose [162 mg/dL] were obtained at this visit).

The patient returned for an interim visit/End of Treatment evaluation on October 8, 1990, while on glyburide, 20 mg/day, only. At that time, her fasting plasma lactate was 2.7 mmol/L and the fasting plasma glucose was 272 mg/dL and there was no detectable metformin present in a plasma sample. In view of the patient's age (at that time, 72 years of age) and the fact that she lived in South Carolina, although she was being followed at Georgetown University Hospital, Washington, D.C., it was mutually agreed that the patient's participation in the study should be terminated. *(See **Item 3**, cover letter and Pages 085-089 and Page 143 of the Metformin Annual Progress Report for 1990 [Serial #048, IND #27,966], concerning this patient's termination).*

During the open-label study, her serum bicarbonate level varied from 18.5 to 22.7 mEq/L, with a calculated anion gap varying from 10.3 to a maximum of 12.5 mEq/L, given as [Na+] - ([Cl] + [HCO^3]) = anion gap. *(**NOTE:** At Visit 1 of this study, while on glyburide alone, the patient's calculated anion gap was 12.3 mEq/L, with a bicarbonate of 21.7 mEq/L. At the termination visit, while on glyburide alone, the serum bicarbonate level was 20.5 mEq/L and the calculated anion gap was 11.5 mEq/L).*

At a subsequent site-monitoring visit, it was noted that one of the study physicians (an Endocrinology Fellow) had indicated "*Abnormal Lab Result*" (specifically, "elevated lactate levels + mild acidosis") as the reason for termination, amongst possible additional choices of: *Adverse Experience, Intercurrent Illness, Treatment Failure, Protocol Violation, Non-Compliance, Patient*

Decision, Lost to Follow-Up, Other, Death. Thereafter, the Principal Investigator, Dr. Terry Taylor, (at the time, Acting Chief of the Division of Endocrinology at Georgetown University Hospital) wrote a letter for the record, to clarify as to why this patient had been terminated (see **Item 4**).

As noted above, we concurred in the decision to prematurely terminate the participation of this elderly patient in the metformin study for a number of reasons: her advanced age, the fluctuations of lactate level which did not seem to be related to study medication and the geographic constraints on close follow-up. However, at no time was there any clinical or biological evidence of "acidosis".

Please provide Dr. Innerfield with one of the enclosed clinical copies of this information.

Should you have any questions regarding this submission or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG
1 Archival Copy, 2 Clinical Copies

LIPHA PHARMACEUTICALS LLC
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL: 212-223 1280 • FAX: 212-223 1398

November 23, 1993
#05-93

VIA FEDERAL EXPRESS, #1092660752
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In response to a telephone conversation with Dr. Ronald Innerfield and this office on November 18, 1993, enclosed in triplicate (one ARCHIVAL copy and two CLINICAL copies) are tabular summaries of safety information on dropped subjects from the non-U.S. Category III metformin studies. This safety information (where available), has already been submitted as part of each individual study synopsis (presented in Volumes 1.202-1.204 of the NDA) but the tables permit a more global perspective of these safety data. (*NOTE: These tables were transmitted by FAX directly to Dr. Innerfield today*).

The studies are listed in the same order as in tabular displays already included in the NDA and according to features of study design: Table 1 consists of non-U.S. Category III *controlled* clinical trials related to indications sought in this NDA; Table 2 consists of non-U.S. Category III *uncontrolled* clinical trials related to indications sought in this NDA; Table 3 consists of non-U.S. Category III *controlled* clinical trials of uses other than those sought in this NDA; Table 4 consists of non-U.S. Category III *uncontrolled* clinical trials of uses other than those sought in this NDA; and Table 5 consists of non-U.S. Category III *Clinical Pharmacology/Pharmacokinetic* studies. The studies are further grouped according to their completion status and the presence or absence of case report forms.

Please provide Dr. Innerfield with one of the enclosed clinical copies.

Should you have any questions regarding this submission or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D./gf

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG
1 Archival Copy, 2 Clinical Copies

LIPHA PHARMACEUTICALS LTD
Lipha
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TEL: 212-223 1280 • FAX: 212-223 1398

November 19, 1993
#04-93

VIA FEDERAL EXPRESS, #0456213273
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

During the course of a telephone conversation with Dr. Ronald Innerfield on November 9, 1993, the subject of which was Lipha's rationale behind changing the Upper Limit of Normal (ULN) for fasting plasma lactate used in our U.S. Phase III pivotal trials from 1.3 mmol/L (as given by SciCor, the central laboratory used for these studies) to 2 mmol/L, Dr. Innerfield requested that we submit SciCor's methodology for plasma lactate determination as well as the instructions given to the investigational sites regarding processing of blood samples for this analyte.

At the time of that telephone contact, Dr. Innerfield was advised that Lipha had previously submitted background information to the Division as to our decision to utilize a higher ULN for fasting plasma lactate for U.S. Study Nos. 87-1D-6023 and 87-2D-6023, based on results obtained for pre-randomization, baseline fasting plasma lactate levels for these patient populations (mean value of 1.48 ± 0.51 mmol/L, range 0.6 to 3.4 mmol/L in November, 1988, N = 143)(***Serial Submission #024 [August 15, 1989], IND***

In that submission to the IND, a protocol addressing some of the factors which might affect plasma lactate values (presence of diabetes, obesity, physical factors, sample processing, etc.) was also provided: Lipha Study No. 89-3C-6023 (***"An Assessment of Factors which may Influence Fasting Plasma Lactate Concentrations in Ambulatory Subjects"***). The report of that study, which did not involve any pharmacologic agents, has been accepted for publication by **Diabète et Metabolisme** and will appear in issue No. 4, 1993 (see below, item 3).

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room, #14B-30

November 19, 1993
#04-93

For further clarification and in response to Dr. Innerfield's request, the following documents are enclosed in triplicate (one ARCHIVAL copy and two CLINICAL copies):

Item 1. SciCor's methodology for plasma lactate determination and instructions provided to investigators for sample processing.

Item 2. A copy of Serial #024, Submission to IND (August 15, 1989), for ease of review. (***NOTE:*** *This also includes additional information provided to all investigators regarding blood sample handling and processing for lactate determinations* ***[Attachment B]***).

Item 3. A copy of the manuscript submitted to **Diabète et Metabolisme**, related to Study No. 89-3C-6023, providing some additional insight into factors affecting lactate values.

Please provide Dr. Innerfield with one of the enclosed clinical copies.

Should you have any questions regarding this submission or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D./gj

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

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1 Archival Copy, 2 Clinical Copies

BM

LIPHA PHARMACEUTICALS INC
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TEL 212-223 1280 • FAX 212-223 1398

NDA ORIG AMENDMENT

November 18, 1993
#03-93

VIA FEDERAL EXPRESS, #0456213262
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

Dr. Ronald Innerfield requested additional clinical information on Patients #29, 35, 59 and 87, who had participated in Lipha non-U.S. Study No. MET/D/86/BERGI and who, according to the data base listings, had been terminated prematurely from the study. (Patients #29, 35 and 87 were on metformin plus diet whereas Patient #59 was on diet alone).

An inquiry for this information was made through Lipha's German subsidiary, and, attached, as Items 1 and 2, is the response from the Co-Investigator in this study, Dr. Bernhard R. Teupe, consisting of his letter, in German (Item 1), as well as an English translation thereof (Item 2). If, as mentioned in the letter, additional information is forthcoming on Patient #59 (on diet alone), it will be promptly transmitted to the Division. The currently available information is provided as one ARCHIVAL copy and two CLINICAL copies.

Please provide Dr. Innerfield with one of the clinical copies.

Should you have any questions regarding this submission or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

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1 Archival Copy, 2 Clinical Copies

LIPHA PHARMACEUTICALS
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

November 16, 1993
#02-93

VIA FEDERAL EXPRESS, #0456213251
ACKNOWLEDGEMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357), submitted to the FDA on September 29, 1993.

In response to several telephone conversations between Dr. Ronald Innerfield and this office on November 8 and 9, 1993, and at his request, enclosed, in triplicate (an ARCHIVAL copy and two CLINICAL copies) are the following documents concerning Patient 13/17 (AML, date of birth: 11/10/35), a participant in U.S. Study No. 87-2D-6023:

Item 1. The complete case report form.

Item 2. A copy of this patient's hospital record related to her hospitalization from Aug. 9, 1990 through Aug. 14, 1990.

Please provide Dr. Innerfield with one of the copies of these records.

Should you have any questions regarding this submission or if additional information is needed, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D./gf

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/AMG
1 Archival Copy, 2 Clinical Copies

BZ

ORIGINAL

LIPHA PHARMACEUTICALS INC

9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

November 12, 1993

VIA FEDERAL EXPRESS #0456213214
ACKNOWLEDGMENT OF DELIVERY REQUESTED

Food and Drug Administration
CDER, HFD-510
Attention: Document Control Room #14B03
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Reference: NDA #20-357 Metformin HCl Oral

Dear Dr. Sobel:

Reference is made to our New Drug Application for Metformin Hydrochloride Oral (#20-357) submitted to the FDA on September 29, 1993.

Pursuant to the telecons with Dr. Nevius, Capt. John Short and this office on November 5, 1993 and in accordance with our subsequent FAX to the Division on the same date, we are submitting a revised INDEX to the above NDA. This is identified as "REVISED INDEX, November 12, 1993". In addition to an ARCHIVAL copy, we have enclosed copies for each reviewer to include CHEMISTRY, PHARMACOLOGY, PHARMACOKINETICS, CLINICAL (two copies) and STATISTICS. Note that the INDEX has been revised to present a more detailed listing of the information in Item 6 - Human Pharmacokinetics and Bioavailability, Item 8 -- Clinical Data Section and Item 10 -- Statistical Section. Thus, there are no changes in the substantive contents of the NDA.

Should you have any questions regarding this submission or if additional information is required, please advise.

Sincerely yours,

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/eg

C

ORIGINAL

LIPHA PHARMACEUTICALS INC
9 WEST 57TH STREET • SUITE 3825 • NEW YORK NEW YORK 10019-2701
TEL 212-223 1280 • FAX 212-223 1398

September 29, 1993

NEW CORRESP

VIA FEDEX #045621315

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 211
12420 Parklawn Drive
Rockville, MD 20852

Reference: **IND #27,966 Metformin HCl Oral**
NEW DRUG APPLICATION
NDA #20-357 (Preassigned Number)

Gentlemen:

Reference is made to our Notice of Claimed Investigational Exemption for a New Drug for Metformin, IND

Attached herewith is the ORIGINAL of our cover letter submitting the above New Drug Application which was inadvertently left out of the volumes delivered to the FDA on September 29, 1993. We ask that you incorporate the Form 365h, original cover letter and attachments into the first volume of the archival copy in your possession. Also attached is a copy of the cover letter with the FDA time, date and receipt stamp.

If there are any questions, please call me at (212) 223-1392.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
CSO INITIALS DATE

Sincerely,

I put note on archival ~~copy~~ cover letter that these originals are here.
10/12/94

LIPHA PHARMACEUTICALS, INC.

Gerard L. Daniel

Gerard L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/eg
Attachments as above

N 20-357

LIPHA
PHARMACEUTICALS

September 29, 1993

HAND CARRIED

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Sent 9/29/93 submission other than original 7th cover letter, and original 356H, and original letter dated 7/26/93 from Janet Foss 10/12/93

Reference: **IND #27,966 Metformin HCl Oral**
NEW DRUG APPLICATION
NDA #20-357 (Preassigned Number)

Gentlemen:

Reference is made to our Notice of Claimed Investigational Exemption for a New Drug for Metformin, IND Submitted herewith is the New Drug Application for this drug. The preassigned NDA number is **20-357**. Request is hereby submitted for an expeditious review and approval.

For ease of review, we have placed a listing of the volumes contained in the ARCHIVAL and REVIEWER copies under Attachment I. Please note that the clinical report volumes contained in Item 8 are provided in full and intact, as presented in Item 8, in Item 10 for the STATISTICAL review copy. By prior agreement with Captain John Short, however, the Final Study Reports in Item 8 are referenced in Item 10 of the ARCHIVAL copy.

Note that Items 7 (Microbiology) and 14 (Patent Certification) are not applicable to this NDA. Item 13 (Patent Information) is attached to the application form in Volume 1.1.

Lipha Pharmaceuticals, Inc. hereby requests for Metformin the five-year post-approval exclusivity period provided for under sections 505 (c) (3) (D) (ii) and 505 (j) (4) J(D) (ii) of the Federal Food, Drug, and Cosmetic Act on the ground that neither Metformin's active ingredient, nor any ester or salt of that active ingredient, has been approved in any other application submitted under section 505 (b) of the Act.

Lipha Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under section 306 of the Act in connection with this application.

For your information, a check in the amount of representing of the application fee for the Metformin NDA (including clinical data) has already been submitted with our letter #082 dated September 23, 1993 (see Attachment II).

A letter of authorization from our parent company, Lyonnaise Industrielle Pharmaceutique (LIPHA, S.A.), appears as Attachment III. The contact person at Lipha Pharmaceuticals, Inc. is the undersigned. Should there be any questions, please call me at (212) 223-1392.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

Gerard-L. Daniel, M.D.
Chairman, President &
Chief Executive Officer

GLD/eg

Letter and Attachments in Triplicate

NDA 20-357
Glucophage (metformin hydrochloride)
Lipha Pharmaceuticals Inc.

May 26, 1994

MEMORANDUM OF MEETING

Lipha Representatives:

Bruce Goddard, RAC, Senior Director of Compliance & Regulatory Affairs
Barbara Weil, Ph.D., Senior Director, Science and Technology
Robert Harris, Ph.D., President, Harris FRC Corporation (Consultant)
Ranga Velagaleti, Ph.D., Vice President, Environmental Fate and Assessment, Analytical Bio-Chemistry Laboratories, Inc.

FDA Staff:

Dr. Ysern
Mr. Short (CSO)
Dr. Vincent (HFD-102)
Mr. Glen Smith (HFD-102)
Ms. Christina Good (HFD-102)

Purpose: Lipha requested the meeting to discuss our concerns regarding their Environmental Assessment included in the NDA. Comments from HFD-102 were FAX'd to Lipha on May 4, 1994, and they responded with an NDA amendment dated May 20, 1994 (received May 23), which included a revised Environmental Assessment.

Discussion and Conclusions: Mr. Goddard noted that the drug substance (DS) is manufactured in Calais, France and the dosage form (DF) is manufactured in Hitchin, U.K. He said that when Lipha looked at their EA in light of the HFD-102 comments, they realized how it could be improved and hoped that the revision provided in the May 20 amendment was a substantial improvement.

Mr. Smith said that the new version of the EA is an improvement but still lacks many things, as determined from his cursory review of the document (given the limited time to review it by the meeting today). He said he still noted deficiencies in some of the areas as follows:

1) Items 5 & 6. They still have not provided an identification of the impurities for the DS. He said they should provide either the CAS #s or structures of the impurities. Dr. Weil noted that the impurities are identified in the Chemistry section of the application and all are present at less than 30 ppm. Mr. Smith said that even though the information is in one part of the application, the EA must stand alone and the information must be included therein. Mr. Smith noted that

if this information is considered confidential, it can be submitted as an appendix to the EA and stamped "CONFIDENTIAL".

2) Manufacture of the DS. For the xylene used, Lipha must revise the control statement to show how it is reclaimed or discarded.

3) Manufacture of the DF. For items like spraying the tablets and washing the equipment, there must be a detailed description of what happens to the residual material.

4) Letter of Authorization for Foreign Countries Stating that the Facility or Process is in Compliance with Local Regulations. Lipha has no problem getting such a statement from Calais, France where the DS is manufactured, but they are unable to get such a document from the UK because there are no permits required for production of the DF and no inspections are done. It was noted that Appendix 5 of the current EA contains the "Proposed Guidelines Regulating Pharmaceutical Industry in the U.K.". Mr. Goddard said that this document is not in effect, and he was told it will not go into effect in the foreseeable future. Dr. Vincent said that if a letter of authorization cannot be obtained for the manufacture of the DF, completing Item 6 would be sufficient. Ms. Good said she would check with the British Embassy as to their requirements for pollution control for the manufacture of drug dosage forms and get back to Lipha.

5) Items 7 and 8. Mr. Smith noted that Lipha's information for Item 7 (Fate of Emitted Substances in the Environment) and Item 8 (Environmental Effects of Released Substances) is inadequate. Tests (or adequate literature references) must be performed to know the fate and effect of metformin if released into the air, water, or ground. He said that we need results of tests performed as per the Environmental Assessment Technical Handbook (FDA, March 1987). Mr. Smith also noted that we do NOT want raw data, but we do want results from each test, not just mean values. Refereed journal articles are acceptable for evidence on fate and/or effects if the articles show or discuss specific testing on the drug.

Mr. Goddard noted that the company (not identified) who will market metformin in the U.S. (a licensee, not Lipha) will surely submit a supplement (following approval of the NDA) providing for them to manufacture the DF in the U.S. He asked what testing and paperwork would be required as far as the EA is concerned. Dr. Vincent said that they would need to supplement the EA approved with the NDA, providing only for the changes; he said they possibly might have to address Items 5, 6, and 9, as they pertain to the new facility.

Mr. Smith also informed the Lipha representatives that all English translations must be certified, e.g., court certified.

Mr. Goddard asked how they should proceed from here, especially regarding item 5) of this memo. It was agreed that Lipha could provide informal information to Mr. Smith to determine if they are approaching the solution in the right direction. But, it was made very clear that none of these informal communications would be part of the NDA until an official submission to the NDA is received. Mr. Smith also indicated that he would not do a detailed review the informal information; he would merely look it over in sufficient detail to determine if Lipha is on the right track.

ACTION ITEM:

Ms. Good to check with the British Embassy to determine if the U.K. has any requirements for pollution control for the manufacture of drug dosage forms, and she will get back to Lipha with the answer.

John R. Short, CSO

Attachments
Revisions to Item 3 of EA (handed out at the meeting)

cc: NDA Arch
HFD-510
attendees
HFD-510/YYChiu, AFleming, EGalliers, DJenkins
HFD-511/JShort 5/27/94/ft/lp/6/2/94/N20357MM.2JS
Concurrence: GSmith, CGood 5/27, PVincent, XYsern 5/31/94

NDA 20-357 November 4, 1993
Glucophage (metformin hydrochloride)
Lipha Pharmaceuticals

MEMORANDUM OF 45-DAY MEETING

FDA Staff:

Dr. Sobel
Dr. Troendle
Dr. Fleming
Dr. Gueriguian
Dr. Innerfield
Dr. Jordan
Mr. Hertig
Dr. Chiu
Dr. Ysern
Mr. Short (CSO)
Mr. Cerny (HFD-009)
Dr. Gordin (HFD-426)
Dr. Nevius (HFD-713)

Purpose: 45-day meeting to determine if we can file the NDA and to set projected completion dates (PCD) for each discipline's review.

Discussion and Conclusions:

Medical: OK to file. This NDA will be reviewed for efficacy by Dr. Gueriguian and for safety by Dr. Innerfield. *PCD = End of January 17, 1994.* Attempting to schedule the E&M Advisory Committee to meeting in March 1994. Dr. Gueriguian is concerned about a lack to definitive dose-response data. Mr. Short to ask Lipha to provide either a "clean, purposeful study" or a compilation of all data in one submission. Dr. Innerfield is concerned about the high dose of metformin and the higher incidence of lactic acidosis at higher doses.

Pharmacology: OK to file. *PCD = February 28, 1994.*

Chemistry: OK to file. *PCD = January 8, 1994.*

Biopharmaceutics: OK to file. *PCD = February 28, 1994.*

Statistics: OK to file as long as a more detailed index is provided before November 28, 1993. *PCD = February 14, 1994.* [Note: Dr. Anita Goodman of Lipha was contacted by Dr. Nevius and Mr. Short on November 5, 1993, and she agreed to provide a more detailed index for both the Statistical and Medical review copies within a few days. The index for the entire submission will not be changed.]

Project Management: OK to file.

DSI: Not present. Will have to coordinate with Dr. Gueriguian to determine what studies need investigation.

Advisory Committee: Will attempt to set E & M Advisory Committee meeting for March 1994.

This drug is rated 1P.

Dr. Fleming announced that he and Mr. Short would be co-project managers for this NDA. Dr. Fleming noted that the purpose of the project manager will not to be looking over everyone's shoulder, but assist each discipline in meeting the Projected Completion Dates. He emphasized that quality should be first and timing second.

CONCLUSION: The application will be filed on November 28, 1993.

ACTION ITEMS:

1. Mr. Short to ask Lipha to provide dose-response data, either a "clean, purposeful study" or a compilation of all data in one submission

2. Mr. Short to find and make copy of the E&M Advisory Committee meeting minutes when metformin was previously reviewed.

3. Dr. Young (DSI) to contact Dr. Gueriguian regarding studies to be investigated.

John R. Short, CSO

cc: NDA Arch
HFD-510
attendees
HFD-344/RYoung
HFD-426/JHunt
HFD-510/EGalliers, DJenkins
HFD-511/JShort 11/8/93 \N20357MM.JRS
Concurrence: JGueriguian, RInnerfield, AFleming 11/8, DHertig, AJordan 11/9, XYsern, YYChiu 11/10, ENevius 12/7, DGordin 12/9, GTroendle, SSobel 12/13/93

pre-NDA/IND
Glucophage (metformin hydrochloride)
Lipha Pharmaceutical

July 9, 1992

Memorandum of Meeting

Lipha Pharmaceutical Representatives:

G. Daniel, M.D. - Chairman and President
A. Goodman, M.D. - Vice President, Medical Affairs
M. Fencik - Senior Director, Data Management
B. Goddard - Director, Compliance and Regulatory Affairs

Consultants for Lipha Pharmaceutical:

R. DeFronzo, M.D. - Chief, Diabetes Division, University of Texas
R. Harris, Ph.D. - President, Harris FRC Corporation
E. Vander Elst, M.D. - Corporate Vice President, Quintiles
W. Solleçito, D.Ph. - Executive Vice President, Quintiles

FDA Staff:

Dr. Sobel
Dr. Troendle
Dr. Gueriguian
Dr. Innerfield
Dr. Chiu
Dr. Ysern
Dr. Jordan
Mr. Hertig
Ms. Braithwaite
Dr. Dorantes (HFD-426)
Mr. Marticello (HFD-713)

Purpose:

The meeting was requested by Lipha to discuss their NDA for Glucophage (metformin). Lipha plans to submit the NDA at the end of 1992. Please refer to the background material dated June 29, 1992 (submitted to IND 27,966), and the attachments for further details.

Discussion and Conclusions:

Dr. Daniel began the meeting with a brief overview of the Lipha organization and the proposed agenda.

Dr. Goodman presented an overview of the two pivotal trials as follows:

87-1D-6023: A double-blind, randomized, parallel trial in obese patients with NIDDM, that have failed to control their glycemia with diet alone. Patients are randomized to receive either metformin [850 mg - 2,550 mg (dose dependent upon 5 week titration phase)] or placebo. The primary efficacy parameters are a reduction in FPG, HbA1C, OGTT, total cholesterol (HDL/LDL), and body weight.

87-2D-6023: A double-blind, randomized, parallel trial in obese patients with NIDDM, that have "failed" maximum sulfonylurea (SU) therapy. Patients are randomized to receive either metformin [500 mg - 2,500 mg (dose dependent upon titration phase)], glyburide (20 mg) or metformin [500 mg - 2,500 mg (dose dependent upon titration phase)] + glyburide (20 mg). The primary efficacy parameters are a reduction in FPG, HbA1C, OGTT, total cholesterol (HDL/LDL), and body weight.

Study 1D demonstrated that metformin reduces FPG, HbAlc and plasma glucose levels. Study 2d demonstrated that the addition of metformin to glyburide reduced FPG, HbAlc and plasma glucose levels.

Both studies demonstrated a high incidence of gastrointestinal adverse reactions (approximately 50%), however, all were rate as mild or moderate.

Dr. Daniel the presented the proposed labelling for metformin (refer to the attachment for specific wording). The Division suggested several modifications, including the deletion of point #3. In addition, Dr. Sobel stated that the treatment benefits, if allowed, would be moved to the **CLINICAL PHARMACOLOGY** section of the package insert.

Dr. Sobel stated that the primary hindrance to approval would be the similarity between metformin and phenformin (removed from the market as an "imminent hazard" due to the incidence of lactic acidosis). Therefore, any additional supporting information regarding safety would be important and should be submitted.

Dr. Daniel stated that both the chemical structure and the metabolic pathway of each drug are different. He also indicated that no country, in which the drug has been approved, has withdrawn it from the market for safety reasons, and that post-marketing surveillance is on-going.

Dr. Daniel also requested input from the Division in regard to the amount of supporting data required for the application. He indicated that efficacy data was available from 1982 to present, however, safety data could be traced back prior to that time. Dr. Sobel indicated that because the two pivotal trials consisted of a total of only 500 patients, all data available (both safety and efficacy) should be submitted.

Dr. Troendle indicated that if possible, sub-group analyses should be prepared in regard to gender and ethnicity.

Mr. Hertig asked the status of the carcinogenicity testing. He indicated that the final report must be included in the NDA submission. Dr. Harris stated that the final report may not be completed, however, a preliminary report would be included. Ms. Braithwaite indicated that if the report submitted was not considered satisfactory at the time the application was considered for filing (approximately 45 days after submission), the entire application would be refused for filing.

The meeting concluded with representatives from Lipha expressing their gratitude to the Division for their comments and suggestions in order to aid them in the preparation of their forthcoming application.

Lana L. Braithwaite

Attachments
Overheads used during presentation

IND
Metformin Hydrochloride
Lipha Chemicals, Inc.

December 2, 1987

Memorandum of Meeting

Lipha Representatives:

Gerard L. Daniel, M.D., President
Bruce E. Goddard, B.S., Director, Compliance & Regulatory Affairs
Anita M. Goodman, M.D., Medical Director
Clifford J. Bailey, Ph.D., Consultant, U. of Aston in Birmingham, U.K.
Ralph A. DeFronzo, M.D., Investigator, Yale University Medical Center
Robert H. Harris, Ph.D., Consultant, President, Harris FRC Corporation
Gerald M. Reaven, M.D., Investigator, Stanford Univ. School of Medicine

FDA Staff:

Dr. Sobel
Dr. G. Troendle
Dr. Fleming
Dr. Jordan
Mr. Hertig
Mr. Short
Dr. Fan (HFN-713)

Purpose: Pre-Phase III meeting. Lipha Chemicals requested the meeting as a follow-up to the last meeting of December 3, 1986, to discuss three Phase III protocols. The protocols were submitted October 29, 1987.

Discussion and Conclusions:

Dr. Daniel described the sequence of events leading up to the meeting and also provided an overview of the proposed. ongoing, and cancelled Phase I & II studies. The studies to be conducted by Karem (2) and Arieff in California had to be cancelled due to external circumstances beyond Lipha's control. The metabolic studies by Drs. DeFronzo (86-1-6023) and Reaven (86-2-6023) are about half finished and another by Dr. Reaven (87-4B-6023) has just begun. Dr. Daniel noted that the adverse reactions reported to date are not remarkable:

Drs. DeFronzo and Reaven each provided results of their above-mentioned studies. Both were pleased with the results obtained to date.

Dr. Jordan asked whether metformin uncouples oxidative phosphorylation. Dr. Bailey replied that he does not think so.

Dr. Goodman then provided an outline of each of the Phase III studies for which Lipha is seeking concurrence or guidance (see attached copies of overheads used).

Protocol 87-1D-6023 -- to determine safety and effectiveness in the control of obese, Type II diabetics who are not adequately controlled with diet alone. The Division had no objection to this study.

Protocol 87-2D-6023 -- to determine the safety and effectiveness in combination with glyburide in the control of obese, Type II diabetics who are not well-controlled on first or second generation sulfonylureas. The only objection to this protocol is that it should contain an additional arm with metformin alone and placebo alone to see if metformin is effective without also using glyburide. If metformin alone is not effective, then this would also provide evidence to support the combination of glyburide plus metformin according to our combination policy. Lipha agreed to add this arm.

Protocol 87-3A-6023 -- to demonstrate the ability of metformin to reduce insulin requirements and still maintain acceptable glycemic control in Type II diabetics who are poorly controlled with insulin. Dr. Troendle noted that merely demonstrating a lowering of insulin requirements probably will not be sufficient to obtain approval of an indication for metformin; other benefits must be demonstrated.

When asked whether good results from the first two studies would be sufficient for filing an NDA, Dr. Troendle responded in the affirmative.

Mr. Hertig noted that no animal carcinogenicity data had been submitted.

Dr. Fan noted that for each of the studies they should include: 1) the "evaluable population" in addition to the "intend-to-treat population" in the efficacy analysis, and 2) an analysis of the poolability of the data. Also, for the third study, they should include a sample-size determination and a statistical plan for analyzing the data.

It was agreed that Lipha Chemical will proceed with the first two protocols (the second one amended with an additional arm) but the third one will be revised and resubmitted for comment. The first two also will be resubmitted but in final form.

John R. Short, CSO

Attachments
Overheads used by Dr. Goodman

cc: IND Orig
HFN-810
HFN-713/MFan
HFN-810/attendees, JGueriguian
HFN-810/JShort 12/3/87/ft/jaf/12/7/87 (WANG 0362r)
Concurrence:Fleming/12/3/87/Hertig/Jordan/Troendle/12/4/87
Sobel/12/5/87

IND
Metformin hydrochloride
Lipha Chemicals, Inc.

May 29, 1986

Memorandum of Meeting

Lipha Representatives:

Gerard L. Daniel, M.D., President and Medical Director
Lorraine D. Long, Asst. to the President and IND Coordinator
Katherine M. Farragher, B.S., Clinical Research Associate
Richard A. Guarino, M.D., Consultant, Oxford Research Int'l Corp.
Robert H. Harris, Ph.D., Consultant, Harris FRC Corp. (reg affairs)

FDA Staff:

Dr. Sobel
Dr. Gueriguian
Dr. Troendle
Dr. Pierce
Mr. Hertig
Mr. Short

Purpose: To outline future clinical trials, to express our concern regarding the past experience with this type of compound, and to consider clinically-relevant efficacy criteria beyond glycemic control.

Discussion and Conclusions:

This meeting was requested by the Division to find out where the company was headed and to express our concerns regarding this type of compound.

Dr. Daniel gave a brief historical perspective of the company (they are new to the Division) and of the treatment of diabetes. He also reviewed the basic safety considerations in favor of metformin and then summarized its benefits as follows:

- does not cause hypoglycemia in normal doses
- does not cause additional hyperinsulinemia
- may lessen morbidity and diabetic complications
- is effective in sulfonylurea failures
- low incidence of lactic acidosis (0.006/1,000 pt. yrs.)

Dr. Daniel also described the various metabolic clinical studies they intend to perform. One by DeFRanzo is provided for in the IND and will start in about 10 days. They also intend to do a special pharmacokinetics study, an analysis of foreign safety data (see attached proposal), and certain efficacy studies.

Dr. Sobel asked how hard is the data (0.006/1,000 pt. yrs.) for the incidence of lactic acidosis. Dr. Daniel said that they intend to confirm this figure. Dr. Sobel informed them that they must consider the broader safety picture and not just concentrate on lactic acidosis.

The Division staff emphasized that they would have to take a very hard look at the effectiveness of metformin. The firm was told that just demonstrating a reduction in blood sugar would not be sufficient for approval of an NDA; they would also have to demonstrate effectiveness on other parameters which improve the condition of the diabetic. Two suggestions were: 1) an improvement in lipid profile and 2) increased sensitivity to insulin.

The sponsor was informed that if this drug went as far as an NDA, it would probably be subjected to an advisory committee review.

The firm asked whether it would be OK to proceed directly to a large Phase III study after the Phase I studies were completed. They were told that this would be OK, i.e., they could skip Phase II.

It was agreed that they would work closely with the Division reviewer in generating the Phase III protocols.

John R. Short, CSO

cc: IND Orig.
HFN-810
HFN-810/attendees
✓HFN-810/JShort/6-2-86
KG/6-13-86/#1693R
Concurrences: REastep/6-4, LPierce/6-9, GTroendle/6-11, DHertig/6-11, SSobel/6-11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND
Metformin Hydrochloride
Lipha Chemicals Inc.

December 3, 1986

Memorandum of Meeting

Lipha Representatives:

Gerard L. Daniel, M.D., President and Medical Director
Richard A. Guarino, M.D., Consultant, Oxford Research Int'l. Corp.

FDA Staff:

Dr. Sobel
Dr. Gueriguian
Dr. Troendle
Dr. Pierce
Mr. Short

Purpose: The meeting was requested by Lipha to discuss Phase III protocol designs, in particular effectiveness endpoints other than glycemic control. (Note: The protocols were first presented to the Division at this meeting, i.e., they were not submitted previously nor were they submitted at the time of the meeting.)

Discussion and Conclusions:

Dr. Daniel gave a brief presentation on the progress of the various metabolic clinical studies. Only two have begun with a total of only 10 patients receiving the drug.

Dr. Daniel indicated that he soon will respond to the manufacturing/quality control concerns itemized in our May 19, 1986 letter.

Dr. Guarino presented a number of proposed Phase III studies in order to get our imput. All were unacceptable because they were not double-blind, in some cases they were uncontrolled, and they did not properly evaluate efficacy endpoints other than glycemic control.

In order to give them a better idea of what we are looking for, Dr. Pierce outlined the following two studies:

1. A double-blind, placebo-controlled study in which metformin is administered to Type II diabetics who are well controlled on insulin. The question to be answered would be whether or not insulin action is improved by metformin administration, i.e., is the insulin requirement reduced and to what degree. HbAlC levels should not be more than 120% above the upper limit of normal.

2. A double-blind, placebo-controlled study in which metformin is evaluated with other oral therapy to determine which drug is more effective. This would be done with Type II obese diabetics who had never before received oral therapy or those who are sulfonylurea failures. Either glyburide or glipizide should be used for comparison to metformin.

Dr. Daniel was upset that we did not agree with the firm's approaches. He also had difficulty understanding Dr. Pierce's approach #1, even though it differed from one of his proposals only by the fact that Dr. Pierce suggested using patients who were controlled on insulin and the firm proposed using patients uncontrolled on insulin.

Dr. Gueriguian reiterated the Division's concern that we cannot perpetuate the mistakes of the past and that the future approval of oral diabetic therapy will hinge on a demonstration that the drug does more for the diabetic than just maintain an optimal blood sugar level. The following endpoints were proposed by the Division staff for their consideration: 1) an improvement in lipid profile, 2) increased sensitivity to insulin (such as indicated in our proposed study #1 above), 3) improved peripheral vascular flow, and 4) fibrinolysis. An increase in fibrinolysis would not be the basis for approval but if found, could result in further studies designed to show whether or not there was a beneficial effect on atherosclerotic plaque.

Dr. Daniel agreed to reconsider their proposed studies and would submit revised protocols.

John R. Short, CSO

cc: IND Orig.
HFN-810
HFN-810/attendees
HFN-810/JShort 12/4/86 (WANG 2574R)
Revised as per Drs. Pierce & Troendle comments 1/22/87
Concurrence: RPierce, JGueriguian 12/5/86, GTroendle 12/8/86,
SSobel 1/15/87/ft/pdz/1/27/87

ADVERTISING MATERIAL

Requested in AP Letter

INTEGRATED SUMMARY OF SAFETY

This Consists of 11 Volumes (1.73 through 1.83)
(They are in a box to accompany the AP Action Package)

Federal Register

April 6, 1979

Pharmacy Withdrawal

Federal Register

Friday
April 6, 1979

Part V

Department o
Health, Educa
and Welfare

Food and Drug Administrati

Phenformin Hydrochloride

C. Patients for Whom Benefit of Phenformin Therapy May Outweigh Risks.

The purpose of this proceeding is to determine whether phenformin is shown to be safe for general marketing under the conditions prescribed, recommended, or suggested in its labeling. See my response to CCD exception, para. 1 at 7–10, *supra*. The existence of a more limited patient population for whom the benefits of phenformin therapy may outweigh the risks is not at issue. *Id.* The question of a voluntary, limited distribution program raised in the Secretary's suspension order is also not part of this proceeding.

For these reasons and in view of pending litigation concerning the propriety of the Secretary's invocation of the imminent hazard provisions, I do not adopt this section of the Initial Decision (at 42–44) but rather find as follows: The effect of withdrawal of phenformin on certain employment opportunities of diabetics does not preclude a decision that phenformin has no longer been shown to be safe. Limitations on occupational options because of health problems are not unique. Because phenformin is not currently labeled for use in only those patients who are allergic to insulin or unresponsive to desensitization, such use for that population is not an issue in this proceeding; and even a finding of safety for such use would not constitute a finding of general safety for use under phenformin's labeling and would not be sufficient to avoid withdrawal.

H. CCD Witnesses.

I adopt the Administrative Law Judge's summary of the CCD data submitted in this proceeding. See my response to CCD exception, para. 13 at 28–29, *supra*.

I. Discussion and Conclusions/Ultimate Findings and Order.

Having made reference to the administrative record throughout his opinion, the Administrative Law Judge summarized the evidence, without citation, and stated his conclusions and findings with respect to the issues designated at the August 30 prehearing conference. See Initial Decision at 45–48. I am issuing Findings of Fact, Conclusions of Law, and a Final Order. In most instances, these will supplement the discussion, conclusions, and findings of the Initial Decision. However, to the extent that my findings are inconsistent with those of the Administrative Law Judge, the Initial Decision is superseded. As modified by my Findings of Fact, responses to CCD exceptions and comments on the Initial Decision, contained in this order, the Initial Decision is adopted and made a part of the final order.

IV. Findings of Fact and Conclusions of Law.

A. Findings of Fact.

1. Phenformin hydrochloride (phenformin) is a new drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p), which has been shipped in interstate commerce pursuant to new drug applications filed by Geigy Pharmaceuticals, Division of Ciba-Geigy Corporation (NDA's 11–624 and 12–752), and USV Laboratories, Division of USV Pharmaceutical Corporation (NDA's 17–128 and 17–127) and approved by the United States Food and Drug Administration.

2. Phenformin is indicated only for symptomatic, adult onset, nonketotic diabetes mellitus (diabetes) (B–506(n)). According to its labeling, phenformin lowers elevated blood glucose levels in diabetics.

3. Phenformin is recommended for use only if diet and weight reduction have first been tried and have failed and only when insulin cannot be used and the sulfonylurea drugs do not achieve adequate control. *Id.*

4. Diabetes is a chronic metabolic disorder in which there is an inadequate secretion or utilization of insulin for normal metabolism (B–497 at 1, B–487 at 12–14, Tr. 92). Diabetes is characterized by an abnormal elevation in blood sugar, which has been used as a principal benchmark in its diagnosis and treatment (B–497 at 2, 8–9, Tr. 87–88, 294).

5. Diabetes is frequently accompanied by severe complications, most particularly cardiovascular and kidney diseases (Tr. 106–107, 295, B–497 at 9–10, CG–43 at 7). Diabetes is the fifth leading cause of death in the United States (CG–43 at 7).

6. There are approximately 5 million diagnosed diabetics in the United States today, most of whom are under treatment (CG–43). About 8 to 12% of these persons were taking phenformin during 1975–1976 (CG–43, CG–20 at 2, CG–11 at 2). The number of persons being treated with phenformin declined from 481,000 in 1974 to approximately 337,000 in 1977 (CG–43, CG–80).

7. The great majority (80–90%) of adult-onset diabetics are overweight (Tr. 406, CG–9 at 2, CG–11 at 2).

8. Dietary control is the most preferred and most effective means for treating adult onset diabetes (B–506(n), B–469 at 3, B–473 at 5, B–499 at 19–20, B–495 at 7, CG–2 at 2, CG–11 at 3). Dietary regulation is the treatment of choice because, when a diabetic's caloric intake is decreased, there is less stress on the available insulin supply, insulin sensitivity is improved (Tr. 11, 94), and the ability to utilize naturally produced insulin is enhanced (B–495 at 10, B–487 at 14–15).

9. The use of exogenous (not produced naturally in the body) insulin is effective in the treatment of adult-onset diabetes by rectifying the insulin deficiency. (B–479 at 17, B–475 at 7). There is evidence that the administration of exogenous insulin also retards the vascular complications of diabetes (Tr. 24, 292–296, B–487 at 12).

10. Phenformin is effective in lowering blood sugar, but this effect is frequently limited to two years or less (Tr. 200–201, 296–297, 303–310, B–475 at 8–9, B–473 at 6, B–489 at 26, B–469 at 9, 13–14, 31). Moreover, the apparent effectiveness is difficult to measure and verify because phenformin is often used in combination with diet and/or sulfonylurea drugs (Tr. 167, 408, 426, 479–483, 523, B–499 at 4, CG–61, CG–20 at 2, CG–15 at 1–2).

11. Phenformin does not stimulate insulin production (B–500(n)). Phenformin does not promote the use of naturally produced insulin (B–495 at 10, Tr. 278–280). Phenformin does not aid or correct the metabolic abnormalities of diabetes (Tr. 295–297, B–497 at 4–5, B–487 at 12–14, B–499 at 20–21). Phenformin does not correct the complications of diabetes (Tr. 443–451, B–344 at 1060). Phenformin does not promote weight reduction (Tr. 450–451, B–509 at 4, 11, B–503 at 6–7, B–475 at 13, B–487 at 16–19, B–72 at 642, B–390 at 105, B–497 at 4).

12. There are essentially no adverse effects involved in the treatment of diabetes by diet and weight reduction. The adverse effects of insulin are far outweighed by its beneficial effects (Tr. 20–21, 198–199, 292–293, 410–411, B–177 at 1, B–475 at 7).

13. Some diabetologists experience difficulty in achieving patient compliance with diet and/or insulin therapies. These problems can be and usually are overcome by diabetologists (Tr. 20–21, 199–200, CG–2 at 2, B–465 at 2–8, 13, B–469 at 3–4, B–503 at 4, B–497 at 24–25).

14. Lactic acidosis is a disorder of intermediary metabolism, in which there is an abnormal accumulation of lactic acid in the blood and tissues (B–489 at 5, B–412 at 40, Tr. 261–262).

15. The fatality rate among persons who suffer from lactic acidosis is

approximately 50% (CG–26, Tables 4 and 5, B–94).

16. Diabetes does not itself cause lactic acidosis (Tr. 262–263, 270, B–499 at 6–10, 17–20, B–475 at 15–17, B–184, B–412 at 50, B–467 at 7–10).

17. A biochemical basis supports the relationship between phenformin and the under utilization and over production of lactate, and the evidence of the modes of phenformin activity provides a probable explanation for this relationship (Tr. 266, 269–277, 461–462, 633–636, B–274, B–68 at 186, B–501 at 2–6, CG–24 at 12, 23, B–487 at 10–11, 18–19, B–497 at 18–23, B–499 at 10–15). The relationship is also supported by the frequently short time between the ingestion of phenformin and the onset of lactic acidosis (B–63 at 44, B–479 at 12–14, B–272 at 70–72, B–467 at 10–11, B–412 at 180).

18. There is a disproportionate incidence of lactic acidosis among diabetics taking phenformin (Tr. 47, 276, B–485 at 11–12, B–473 at 6–9, B–475 at 11–12, 15–17, B–499 at 5–10, 17–18, B–467 at 7–10, B–503 at 10, B–509 at 3, B–479 at 6–10, B–485 at 10, B–64, B–471 at 2, 7–9, CG–20 at 4).

19. Reports in the published medical literature and in retrospective studies constitutes substantial and convincing evidence of the association between lactic acidosis and phenformin, when used alone or in combination with the sulfonylurea drugs (B–64, B–65, B–471, B–290, B–94, B–493 at 3–10, B–92, B–93, B–235, B–236, B–338, B–390, B–33, B–42, B–15, B–96, B–272, B–473 at 6–9, B–475 at 15–18, B–467 at 8–13, B–479 at 3–11, Tr. 634).

20. The association between phenformin and lactic acidosis appears to be dose-related (B–509 at 2–4, B–59, CG–26, Tables 6 and 7, B–481 at 29–30, B–495 at 5, B–64, B–471 at 12–17, B–479 at 11–13, B–63). The association is also supported by evidence involving suicide attempts by use of phenformin (B–479 at 11–14, B–63 at 43–44).

21. An association between phenformin and lactic acidosis need not be based upon quantification of the background incidence of lactic acidosis among the population at large or among the diabetic population not taking phenformin. The background occurrence or incidence is unknown for the vast majority of nonreportable diseases (Tr. 218–219, 383–386, 493–494).

22. A precautionary warning about the possible association between lactic acidosis and phenformin was added by USV to the phenformin labeling in 1964 (CG–25 at 1–2, B–506(e)). A strengthened lactic acidosis warning and statement of contraindications, designed to screen diabetic patients predisposed to lactic acidosis, were added to the labeling in 1970 (CG–25 at 3). In 1974, the lactic acidosis warning was strengthened and a more detailed description of medical conditions predisposing patients to *lactic acidosis was* included (CG–25 at 7, B–506(k)). A black box warning concerning lactic acidosis was included in phenformin labeling approved June 1976 (CG–25 at 7–8, B–506(m)).

23. The 1970–1976 labeling did not result in limiting the use of phenformin to those patients for whom it was not contraindicated (CG–26, CG–25 at paras. 24, 25, 28 and Exs. 2 and AA, CCD–5, CG–61, CG–63 at 19–20, CG–20 at 2–4, Tr. 348, 357, 383, compare Tr. 555–560 with B–24 at 102 and B–23 at 339, CG–49 at 3).

24. The current (January 1977) labeling for phenformin (B–500(n), Ex. V to CG–25) is designed to restrict its use to only those patients with none of the lactic acidosis predisposing risk factors.

25. The current labeling cannot reasonably be expected to result in the detection of those persons for whom phenformin is contraindicated:

a. With respect to screening for predisposing renal dysfunction, the recommended tests are inadequate and are frequently not performed by general practitioners (B–503 at 12–13, B–495 at 4, B–497 at 4–5, B–487 at 20–22, B–483 at 7–10, B–467 at 11–13, B–489 at 11–14, Tr. 112–116, 592–594).

b. With respect to screening for predisposing liver disease, routine workup is inadequate (Tr. 29–32, 112–121). Thus, compliance with the labeling requirements by general practitioners is unlikely to prevent the occurrence of lactic acidosis (B–471 at 29–30, B–467 at 8–11, 17–18).

26. Lactic acidosis is associated with the use of phenformin even in compliance with the January 1977 labeling, that is, at or below 100 mgs. daily dose and without predisposing risk factors (CG–26, Table 6, B–59 at 4–8, 14–15, and Table 3, B–481 at 29–30, B–495 at 4, B–412 at 180–185, B–272 at 70–72, B–86 at 974–975, B–471 at 2–7, 13–14, 20–31, B–467 at 4–13, 18–19, B–236, B–64, B–493 at 4–13, B–64, Tr. 359–360).

27. The Ciba-Geigy study of the cases of confirmed lactic acidosis associated with phenformin (CG–26) is deficient, and the incidence of lactic acidosis suggested by the data in that study is unreliably low.

a. The study included only those reports in the United States medical literature, whereas several of the retrospective studies are reported in the foreign medical literature (e.g., B–63, B–275, B–276, B–412). Moreover, occurrences of lactic acidosis are likely to be underreported due to a loss of interest in the medical community once a significant number of such reports have been published (B–475 at 12).

b. Physicians are under no legal obligation to report adverse reactions to drug firms. Voluntary reporting, upon which the study is based, significantly understates the true number of adverse reactions (B–479 at 11, B–481 at 8–11, CG–1 at 8, Tr. 43, 336–339, 342–345, 492–505). In measuring adverse reactions, retrospective and prospective patient record reviews, while not ideal, are entitled to greater weight than voluntary reporting to manufacturers (B–481 at 11–14, Tr. 342–345; compare B–479 at 2–11 with Tr. 564–566).

c. The study excluded those cases where there were data indicating impaired renal function. Although impaired renal function is a predisposing factor, those responsible for the study did not determine whether the impaired renal function preexisted use of phenformin or appeared as a consequence of the phenformin-associated lactic acidosis. Thus exclusion of these data was unjustified. (Tr. 552, 568, 592–594, CG–26 at 5–6, B–475 at 14–15, B–483 at 10–12, B–467 at 11–13, B–493 at 4–8, B–471 at 21–32).

d. The study excluded cases where the data were inadequate to determine the presence of predisposing factors; no attempt to obtain such information was documented in the record (CG–26 at 9).

e. The criteria used in the study to determine the presence of lactic acidosis were more conservative than those used by most investigators (CG–49 at 3, B–471 at 1–5).

28. The reported decrease in the incidence of phenformin-associated lactic acidosis during 1974–1977 must be discounted due to *underreporting*, a corresponding decrease in the number of diabetics taking phenformin from 481,000 in 1974 to 337,000 in 1977, and a reporting lag time of approximately 9 months (printout attached to CG–26; see Ciba-Geigy/USV Proposed Findings of Fact, para. 22b; Tr. 623–625).

29. Most diabetics in this country who are treated for diabetes by a physician are not treated by a diabetologist (B–483 at 10, B–471 at 23, B–499 at 18–20, Tr. 116–117).

30. The evidence strongly suggests that the incidence of lactic acidosis is greater among patients of general practitioners than among patients of diabetologists (B–477 at 5, B–493 at 4, CG–2 at 4, CG–12 at 9, CG–14 at 2, CG–10 at 3, B–471 at 23, B–499 at 18–20, Tr. 116–119, 347–348, 383, 425–430, 518–524).

31. The testimony of diabetologists about the absence of lactic acidosis among their patients is evidence that the great majority of phenformin-associated lactic acidosis occurs among patients of those physicians with the least special training in screening and testing patients for use of phenformin and in recognizing the consequent lactic acidosis. *Id.* In addition, a significant number of cases of lactic acidosis could exist among the patients treated by diabetologists and general practitioners in the course of their individual practice and be undetected due to their relative infrequency. See Tr. 298–300; *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973).

32. Phenformin has not been shown to be uniquely useful in treating the obese adult-onset diabetic who is "hyperinsulinemic" (B–497 at 5–13 and 25–26, B–509 at 10–11, B–362 at 363–387, B–475 at 18–19, B–503 at 3–4, and B–495 at 9–10, B–469 at 11–13).

33. The removal of phenformin from the market will not seriously disrupt treatment of diabetic patients (CG–10 at 4, B–509 at 3–4, B–467 at 19, B–465 at 4–5, 9–10, B–469 at 8–9, B–479 at 17–19, B–495 at 6–7, B–503 at 7, 14, B–499 at 18–20, B–471 at 22–23, 32, Tr. 298–300).

B. Conclusions of Law.

1. The Bureau of Drugs has sustained its burden of showing, based on new evidence of clinical experience, evaluated together with the data available when the NDA's for phenformin were approved, that phenformin is not shown to be safe for use under the conditions approved in its new drug applications.

2. The Bureau of Drugs has established an association between lactic acidosis and phenformin. Although this relationship has not been conclusively shown to be causal, there is a substantially disproportionate incidence of lactic acidosis among diabetics treated with phenformin.

3. Lactic acidosis is associated with phenformin at dosage levels at or below those prescribed in the January 1977 labeling. Lactic acidosis is associated with phenformin absent the "predisposing factors" for which phenformin is contraindicated.

4. It has not been shown that the current labeling contraindications will reduce the incidence of phenformin-associated lactic acidosis so as to render phenformin safe for use.

5. The risks of the use of phenformin outweigh its benefits.

V. Final Order

Therefore, on the basis of the foregoing Findings of Fact and Conclusions of Law, the Initial Decision of the Administrative Law Judge, as modified by this order, and the record of the proceedings, and under the Federal Food, Drug, and Cosmetic Act (sec. 505(e)(2), 52 Stat. 1052 as amended (21 U.S.C. 355(e)(2))) and the authority delegated to the Commissioner (21 CFR 5.1), the new drug applications for phenformin, and all the amendments and supplements thereto, are hereby withdrawn, effective November 15, 1978. The introduction or delivery for introduction into interstate commerce of phenformin, except pursuant to an exemption granted under section 505(i) of the act, is prohibited. 21 U.S.C. 331(d).

Dated: November 15, 1978.

Donald Kennedy,
Commissioner of Food and Drugs.

[Docket No. 77N-0150]

[FR Doc. 79-10363 Filed 4-5-79; 8:45 am]
BILLING CODE 4110-03-M

Phenformin Hydrochloride; Proposal to Withdraw Approval of New Drug Applications; Initial Decision

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency is issuing the Administrative Law Judge's Initial Decision on the proposal to withdraw approval of new drug applications for phenformin hydrochloride.

ADDRESS: The Initial Decision may be seen in the office of the Hearing Clerk (HFA–305), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Richard A. Anderson, Office of the Associate Commissioner for Health Affairs (HYF–21), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1170.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the Federal Register, the agency is publishing the Commissioner's final decision on withdrawal of approval of new drug applications for phenformin hydrochloride and his denial of a petition for reconsideration. The Administrative Law Judge's Initial Decision on phenformin hydrochloride is set forth below:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

Initial Decision [1]

[Docket No. 77N-0150]

Proposal to Withdraw Approval of the New Drug Applications for Phenformin Hydrochloride

1. Phenformin found to have limited short-term beneficial effects in the treatment of diabetics under the conditions of use prescribed, recommended or suggested in its labeling.

2. The conditions of use prescribed, recommended or suggested in the labeling for phenformin found inadequate to exclude from treatment those persons for whom the drug is contraindicated as a result of factors which predispose patients to lactic acidosis.

3. The occurrence of lactic acidosis found associated with the use of phenformin in patients for whom the drug is indicated under its current labeling and the incidence of such occurrences as compared to the diabetic population at large is not susceptible of quantification on this record.

4. Therapeutic modalities other than phenformin found shown to be effective for treating patients for whom phenformin is indicated in its labeling without the same degree of risk associated with the use of phenformin.

5. The limited benefits of phenformin found insufficient to support a finding of safety in light of the risks attending its general marketing under the approved NDA's. Approval of the NDA's for phenformin ordered withdrawn pursuant to § 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e).

William Bickerstaff, George Doherty, Richard Morey, Richard Nolan, Richard Serbin, Alfred Schretter, Nicholas Weiskopf, for the manufacturing parties.

Neil Chayet, Michael Morrell, Anthony Roccograndi, and *Daniel Shaw* for the Committee for the Care of the Diabetic.

Arnold Friede, Frederick Degnan, for the Bureau of Drugs, Food and Drug Administration.

By DANIEL J. DAVIDSON, Administrative Law Judge

By notice published in the Federal Register of August 12, 1977 (42 FR 40959), this matter was assigned for formal evidentiary public hearing by

[1] Pursuant to § 12.125(a) (21 CFR 12.125(a)), exceptions to this initial decision must be received by the Hearing Clerk not more than 30 days after the date hereof. Replies to exceptions must be received by the Hearing Clerk not more than 20 days thereafter.

Bristol-Myers, Merck in deals for new pharmaceuticals

By IRIS TAYLOR

Bristol-Myers Squibb Co. of Princeton said it has licensed the U.S. rights to a French Type II diabetes drug currently under review at the U.S. Food and Drug Administration (FDA).

Separately, Merck & Co. of Whitehouse Station said its West Point Pharma unit will begin marketing five new generic drugs, giving it a total portfolio of about 16 products and a strengthened presence in the generic market. In New Jersey, Merck's new generic drugs will take market share from Warner-Lambert Co.'s cholesterol lower Lopid and American Home Products Co.'s athritis drug Orudis.

BMS, a player in the diabetes market since the 1980's when it marketed insulin for Novo Nordisk A/S, agreed to market Glucophage, a Lipha S.A. of France product, assuming it wins FDA approval.

Bristol-Myers Squibb spokeswoman Peggy Ballman said Glucophage has been on the fast track since its application was filed with the FDA last September. The FDA's Endocrine and Metabolic Advisory Committee on March 18 unanimously recommended its approval as a first-line treatment for Type II diabetes when patients have failed a diet and exercise regimen.

Usually, the FDA approves drugs within weeks or months of a recommendation by an advisory committee.

Over 13 million Americans suffer from diabetes, according to Jerry Franz, a spokesman for the American Diabetes Association (ADA) in Chicago. Nearly half of them do not know they have the disease because its symptoms are silent for years. "It affects the eyes, kidneys and heart," said Franz. "If a person is unaware and not treated, it can have significant complications and cause death later on."

Of the other half, nearly 7 million, 90 percent have been diagnosed with Type II diabetes. "It's a large market and growing because of the increasing elderly population," said Ballman.

'Important drug'

ADA's Franz said in Type I diabetes, a patients' body produces no insulin and must be injected daily with a synthetically produced insulin product. In Type II diabetes, the body produces some insulin but may need drugs "to stimulat the body to use its insulin more efficiently or stimulate the pancrease to make more. There are many companies that make oral drugs for Type II," he said.

"Getting body weight down can control blood sugars," Franz said. "But, that doesn't work for all people."

Franz said the ADA has no position on Glucophase yet because its not approved.

"We're waiting to see what the FDA does with it."

Glucophase belongs to a new class of drugs called biguanide hypoglycemic agents. If approved, it will compete with the existing class of drugs called sulfonylureas. The Upjohn Co. of Michigan, Pfizer Inc. of New York and Hoechst Roussel Pharmaceuticals Inc. of Bridgewater make sulfonylureas.

Glucophase is in tablet form and can be taken alone twice a day by the majority of patients and three times by others, or in combination with another drug.

"It's going to be an important drug for us," said Ballman. "We believe it's an important market for the future on its own because there are some unmet medical needs there. For Type II diabetes, which this product treats, patients are not always successful in controlling blood sugar. Also, it's related to our cardiovascular portfolio. Hypertension is a common side effect of diabetes. It's a nice addition to our cardiovascular portfolio and will help us increase our presence in the diabetes market."

Glucophage, developed by Lipha's U.S. subsidiary Lipha Pharmaceuticals Inc. in New York, and first launched in France in 1959, is on the market in 80 countries. Ballman said the FDA

Please turn to next page

Squibb, Merck in deals for pharmaceuticals

From preceding page

tracked the drug "because it had such a strong clinical file outside the United States."

Bristol-Myers Squibb's big-selling heart drug Capoten ntly received additional approval as a therapy for Type ibetes. That gives the $11.4 billion pharmaceutical giant vo-product diabetes portfolio. Bristol-Myers Squibb tinues to distribute Novo's insulin products.

Merck & Co.'s five newly acquired generic drugs are: alolam (C-IV), an anti-anxiety drug which Upjohn markas Xanax; carbidopa/levodopa for Parkinson's Disease; fibrozil, a cholesterol drug that Warner Lambert markets as Lopid; ketoprofen, the generic version of American Home Products Co.'s Orudis for arthritis; and, naproxen, another arthritis drug marketed by Syntex Laboratories Inc. markets as Naprosyn.

These are the first products marketed by West Point Pharma that are not off-patent Merck drugs.

Merck said the products are manufactured for its West Point Pharma label by leading generic drug companies.

David Doll, West Point Pharma's general manager, said expanded portfolio demonstrates "that Merck will be involved in generic pharmaceuticals for the long term. We will significantly expand our product offering in the coming months."

END

J.H.M. RESEARCH &DEVELOPMENT, INC. 5776 SECOND STREET,N.E. WASH. DC 20011

20357

NDA 20-357/S-021

AUG 4 2000

Bristol-Myers Squibb
Attention: William J. Regan
Director - CMC for Marketed Products
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Regan:

Please refer to your supplemental new drug application dated June 27, 2000, received July 5, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage® (metformin hydrochloride) Tablets, 500 mg, 850 mg, and 1000 mg.

This "Special Supplemental - Changes Being Effected in 30 Days," provides for an increase in the amount of material charged to the coating equipment in the manufacture of the 500 mg tablets.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Ms. Jena Weber, Regulatory Health Project Manager, at 301-827-6422.

Sincerely,

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

[redacted]

CHEMIST'S REVIEW

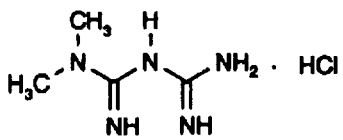
Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 20-357** Approved: 29-DEC-1994
Name and Address of Applicant: Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute Princeton, NJ 08543-400 P.O Box 4000 (609) 252-4000 (609) 252-4732	**Supplement** SCM-021 Doc 27-JUN-2000 Rec. 05-JUL-2000 **Name Of The Drug** Glucophage Tablets **Nonproprietary Name** Metformin Hydrochloride Tablets
Supplement provides for provide for an increase in the amount of material charged to the coating equipment in the manufacture of the 500 mg tablets	**New Correspondence** --

Pharmacological Category	**How Dispensed**	**Supporting Documents**
Antihyperglycemic Agent	Oral Rx	--
Dosage Form Tablets	**Potencies** 500, 850 and 1000 mg	

Chemical Name and Structure

Metformin Hydrochloride

$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)



N,N-Dimethylbiguanide hydrochloride or *N,N*-Dimethylimidodicarbonimidic diamide monohydrochloride

Comments: The main change proposed in this SUPAC supplement is to allow for an increase in the amount of material charged to the coating equipment in the manufacture of the 500 mg tablets at the approved manufacturing facility in Humacao, Puerto Rico. In support of this submission the applicant provides: (1) Description of the minor changes that correspond to adjustments in the coating steps of the manufacturing procedure, (2) Master and executed batch records incorporating the proposed changes, (3) Dissolution profile comparisons, and (4) Stability Commitment. Dissolution profiles of tablets manufactured with current and proposed changes are basically superposed (similarity factor, f_2, ~ The Humacao facility has been found acceptable based on profile by the District Office (EER Summary Report dated 26-JUL-2000). The submission is in accordance with SUPAC-IR Level 2 changes, and the required information has been adequately provided.

Conclusions and Recommendations Satisfactory CMC information has been provided to support the increase in the amount of material charged to the coater in the manufacture of Glucophage 500-mg tablets at the Humacao facility. From the chemistry point of view, this supplement can be approved.

Reviewer Name (and signature) **Date Completed:** 26-JUL-2000
Xavier Ysern, PhD

R/D Init.

filename: /nda/20537s21.doc

DISTRIBUTION: Original: NDA 20-357 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20357/021 Priority: 1P Org Code: 510
Stamp: 05-JUL-2000 Regulatory Due: 05-JAN-2001 Action Goal: District Goal: 01-DEC-2000
Applicant: BRISTOL MYERS SQUIBB
4000
PRINCETON, NJ 085434000
Brand Name: GLUCOPHAGE (METFORMIN HCL) 500 / 850 MG
Established Name:
Generic Name: METFORMIN HCL
Dosage Form: TAB (TABLET)
Strength: 500, 850 AND 1000 MG

FDA Contacts:			
	J. WEBER	(HFD-510)	301-827-6422 , Project Manager
	X. YSERN	(HFD-510)	301-827-6420 , Review Chemist
	S. MOORE	(HFD-510)	301-827-6430 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-JUL-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2623458
SQUIBB MANUFACTURING INC
STATE RD #3 KM77.5
HUMACAO, PR 00791
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JUL-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

[redacted]

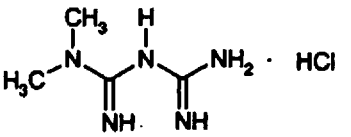
CHEMIST'S REVIEW

Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 20-357** Approved: 29-DEC-1994
Name and Address of Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute Princeton, NJ 08543-400 P.O Box 4000 (609) 252-4000 (609) 252-4732	**Supplement** SCM-016 Doc 01-FEB-1999 Rec 05-FEB-1999 **Name Of The Drug** Glucophage Tablets **Nonproprietary Name** Metformin Hydrochloride Tablets
Supplement provides for an alternate stand alone packaging operation site change for Glucophage 1000-mg tablets at BMS' facility in Mayagüez, Puerto Rico.	**New Correspondence** --

Pharmacological Category	**How Dispensed**	**Supporting Documents**
Antihyperglycemic Agent	Oral Rx	--
Dosage Form Tablets	**Potencies** 500, [redacted] 850 and 1000 mg	

Chemical Name and Structure

$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)



N,N-Dimethylbiguanide hydrochloride or
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride

Comments: This **SUPAC Changes Being Effected (CBE) Special Supplement** for an alternate stand alone packaging operation site change for Glucophage 1000-mg tablets in HDPE bottles containing [redacted] 100, [redacted] tablets, using the same container/closure system in the approved application. The packaging site, the Bristol-Myers Squibb Laboratories Company in Mayagüez, Puerto Rico, is an approved facility to package Glucophage 500-mg and 850-mg tablets in HDPE bottles and PVC [redacted] blisters. As stated by the applicant, Glucophage (metformin hydrochloride) 1000-mg tablets packaged at Mayagüez will be placed into the routine marketed product stability testing program. Also, a statement of compliance with cGMP and the date of the latest FDA inspection (October 26 – December 17, 1998) in Mayagüez are included in this supplement. The facility has an acceptable status based on profile (EER Summary Report attached).

Conclusions and Recommendations Stand alone packaging operations site changes for immediate release solid oral dosage forms, utilizing approved container(s)/closure(s) can be submitted as CBE supplement (February 18, 1997, letter from the Agency). Satisfactory CMC information has been provided to support the packaging of Glucophage 1000-mg tablets at Mayagüez. From the chemistry point of view, this supplement can be approved.

Reviewer Name (and signature) **Date Completed:** 01-MAR-1999
Xavier Ysern, PhD

R/D Init.

filename:
/nda/20537s16.doc

DISTRIBUTION: Original: NDA 20-357 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern

[redacted]

AP SUBAC-IR CBE

APPEARS THIS WAY
ON ORIGINAL

[redacted]

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20357/016 Priority: 1P Org Code: 510
Stamp: 05-FEB-1999 Regulatory Due: 05-AUG-1999 Action Goal: District Goal: 01-JUL-1999
Applicant: BRISTOL MYERS SQUIBB 4000
PRINCETON, NJ 085434000
Brand Name: GLUCOPHAGE (METFORMIN HCL) 500 / 850 MG
Established Name:
Generic Name: METFORMIN HCL
Dosage Form: TAB (TABLET)
Strength: 500, 850 AND 1000 MG

FDA Contacts: X. YSERN (HFD-510) 301-827-6430 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 26-FEB-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 2627673
BRISTOL LABORATORIES INC DIV
FOREIGN TRADE ZONE #7 RD #114
MAYAGUEZ, PR 00680
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-FEB-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: FINISHED DOSAGE PACKAGER

APPEARS THIS WAY
ON ORIGINAL

[redacted]

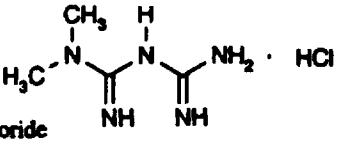
CHEMIST'S REVIEW

Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA #** 20-357 Approved: 29-DEC-1994
Name and Address of Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute Princeton, NJ 08543-400 P.O Box 4000 (609) 252-4000 (609) 252-4732	**Supplement** SCM-015 Doc 29-JAN-1999 Rec 02-FEB-1999 **Name Of The Drug** Glucophage Tablets **Nonproprietary Name** Metformin Hydrochloride Tablets
Supplement provides for the manufacture of the metformin hydrochloride and magnesium stearate [redacted] at the [redacted] approved facility.	**New Correspondence** –

Pharmacological Category Antihyperglycemic Agent	**How Dispensed** Oral Rx	**Supporting Documents** DMF [redacted]
Dosage Form Tablets	**Potencies** 500, [redacted] 850 and 1000 mg	

Chemical Name and Structure

Metformin hydrochloride
$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-24-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylbiguanide hydrochloride or
N,N-Dimethylimidodicarbonimidic diamide monohydrochloride



Comments: This Supplement, SCM-015, provides for the manufacture of the metformin HCl and magnesium stearate [redacted] at the [redacted] approved facility. The [redacted] produced at [redacted] will be used in the formulation of Glucophage Tablets at all manufacturing approved sites. The [redacted] manufacturing process is the same as the approved process at [redacted] The use of this [redacted] was proposed in supplement S-003 and approved on 30-APR-1996. The presence of magnesium stearate in the [redacted] The use of this [redacted] considered as an improvement, is a minor modification in the drug product manufacturing process. There are no changes in the total formulation quantity of magnesium stearate [redacted] the quantitative composition of the tablets, or the drug product specifications. [redacted] release specifications for the metformin HCl and magnesium stearate [redacted] are adequately provided. Stability testing of the [redacted] for three different lots (six months data at 40°C/75% RH, 25°C/60% RH and ambient) showed basically no changes from release values. [redacted] An acceptable District recommendation, based on profile, was given (17-MAY-1999) to [redacted]

Conclusions and Recommendations Satisfactory CMC information has been provided to support the use of the metformin hydrochloride and magnesium stearate [redacted] at the [redacted] for the manufacture of glucophage (metformin HCl) tablets. From the chemistry point of view, this supplement can be approved.

Reviewer Name (and signature) **Date Completed:** 25-MAY-1999
Xavier Ysern, PhD

R/D Init.

filename: /nda/20537s15.doc

DISTRIBUTION: Original: NDA 20-357 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern

AP

[redacted]

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20357/015 Priority: 1P Org Code: 510
Stamp: 02-FEB-1999 Regulatory Due: 02-JUN-1999 Action Goal: District Goal: 28-APR-1999
Applicant: BRISTOL MYERS SQUIBB
4000
PRINCETON, NJ 085434000
Brand Name: GLUCOPHAGE (METFORMIN HCL) 500 / 850 MG
Established Name:
Generic Name: METFORMIN HCL
Dosage Form: TAB (TABLET)
Strength: 500, 850 AND 1000 MG

FDA Contacts: X. YSERN (HFD-510) 301-827-6420 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 17-MAY-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-MAY-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

[redacted]

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000 609 252-4000

April 28, 1995

NDA 20-357

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

/S/
5/8/95

Dear Sir or Madam:

Pursuant to 21 CFR 314.80(c)(2), the Periodic Adverse Drug Experience Report for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357, is enclosed.

Glucophage® (metformin hydrochloride) Tablets received conditional FDA approval on December 29, 1994, Glucophage® marketing was not possible until final FDA approval of the patient package insert. Bristol-Myers Squibb will base its post-marketing periodic reporting submission on the December 29, 1994 approval letter.

The period covered by this report is January 1, 1995 to March 31, 1995. There are no initial or follow-up facsimile Forms FDA-3500A in this submission.

/S/
8 May 95

Sincerely yours,

Esther B. Brecher, D.O.
Director
Worldwide Safety & Surveillance

/S/
5/10/95

EBB:sk
Attachments

Pool Dr-510

ORIGINAL

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

January 1, 1995 to March 31, 1995

TABLE OF CONTENTS

Bristol-Myers Squibb Company

Facsimile Form FDA-3500A Initial Reports

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Received January 1, 1995 to March 31, 1995

Serious Expected Spontaneous Domestic Adverse Events
By Manufacturer File Number

There were no initial reports of serious expected adverse events for this reporting period.

Bristol-Myers Squibb Company

Facsimile Form FDA-3500A Follow-Up Reports

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Received January 1, 1995 to March 31, 1995

Serious Expected Spontaneous Domestic Adverse Events
By Manufacturer File Number

There were no follow-up reports of serious expected adverse events for this reporting period.

Bristol-Myers Squibb Company

Facsimile Form FDA-3500A Initial Reports

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Received January 1, 1995 to March 31, 1995

Nonserious Spontaneous Domestic Adverse Events
By Manufacturer File Number

There were no initial reports of nonserious adverse events for this reporting period.

Bristol-Myers Squibb Company

Facsimile Form FDA-3500A Follow-Up Reports

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Received January 1, 1995 to March 31, 1995

Nonserious Spontaneous Domestic Adverse Events
By Manufacturer File Number

There were no follow-up reports of nonserious adverse events for this reporting period.

Bristol-Myers Squibb Company

GLUCOPHAGE TABS
(metformin hcl)

NDA 20-357

Index of Serious Expected Initial and Follow-Up Reports

By Manufacturer File Number

Received 01/01/95 to 03/31/95
Initial Reports: Section IA; Follow-Up Reports: Section IB

MFR (CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
No Reports For This Period			

Bristol-Myers Squibb Company

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Index of Suspected Interacting Drugs
From Spontaneous and Literature Sources

By Manufacturer File Number

Received January 1, 1995 to March 31, 1995

There were no reports of drug interactions received during this reporting period.

Bristol-Myers Squibb Company

GLUCOPHAGE TABS
(metformin hcl)

NDA 20-357

Index of Nonserious Initial and Follow-Up Reports

By Manufacturer File Number

Received 01/01/95 to 03/31/95
Initial Reports: Section IA; Follow-Up Reports: Section IB

MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE

No Reports For This Period

Bristol-Myers Squibb Company

Narrative Summary and Analysis of Information in This Report

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

January 1, 1995 to March 31, 1995

FDA MEDWATCH PROGRAM

There were no reports received through the FDA MedWatch Program.

NONSERIOUS

There are no initial and no follow-up nonserious adverse drug experience reports included in this submission.

SERIOUS EXPECTED

There are no initial and no follow-up serious expected adverse drug experience reports included in this submission.

SERIOUS UNEXPECTED

There were no initial and no follow-up 15-Day Alert reports submitted by Bristol-Myers Squibb during this reporting period.

Bristol-Myers Squibb Company

GLUCOPHAGE TABS
(metformin hcl)

NDA 20-357

Index of 15-Day Initial and Follow-Up Reports

By Manufacturer File Number

Submitted 01/01/95 to 03/31/95

MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE	LETTER DATE(S)
No Reports For This Period				

Bristol-Myers Squibb Company

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Index of 15-Day Increased Frequency Alert Reports

Submitted January 1, 1995 to March 31, 1995

There were no increased frequency alert reports submitted during this reporting period.

Bristol-Myers Squibb Company

GLUCOPHAGE TABS
(metformin hcl)

NDA 20-357

Tabulation and Index of 15-Day Initial and Follow-Up Reports

By Body System

Submitted 01/01/95 to 03/31/95

BODY SYSTEM/ EXPANDED COSTART TERM	REPORTED TERM	MFR(CTU) FILE NO.	NO. OF FILES PER EXPANDED COSTART TERM
No Reports For This Period			

Bristol-Myers Squibb Company

GLUCOPHAGE TABS
(metformin hcl)

NDA 20-357

Tabulation and Index of Serious Expected Initial and Follow-Up Reports

By Body System

Received 01/01/95 to 03/31/95
Initial Reports: Section IA; Follow-Up Reports: Section IB

BODY SYSTEM/ EXPANDED COSTART TERM	REPORTED TERM	MFR(CTU) FILE NO.	NO. OF FILES PER EXPANDED COSTART TERM
No Reports For This Period			

Bristol-Myers Squibb Company

GLUCOPHAGE TABS
(metformin hcl)

NDA 20-357

Tabulation and Index of Nonserious Initial and Follow-Up Reports

By Body System

Received 01/01/95 to 03/31/95
Initial Reports: Section IA; Follow-Up Reports: Section IB

BODY SYSTEM/ EXPANDED COSTART TERM	REPORTED TERM	MFR(CTU) FILE NO.	NO. OF FILES PER EXPANDED COSTART TERM
No Reports For This Period			

Bristol-Myers Squibb Company

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Index of Adverse Drug Events Reported Under Another NDA

Received January 1, 1995 to March 31, 1995

There were no reports received during this reporting period submitted under another NDA.

Bristol-Myers Squibb Company

Current Prescribing Information

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

January 1, 1995 to March 31, 1995

The current package insert number is P8330-00, issued: February 1995.

Bristol-Myers Squibb Company

New Safety Information

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

January 1, 1995 to March 31, 1995

We are unaware of any new safety information released during this reporting period.

Bristol-Myers Squibb Company

Summary of Non-U.S.A. Product Safety Actions

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

January 1, 1995 to March 31, 1995

We are unaware of any non-U.S.A. product safety actions taken during this reporting period.

Bristol-Myers Squibb Company

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

Index of Company Sponsored Studies

January 1, 1995 to March 31, 1995

One company sponsored study was approved for initiation during this reporting period. This study is listed below:

Country	Protocol Number	Protocol Title
United States	MET/69-94.001	Dose-Response Study Of Various Levels Of Metformin Hydrochloride Compared To Placebo On Patients With Non-Insulin Dependent Diabetes Mellitus.

Bristol-Myers Squibb Company

Description of Prescribing Changes Since the Previous Reporting Period

Glucophage® Tablets

(metformin hydrochloride)

NDA 20-357

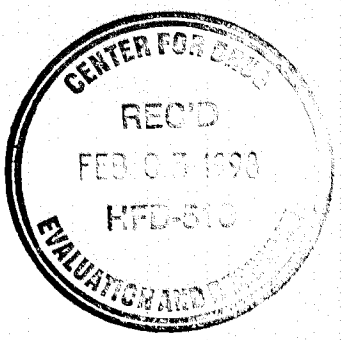
January 1, 1995 to March 31, 1995

Package insert number P8330-00 is the first package insert to be issued. Therefore, there are no changes to report.

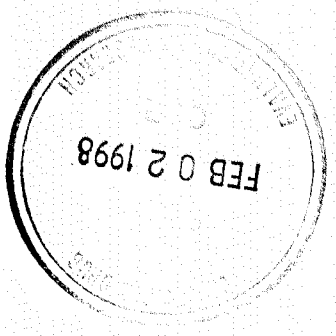
ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000



January 30, 1998



NDA 20-357

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Noted
/S/ 2/9/98

Dear Sir or Madam:

Pursuant to 21 CFR 314.80(c)(2), the twelfth quarterly Periodic Adverse Drug Experience Report for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357, is enclosed.

The period covered by this report is October 1, 1997 to December 31, 1997.

There are one hundred forty three initial and eleven follow-up facsimile Forms FDA-3500A in this submission.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

/S/ 2-10-98
CSO INITIALS DATE

Sincerely yours,

Kate Belgum for

Savian P. Nicholas, M.D.
Director
Worldwide Safety & Surveillance

SN:cg
Attachments

Noted
/S/
2/9/98

ORIGINAL
P-013
DIV-510

/S/

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

October 1, 1997 to December 31, 1997

TABLE OF CONTENTS

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Facsimile Form FDA-3500A Initial Reports
Serious Expected Spontaneous Domestic Adverse Events
By Manufacturer File Number

Received October 1, 1997 to December 31, 1997

There is one initial report of a serious expected adverse events received during this reporting period.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074209

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 52 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 12/04/97

4. Date of this report: 01/21/98

5. Describe event or problem

A HEALTH PROFESSIONAL FROM A POISON CONTROL CENTER REPORTED THAT A 52-YEAR-OLD MALE PATIENT TOOK AN OVERDOSE OF GLUCOPHAGE (METFORMIN HCL) AND DEVELOPED AN INCREASED LACTIC ACID LEVEL. ON DECEMBER 4, 1997, THE PATIENT WAS ADMITTED TO A HOSPITAL FOR OBSERVATION FOLLOWING THE INGESTION OF 10-12 500 MG TABLETS OF GLUCOPHAGE. LABORATORY STUDIES REVEALED THE FOLLOWING: LACTIC ACID 2.6 (N= 0.5-2.2), GLUCOSE 198, BUN 20, CREATININE 0.9, O2 SATURATION 97%; VITAL SIGNS SHOWED B/P 137/93, RESPIRATIONS 20, BODY TEMPERATURE 97, PULSE 86. REPORTEDLY, THE PATIENT WAS "RUNNING OUT THE DOOR AND THOUGHT THE GLUCOPHAGE WERE HIS MULTIVITAMINS." THE PATIENT WAS ASYMPTOMATIC WITH REGARD TO THE OVERDOSE. ADDITIONAL INFORMATION WAS PURSUED VIA TELEPHONE WITHOUT SUCCESS. FURTHER DETAILS HAVE BEEN REQUESTED IN WRITING.

6. Relevant tests/laboratory data

GLUCOSE 198
12/04/97
O2 SATURATION 97 %
12/04/97
LACTATE 2.6
12/04/97
BLOOD PRESSURE 137/93
12/04/97
RESPIRATIONS 20
12/04/97
BODY TEMPERATURE 97
12/04/97

(CONTINUED)

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 5000-6000 MG ORAL

3. Therapy dates
#1. 12/04/97-12/04/97
1 DOSES

4. Diagnosis for use
#1. NI

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
12/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
OVERDOSE ACCID
LAB TEST ABNORM

9. Mfr.report number
M074209

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
HEALTH PROFESSIONAL

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074209

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data

```
PULSE 86
   12/04/97
BUN 20
   12/04/97
CREATININE 0.9
   12/04/97
```

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Facsimile Form FDA-3500A Initial Reports
Nonserious Spontaneous Domestic Adverse Events
By Manufacturer File Number

Received October 1, 1997 to December 31, 1997

There were one hundred forty two initial reports of nonserious adverse events received during this reporting period.

APPEARS THIS WAY
ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071924

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [X] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death ____
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: 09/00/97
4. Date of this report: 01/21/98
5. Describe event or problem

A FEMALE CONSUMER REPORTED THAT SHE DEVELOPED AN UPSET STOMACH AS THE TABLETS HAD A "BAD ODOR" AFTER TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN SEPTEMBER, 1997; SHE WAS NOT TAKING ANY CONCOMITANT DRUGS. AFTER EXPERIENCING THE ABOVE EVENT, SHE "CHANGED TABLETS" AND THE EVENT RESOLVED (DETAILS NOT PROVIDED). CROSS REFERENCE PRODUCT COMPLAINT #23121.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 09/00/97-UNK

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DYSPEPSIA

9. Mfr.report number
M071924

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071941

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence
2. Age at time of event: or 79 YRS; Date of birth:
3. Sex: [ ] female [X] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: 09/30/97
4. Date of this report: 01/21/98
5. Describe event or problem

A 79 Y/O MALE PATIENT REPORTED THAT HE DEVELOPED DROWSINESS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 250 MG BID FOR TREATMENT OF DIABETES MELLITUS TYPE II. THE PATIENT STARTED TAKING GLUCOPHAGE ON SEPTEMBER 30, 1997; AFTER 2 DOSES HE DEVELOPED THE ABOVE SYMPTOM. HIS MEDICAL HISTORY INCLUDED FIRST DEGREE HEART BLOCK AND ALLERGIES TO PENICILLIN AND CORTISONE. HE WAS CONCOMITANTLY TAKING VICODIN (HYDROCODONE/APAP), STEROID SHOTS, SYNTHROID (LEVOTHYROXINE SODIUM), CARDIZEM (DILTIAZEM HCL) AND ASPIRIN. OUTCOME AND STATUS OF GLUCOPHAGE THERAPY WAS NOT REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
FIRST DEGREE HEART BLOCK
ALLERGY PENICILLIN
CORTISONE ALLERGY

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG
2. Dose, frequency & route used: #1. 250 MG BID ORAL
3. Therapy dates: #1. 09/30/97-UNK 2 DOSES
4. Diagnosis for use: #1. DIABETES MELLITUS TYPE II
5. Event abated after use stopped or dose reduced: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction: [ ] yes [ ] no [X] doesn't apply; #1 [ ] yes [ ] no [ ] doesn't apply
9. NDC #: NOT REPORTED
10. Concomitant medical products
CARDIZEM
SYNTHROID
STEROIDS
VICODIN

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [X] consumer
   - [ ] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:

4. Date received by manufacturer: 10/01/97
5. (A)NDA # 20-357; IND #; PLA #; pre-1938 [ ] yes; OTC product [ ] yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - [ ] 5-day [ ] 15-day
   - [ ] 10-day [X] periodic
   - [X] initial [ ] follow-up# ____
8. Adverse event term(s): SOMNOLENCE
9. Mfr.report number: M071941

E. Initial reporter

1. Name, address & phone number
2. Health professional? [ ] yes [X] no
3. Occupation: CONSUMER
4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071941

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
ASPIRIN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071962

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE DEVELOPED SORENESS IN THE LEFT RIBCAGE AREA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 11 WEEKS. THE PAIN OCCURS REPORTEDLY AFTER THE PATIENT EATS. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
11 WEEKS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
LOPID
AMARYL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/02/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
PAIN ABDO

9. Mfr.report number
M071962

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071968

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 55 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 06/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 55 Y/O FEMALE CONSUMER REPORTED THAT SHE DEVELOPED URINARY FREQUENCY WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT'S MEDICAL HISTORY INCLUDED HERNIA SURGERY (THREE HERNIAS) IN 1993 AND IN JUNE, 1997 AND SHE REPORTED THAT SHE USUALLY HAS TROUBLE URINATING AFTER INTERCOURSE. WHILE SHE WAS IN THE HOSPITAL IN JUNE FOR THE HERNIA SURGERY, SHE TOOK ONE GLUCOPHAGE TABLET AND HOURS LATER WAS URINATING MORE FREQUENTLY. SHE THEN STOPPED THE GLUCOPHAGE. HER HISTORY ALSO INCLUDED BEING "VERY NERVOUS; HAS ANXIETY ATTACKS" AND A BAD REACTION DURING A PREGNANCY 30 YEARS AGO TO A DRUG FOR WHICH SHE COULD NOT RECALL THE NAME. SHE REPORTED THAT THE REACTION HAD MADE HER DIZZY AND TIRED. CONCOMITANT DRUGS INCLUDED ENTEX (GUAIFENESIN/PHENYLPROP) AT HS FOR "SINUS." A FEW MONTHS AFTER THE EVENT, THE PATIENT AGAIN STARTED GLUCOPHAGE, AND "THE SAME PROBLEM RETURNED."

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
DYSURIA
HERNIA
HERNIA REPAIRS
NERVOUSNESS
ANXIETY ATTACKS
DRUG REACTION

(CONTINUED)

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. 06/00/97-UNK

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ENTEX

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/02/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
URIN FREQUENCY

9. Mfr.report number
M071968

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071968

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

THE OUTCOME OF THE EVENT AND CURRENT STATUS OF GLUCOPHAGE THERAPY WAS NOT REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

PREGNANCY

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072013

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or 81.7 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/01/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT A 28-YEAR-OLD FEMALE DEVELOPED FATIGUE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE AT 500 MG QD AND AFTER ONE TO TWO WEEKS, THE DOSE WAS INCREASED TO 500 MG BID. THE PATIENT HAD GOOD CONTROL OF BLOOD SUGAR AT THIS DOSE; HOWEVER, SHE HAD DEVELOPED FATIGUE AFTER THIS INCREASE. SHE WAS NOT TAKING ANY CONCOMITANT DRUGS. TOTAL THERAPY DURATION HAS NOW BEEN APPROXIMATELY FOUR WEEKS. AS OF OCTOBER 1, 1997 THE EVENT IS UNRESOLVED.

SUPPLEMENTAL INFORMATION REVEALED THAT THE INITIAL REPORTER WAS A PHYSICIAN; THIS INFORMATION NOW RECEIVED ON OCTOBER 28, 1997 WAS SUBMITTED BY THIS PHYSICIAN, VIA A DOCTOR OF PHARMACY. IT WAS REPORTED THAT THE

(CONTINUED)

6. Relevant tests/laboratory data
SERUM GLUCOSE CONTROLLED

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
CONTINUING 4 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
ASTHENIA

9. Mfr.report number
M072013

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [X] no [ ] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072013

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

PATIENT, A 26-YEAR-OLD FEMALE WEIGHING 180 POUNDS, INITIALLY DEVELOPED THE FATIGUE ON OCTOBER 1, 1997. THE FATIGUE EVENTUALLY RESOLVED AFTER ADDITIONAL WEEKS ON GLUCOPHAGE THERAPY. THE DOSAGE OF GLUCOPHAGE WAS NOT CHANGED, AND THERAPY WAS NOT INTERRUPTED. IT WAS CONFIRMED THAT THE PATIENT WAS NOT TAKING ANY CONCOMITANT DRUGS. LOT NUMBER AND EXPIRATION DATE FOR THE PATIENT'S GLUCOPHAGE PRESCRIPTION WAS UNKNOWN. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072037

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or 56 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 09/04/97

4. Date of this report: 01/21/98

5. Describe event or problem
A PHYSICIAN REPORTED THAT A 56-YEAR-OLD MALE PATIENT DEVELOPED AN INCREASED LACTIC ACID LEVEL WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON AUGUST 8, 1997. PRIOR TO THAT TIME, HIS SERUM CHEMISTRIES WERE NORMAL; HE HAD NO RENAL OR HEPATIC IMPAIRMENT. ON SEPTEMBER 4, 1997 HE DEVELOPED FATIGUE AND WEAKNESS. A LACTIC ACID LEVEL WAS NOTED TO BE 41 MG/DL (N=8-12 MG/DL) AND HIS ERYTHROCYTE SEDIMENTATION RATE (ESR) WAS 41. HIS SERUM ELECTROLYTES WERE NORMAL; ARTERIAL BLOOD GASES WERE NOT PERFORMED AND HE WAS NOT ADMITTED TO A HOSPITAL. GLUCOPHAGE THERAPY WAS STOPPED ON SEPTEMBER 4, 1997. BY SEPTEMBER 22, 1997, HIS LACTATE LEVEL WAS STILL MILDLY ELEVATED AT 15 MG/DL. THE SYMPTOMS OF FATIGUE AND WEAKNESS HAVE RESOLVED. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
LACTIC ACID 41 MG/DL
09/04/97
SED RATE 41
09/04/97
ELECTROLYTES NORMAL
09/04/97
LACTIC ACID 15 MG/DL
09/22/97

7. Other relevant history, including preexisting medical conditions
NONE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 08/08/97-09/04/97
28 DAYS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ initial ☐ follow-up# ____

8. Adverse event term(s)
LAB TEST ABNORM
ASTHENIA
ESR INC

9. Mfr.report number
M072037

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072068

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER REPORTED THAT SHE BECAME "SICK TO HER STOMACH" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT WAS ALSO TAKING GLIPIZIDE. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLIPIZIDE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/06/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
NAUSEA

9. Mfr.report number
M072068

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072101

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 55 YRS
Date of birth:

3. Sex: [ ] female [X] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT HER 55-YEAR-OLD HUSBAND DEVELOPED SHORTNESS OF BREATH AND CHEST PAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF DIABETES MELLITUS. DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT WAS CONCOMITANTLY TAKING GLUCOTROL XL (GLIPIZIDE). THE CONSUMER DID NOT WISH TO PROVIDE ANY FURTHER INFORMATION.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL XL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DYSPNEA
PAIN CHEST

9. Mfr.report number
M072101

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072103

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE THAT A FEMALE PATIENT, AGE UNSPECIFIED, DEVELOPED INCREASED LIVER FUNCTION TESTS AND A FATTY LIVER WHILE TAKING GLUCOPHAGE (METFORMIN HCL) AND ZOCOR (SIMVASTATIN) THERAPIES. DAILY DOSAGE AND THERAPY DATES FOR THESE DRUGS WERE NOT PROVIDED. THE PATIENT WAS FOUND TO HAVE INCREASED LIVER FUNCTION TESTS, AND WAS LATER FOUND TO HAVE A FATTY LIVER (DIAGNOSTIC PROCESS NOT REPORTED). GLUCOPHAGE AND ZOCOR THERAPIES WERE STOPPED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

LIVER FUNCTION INCREASED

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS
#2. ZOCOR

2. Dose, frequency & route used
#1. ORAL
#2. NI

3. Therapy dates
#1. NI
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. NI

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
LIVER FATTY
LIVER FUNC ABNORM

9. Mfr.report number
M072103

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072116

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 65 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 06/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 65-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED ELEVATED BLOOD PRESSURE, HEARTBURN, RAPID PULSE AND DEPRESSION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT HAS BEEN TAKING GLUCOPHAGE FOR GREATER THAN ONE YEAR, AND SINCE JUNE, 1997 HAS BEEN EXPERIENCING THE ABOVE EVENTS. CONCOMITANT DRUGS INCLUDED ZESTRIL (LISINOPRIL) AND ZESTORECTIC (LISINOPRIL/HCTZ). HER BLOOD PRESSURE WAS NOTED TO BE 203/100 AND HER PULSE WAS 96. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
BLOOD PRESSURE 203/100 MMHG
06/00/97
PULSE 96 BPM
06/00/97

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG BID ORAL

3. Therapy dates
#1. UNK
>1 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ZESTORETIC
ZESTRIL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
HYPERTENS
TACHYCARDIA
DEPRESSION
DYSPEPSIA

9. Mfr.report number
M072116

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072313

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 62-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED FLATULENCE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG TID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 3-4 MONTHS. THE PATIENT HAD BEEN TAKING GLUCOPHAGE 500 MG QID; WHEN THE DOSE WAS RECENTLY INCREASED TO 850 MG TID, SHE BEGAN EXPERIENCING THE ABOVE SYMPTOM.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 2000-2550 MG QD ORAL

3. Therapy dates
#1. UNK
3-4 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NORVASC

LANOXIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/09/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
FLATUL

9. Mfr.report number
M072313

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072322

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex NI — ☐ female ☐ male
4. Weight ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI
4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A PATIENT (AGE AND GENDER NOT REPORTED) DEVELOPED AN INCREASE IN VITAMIN B-12 LEVELS WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT REPORTED. GLUCOPHAGE THERAPY WAS STOPPED IN LIGHT OF THE EVENT. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/02/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
LAB TEST ABNORM

9. Mfr.report number
M072322

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072323

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 52 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 52-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED INCREASING GLUCOSE LEVELS AFTER GLUCOPHAGE (METFORMIN HCL) WAS ADDED TO INSULIN THERAPY FOR TREATMENT OF NON-INSULIN-DEPENDENT DIABETES MELLITUS. THE PATIENT HAD BEEN TAKING INSULIN 70/30 40 UNITS QAM AND 45 UNITS QPM FOR 3 YEARS. WHEN GLUCOPHAGE WAS ADDED, HER GLUCOSE LEVELS INCREASED; GLUCOPHAGE WAS STOPPED AND THE LEVELS DROPPED. HER MEDICAL HISTORY INCLUDED HYPERTENSION AND SHE WAS TAKING AN UNSPECIFIED CHOLESTEROL-LOWERING DRUG.

6. Relevant tests/laboratory data

SERUM GLUCOSE INCREASED

SERUM GLUCOSE IMPROVED

7. Other relevant history, including preexisting medical conditions

HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. HUMULIN INSULIN

2. Dose, frequency & route used
#1. 500 MG BID ORAL
#2. 85 U QD SQ

3. Therapy dates
#1. NI
#2. UNK CONTINUING 3 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES
#2. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/10/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
HYPERGLYCEM
REACT AGGRAV

9. Mfr.report number
M072323

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072336

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 82 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

AN 82-YEAR-OLD MALE CONSUMER EXPERIENCED DIARRHEA AND HEARTBURN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TWICE DAILY. GLUCOPHAGE THERAPY WAS STARTED IN MARCH, 1997. THE ONSET DATE OF THE EVENT WAS NOT REPORTED. CONCOMITANT MEDICATIONS INCLUDED GLUCOTROL XL (GLIPIZIDE) THERAPY.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 03/00/97-UNK
7 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL XL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/10/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ initial ☐ follow-up# ____

8. Adverse event term(s)
DIARRHEA
DYSPEPSIA

9. Mfr.report number
M072336

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072363

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 68 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 10/07/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT A 68-YEAR-OLD MALE PATIENT WAS NOTED TO HAVE ELEVATED LEVELS OF SERUM GLUTAMIC OXALOACETIC TRANSAMINASE (SGOT) AND SERUM GLUTAMIC PYRUVIC TRANSAMINASE (SGPT) LEVELS, AS WELL AS INCREASED LACTIC DEHYDROGENASE (LDH), AND BILIRUBIN LEVELS DURING GLUCOPHAGE (METFORMIN HCL) THERAPY. THE ONSET DATE OF THE EVENTS WAS REPORTED AS OCTOBER 7, 1997. SGOT AND SGPT LEVELS WERE REPORTED AS "EXTREMELY HIGH" AND LDH AND BILIRUBIN LEVEL WERE NOTED ONLY AS "INCREASED"; SPECIFIC VALUES WERE NOT REPORTED. GLUCOPHAGE 500 MG TWICE DAILY WAS STARTED IN AUGUST, 1997, ("A COUPLE OF MONTHS") PRIOR TO THE EVENT FOR THE TREATMENT OF TYPE II DIABETES MELLITUS. AS OF OCTOBER 8, 1997, THE PATIENT REMAINS ON GLUCOPHAGE THERAPY.

6. Relevant tests/laboratory data

SGOT ELEVATED
10/07/97
SGPT ELEVATED
10/07/97
LDH INCREASED
10/07/97
BILIRUBIN INCREASED
10/07/97

7. Other relevant history, including preexisting medical conditions

GOITER

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG BID ORAL

3. Therapy dates: #1. 08/00/97-UNK CONTINUING 2 MONTHS

4. Diagnosis for use: #1. DIABETES MELLITUS TYPE II

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products

SYNTHROID

DIABETA

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer: 10/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

LIVER FUNC ABNORM

LDH INC

BILIRUBINEM

9. Mfr.report number: M072363

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: PHARMACIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072386

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 57 YRS — Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 58-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED GAS, CRAMPS AND A TERRIBLE TASTE IN HER MOUTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TEN DAYS. THE PATIENT'S MEDICAL HISTORY INCLUDED EDEMA AND GOUT. THE ABOVE EVENTS STARTED AT THE TIME GLUCOPHAGE THERAPY WAS INITIATED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

GOUT

EDEMA

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG BID ORAL

3. Therapy dates: #1. UNK 10 DAYS

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products

SYNTHROID

PREMPRO

SPIRONOLACTONE

ALLOPURINOL

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 10/13/97

5. (A)NDA # 20-357

IND # ____

PLA # ____

pre-1938 [ ] yes

OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)

FLATUL

PAIN

TASTE PERVERS

9. Mfr.report number: M072386

E. Initial reporter

1. Name, address & phone number

2. Health professional? [ ] yes [X] no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072393

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A FEMALE CONSUMER (AGE NOT SPECIFIED) REPORTED THAT SHE DEVELOPED RED, ITCHY SKIN UNDER THE AREA WHERE THE CLIMERA (ESTRADIOL) PATCH WAS APPLIED, WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS ONE YEAR. THE PATIENT WAS CONCOMITANTLY TAKING ESTROPIPATE 0.625 MG AND GLUCOTROL (GLIPIZIDE). THE PATIENT NOTED THAT SINCE STARTING GLUCOPHAGE, THE AREA OF SKIN UNDERNEATH THE CLIMARA PATCH HAS BECOME RED AND ITCHY. THE STATUS OF GLUCOPHAGE AND CLIMARA THERAPIES, AND THE OUTCOME OF THE EVENT WAS NOT REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. CLIMARA
2. Dose, frequency & route used
#1. 500 MG TID ORAL
#2. PATCH
3. Therapy dates
#1. 00/00/96-UNK 1 YEARS
#2. NI
4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES
#2. UNK
5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply
6. Lot #
#1. NI
#2. NI
7. Exp.date
#1. NI
#2. NI
8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply
9. NDC #
NOT REPORTED
10. Concomitant medical products
GLUCOTROL
ESTROPIPATE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000
2. Phone number
609-252-3737
3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [X] consumer
   - [ ] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:
4. Date received by manufacturer
10/13/97
5. (A)NDA # 20-357
   IND # ____
   PLA # ____
   pre-1938 [ ] yes
   OTC product [ ] yes
6. If IND, protocol #
NA
7. Type of report (check all that apply)
   - [ ] 5-day [ ] 15-day
   - [ ] 10-day [X] periodic
   - [X] Initial [ ] follow-up# ____
8. Adverse event term(s)
RASH
PRURITUS
9. Mfr.report number
M072393

E. Initial reporter

1. Name, address & phone number
2. Health professional? [ ] yes [X] no
3. Occupation
CONSUMER
4. Initial reporter also sent report to FDA [ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072394

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 64 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 64-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED CHEST PAIN, MUSCULOSKELETAL PAIN, DIARRHEA AND LIGHTHEADEDNESS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS ONE YEAR. THE PATIENT'S MEDICAL HISTORY INCLUDED HYPERTENSION. AS OF OCTOBER 13, 1997, THE ABOVE EVENTS ARE UNRESOLVED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

HYPERTENSION

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used

#1. 850 MG TID ORAL

3. Therapy dates

#1. 00/00/96-UNK
1 YEARS

4. Diagnosis for use

#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

GLYNASE

INSULIN

SYNTHROID

TENORMIN

(CONTINUED)

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 10/13/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)

PAIN CHEST
PAIN
DIARRHEA
DIZZINESS

9. Mfr.report number: M072394

E. Initial reporter

1. Name, address & phone number

2. Health professional?: [ ] yes [X] no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072394

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

MOTRIN

NORVASC

NITROSTAT

VASOTEC

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072394

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
    IMDUR
    ZANTAC

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072451

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 70 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 70-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE "DID NOT FEEL WELL", WITH SYMPTOMS INCLUDING INCREASED HUNGER, SWEATING AND MUSCLE WEAKNESS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION FOR GLUCOPHAGE WAS APPROXIMATELY SIX MONTHS. THE PATIENT STOPPED GLUCOPHAGE "FOR A FEW DAYS" AND STATED THAT SHE "FELT BETTER." IT WAS NOT REPORTED IF SHE RESUMED GLUCOPHAGE THERAPY; HOWEVER, THE SYMPTOMS WERE PERSISTING AS OF OCTOBER 14, 1997.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG BID ORAL

3. Therapy dates
#1. 00/00/97-UNK
6 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYNASE

AXID

SYNTHROID

PRINIVIL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/14/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
APPETITE INC

SWEAT

MYASTHENIA

9. Mfr.report number
M072451

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072473

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE PATIENT, AGE NOT REPORTED, DEVELOPED SEVERE GASTROINTESTINAL UPSET WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT'S MEDICAL HISTORY INCLUDED CELIAC DISEASE (GLUTEN INTOLERANCE). THE DURATION OF GLUCOPHAGE THERAPY WAS FOUR DAYS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
CELIAC DISEASE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. UNK
4 DAYS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/14/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DYSPEPSIA

9. Mfr.report number
M072473

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072474

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 52 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A 52-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED LOW BACK PAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS THREE MONTHS. THE PHYSICIAN ADVISED THE PATIENT TO STOP GLUCOPHAGE, AND AFTER STOPPING THE DRUG, THE EVENT ABATED. GLUCOPHAGE THERAPY WAS RESTARTED, AND THE LOW BACK PAIN RESUMED. THE CURRENT STATUS OF GLUCOPHAGE THERAPY AND THE OUTCOME OF THE EVENT WERE NOT PROVIDED. THE PATIENT WAS NOT TAKING ANY CONCOMITANT DRUGS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
3 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/14/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ initial ☐ follow-up# ____

8. Adverse event term(s)
PAIN BACK

9. Mfr.report number
M072474

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072513

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 57 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 09/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 67-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED NAUSEA, DIARRHEA, CHILLS AND WEAKNESS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS "THREE YEARS." IN MID TO LATE SEPTEMBER, 1997, THE PATIENT BEGAN TO DEVELOP THE ABOVE SYMPTOMS. SHE WAS ALSO TAKING LIPITOR (ATORVASTATIN) FOR HYPERCHOLESTEROLEMIA. IN LIGHT OF HER SYMPTOMS, BOTH GLUCOPHAGE AND LIPITOR WERE STOPPED ON APPROXIMATELY OCTOBER 5, 1997. AS OF OCTOBER 15, 1997 (TEN DAYS LATER), THE SYMPTOMS PERSIST. UNSPECIFIED BLOOD TESTS ARE PENDING. THE PATIENT'S MEDICAL HISTORY INCLUDES ALLERGY TO ZOCOR (SIMVASTATIN) MANIFESTED BY RASH. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERCHOLESTEROLEMIA

ALLERGY ZOCOR

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. LIPITOR

2. Dose, frequency & route used
#1. 1000 MG BID ORAL
#2. ORAL

3. Therapy dates
#1. UNK-10/05/97 3 YEARS
#2. UNK-10/05/97

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES
#2. HYPERCHOLESTEROLEMIA

5. Event abated after use stopped or dose reduced
#1 [ ] yes [X] no [ ] doesn't apply
#2 [ ] yes [X] no [ ] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 10/15/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
NAUSEA
DIARRHEA
CHILLS
ASTHENIA

9. Mfr.report number
M072513

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072622

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or 73 YRS
Date of birth:

3. Sex
[X] female
[ ] male

4. Weight
____ lbs
or
NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
[ ] death
[ ] life-threatening
[ ] hospitalization-initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other:

3. Date of event: 10/10/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 73-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED A RASH AND ITCHING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO YEARS. CONCOMITANT DRUGS INCLUDED GLYNASE (GLYBURIDE) FOR A DURATION OF FIVE YEARS. ON OCTOBER 10, 1997, THE PATIENT DEVELOPED THE RASH AND ITCHING; AS OF OCTOBER 17, 1997 THE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG TID ORAL

3. Therapy dates
#1. 00/00/95-UNK
2 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYNASE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
[ ] foreign
[ ] study
[ ] literature
[X] consumer
[ ] health professional
[ ] user facility
[ ] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer
10/17/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
[ ] 5-day [ ] 15-day
[ ] 10-day [X] periodic
[X] Initial [ ] follow-up# ____

8. Adverse event term(s)
RASH
PRURITUS

9. Mfr.report number
M072622

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072623

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 60 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/13/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 60-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED NAUSEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APPROXIMATELY APRIL, 1997; THERAPY DURATION WAS REPORTED AS SIX MONTHS. FROM OCTOBER 13, 1997 UNTIL OCTOBER 15, 1997, THE PATIENT EXPERIENCED NAUSEA. SHE STOPPED GLUCOPHAGE THERAPY ON OCTOBER 15, 1997 AND THE NAUSEA RESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. 04/00/97-10/15/97
6 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
MICRONASE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/17/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
NAUSEA

9. Mfr.report number
M072623

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072653

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A SALES REPRESENTATIVE, THAT A PATIENT (AGE AND GENDER NOT PROVIDED) DEVELOPED INCREASED PERSPIRATION WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THE PATIENT STARTED EXPERIENCING THE EVENT WHEN THE DOSAGE OF GLUCOPHAGE WAS INCREASED. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING. B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
09/10/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
SWEAT

9. Mfr.report number
M072653

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072654

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem:

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A FEMALE PATIENT (AGE NOT SPECIFIED) DEVELOPED INCREASED LIVER FUNCTION TESTS WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THE PATIENT WAS TAKING GLUCOTROL XL CONCOMITANTLY. AFTER FOUR MONTHS OF TAKING GLUCOPHAGE, THE PATIENT DEVELOPED AN INCREASE IN LIVER ENZYMES: GGT=54, AST=54 AND ALT=91. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data:

AST 54

ALT 91

GGT 54

7. Other relevant history, including preexisting medical conditions:

UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS
2. Dose, frequency & route used: #1. ORAL
3. Therapy dates: #1. UNK 4 MONTHS
4. Diagnosis for use: #1. DIABETES MELLITUS
5. Event abated after use stopped or dose reduced: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply
9. NDC #: NOT REPORTED
10. Concomitant medical products: GLUCOTROL XL

G. All manufacturers

1. Contact office - name/address:

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737
3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [ ] consumer
   - [X] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:
4. Date received by manufacturer: 09/25/97
5. (A)NDA # 20-357; IND # ____; PLA # ____; pre-1938 [ ] yes; OTC product [ ] yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - [ ] 5-day [ ] 15-day
   - [ ] 10-day [X] periodic
   - [X] Initial [ ] follow-up# ____
8. Adverse event term(s): LIVER FUNC ABNORM
9. Mfr.report number: M072654

E. Initial reporter

1. Name, address & phone number
2. Health professional? [X] yes [ ] no
3. Occupation: PHYSICIAN
4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072697

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: xxx — In confidence
2. Age at time of event: or 75 YRS — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: 10/13/97
4. Date of this report: 01/21/98
5. Describe event or problem

A 75-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED BOUTS OF HYPOGLYCEMIA "MANIFESTED BY SWEATING AND SHAKINESS" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) AND GLUCOTROL (GLIPIZIDE) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT HAS BEEN TAKING GLUCOPHAGE 500 MG BID FOR ONE YEAR; DURATION OF GLUCOTROL THERAPY WAS NOT REPORTED. ON OCTOBER 13, 1997, THE PATIENT BEGAN EXPERIENCING THE ABOVE EVENT. SERUM GLUCOSE LEVELS WERE NOT PROVIDED. AS OF OCTOBER 20, 1997, THE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. GLUCOTROL
2. Dose, frequency & route used
#1. 500 MG BID ORAL
#2. ORAL
3. Therapy dates
#1. 00/00/96-UNK 1 YEARS
#2. NI
4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES
#2. NON-INSULIN-DEPENDENT DIABETES
5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply
6. Lot #
#1. NI
#2. NI
7. Exp.date
#1. NI
#2. NI
8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply
9. NDC #
NOT REPORTED
10. Concomitant medical products
LASIX

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000
2. Phone number
609-252-3737
3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [X] consumer
   - [ ] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:
4. Date received by manufacturer
10/20/97
5. (A)NDA # 20-357
   IND # ____
   PLA # ____
   pre-1938 [ ] yes
   OTC product [ ] yes
6. If IND, protocol #
NA
7. Type of report (check all that apply)
   - [ ] 5-day [ ] 15-day
   - [ ] 10-day [X] periodic
   - [X] Initial [ ] follow-up# ____
8. Adverse event term(s)
HYPOGLYCEM
9. Mfr.report number
M072697

E. Initial reporter

1. Name, address & phone number
2. Health professional?
[ ] yes [X] no
3. Occupation
CONSUMER
4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072698

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 70 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/19/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 70-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. THE PATIENT'S DURATION OF GLUCOPHAGE THERAPY WAS FIVE DAYS; ON OCTOBER 19, 1997 SHE DEVELOPED THE ABOVE EVENT. CONCOMITANT DRUGS INCLUDED ZANTAC (RANITIDINE) AND ZESTRIL (LISINOPRIL). NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. 10/00/97-UNK
5 DAYS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ZANTAC

ZESTRIL

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/20/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA

9. Mfr.report number
M072698

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072703

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 48 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or 149.8 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/03/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 48-YEAR-OLD FEMALE PATIENT EXPERIENCED A POSSIBLE DRUG INTERACTION CHARACTERIZED BY TWO EPISODES OF HYPOGLYCEMIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) AND ERYTHROMYCIN THERAPIES. GLUCOPHAGE THERAPY WAS STARTED IN SEPTEMBER, 1997 FOR THE TREATMENT OF TYPE II DIABETES MELLITUS. GLUCOPHAGE DOSAGE AT THE TIME OF THE EVENTS WAS 1000 MG IN THE MORNING AND 500 MG AT NIGHT. ERYTHROMYCIN (DOSAGE NOT REPORTED) THERAPY WAS STARTED ON APPROXIMATELY OCTOBER 2, 1997. ON OCTOBER 3, 1997, THE PATIENT AWOKE FEELING "SHAKY AND WEAK". HER GLUCOSE MONITORING DEVICE SHOWED A GLUCOSE LEVEL OF APPROXIMATELY 50. SHE ATE AND HER SYMPTOMS RESOLVED; NO FURTHER TREATMENT WAS NECESSARY. ERYTHROMYCIN THERAPY WAS DISCONTINUED ON AN UNSPECIFIED DATE AND GLUCOPHAGE THERAPY WAS CONTINUED. ERYTHROMYCIN THERAPY

(CONTINUED)

6. Relevant tests/laboratory data

SERUM GLUCOSE 50
10/03/97
SERUM GLUCOSE 41
10/16/97
SERUM GLUCOSE 120
10/16/97

7. Other relevant history, including preexisting medical conditions

OBESITY

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. ERYTHROMYCIN

2. Dose, frequency & route used
#1. 1500 MG QD ORAL
#2. ORAL

3. Therapy dates
#1. 09/16/97-UNK CONTINUING
#2. 10/02/97-10/03/97 CONTINUING 2 DAYS

4. Diagnosis for use
#1. DIABETES MELLITUS TYPE II
#2. UNK

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [X] yes [ ] no [ ] doesn't apply

6. Lot #
#1. UNKNOWN
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [X] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
IMDUR
LOPRESSOR
RISPERDAL
ZOLOFT

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/17/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
HYPOGLYCEM
DRUG INTERACTION

9. Mfr.report number
M072703

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072703

UF/Dist report # N.A.

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

WAS RESTARTED ON OCTOBER 15, 1997. ON OCTOBER 16, 1997, THE PATIENT AGAIN EXPERIENCED MORNING HYPOGLYCEMIA WITH A BLOOD GLUCOSE LEVEL OF 41. THE PATIENT'S GLUCOSE LEVEL ROSE TO 120 AFTER TAKING ORANGE JUICE; NO FURTHER TREATMENT WAS NECESSARY. BOTH GLUCOPHAGE AND ERYTHROMYCIN THERAPY WERE CONTINUED. THE PATIENT DENIED CHANGES IN DIETARY INTAKE OR ACTIVITY LEVELS AT THE TIME OF THE EVENTS. AS OF OCTOBER 23, 1997, THE PATIENT HAS REPORTED NO ADDITIONAL EPISODES OF HYPOGLYCEMIA. THE PHYSICIAN STATED THAT HE "BELIEVES GLUCOPHAGE DID NOT CAUSE THE HYPOGLYCEMIA AND SUSPECTS ERYTHROMYCIN" THERAPY. CONCOMITANT MEDICATIONS INCLUDED IMDUR (ISOSORBIDE MONONITRATE) FOUR TIMES DAILY, LOPRESSOR (METOPROLOL TARTRATE) 25 MG TWICE DAILY, RISPERDAL (RISPERIDONE), AND ZOLOFT (SERTRALINE HCL) THERAPIES. MEDICAL HISTORY

(CONTINUED)

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072703

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

INCLUDED OBESITY.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN ON NOVEMBER 14, 1997. IT WAS REPORTED THAT THE PATIENT STARTED TAKING GLUCOPHAGE ON SEPTEMBER 16, 1997. HER WEIGHT WAS NOTED TO BE 330 POUNDS. HE STATED THAT ERYTHROMYCIN THERAPY WAS STOPPED ON OCTOBER 3, 1997. THE DRUG WAS REINTRODUCED ON OCTOBER 15, 1997 AND THE HYPOGLYCEMIA REAPPEARED. SUBSEQUENTLY, THE HYPOGLYCEMIA DID RESOLVE; HOWEVER, THE STATUS OF ERYTHROMYCIN THERAPY WAS NOT PROVIDED. GLUCOPHAGE THERAPY CONTINUES. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072737

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 74 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 08/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 74-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED NAUSEA, VOMITING AND STOMACH UPSET WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN AUGUST, 1997; TOTAL THERAPY DURATION WAS ONE MONTH. SINCE STARTING GLUCOPHAGE, SHE HAS BEEN EXPERIENCING THE ABOVE SYMPTOMS. GLUCOPHAGE WAS STOPPED IN SEPTEMBER, 1997 AND AS OF ONE MONTH LATER, THE ABOVE SYMPTOMS PERSIST. HER MEDICAL HISTORY INCLUDED ULCER; SHE WAS CONCOMITANTLY TAKING DYAZIDE (TRIAMTERENE, HCTZ), POTASSIUM, TAGAMET (CIMETIDINE), ADALAT (NIFEDIPINE) AND ORINASE (TOLBUTAMIDE). NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
ULCER

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 08/00/97-09/00/97
1 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [X] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
DYAZIDE
POTASSIUM
TAGAMET
ADALAT

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/21/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
NAUSEA
VOMIT
DYSPEPSIA

9. Mfr.report number
M072737

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072737

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
ORINASE

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072748

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 76 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A 76-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED A SALTY TASTE IN HIS MOUTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QHS FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS FOUR MONTHS. THE PATIENT STOPPED GLUCOPHAGE, AND THE EVENT RESOLVED. HE WAS RECHALLENGED WITH THE DRUG, AND THE SALTY TASTE REAPPEARED. THE CURRENT STATUS OF GLUCOPHAGE THERAPY AND THE OUTCOME OF THE EVENT WERE NOT PROVIDED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QHS ORAL

3. Therapy dates
#1. UNK
4 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
SYNTHROID
LIPITOR
VITAMINS

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/22/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
TASTE PERVERS

9. Mfr.report number
M072748

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072754

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 59 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 09/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 59-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED A TERRIBLE BODY ODOR ("SMELLED LIKE FISH") WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN-DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN JUNE, 1997; SINCE SEPTEMBER 1997, SHE HAS NOTED THE ABOVE EVENT. CONCOMITANT DRUGS INCLUDED AN UNSPECIFIED THYROID MEDICATION. AS OF OCTOBER 22, 1997 THE PATIENT REMAINS ON GLUCOPHAGE THERAPY, AND THE ABOVE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 06/00/97-UNK CONTINUING

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/22/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
BODY ODOR

9. Mfr.report number
M072754

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072755

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 67 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/00/96

4. Date of this report: 01/21/98

5. Describe event or problem

A 67-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APPROXIMATELY OCTOBER, 1996; THERAPY DURATION WAS REPORTED AS ONE YEAR. SINCE APRIL, 1997, SHE HAS BEEN EXPERIENCING DIARRHEA. GLUCOPHAGE THERAPY WAS STOPPED ON OCTOBER 20, 1997. THE CONSUMER "DIDN'T KNOW" IF THE EVENT HAD COMPLETELY SUBSIDED SINCE STOPPING GLUCOPHAGE THERAPY.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON NOVEMBER 14, 1997. SHE REPORTED THAT THE DOSAGE FOR HER GLUCOTROL XL WAS "3 PILLS DAILY" AND THE SYNTHROID WAS .05 MG ONCE DAILY. THE GLUCOPHAGE 850 MG SHE WAS TAKING TWICE DAILY WITH MEALS. DIARRHEA, IN ADDITION

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG BID ORAL

3. Therapy dates
#1. 10/00/96-10/20/97
1 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL

SYNTHROID

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/22/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA

FLATUL

9. Mfr.report number
M072755

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072755

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

TO GAS, FIRST OCCURRED COINCIDENT TO THE INITIATION OF GLUCOPHAGE THERAPY. AT FIRST SHE HAD DIARRHEA EVERY OTHER WEEK; "SOMETIMES FOUR DAYS IN A ROW." WHEN THE SYMPTOMS BECAME INTOLERABLE, SHE STOPPED GLUCOPHAGE THERAPY. THE EVENTS RESOLVED FOLLOWING DISCONTINUATION OF GLUCOPHAGE. SHE WAS PLACED ON "ANOTHER PILL" WHICH SHE REPORTED IS NOT PROVIDING GOOD DIABETIC CONTROL. NO FURTHER DETAILS WERE REPORTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED ON DECEMBER 17, 1997 FROM THE TREATING PHYSICIAN. HE CONFIRMED THAT THE DIARRHEA RESOLVED FOLLOWING DISCONTINUATION OF GLUCOPHAGE. THE PATIENT WAS NOT RECHALLENGED WITH GLUCOPHAGE THERAPY. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072780

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE REGISTERED NURSE (WHO IS ALSO THE PATIENT) REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT SHE HAD BLOOD SUGARS THAT WERE "NOT NORMAL" AND WAS "FEELING BAD" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG STRENGTH TABLETS. THERAPY DATES AND EXACT DAILY DOSAGE FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT WAS TAKING GLUCOPHAGE FROM LOT NUMBER D7J197A, EXPIRATION DATE NOVEMBER 1999. IT WAS NOT CLARIFIED WHAT WAS MEANT BY HER GLUCOSE LEVELS BEING "NOT NORMAL." ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
BLOOD SUGAR "ABNORMAL"

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. DJ7197A

7. Exp.date
#1. 11/99

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/23/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
MALAISE
LAB TEST ABNORM

9. Mfr.report number
M072780

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
REGISTERED NURSE

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072824

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 48 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A REGISTERED NURSE REPORTED THAT A 48-YEAR-OLD FEMALE PATIENT DEVELOPED FACIAL TWITCHING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATENT OF DIABETES MELLITUS. DAILY DOSE OF GLUCOPHAGE WAS NOT PROVIDED; FREQUENCY OF ADMINISTRATION WAS TWICE DAILY. THERAPY DATES WERE NOT REPORTED; HOWEVER, DURATION WAS STATED TO BE "AT LEAST A COUPLE OF WEEKS." THE PATIENT WAS ALSO TAKING AMARYL (GLIMERIRIDE), ASPIRIN AND AN UNSPECIFIED DRUG "FOR CHOLESTEROL." "AMARYL, OTHER MEDS (EG., FOR CHOLESTEROL AND ASA) WERE STOPPED WITHOUT RESOLUTION OF THE EVENT".ITWAS UNCLEAR IF GLUCOPHAGE WAS STOPPED DUE TO THE EVENT. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. AMARYL
(CONTINUED)

2. Dose, frequency & route used
#1. BID ORAL
#2. ORAL

3. Therapy dates
#1. NI
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/23/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
TWITCH

9. Mfr.report number
M072824

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
REGISTERED NURSE

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072824

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name: #3. ASPIRIN
2. Dose, frequency & route used: #3. NI
3. Therapy dates: #3. NI
4. Diagnosis for use: #3. UNK
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☒ doesn't apply
   #3 ☐ yes ☐ no ☐ doesn't apply
6. Lot #: #3. NI
7. Exp.date: #3. NI
8. Event reappeared after reintroduction: ☐ yes ☐ no ☒ doesn't apply
   #3 ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072832

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex NI ☐ female ☐ male

4. Weight ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT APPROXIMATELY FOUR PATIENTS DEVELOPED INCREASED LACTATE LEVELS, MUSCLE ACHES AND SHORTNESS OF BREATH WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THIS FILE REPRESENTS PATIENT #1 OF 4. THE AGE AND GENDER OF THE PATIENT WAS NOT REPORTED. THE PATIENT HAD NORMAL RENAL AND HEPATIC FUNCTION. IT WAS NOTED THAT THE PATIENT DID NOT DEVELOP LACTIC ACIDOSIS. ADDITIONAL INFORMATION WAS REQUESTED, INCLUDING THE LACTATE LEVEL, HAS BEEN REQUESTED. CROSS REFERENCE CARES FILE NUMBERS M073399, M073400 AND M073401.

6. Relevant tests/laboratory data

LACTIC ACID INCREASED

RENAL FUNCTION NORMAL

HEPATIC FUNCTION NORMAL

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no [X] doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no [X] doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- [X] health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/23/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day [X] periodic
- [X] Initial ☐ follow-up# ____

8. Adverse event term(s)
LAB TEST ABNORM
DYSPNEA
MYALGIA

9. Mfr.report number
M072832

E. Initial reporter

2. Health professional?
[X] yes ☐ no

3. Occupation
PHARMACIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072844

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 09/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER (AGE NOT SPECIFIED) REPORTED THAT SHE DEVELOPED FATIGUE/WEAKNESS AND A 25-POUND WEIGHT LOSS OVER THE PAST MONTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. DURATION OF THERAPY WAS "THREE DAYS." IN SEPTEMBER, 1997, THE ABOVE EVENTS FIRST STARTED, AND OVER THE ENSUING MONTH, SHE LOST A TOTAL OF 25 POUNDS. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. 00/00/97-00/00/97
3 DAYS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/24/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
ASTHENIA
WEIGHT DEC

9. Mfr.report number
M072844

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072853

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event:
or 65 YRS
Date of birth:

3. Sex
☐ female
☒ male

4. Weight
____ lbs
or
NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 65-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED STOMACH CRAMPS AND SWEATING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO YEARS. IN OCTOBER, 1997 (FOR THE PAST FEW WEEKS), THE PATIENT HAS BEEN EXPERIENCING SWEATING AFTER THE MORNING DOSE OF GLUCOPHAGE AND STOMACH CRAMPS. AS OF OCTOBER 24, 1997, THE ABOVE EVENTS ARE UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. 00/00/95-UNK
2 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
MONOPRIL
BABY ASPIRIN
VERAPAMIL
GLUCOTROL XL

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/24/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
PAIN ABDO
SWEAT

9. Mfr.report number
M072853

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072853

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
PEPCID

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072894

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 90 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 10/20/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 90-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED "STOMACHACHES", CRAMPS AND DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. THE PATIENT STARTED TAKING GLUCOPHAGE ON APPROXIMATELY OCTOBER 17, 1997; BY OCTOBER 20, 1997 HE HAD DEVELOPED THE ABOVE SYMPTOMS. AS OF OCTOBER 27, 1997 THE EVENTS ARE UNRESOLVED. CONCOMITANT DRUGS INCLUDED LANOXIN, ZANTAC (RANITIDINE) AND CAPOTEN (CAPTOPRIL). NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. 10/17/97-UNK
CONTINUING 10 DAYS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
CAPOTEN
LANOXIN
ZANTAC

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/27/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
DYSPEPSIA
PAIN
DIARRHEA

9. Mfr.report number
M072894

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072905

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex NI
☐ female ☐ male

4. Weight
____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A PATIENT (AGE AND GENDER NOT SPECIFIED), DEVELOPED "GREYING OF SKIN", MUSCLE TIGHTNESS AND UPSET STOMACH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG QD. NO FURTHER DETAILS WERE REPORTED. FURTHER INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
NI

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG QD ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/17/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
EDEMA
PALLOR
HYPERTONIA

9. Mfr.report number
M072905

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M072988

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 82 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 01/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

AN 82-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED INSOMNIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. THE PATIENT STARTED TAKING GLUCOPHAGE IN NOVEMBER, 1996; BY JANUARY, 1997 SHE HAD DEVELOPED THE ABOVE SYMPTOM. SHE WAS CONCOMITANTLY TAKING GLIPIZIDE. AS OF OCTOBER 27, 1997 THE ABOVE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 11/00/96-UNK

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLIPIZIDE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/27/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
INSOMNIA

9. Mfr.report number
M072988

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073028

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 61 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 61-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED SEVERE DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT WAS NOT TAKING ANY CONCOMITANT DRUGS. IN OCTOBER, 1997, THE PATIENT TOOK A SINGLE 500 MG TABLET OF GLUCOPHAGE, AND AFTER THIS ONE DOSE SHE DEVELOPED SEVERE DIARRHEA. SHE STOPPED GLUCOPHAGE, AND THE EVENT RESOLVED. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG ORAL

3. Therapy dates
#1. 10/00/97-10/00/97
1 DOSES

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/28/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA

9. Mfr.report number
M073028

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073072

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 04/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT HIS WIFE (AGE NOT SPECIFIED) DEVELOPED BLOODY STOOLS, CRAMPING AND DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APPROXIMATELY APRIL, 1997. SHE SUBSEQUENTLY BEGAN EXPERIENCING THE ABOVE EVENT. GLUCOPHAGE THERAPY WAS STOPPED AND THEN RESTARTED ONE MONTH LATER AT 500 MG QD; THE DOSE WAS SUBSEQUENTLY AGAIN INCREASED TO 500 MG BID. THE PATIENT INITIALLY WAS "FINE" WITH A FASTING BLOOD SUGAR OF 104. THE PATIENT AGAIN COMPLAINED OF CRAMPING, DIARRHEA AND BLOOD IN THE STOOL. GLUCOPHAGE THERAPY WAS STOPPED AND THE PATIENT "GOT BETTER" (NOT SPECIFIED IF EVENTS COMPLETELY RESOLVED). THE REPORTER STATED THAT HE CONSIDERS GLUCOPHAGE TO BE THE CAUSE OF THE EVENT. THE PATIENT IS NOT CURRENTLY TAKING (AS OF OCTOBER 28, 1997) ANY ANTI-DIABETIC THERAPY. NO FURTHER DETAILS WERE

(CONTINUED)

6. Relevant tests/laboratory data
FASTING BLOOD SUGAR 104
05/00/97

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 04/00/97-00/00/97
6 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [X] yes [ ] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/28/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
MELENA
PAIN
DIARRHEA

9. Mfr.report number
M073072

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073072

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073080

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 62 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 62-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID. THE PATIENT STARTED TAKING GLUCOPHAGE IN FEBRUARY, 1997. THE ONSET DATE OF THE EVENT WAS NOT REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 02/00/97-UNK

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NORVASC

IMODIUM

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA

9. Mfr.report number
M073080

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073082

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — in confidence

2. Age at time of event: or 71 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 71-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED ODOR IN THE URINE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG QD. THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. CONCOMITANT DRUGS INCLUDED ALLOPURINOL QD AND ZOCOR QD. NO FURTHER DETAILS WERE REPORTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON NOVEMBER 18, 1997. THE EXPIRATION DATE FOR HER GLUCOPHAGE PRESCRIPTION WAS APRIL, 2000; SHE GAVE A LOT NUMBER OF "BMS6070." NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG QD ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. "BMS6070"

7. Exp.date
#1. 4/2000

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ALLOPURINOL

ZOCOR

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
URIN ABNORM

9. Mfr.report number
M073082

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073087

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 66 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 01/24/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 66-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED "NERVE DAMAGE" WITH UPPER BACK PAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON JANUARY 14, 1997; BY JANUARY 24, 1997 SHE WAS EXPERIENCING THE ABOVE SYMPTOMS. SHE STOPPED TAKING GLUCOPHAGE IN APRIL, 1997. AS OF OCTOBER 19, 1997 (MORE THAN SIX MONTHS AFTER STOPPING GLUCOPHAGE), THE ABOVE SYMPTOMS PERSIST. HER MEDICAL HISTORY INCLUDED HYPERTENSION. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 01/14/97-04/00/97
3 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [X] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ACCUPRIL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN BACK
NEUROPATHY

9. Mfr.report number
M073087

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073092

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
   [redacted]
   In confidence

2. Age at time of event: or 63 YRS
   Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:

3. Date of event: 00/00/96

4. Date of this report: 01/21/98

5. Describe event or problem

A 63-YEAR-OLD MALE PATIENT REPORTED THAT HE DEVELOPED A LOSS OF APPETITE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS TYPE II. HE STARTED TAKING GLUCOPHAGE IN 1996; THERAPY DURATION IS APPROXIMATELY 1.5 YEARS. SINCE STARTING GLUCOPHAGE THERAPY, THE PATIENT HAS EXPERIENCED A LOSS OF APPETITE; HE REPORTED THAT HE "FEELS FULL ALL DAY LONG, IT'S HARD TO EAT NOT DUE TO NAUSEA BUT DUE TO THE FULL FEELING." HIS MEDICAL HISTORY INCLUDED ALLERGY TO TALWIN (PENTAZOCINE LACTATE).

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
TALWIN ALLERGY

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 00/00/96-UNK
1.5 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS TYPE II

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYNASE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
ANOREXIA

9. Mfr.report number
M073092

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073159

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [X] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT HIS WIFE (AGE NOT SPECIFIED) DEVELOPED "LOTS OF BLOATING", SOFT BOWEL MOVEMENTS AND WAS PASSING "ALOT OF PROTEIN" IN THE URINE WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THE PATIENT WAS TAKING THE 500 MG STRENGTH OF GLUCOPHAGE TABLETS; DAILY DOSE NOT SPECIFIED. THE PATIENT ALSO COMPLAINED THAT THE TABLETS HAD AN ODOR "LIKE DEAD FISH." ADDITIONAL INFORMATION WAS REQUESTED. CROSS REFERENCE PRODUCT COMPLAINT NUMBER 23335.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. UNKNOWN

7. Exp.date
#1. UNKNOWN

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/31/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
FLATUL
ALBUMINURIA
STOOL ABNORM

9. Mfr.report number
M073159

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
PATIENT'S HUSBAND

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073188

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 43 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT HER 43-YEAR-OLD HUSBAND DEVELOPED FLATULENCE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS FOUR WEEKS. CONCOMITANT DRUGS INCLUDED GLYBURIDE QD. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG BID ORAL

3. Therapy dates
#1. UNK 4 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYBURIDE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/31/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
FLATUL

9. Mfr.report number
M073188

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073213

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 45 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 45-YEAR-OLD FEMALE PATIENT DEVELOPED HYPOGLYCEMIA WITH ASSOCIATED SYMPTOMS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF DIABETES MELLTUS TYPE II. THE EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS THREE MONTHS. THE PATIENT WAS NOT TAKING ANY CONCOMITANT DRUGS, AND HAD NO COEXISTING OR SIGNIFICANT PAST MEDICAL CONDITIONS. WHILE TAKING GLUCOPHAGE, THE PATIENT HAS DEVELOPED HYPOGLYCEMIA (BLOOD SUGAR IN THE 50'S), WITH ASSOCIATED SYMPTOMS INCLUDED SWEATING, SHAKINESS AND NERVOUSNESS. THE PATIENT DENIED FASTING OR PROLONGED EXERCISE. NO FURTHER DETAILS WERE REPORTED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
BLOOD SUGAR 50'S

7. Other relevant history, including preexisting medical conditions
NONE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. UNK
3 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS TYPE II

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/31/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
HYPOGLYCEM

9. Mfr.report number
M073213

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073216

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 52 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 52-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED BLURRED VISION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2 WEEKS. A FEW DAYS AFTER STARTING GLUCOPHAGE, SHE DEVELOPED THE ABOVE SYMPTOM. HER MEDICAL HISTORY INCLUDED HYPERTENSION.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
2 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
MICRONASE

ALTACE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/31/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
VISION ABNORM

9. Mfr.report number
M073216

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073238

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [ ] female [X] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
[ ] death ____
[ ] life-threatening
[ ] hospitalization-initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER (AGE NOT PROVIDED) REPORTED THAT HE DEVELOPED BLOATING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 2500 MG QD. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO YEARS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 2500 MG QD ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
[ ] foreign
[ ] study
[ ] literature
[X] consumer
[ ] health professional
[ ] user facility
[ ] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer
11/03/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
[ ] 5-day [ ] 15-day
[ ] 10-day [X] periodic
[X] Initial [ ] follow-up# ____

8. Adverse event term(s)
FLATUL

9. Mfr.report number
M073238

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073255

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or 60 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [X] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 60-YEAR-OLD FEMALE CONSUMER COMPLAINED THAT THE PRODUCT "WAS NOT WORKING" AND THAT SHE WAS PASSING THE TABLET IN THE STOOL WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF DIABETES MELLITUS. HER MEDICAL HISTORY, HOWEVER, INCLUDED AN ILEOSTOMY. SHE WAS NOT TAKING ANY CONCOMITANT DRUGS. TOTAL DURATION OF GLUCOPHAGE THERAPY IS ONE WEEK. ADDITIONAL INFORMATION WAS REQUESTED. CROSS REFERENCE PRODUCT COMPLAINT #23428.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
ILEOSTOMY

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. UNK
1 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/03/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
NO DRUG EFFECT

9. Mfr.report number
M073255

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073262

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A FEMALE PATIENT (AGE NOT REPORTED) DEVELOPED DECREASED SWEATING WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. WHILE TAKING GLUCOPHAGE, THE PATIENT NOTED THAT SHE IS "NOT SWEATING WHEN SHE EXERCISES." NO FURTHER DETAILS WERE REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/22/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
SWEAT DEC

9. Mfr.report number
M073262

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073267

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 76 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 08/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 76-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED AN ECZEMATOUS RASH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 2000 MG QD FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 9 MONTHS. IN APPROXIMATELY AUGUST, 1997, THE PATIENT DEVELOPED THE ABOVE SYMPTOM. HIS MEDICAL HISTORY INCLUDED ARTHRITIS AND RASH RESULTING FROM USE OF TOLBUTAMIDE. HE WAS CONCOMITANTLY TAKING NAPROSYN (NAPROXEN SODIUM). AS OF NOVEMBER 4, 1997, THE EVENT IS DESCRIBED AS "GETTING WORSE." NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
ARTHRITIS

ALLERGY TOLBUTAMIDE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 2000 MG QD ORAL

3. Therapy dates
#1. UNK
9 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NAPROSYN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
RASH

9. Mfr.report number
M073267

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073298

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 70 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/20/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER IN HER 70'S REPORTED THAT SHE DEVELOPED HEART PALPITATIONS, DIZZINESS AND NAUSEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO WEEKS. ON OCTOBER 20, 1997, THE PATIENT DEVELOPED THE ABOVE SYMPTOMS. HER MEDICAL HISTORY INCLUDED HYPOTHYROIDISM, IRREGULAR HEART BEAT AND ALLERGIES TO CODEINE AND IODINE. CONCOMITANT DRUGS INCLUDED DIGOXIN, SYNTHROID (LEVOTHYROXINE SODIUM), GLUCOTROL (GLIPIZIDE) AND VITAMINS. THE SYMPTOMS RESOLVED; IT WAS NOT NOTED IF GLUCOPHAGE THERAPY WAS CONTINUED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPOTHYROIDISM
IRREGULAR HEARTBEAT
ALLERGY CODEINE
ALLERGY IODINE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG BID ORAL

3. Therapy dates
#1. 00/00/97-UNK
2 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
SYNTHROID
LANOXIN
GLUCOTROL
VITAMINS

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
PALPITAT
DIZZINESS
NAUSEA

9. Mfr.report number
M073298

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073363

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier: In confidence

2. Age at time of event: or 67 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 67-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED TINGLING AROUND THE MOUTH INCLUDING THE THROAT AREA WHILE TAKING GLUCOPHAGE (METFORMIN HCL 500 MG BID) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APPROXIMATELY NOVEMBER, 1996; IN OCTOBER 1997 (FOR THE PAST MONTH), HE HAS BEEN EXPERIENCING THE ABOVE SYMPTOMS. AS OF NOVEMBER 6, 1997, THE ABOVE EVENT IS UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 11/00/96-UNK
1 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYNASE

VITAMINS

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ initial ☐ follow-up# ____

8. Adverse event term(s)
PARESTH CIRCUMORAL

9. Mfr.report number
M073363

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073366

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier

In confidence

2. Age at time of event: or 71 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 71-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED AN INCREASE IN SERUM GLUCOSE LEVELS AFTER STARTING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 23 WEEKS. PRIOR TO GLUCOPHAGE THERAPY, THE PATIENT WAS TAKING GLIPIZIDE. GLIPIZIDE THERAPY WAS STOPPED WHEN GLUCOPHAGE WAS STARTED. THE PATIENT WAS NOT TAKING ANY CONCOMITANT DRUGS. THE ACTUAL SERUM GLUCOSE READINGS WERE NOT PROVIDED. AS OF NOVEMBER 6, 1997, THE EVENT IS UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
SERUM GLUCOSE INCREASED

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 00/00/97-UNK
23 WEEKS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ initial ☐ follow-up# ____

8. Adverse event term(s)
HYPERGLYCEM
REACT AGGRAV

9. Mfr.report number
M073366

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073372

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 07/16/97

4. Date of this report: 01/21/98

5. Describe event or problem

THIS IS A SPONTANEOUS REPORT, WHICH WAS REFERRED BY SMITHKLINE-BEECHAM PHARMACEUTICALS.

A MALE CONSUMER, AGE NOT PROVIDED, REPORTED THAT HE DEVELOPED DIARRHEA AND BLOATING WHILE TAKING GLUCOPHAGE (METFORMIN HCL), MIACALCIN (CALCITONIN SALMON), SALAGEN (PILOCARPINE HCL) AND OS-CAL (CALCIUM CARBONATE). THE PATIENT BEGAN DEVELOPING THE ABOVE EVENTS ON APPROXIMATELY JULY 16, 1997. BY OCTOBER 20, 1997, HE HAD STOPPED USING OS-CAL FOR A TIME, AND THEN RESTARTED THE PRODUCT. HE STATED THAT THE BLOATING AND DIARRHEA WEREN'T AS BAD WHEN HE RESTARTED THE OS-CAL. HE ALSO QUESTIONED IF MIACALCIN, SALAGEN AND GLUCOPHAGE THERAPIES COULD BE CAUSING THE SYMPTOMS. THE DOSAGE AND THERAPY DATES FOR THE ABOVE MEDICATIONS WERE NOT PROVIDED. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS
#2. OS-CAL (CONTINUED)

2. Dose, frequency & route used
#1. ORAL
#2. NI

3. Therapy dates
#1. NI
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. UNK

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
DIARRHEA
FLATUL

9. Mfr.report number
M073372

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073372

UF/Dist report # NA

FDA Use Only

APPEARS THIS WAY ON ORIGINAL

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
   #3. MIACALCIN
   #4. SALAGEN
2. Dose, frequency & route used
   #3. NI
   #4. NI
3. Therapy dates
   #3. NI
   #4. NI
4. Diagnosis for use
   #3. UNK
   #4. UNK
5. Event abated after use stopped or dose reduced
   #3 ☐ yes ☐ no ☒ doesn't apply
   #4 ☐ yes ☐ no ☒ doesn't apply
6. Lot #
   #3. NI
   #4. NI
7. Exp.date
   #3. NI
   #4. NI
8. Event reappeared after reintroduction
   #3 ☐ yes ☐ no ☒ doesn't apply
   #4 ☐ yes ☐ no ☒ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073399

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth: NI
3. Sex NI — ☐ female ☐ male
4. Weight ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A PHARMACIST REPORTED THAT APPROXIMATELY FOUR PATIENTS DEVELOPED INCREASED LACTATE LEVELS, MUSCLE ACHES AND SHORTNESS OF BREATH WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THIS FILE REPRESENTS PATIENT #2 OF 4. THE AGE AND GENDER OF THE PATIENT WAS NOT REPORTED. THE PATIENT HAD NORMAL RENAL AND HEPATIC FUNCTION. IT WAS NOTED THAT THE PATIENT DID NOT DEVELOP LACTIC ACIDOSIS. ADDITIONAL INFORMATION WAS REQUESTED, INCLUDING THE LACTATE LEVEL, HAS BEEN REQUESTED. CROSS REFERENCE CARES FILE NUMBERS M72832, M73401 AND M73400.

6. Relevant tests/laboratory data

LACTIC ACID INCREASED

RENAL FUNCTION NORMAL

HEPATIC FUNCTION NORMAL

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS
2. Dose, frequency & route used: #1. ORAL
3. Therapy dates: #1. NI
4. Diagnosis for use: #1. DIABETES MELLITUS
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☐ no ☒ doesn't apply
   - ☐ yes ☐ no ☐ doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☒ doesn't apply
   - ☐ yes ☐ no ☐ doesn't apply
9. NDC #: NOT REPORTED
10. Concomitant medical products: UNK

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☒ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer: 10/23/97
5. (A)NDA # 20-357; IND # ____; PLA # ____; pre-1938 ☐ yes; OTC product ☐ yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☒ periodic
   - ☒ Initial ☐ follow-up# ____
8. Adverse event term(s)

LAB TEST ABNORM

DYSPNEA

MYALGIA

9. Mfr.report number: M073399

E. Initial reporter

2. Health professional? ☒ yes ☐ no
3. Occupation: PHARMACIST
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073400

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex NI — ☐ female ☐ male
4. Weight ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT APPROXIMATELY FOUR PATIENTS DEVELOPED INCREASED LACTATE LEVELS, MUSCLE ACHES AND SHORTNESS OF BREATH WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THIS FILE REPRESENTS PATIENT #3 OF 4. THE AGE AND GENDER OF THE PATIENT WAS NOT REPORTED. THE PATIENT HAD NORMAL RENAL AND HEPATIC FUNCTION. IT WAS NOTED THAT THE PATIENT DID NOT DEVELOP LACTIC ACIDOSIS. ADDITIONAL INFORMATION WAS REQUESTED, INCLUDING THE LACTATE LEVEL, HAS BEEN REQUESTED. CROSS REFERENCE CARES FILE NUMBERS M72832, M73399 AND M73401.

6. Relevant tests/laboratory data

LACTIC ACID INCREASED

RENAL FUNCTION NORMAL

HEPATIC FUNCTION NORMAL

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/23/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
LAB TEST ABNORM
DYSPNEA
MYALGIA

9. Mfr.report number
M073400

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHARMACIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073401

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex NI
☐ female
☐ male

4. Weight
___ lbs
or
NI ___ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ___
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A PHARMACIST REPORTED THAT APPROXIMATELY FOUR PATIENTS DEVELOPED INCREASED LACTATE LEVELS, MUSCLE ACHES AND SHORTNESS OF BREATH WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THIS FILE REPRESENTS PATIENT #4 OF 4. THE AGE AND GENDER OF THE PATIENT WAS NOT REPORTED. THE PATIENT HAD NORMAL RENAL AND HEPATIC FUNCTION. IT WAS NOTED THAT THE PATIENT DID NOT DEVELOP LACTIC ACIDOSIS. ADDITIONAL INFORMATION WAS REQUESTED, INCLUDING THE LACTATE LEVEL, HAS BEEN REQUESTED. CROSS REFERENCE CARES FILE NUMBERS M72832, M73399 AND M73400.

6. Relevant tests/laboratory data
LACTIC ACID INCREASED
RENAL FUNCTION NORMAL
HEPATIC FUNCTION NORMAL

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/23/97

5. (A)NDA # 20-357
IND # ___
PLA # ___
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ___

8. Adverse event term(s)
LAB TEST ABNORM
DYSPNEA
MYALGIA

9. Mfr.report number
M073401

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHARMACIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073404

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death ____
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A FEMALE CONSUMER REPORTED THAT SHE DEVELOPED WEIGHT LOSS AND PRESSURE IN THE BACK OF THE HEAD AND NECK WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT REPORTED THAT SHE IS AFRAID THAT SHE MAY BE DEVELOPING LACTIC ACIDOSIS. NO FOLLOW-UP IS POSSIBLE; HOWEVER, AS THE PATIENT REFUSED TO PROVIDE AN ADDRESS OR PHONE NUMBER. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/07/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
WEIGHT DEC
HEADACHE

9. Mfr.report number
M073404

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073421

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 35 YRS — Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER IN HER 30'S REPORTED THAT SHE DEVELOPED SIGNIFICANT HAIR LOSS, WITH DRY/BREAKING HAIR WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 30 DAYS. IN OCTOBER, 1997 SHE BEGAN EXPERIENCING THE ABOVE EVENT. HER MEDICAL HISTORY INCLUDED DEPRESSION. AS OF NOVEMBER 7, 1997, THE ABOVE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

DEPRESSION

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used

#1. 500 MG BID ORAL

3. Therapy dates

#1. UNK
30 DAYS

4. Diagnosis for use

#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

LITHIUM

SYNTHROID

DESYREL

DESIPRAMINE

(CONTINUED)

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 11/07/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

NA

7. Type of report (check all that apply)

- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)

ALOPECIA
HAIR DIS

9. Mfr.report number

M073421

E. Initial reporter

1. Name, address & phone number

2. Health professional? [ ] yes [X] no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073421

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
    BENADRYL

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073473

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE PATIENT, AGE NOT SPECIFIED, REPORTED THAT SHE DEVELOPED A METALLIC TASTE IN HER MOUTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1 TABLET BID. EXACT THERAPY DATES AND DAILY DOSAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2 MONTHS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. 1 TAB BID ORAL

3. Therapy dates
#1. UNK
2 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/10/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
TASTE PERVERS

9. Mfr.report number
M073473

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073480

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — in confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 09/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER (AGE NOT SPECIFIED) REPORTED THAT SHE DEVELOPED DIZZINESS/LIGHTHEADEDNESS, GASTROINTESTINAL UPSET CHARACTERIZED BY DIARRHEA AND STOMACH CRAMPS, "DECREASED THIRST AND HUNGER", BACK PAIN AND RIGHT LEG PAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID AND GLYBURIDE FOR TREATMENT OF DIABETES MELLITUS. PRIOR TO THIS TIME, THE PATIENT WAS TAKING AN UNSPECIFIED "DIABETIC DRUG." SHE THEN SWITCHED TO GLYBURIDE AND GLUCOPHAGE THERAPY ON SEPTEMBER 9, 1997. "SOON AFTER STARTING THE MEDICATION", SHE DEVELOPED THE ABOVE SYMPTOMS. HER MEDICAL HISTORY INCLUDED RAPID HEARTBEAT AND HYPERTENSION. CONCOMITANT DRUGS INCLUDED ATENOLOL AND LANOXIN. IN LIGHT OF THE ABOVE SYMPTOMS, THE PATIENT "WAS EVALUATED EXTENSIVELY FOR A PINCHED NERVE AND ARTHRITIS." THE RESULTS OF HER EVALUATION WERE NOT REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

RAPID HEART BEAT

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. GLYBURIDE

2. Dose, frequency & route used
#1. 500 MG BID ORAL
#2. ORAL

3. Therapy dates
#1. 09/09/97-UNK
#2. 09/09/97-UNK

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ATENOLOL

LANOXIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/10/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN ABDO
PAIN BACK
PAIN
DIZZINESS
ANOREXIA

9. Mfr.report number
M073480

(CONTINUED)

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073480

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — in confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
   DIARRHEA
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073490

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI
4. Date of this report: 01/21/98

5. Describe event or problem

A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE DEVELOPED STOMACH PAIN AND DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF DIABETES MELLITUS. THE EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO WEEKS. THE PATIENT'S DAILY DOSAGE OF GLUCOPHAGE WAS 500 MG. HE REPORTED THAT HE WILL "CONTINUE TO TAKE THE MEDICATION." NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. UNK CONTINUING 2 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/11/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
PAIN ABDO
DIARRHEA

9. Mfr.report number
M073490

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073515

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A CONSUMER REPORTED THAT HER HUSBAND (AGE NOT SPECIFIED) DEVELOPED "STOMACH PROBLEMS" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS A "COUPLE OF MONTHS." EVER SINCE STARTING GLUCOPHAGE THERAPY, THE PATIENT HAS BEEN EXPERIENCING THESE STOMACH PROBLEMS. NO FURTHER DETAILS ARE AVAILABLE, AS THE REPORTER REFUSED TO PROVIDE AN ADDRESS OR PHONE NUMBER.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/11/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
DYSPEPSIA

9. Mfr.report number
M073515

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073519

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☒ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A PHARMACIST REPORTED THAT A MALE PATIENT (AGE NOT PROVIDED) EXPERIENCED A LACK OF EFFECT WHILE TAKING GLUCOPHAGE (METFORMIN HCL) TABS 500 MG STRENGTH (FREQUENCY NOT STATED) FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT WAS TAKING GLUCOPHAGE FROM LOT NUMBER J7J134A, EXPIRATION DATE NOT SPECIFIED, AND WAS EXPERIENCING ELEVATED GLUCOSE LEVELS. THE REPORTER STATED THAT THE GLUCOPHAGE WAS "INEFFECTIVE." ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
SERUM GLUCOSE ELEVATED

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. J7J134A

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
NO DRUG EFFECT

9. Mfr.report number
M073519

E. Initial reporter

2. Health professional?
☒ yes ☐ no

3. Occupation
PHARMACIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073525

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT SHE DEVELOPED CHEST PAIN ON EXERTION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID. THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. IN LATE OCTOBER, 1997 (APPROXIMATELY TWO WEEKS AGO), THE PATIENT'S DOSAGE OF GLUCOPHAGE WAS INCREASED TO 500 MG BID (INITIAL DOSE NOT REPORTED). FOLLOWING THIS DOSAGE INCREASE, SHE BEGAN EXPERIENCING THE CHEST PAIN. SHE STATED THAT WHEN SHE IS ACTIVE OR EXERTS HERSELF, SHE DEVELOPS THE SYMPTOM. CONCOMITANT DRUGS INCLUDED MICRONASE (GLYBURIDE) QD. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
MICRONASE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/12/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN CHEST

9. Mfr.report number
M073525

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073526

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 76 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A 76-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED A LOSS OF APPETITE WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES WERE NOT REPORTED. NO FURTHER DETAILS WERE PROVIDED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. UNK

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
ANOREXIA

9. Mfr.report number
M073526

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073530

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or 92 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 92-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED A METALLIC TASTE IN HER MOUTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS ONE MONTH. SINCE STARTING THE PRODUCT, SHE HAS BEEN EXPERIENCING THE ABOVE SYMPTOM, AND AS OF NOVEMBER 12, 1997, THE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
1 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
DIGOXIN
GLUCOTROL
CARDIZEM
PREDNISONE

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
TASTE PERVERS

9. Mfr.report number
M073530

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073530

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
BIAXIN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073549

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or 67 YRS — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI
4. Date of this report: 01/21/98

5. Describe event or problem

A 67-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA AND A METALLIC TASTE IN HER MOUTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO MONTHS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
2 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA
TASTE PERVERS

9. Mfr.report number
M073549

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? [ ] yes [ ] no
3. Occupation
4. Initial reporter also sent report to FDA [ ] yes [ ] no [ ] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073571

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 88 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

AN 88-YEAR-OLD MALE PATIENT REPORTED THAT HE DEVELOPED RENAL IMPAIRMENT, DIARRHEA, LOSS OF APPETITE, STOMACH UPSET, EXTREME FATIGUE AND EYE PROBLEMS CHARACTERIZED BY "HALO LIKE FLICKERING AND FLOATERS" WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THE PATIENT'S DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. HIS BASELINE GLUCOSE LEVELS WERE IN THE RANGE OF 133 (N=64-105). GLUCOPHAGE THERAPY WAS STARTED, AND THE PATIENT REPORTED IMPROVED GLYCEMIC CONTROL. HE THEN BEGAN TO EXPERIENCE THE ABOVE EVENTS (WITH THE EXCEPTION OF THE RENAL PROBLEMS). HE WAS EVALUATED BY AN EYE DOCTOR, AND A PHYSICAL PROBLEM WAS NOT IDENTIFIED. HE STATED THAT HE "DID NOT EVEN NEED NEW LENSES." AFTER SIX MONTHS, HE WAS EVALUATED BY ANOTHER PHYSICIAN, WHO NOTED THAT THE PATIENT'S "KIDNEYS WERE BEING AFFECTED." HE TOLD THE PATIENT TO STOP GLUCOPHAGE THERAPY. WITHIN TWO

(CONTINUED)

6. Relevant tests/laboratory data
SERUM GLUCOSE 133

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/06/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
KIDNEY FUNC ABNORM
ANOREXIA
DYSPEPSIA
DIARRHEA
EYE DIS

9. Mfr.report number
M073571

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073571

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

WEEKS OF STOPPING THE DRUG, THE PATIENT REPORTED THAT "EVERY SIDE EFFECT DISAPPEARED." NO FURTHER DETAILS WERE REPORTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON DECEMBER 18, 1997. HE REPORTED THAT THE DAILY DOSAGE FOR GLUCOPHAGE HAD BEEN 500 MG BID. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA
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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073582

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence
2. Age at time of event: or 63 YRS; Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: 10/00/97
4. Date of this report: 01/21/98
5. Describe event or problem

A 63-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED AN ALLERGIC REACTION CHARACTERIZED BY "SWELLING OF THE HANDS AND FEET AND A RASH" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 5 DAYS. IN LATE OCTOBER, 1997 (TWO WEEKS AGO), THE PATIENT EXPERIENCED SUDDEN-ONSET SYMPTOMS AS NOTED ABOVE. GLUCOPHAGE THERAPY WAS STOPPED, AND THE SYMPTOMS RESOLVED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG
2. Dose, frequency & route used: #1. 500 MG BID ORAL
3. Therapy dates: #1. 10/00/97-00/00/97 5 DAYS
4. Diagnosis for use: #1. NON-INSULIN-DEPENDENT DIABETES
5. Event abated after use stopped or dose reduced
   #1 ☒ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction
   ☐ yes ☐ no ☒ doesn't apply
   #1 ☐ yes ☐ no ☐ doesn't apply
9. NDC #: NOT REPORTED
10. Concomitant medical products
    UNIPHYL
    CLARITIN
    VENTOLIN
    GLYNASE

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
   LOUISE LOVAS, B.S.N.
   BRISTOL-MYERS SQUIBB
   WORLDWIDE SAFETY & SURVEILLANCE
   MAIL LOCATION D23-07
   P.O.BOX 4000
   PRprinceton,NEW JERSEY 08543-4000
2. Phone number: 609-252-3737
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☒ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer: 11/13/97
5. (A)NDA # 20-357; IND #; PLA #; pre-1938 ☐ yes; OTC product ☐ yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☒ periodic
   - ☒ Initial ☐ follow-up#
8. Adverse event term(s)
   ALLERG REACT
9. Mfr.report number: M073582

E. Initial reporter

1. Name, address & phone number
2. Health professional? ☐ yes ☒ no
3. Occupation: CONSUMER
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073582

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

ASCRIPTIN

TOPROL XL

PROZAC

ZOCOR

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073680

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE DEVELOPED DIFFICULTY BREATHING AND LIGHTHEADEDNESS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF DIABETES MELLITUS. THERAPY DATES AND DAILY DOSAGE FOR GLUCOPHAGE WAS NOT PROVIDED. THE REPORTER REFUSED TO PROVIDE ANY FURTHER INFORMATION.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/17/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ initial ☐ follow-up# ____

8. Adverse event term(s)
DYSPNEA
DIZZINESS

9. Mfr.report number
M073680

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073682

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A FEMALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT SHE DEVELOPED CONSTIPATION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS THREE WEEKS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
3 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/17/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
CONSTIP

9. Mfr.report number
M073682

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073692

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 42 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 09/30/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A 42-YEAR-OLD MALE PATIENT DEVELOPED INCREASED LIVER ENZYMES, INCREASED GLUCOSE, AN INCREASED WHITE BLOOD CELL COUNT (INCLUDING INCREASED BASOPHILS) AND A DECREASED SODIUM LEVEL WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. ON SEPTEMBER 30, 1997, THE PATIENT UNDERWENT LABORATORY TESTING, WHICH YIELDED THE FOLLOWING RESULTS: ALKALINE PHOSPHATASE 205, LDH 279, AST 72, ALT 78, SERUM GLUCOSE 213, LEUKOCYTES 10.5, BASOPHILS INCREASED (VALUE UNKNOWN). THE PATIENT HAS A HISTORY OF OCCUPATIONAL EXPOSURE TO CHEMICAL INHALATION SOLVENTS (SPECIFIC INHALANTS NOT IDENTIFIED). ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data

ALKALINE PHOSPHATASE 205
09/30/97
LDH 279
09/30/97
AST 72
09/30/97
ALT 78
09/30/97
SODIUM 131
09/30/97
BASOPHILS INCREASED
09/30/97

(CONTINUED)

7. Other relevant history, including preexisting medical conditions

CHEMICAL EXPOSURE

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS

2. Dose, frequency & route used: #1. ORAL

3. Therapy dates: #1. NI

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 11/18/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
LIVER FUNC ABNORM
WBC ABNORM
HYPONATREM
BASOPHILIA
HYPERGLYCEM

9. Mfr.report number: M073692

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073692

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data

WBC 10.5
09/30/97
GLUCOSE 213
09/30/97

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073829

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE "BECAME VERY ILL" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF DIABETES MELLITUS. DAILY DOSAGE WAS NOT PROVIDED. THE PATIENT STARTED TAKING GLUCOPHAGE ON APPROXIMATELY JANUARY 1, 1997. HE WAS INSTRUCTED TO TAKE THE PRODUCT ONE-HALF HOUR BEFORE MEALS. HE STATED THAT HE THEN BECAME VERY ILL AND UNDERWENT TESTS INCLUDED AN ULTRASOUND, "HYDROSCAN" AND X-RAYS. FOLLOWING THE DIAGNOSTIC TESTING, IT WAS THEN DEEMED THAT "THE GLUCOPHAGE WAS MAKING HIM ILL." NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1.
ORAL

3. Therapy dates
#1. 01/01/97-UNK

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/11/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
MALAISE

9. Mfr.report number
M073829

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073839

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 11/07/97

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE DEVELOPED ITCHING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 6 MONTHS. ON APPROXIMATELY NOVEMBER 7, 1997 (AND FOR THE ENSUING TWO WEEKS), THE PATIENT HAS BEEN EXPERIENCING ITCHING. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK 6 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NORPACE
LOPRESSOR
COZAAR
LASIX
(CONTINUED)

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/21/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
PRURITUS

9. Mfr.report number
M073839

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073839

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
    K-DUR
    AMARYL
    ASPIRIN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073863

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 55 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 55-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED ELEVATED LIVER FUNCTION TESTS AND AN "INFLAMED LIVER" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID AND REZULIN (TROGLITAZONE) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. SHE PATIENT STARTED GLUCOPHAGE MARCH, 1997; IN OCTOBER, 1997, IT WAS NOTED THAT HER LIVER FUNCTION TESTS WERE ELEVATED. REPEAT STUDIES SHOWED THE LIVER FUNCTION TEST ELEVATION PERSISTING. A "SCAN" IN OCTOBER, 1997 SHOWED THE LIVER TO BE INFLAMED. CONCOMITANT DRUGS INCLUDED GLUCOTROL XL (GLIPIZIDE). AS OF NOVEMBER 21, 1997, THE ABOVE EVENTS ARE UNRESOLVED. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

LIVER FUNCTION INCREASED
10/00/97
SCAN ABNORMAL
10/00/97

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. REZULIN

2. Dose, frequency & route used
#1. 1000 MG BID ORAL
#2. ORAL

3. Therapy dates
#1. 03/00/97-UNK
#2. NI

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES
#2. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL XL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/21/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
LIVER FUNC ABNORM
HEPATITIS

9. Mfr.report number
M073863

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073924

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE DEVELOPED DIARRHEA AND DEHYDRATION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 8 TO 9 MONTHS. THE PATIENT COMPLAINED OF INCREASING DIARRHEA AND DEHYDRATION; THE DIARRHEA PERSISTED FOR ONE MONTH. HE REPORTED THAT HE "BECAME VERY DEHYDRATED;" HOWEVER, HE WAS NOT ADMITTED TO A HOSPITAL. GLUCOPHAGE THERAPY WAS CONTINUED AT 500 MG TID, AND THE DIARRHEA EVENTUALLY RESOLVED WITHOUT TREATMENT. HE REPORTED THAT HIS RENAL AND HEPATIC FUNCTION WERE NORMAL. CONCOMITANT DRUGS INCLUDED: WELLBUTRIN (BUPROPION HCL), MS CONTIN (MORPHINE SULFATE SA) FOR DIABETIC NEUROPATHY, SOMA (CARISOPRODOL), PRILOSEC (OMEPRAZOLE), CLONIDINE, GLYBURIDE 5 MG QD AND DIFLUCAN (FLUCONAZOLE). NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
RENAL FUNCTION NORMAL
HEPATIC FUNCTION NORMAL

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. UNK CONTINUING 8-9 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
WELLBUTRIN
MS CONTIN
SOMA
PRILOSEC

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/25/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
DIARRHEA
DEHYDRAT

9. Mfr.report number
M073924

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073924

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

CLONIDINE

DIFLUCAN

GLYBURIDE

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073947

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 48 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT A 48-YEAR-OLD FEMALE DEVELOPED DIARRHEA, AN INCREASED HEART RATE AND INSOMNIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS FOUR WEEKS. THE PATIENT WAS CONCOMITANTLY TAKING GLUCOTROL (GLIPIZIDE). NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

HEART RATE INCREASED

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used

#1. 500 MG QID ORAL

3. Therapy dates

#1. UNK
4 WEEKS

4. Diagnosis for use

#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [X] doesn't apply

[ ] yes [ ] no [ ] doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

GLUCOTROL

G. All manufacturers

1. Contact office - name/address

LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 11/26/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)

DIARRHEA
TACHYCARDIA
INSOMNIA

9. Mfr.report number: M073947

E. Initial reporter

1. Name, address & phone number

2. Health professional? [ ] yes [X] no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073951

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 78 YRS — Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 78-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE, AND ON THE SECOND DAY OF TREATMENT, SHE BEGAN EXPERIENCING THE ABOVE SYMPTOM. TOTAL THERAPY DURATION HAS BEEN ONE WEEK. SHE WAS CONCOMITANTLY TAKING AN UNSPECIFIED ANTIHYPERTENSIVE AGENT. AS OF NOVEMBER 26, 1997, THE DIARRHEA IS PERSISTING. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. UNK
1 WEEKS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ANTIHYPERTENSIVE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)

- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/26/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)

- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA

9. Mfr.report number
M073951

E. Initial reporter

1. Name, address & phone number
USA

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073962

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 45 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT A MORBIDLY OBESE 45-YEAR-OLD MALE PATIENT DEVELOPED MASSIVE FLUID RETENTION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 2500 MG QD. THERAPY DATES WERE NOT PROVIDED. THE PHYSICIAN REPORTEDLY HAS RULED OUT OTHER CAUSES OF FLUID RETENTION SUCH AS CARDIOVASCULAR DISEASE; LABORATORY STUDIES INLUDING A BUN, SERUM CREATININE, LIVER FUNCTION TESTS AND URINE PROTEIN WERE WITHIN NORMAL LIMITS. THE PATIENT HAS GAINED A TOTAL OF 20 POUNDS IN THE ABDOMEN AND PERIPHERY IN A RELATIVELY "SHORT PERIOD OF TIME." NO FURTHER DETAILS WERE REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

BUN NORMAL

CREATININE NORMAL

URINE PROTEIN NEGATIVE

LIVER FUNCTION NORMAL

7. Other relevant history, including preexisting medical conditions

MORBID OBESITY

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 2500 MG QD ORAL

3. Therapy dates: #1. NI

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1
☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 11/25/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s): EDEMA

9. Mfr.report number: M073962

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: PHARMACIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073983

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT SHE DEVELOPED EXTREME DIARRHEA AND INCONTINENCE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) AND PAXIL (PAROXETINE HCL). DAILY DOSAGE AND EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS ONE YEAR. THE PATIENT WAS REPORTEDLY RESPONDING WELL TO GLUCOPHAGE THERAPY; AFTER THE INTRODUCTION OF PAXIL (DOSE AND START DATE NOT REPORTED), THE PATIENT DEVELOPED THE ABOVE EVENTS. NO FURTHER DETAILS WERE REPORTED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON DECEMBER 19, 1997. SHE REPORTED THAT SHE WAS USING INSULIN CONCOMITANTLY WITH GLUCOPHAGE THERAPY. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS
#2. PAXIL

2. Dose, frequency & route used
#1. ORAL
#2. NI

3. Therapy dates
#1. UNK
1 YEARS
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. UNK

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
INSULIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/02/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA
INCONTIN URIN

9. Mfr.report number
M073983

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073990

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or 67 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 03/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 67-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED INCREASED BLOOD SUGAR "WHEN SHE TAKES AN 'ANTI-INFLAMMATORY' OR ASPIRIN" AND GLUCOPHAGE (METFORMIN HCL). THE PATIENT STARTED TAKING GLUCOPHAGE IN MARCH, 1997. HER MEDICAL HISTORY INCLUDED ULCERATIVE COLITIS, HYPERTENSION AND HYPOTHYROIDISM. THE PATIENT'S BLOOD SUGAR IS 80-110 BEFORE DINNER. AFTER TAKING ASPIRIN OR AN ANTI-INFLAMMATORY AGENT, HER GLUCOSE LEVEL INCREASES TO 135 TO 140. SHE NOTED THAT THIS DID NOT OCCUR PRIOR TO GLUCOPHAGE THERAPY (IT STARTED IN MARCH 1997 AFTER SHE INITIATED GLUCOPHAGE). ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

SERUM GLUCOSE 80-110
00/00/97
SERUM GLUCOSE 135-140
00/00/97

7. Other relevant history, including preexisting medical conditions

ULCERATIVE COLITIS

HYPERTENSION

HYPOTHYROIDISM

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

#2. ASPIRIN

(CONTINUED)

2. Dose, frequency & route used
#1. 500 MG BID ORAL

#2. NI

3. Therapy dates
#1. 03/00/97-UNK

#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

#2. NI

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI

#2. NI

7. Exp.date
#1. NI

#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
SULFASALAZINE

HYZAAR

SYNTHROID

PREMARIN

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
HYPERGLYCEM

DRUG INTERACTION

9. Mfr.report number
M073990

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073990

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: / or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
#3. ANTI-INFLAMMATORY
2. Dose, frequency & route used
#3. NI
3. Therapy dates
#3. NI
4. Diagnosis for use
#3. NI
5. Event abated after use stopped or dose reduced
#3 ☐ yes ☐ no ☒ doesn't apply
#3 ☐ yes ☐ no ☐ doesn't apply
6. Lot #
#3. NI
7. Exp.date
#3. NI
8. Event reappeared after reintroduction
#3 ☐ yes ☐ no ☒ doesn't apply
#3 ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
PROVERA
GLUCOTROL

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073993

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 69 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT HER 69-YEAR-OLD HUSBAND DEVELOPED HYPERTENSION WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2 YEARS. THE PATIENT'S BLOOD PRESSURE WAS 140/80, AND INCREASED TO 170/100 WHILE ON GLUCOPHAGE THERAPY. HE WAS CONCOMITANTLY TAKING ASPIRIN. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

BLOOD PRESSURE 140/80

BLOOD PRESSURE 170/100

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used: #1. 850 MG BID ORAL

3. Therapy dates: #1. UNK 2 YEARS

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: ASPIRIN

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ initial ☐ follow-up# ____

8. Adverse event term(s): HYPERTENS

9. Mfr.report number: M073993

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073994

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 11/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER, AGE NOT PROVIDED, REPORTED THAT SHE DEVELOPED A REDDISH-PURPLE AREA ON HER CHEEKS ("LOOKED LIKE AN INVERTED TRIANGLE") AND A HEADACHE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN NOVEMBER, 1997; THERAPY DURATION WAS TWO WEEKS. IN LATE NOVEMBER, 1997, SHE DEVELOPED THE ABOVE SYMPTOMS. AS OF DECEMBER 1, 1997, SHE REPORTED THAT SHE "WAS FEELING BETTER." HER MEDICAL HISTORY INCLUDED ALLERGY TO PYRIDIUM (PHENAZOPYRIDINE HCL). ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
ALLERGY PYRIDIUM

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 11/00/97-UNK
2 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ASPIRIN
INDERAL
DIURETIC
LASIX

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
SKIN DISCOLOR
HEADACHE

9. Mfr.report number
M073994

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
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Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M073994

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
    CHLORPHENIRAMINE

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074001

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 71 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 11/24/97

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT HER 71-YEAR-OLD HUSBAND DEVELOPED DIZZINESS AND NAUSEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON APPROXIMATELY NOVEMBER 1, 1997; ON APPROXIMATELY NOVEMBER 24, 1997 HE DEVELOPED THE ABOVE EVENTS. HIS MEDICAL HISTORY INCLUDED A STROKE IN FEBRUARY 1997 AND HYPERTENSION. AS OF DECEMBER 1, 1997, THE NAUSEA AND DIZZINESS ARE UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

STROKE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. 11/01/97-UNK
1 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
12/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
NAUSEA
DIZZINESS

9. Mfr.report number
M074001

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074008

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 76 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 11/16/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 76-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED AN ALLERGIC RASH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE (EXACT DATE NOT PROVIDED), AND AFTER 10 DAYS (ON NOVEMBER 16, 1997), HE DEVELOPED AN ALLERGIC SKIN RASH ON HIS LEGS AND STOMACH. HIS MEDICAL HISTORY INCLUDED HEART DISEASE AND NO KNOWN ALLERGIES. THE SKIN RASH RESOLVED; IT WAS NOT REPORTED IF GLUCOPHAGE THERAPY WAS CONTINUED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HEART DISEASE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
10 DAYS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
LANOXIN
MONOKET
ZESTRIL
COUMADIN

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/26/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
ALLERG REACT

9. Mfr.report number
M074008

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074008

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced
   - ☐ yes ☐ no ☐ doesn't apply
   - ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction
   - ☐ yes ☐ no ☐ doesn't apply
   - ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

CARDIZEM CD

PROSCAR

LESCOL

ASPIRIN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074052

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 59 YRS — Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/95

4. Date of this report: 01/21/98

5. Describe event or problem

A 59-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED INSOMNIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN 1995; THERAPY DURATION WAS REPORTED AS APPROXIMATELY 2 YEARS. THE PATIENT NOTICED THE INSOMNIA IMMEDIATELY AFTER STARTING THE DRUG. AS OF DECEMBER 1, 1997, THE ABOVE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 00/00/95-UNK
2 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
PREMARIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/01/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
INSOMNIA

9. Mfr.report number
M074052

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074117

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT HE DEVELOPED PAIN IN THE KIDNEY AREA, FELT "TOXIC" AND HIS URINE WAS "VERY YELLOW" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2 MONTHS. HE STOPPED USING GLUCOPHAGE ON HIS OWN ACCORD, OVER CONCERN THAT HE COULD BE DEVELOPING A MORE SERIOUS PROBLEM, AND HE STARTING TAKING HIS OLD PRESCRIPTION (GLYBURIDE) IN ITS PLACE. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG BID ORAL

3. Therapy dates
#1. 00/00/97-00/00/97
2 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
MALAISE
PAIN KIDNEY
URIN ABNORM

9. Mfr.report number
M074117

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074208

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or 61 YRS
Date of birth:

3. Sex
[X] female
[ ] male

4. Weight
____ lbs
or
NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT A 61-YEAR-OLD FEMALE PATIENT DEVELOPED HYPOGLYCEMIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THERAPY DATES WERE NOT PROVIDED; THE PATIENT HAS BEEN COMPLAINING OF HYPOGLYCEMIA FOR THE PAST TWO TO THREE MONTHS. SHE REPORTED THAT HER POSTPRANDIOL GLUCOSE LEVELS TAKEN AT THIS TIME RANGE FROM 60-70 AND SHE FEELS "COLD" ASSOCIATED WITH THIS SYMPTOM. THE PATIENT IS OTHERWISE HEALTHY, AND SHOWS NO SIGNS OF PROGRESSION OF HER DIABETES. SHE DENIED UNDERGOING STRENOUS EXERCISE. SHE TAKES NO OTHER CONCOMITANT DRUGS; DENIES USE OF A SULFONYLUREA OR INSULIN. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
SERUM GLUCOSE 60-70
00/00/97

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day
- [ ] 15-day
- [ ] 10-day
- [X] periodic
- [X] initial
- [ ] follow-up# ____

8. Adverse event term(s)
HYPOGLYCEM

9. Mfr.report number
M074208

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHARMACIST

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074212

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or 72 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or 90.8 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 72-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED CONTINUING RASH OF THE FACE AND SCALP, WHICH WORSENS WITH INCREASING IN GLUCOSE LEVELS, WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT WAS EXPERIENCING THE RASH "BEFORE GLUCOPHAGE THERAPY." SHE HAS BEEN TAKING GLUCOPHAGE FOR AT LEAST ONE YEAR, AND STILL HAS THE RASH AS OF DECEMBER 3, 1997. SHE DID NOT CLARIFY IF THE INCREASES IN GLUCOSE WERE OUTSIDE OF NORMAL RANGE, OR IN THEY WERE JUST THE DAILY FLUCTUATIONS IN LEVELS (ASSOCIATED WITH AN INCREASE IN SYMPTOMS). SHE HAS NO KNOWN ALLERGIES AND CONCOMITANTLY TAKES DIABETA (GLYBURIDE). NO FURTHER DETAILS WERE REPORTED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
RASH

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG BID ORAL

3. Therapy dates
#1. UNK
>1 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
DIABETA

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/03/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
RASH
REACT AGGRAV

9. Mfr.report number
M074212

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074218

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or 76 YRS
Date of birth:

3. Sex
[X] female
[ ] male

4. Weight
____ lbs
or
NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
[ ] death
[ ] life-threatening
[ ] hospitalization-initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem
A 76-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DRY SKIN, JOINT PAIN AND DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS ONE MONTH. IMMEDIATELY AFTER STARTING THE DRUG, SHE BEGAN EXPERIENCING DIARRHEA; THE DRY SKIN OCCURRED GRADUALLY. INFORMATION REGARDING THE ONSET OF JOINT PAIN WAS NOT REPORTED. HER MEDICAL HISTORY INCLUDED NO KNOWN ALLERGIES. AS OF DECEMBER 3, 1997 THE ABOVE EVENTS ARE UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
1 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
FOSAMAX
LEVOXYL
PREMARIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
[ ] foreign
[ ] study
[ ] literature
[X] consumer
[ ] health professional
[ ] user facility
[ ] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer
12/03/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
[ ] 5-day [ ] 15-day
[ ] 10-day [X] periodic
[X] Initial [ ] follow-up# ____

8. Adverse event term(s)
SKIN DRY
ARTHRALGIA
DIARRHEA

9. Mfr.report number
M074218

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074219

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier: In confidence

2. Age at time of event: or 69 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 69-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED BACK PAIN AND PAIN IN THE ABDOMEN UNDER THE RIBCAGE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON NOVEMBER 18, 1997. SHE WAS NOT TAKING ANY CONCOMITANT DRUGS. ON AN UNSPECIFIED DATE, SHE DEVELOPED THE ABOVE SYMPTOMS. LABORATORY TESTING AND AN ABDOMINAL ULTRASOUND WERE NEGATIVE. GLUCOPHAGE THERAPY WAS RECENTLY INTERRUPTED IN PREPARATION FOR A COMPUTED TOMOGRAPHY SCAN, BUT AS OF DECEMBER 9, 1997, THE ABOVE SYMPTOMS ARE UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
BLOOD TEST NORMAL
00/00/97
ULTRASOUND ABDOMINAL NORMAL
00/00/97

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 11/18/97-12/00/97

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [X] no [ ] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/04/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN BACK
PAIN ABDO

9. Mfr.report number
M074219

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074231

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 58 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 11/15/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 58-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED STOMACH/GAS PAIN AND MUSCLE ACHES WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN EARLY 1997; THERAPY DURATION WAS 8 MONTHS. ON NOVEMBER 15, 1997, SHE INITIALLY DEVELOPED THE ABOVE SYMPTOMS. HER MEDICAL HISTORY INCLUDED HYPERCHOLESTEROLEMIA AND HYPERTENSION. AS OF DECEMBER 3, 1997, THE EVENTS ARE UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERCHOLESTEROLEMIA

HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG BID ORAL

3. Therapy dates
#1. 00/00/97-UNK
8 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLIPIZIDE

CAPOTEN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/03/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN ABDO

MYALGIA

9. Mfr.report number
M074231

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074256

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 65 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/95

4. Date of this report: 01/21/98

5. Describe event or problem

A 65-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE HAS EPISODES OF FEELING SHAKY AND FLUCTUATING GLUCOSE LEVELS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID AND GLYNASE (GLYBURIDE) FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2.5 YEARS. SINCE SHE STARTED GLUCOPHAGE, HER GLUCOSE BEFORE BREAKFAST IS APPROXIMATELY 229. HER GLUCOSE IS THEN APPROXIMATELY 84 BEFORE LUNCH AND ALSO SOMETIME BEFORE DINNER. SHE FEELS SHAKY DURING THESE TIMES. SHE IS ON A 1500 CALORIE DIET. WHEN SHE STOPPED GLUCOPHAGE, HER GLUCOSE READINGS ARE IN THE LOW 200'S. OTHER TIMES WHILE TAKING GLUCOPHAGE, HER GLUCOSE LEVEL IS IN THE RANGE OF 170. THE CURRENT STATUS OF GLUCOPHAGE THERAPY WAS NOT PROVIDED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

SERUM GLUCOSE 229

SERUM GLUCOSE 84

SERUM GLUCOSE LOW 200'S

SERUM GLUCOSE 170

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. GLYNASE

2. Dose, frequency & route used
#1. 500 MG TID ORAL
#2. ORAL

3. Therapy dates
#1. 00/00/95-UNK 2.5 YEARS
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
VITAMIN C
VITAMIN E
GARLIC
CHROMIUM

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/05/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
LAB TEST ABNORM
NERVOUSNESS

9. Mfr.report number
M074256

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074274

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 46 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT A 46-YEAR-OLD FEMALE CONSUMER DEVELOPED FLUSHING AND A "DRUNK FEELING" AFTER TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID AND COINCIDING WITH THE ADMINISTRATION OF UNSPECIFIED EYE DROPS DURING AN OPTOMETRY EXAMINATION. THE PATIENT HAD BEEN TAKING GLUCOPHAGE FOR 1.5 DAYS; SHE UNDERWENT THE OPTOMETRY EXAMINATION AND RIGHT AFTER RECEIVING THE EYE DROPS, THE PATIENT BECAME SYMPTOMATIC. THE NAME OF THE EYE DROPS AND WHETHER OR NOT THEY CONTAINED ATROPINE WAS NOT KNOWN. THE PATIENT'S CURRENT STATUS WAS NOT PROVIDED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG
#2. EYE DROPS

2. Dose, frequency & route used
#1. 500 MG BID ORAL
#2. EYE

3. Therapy dates
#1. 00/00/97-UNK 1.5 DAYS
#2. 00/00/97-00/00/97 1 DOSES

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. DIAGNOSTIC

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYNASE
PRILOSEC
NORTRIPTYLINE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/05/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
VASODILAT
STUPOR

9. Mfr.report number
M074274

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHARMACIST

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074283

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 63 YRS — Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 63-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DECREASED RED BLOOD CELLS, DECREASED WHITE BLOOD CELLS AND DECREASED PLATELETS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. DAILY DOSAGE WAS NOT PROVIDED; THE PATIENT STARTED TAKING GLUCOPHAGE IN JANUARY, 1997. SHE REPORTED THAT SHE "WAS MISDIAGNOSED WITH SHINGLES AND NON-INSULIN DEPENDENT DIABETES UPON AN EMERGENCY ROOM VISIT IN JANUARY, 1997 FOR HEADACHE AND NECK PAIN." SHE THEN HAD BEEN TAKING GLUCOPHAGE AND A SULFONYLUREA FOR FIVE TO SIX MONTHS (STOPPED IN JULY, 1997) AND IS NOW EXPERIENCING THE ABOVE EVENTS. THE EXACT ONSET DATE OF THE EVENTS WERE NOT PROVIDED. HEMATOLOGIC VALUES WERE ALSO NOT PROVIDED. AS OF DECEMBER 5, 1997, THE EVENTS ARE UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

(CONTINUED)

6. Relevant tests/laboratory data

RBC DECREASED
00/00/97
WBC DECREASED
00/00/97
PLATELETS DECREASED
00/00/97

7. Other relevant history, including preexisting medical conditions

HEADACHE

NECK PAIN

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS

2. Dose, frequency & route used: #1. ORAL

3. Therapy dates: #1. 01/00/97-07/00/97 5-6 MONTHS

4. Diagnosis for use: #1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: SULFONYLUREA

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 12/05/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
RBC ABNORM
THROMBOCYTOPENIA
LEUKOPENIA

9. Mfr.report number: M074283

E. Initial reporter

1. Name, address & phone number

2. Health professional? [ ] yes [X] no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074283

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074286

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or 68 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 11/04/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 68-YEAR-OLD MALE PATIENT REPORTED THAT HE DEVELOPED SWELLING OF HIS FEET WHILE TAKING GLUCOPHAGE (METFORMIN HC) 500 MG TID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2 TO 3 YEARS. ON NOVEMBER 4, 1997, HE STARTED EXPERIENCING THE ABOVE EVENT. HIS MEDICAL HISTORY INCLUDED HIATAL HERNIA AND NO KNOWN DRUG ALLERGIES. AS OF DECEMBER 5, 1997, THE SYMPTOMS ARE UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HIATAL HERNIA

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. UNK 2-3 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYBURIDE

PRAZOSIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
12/05/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
EDEMA PERIPH

9. Mfr.report number
M074286

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074311

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 70 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 70-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED "BLEEDING FROM HIS PENIS" AND DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE (DATE UNSPECIFIED) AND AFTER ONE WEEK OF THERAPY, HE BEGAN EXPERIENCING THE ABOVE EVENTS. TOTAL THERAPY DURATION IS TWO MONTHS. HIS MEDICAL HISTORY INCLUDED A TRANSURETHRAL RESECTION OF THE PROSTATE (TURP), AND HE PREVIOUSLY HAD BLOOD IN THE URINE RESULTING FROM THIS SURGERY. AS OF DECEMBER 9, 1997, THE ABOVE EVENTS ARE UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

TRANSURETHRAL RESECTION PROSTATE

HEMATURIA

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used

#1. 500 MG BID ORAL

3. Therapy dates

#1. UNK
2 MONTHS

4. Diagnosis for use

#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

GLYBURIDE

ALTACE

HYDROCHLOROTHIAZIDE

POTASSIUM CHLORIDE

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/09/97

5. (A)NDA # 20-357

IND # ____

PLA # ____

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ initial ☐ follow-up# ____

8. Adverse event term(s)

HEM

DIARRHEA

9. Mfr.report number: M074311

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074322

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 57 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 12/00/96

4. Date of this report: 01/21/98

5. Describe event or problem

A 57-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED "SEVERE CRAMPING" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN 1996; DURATION OF THERAPY WAS THREE MONTHS. IN DECEMBER, 1996, SHE DEVELOPED THE ABOVE SYMPTOMS WHICH PERSISTED FOR SIX WEEKS. HER MEDICAL HISTORY INCLUDED HYPERTENSION AND FIBROMYALGIA. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

FIBROMYALGIA

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 00/00/96-UNK
3 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
INSULIN

HYZAAR

NORVASC

PROVERA

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. # IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN

9. Mfr.report number
M074322

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074322

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
OGEN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074323

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 69 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 12/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 69-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED STOMACH DISTRESS, DIFFICULTY URINATING AND WAS UNABLE TO COMPLETELY EMPTY HIS BLADDER WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS FIVE WEEKS. THE PATIENT'S MEDICAL HISTORY INCLUDED AN ENLARGED PROSTATE; HOWEVER, HE WAS PREVIOUSLY "UNDER CONTROL" WITH REGARD TO THIS PROBLEM. HIS HISTORY ALSO INCLUDED HYPERTENSION AND ALLERGY TO PENICILLIN. THE PATIENT FURTHER DESCRIBED THAT HIS STOMACH DISTRESS OCCURRED WHEN LYING DOWN AT NIGHT; HE DEVELOPED THE URINARY AND THE STOMACH SYMPTOMS IN EARLY DECEMBER 1997 (FOR THE PREVIOUS WEEK). THE PATIENT SKIPPED AN EVENING DOSE, AND NOTED THAT THE SYMPTOMS IMPROVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

ENLARGED PROSTATE

HYPERTENSION

ALLERGY PENICILLIN

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used

#1. 500 MG BID ORAL

3. Therapy dates

#1. 00/00/97-UNK
5 WEEKS

4. Diagnosis for use

#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

VASOTEC

TENORMIN

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

DYSPEPSIA

DYSURIA

URIN RETENT

9. Mfr.report number: M074323

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074325

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 53 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 53-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED A METALLIC TASTE ON HER TONGUE AND NUMBNESS ON THE TIP OF THE TONGUE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN EARLY 1996; THERAPY DURATION WAS REPORTED AS 1.5 YEARS. SINCE THE SUMMER OF 1997, SHE DEVELOPED THE ABOVE SYMPTOMS. SHE NOTED, HOWEVER, THAT SHE UNDERWENT PERIODONTAL WORK IN JULY, 1997. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG BID ORAL

3. Therapy dates
#1. 00/00/95-UNK
1.5 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYNASE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
TASTE PERVERS
PARESTHESIA

9. Mfr.report number
M074325

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074336

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 60 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 00/00/96

4. Date of this report: 01/21/98

5. Describe event or problem

A 60-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED AN UPSET STOMACH, "FOOD TASTED BAD" AND DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS ONE YEAR. THE PATIENT HAS EXPERIENCED THE ABOVE SYMPTOMS SINCE HE STARTED TAKING GLUCOPHAGE THERAPY. AS OF DECEMBER 8, 1997 THE EVENTS ARE UNRESOLVED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG BID ORAL

3. Therapy dates
#1. 00/00/96-UNK
1 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYBURIDE

ZESTRIL

HYDROCHLOROTHIAZIDE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
12/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
DYSPEPSIA

TASTE PERVERS

DIARRHEA

9. Mfr.report number
M074336

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074348

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 68 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A MALE CONSUMER, AGE 68, REPORTED THAT HE DEVELOPED MUSCLE PAIN IN HIS ARMS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS THREE MONTHS. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used

#1. 500 MG BID ORAL

3. Therapy dates

#1. UNK
3 MONTHS

4. Diagnosis for use

#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

HYTRIN

ASPIRIN

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

MYALGIA

9. Mfr.report number

M074348

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074446

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 40 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 12/06/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 40-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED NAUSEA, DIARRHEA AND ABDOMINAL PAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON APPROXIMATELY DECEMBER 6, 1997. SINCE STARTING THE PRODUCT, HE HAS BEEN EXPERIENCING THE ABOVE SYMTPOMS; ON DECEMBER 10, 1997 HE REPORTED FEELING "MUCH WORSE." HE STATED THAT HIS EVENING DOSE, TAKEN AT TIMES WITH FOOD, IS NOT AS UPSETTING TO HIS STOMACH AS THE OTHER DOSE. HE NOTED THAT HE GETS BOUTS OF PAIN "AS IF HE WAS PREGNANT." NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 12/06/97-UNK
CONTINUING 6 DAYS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
SUDAFED

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/11/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
NAUSEA
DIARRHEA
PAIN ABDO

9. Mfr.report number
M074446

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074448

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 12/04/97

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER, AGE NOT REPORTED, STATED THAT SHE DEVELOPED AN INCREASED APPETITE AND WEIGHT GAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2-3 YEARS. THE PATIENT STATED THAT SHE WAS INSTRUCTED TO TAKE GLUCOPHAGE AFTER MEALS. ON DECEMBER 4, 1997, SHE NOTED THE ABOVE SYMPTOMS; WHEN SHE HAD BEEN TAKING GLUCOPHAGE THE "NIGHT BEFORE", SHE DID NOT NOTICE THESE SYMPTOMS. HER MEDICAL HISTORY INCLUDED HYPERTENSION, AND ALLERGY TO PHENOTHIAZINES. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK CONTINUING 2-3 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1 [ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
VASOTEC

KLONOPIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
APPETITE INC

WEIGHT INC

9. Mfr.report number
M074448

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074464

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 59 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 11/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 59-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED NAUSEA, DIARRHEA AND A STOMACHACHE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN LATE NOVEMBER, 1997. IMMEDIATELY AFTER STARTING THE PRODUCT, SHE BEGAN EXPERIENCING THE ABOVE SYMPTOMS. AS OF DECEMBER 12, 1997, THE EVENTS ARE UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 11/00/97-UNK
3 WEEKS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
PREMARIN

PROVERA

ZANTAC

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
NAUSEA

DIARRHEA

DYSPEPSIA

9. Mfr.report number
M074464

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
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MEDWATCH

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Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074469

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 69 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 11/04/96

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 69-YEAR-OLD MALE PATIENT DEVELOPED LYMPHOCYTTOSIS AND LEUKOCYTOSIS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN 1996; THERAPY DURATION WAS REPORTED AS ONE YEAR. HIS MEDICAL HISTORY INCLUDED HYPERTENSION AND HYPERCHOLESTEROLEMIA. ON NOVEMBER 4, 1996, THE PATIENT HAD INCREASED LEUKOCYTES, BUT A NORMAL DIFFERENTIAL COUNT. ON NOVEMBER 6, 1997, THE PATIENT HAD BOTH LEUKOCYTOSIS AND LYMPHOCYTOSIS. AS OF DECEMBER 12, 1997, THE EVENTS ARE UNRESOLVED.

6. Relevant tests/laboratory data

LEUKOCYTES INCREASED
11/04/96
DIFFERENTIAL WBC COUNT NORMAL
11/04/96
LEUKOCYTES INCREASED
11/06/97
LYMPHOCYTES INCREASED
11/06/97

7. Other relevant history, including preexisting medical conditions

HYPERTENSION

HYPERCHOLESTEROLEMIA

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG BID ORAL

3. Therapy dates: #1. 00/00/96-UNK 1 YEARS

4. Diagnosis for use: #1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products

ATENOLOL

PRILOSEC

LOPID

LOTENSIN

(CONTINUED)

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/12/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

LYMPHOCYTOSIS

LEUKOCYTOSIS

9. Mfr.report number: M074469

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: PHYSICIAN

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

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APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074469

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
CLARITIN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074478

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 09/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER, AGE NOT PROVIDED, REPORTED THAT HE DEVELOPED MUSCLE PAIN IN BETWEEN THE THIGHS AND THROUGH THE LEGS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN JULY, 1996. HIS MEDICAL HISTORY INCLUDED HEART SURGERY AND HYPERTENSION. THE PATIENT INITIALLY DEVELOPED THE MUSCLE PAIN IN SEPTEMBER, 1997. A DOPPLER TEST WAS PERFORMED, WHICH WAS NEGATIVE. HE STOPPED TAKING GLUCOPHAGE, AND THE SYMPTOMS RESOLVED. HE THEN RESTARTED TAKING THE PRODUCT AND THE SYMPTOMS REOCCURRED. ON DECEMBER 12, 1997, HE STARTED ON GLUCOPHAGE 250 MG BID AND "FEELS OKAY SO FAR." ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
DOPPLER LEG NEGATIVE
00/00/97

7. Other relevant history, including preexisting medical conditions
HEART SURGERY
HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 07/00/96-UNK CONTINUING

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
PROCARDIA
VASOTEC
LANOXIN
GLUCOTROL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/15/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
MYALGIA

9. Mfr.report number
M074478

E. Initial reporter

1. Name, address

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074480

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 44 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT A 44-YEAR-OLD MALE FAILED A BREATHALIZER TEXT (WITH AN INCREASED BLOOD ALCOHOL LEVEL OF .10) WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. TOTAL DURATION WAS 3-4 MONTHS. HIS MEDICAL HISTORY INCLUDED HERNIA REPAIR SURGERY ON NOVEMBER 12, 1997 (NOT STATED IF PATIENT WAS TAKING GLUCOPHAGE AT THAT TIME). HE WAS CONCOMITANTLY TAKING HYDROCORTONE. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

BLOOD ALCOHOL LEVEL .10

7. Other relevant history, including preexisting medical conditions

HERNIA REPAIR

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG BID ORAL

3. Therapy dates: #1. UNK 3-4 MONTHS

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: HYDROCORTONE

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other: ____

4. Date received by manufacturer: 12/15/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s): DRUG LEVEL INC

9. Mfr.report number: M074480

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074497

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 60 YRS — Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or 68.1 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 06/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 60-YEAR-OLD FEMALE DEVELOPED AN INCREASED LDH WHILE TAKING GLUCOPHAGE (METFORMIN HCL), MEVACOR (LOVASTATIN) AND GLYNASE (GLIPIZIDE). THERAPY DATES FOR GLUCOPHAGE AND DAILY DOSAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO YEARS. MEVACOR WAS BEING TAKEN AT 20 MG BID AND GLYNASE AT 3 MG QD. IN JUNE, 1997, IT WAS NOTED THAT THE PATIENT'S LDH WAS INCREASED (VALUE NOT REPORTED). MEVACOR THERAPY WAS STOPPED IN JUNE, 1997; GLYNASE AND GLUCOPHAGE WERE CONTINUED. A FOLLOW-UP LDH LEVEL WAS NOT REPORTED. HER MEDICAL HISTORY INCLUDED HYPERLIPIDEMIA. ADDITIONAL INFORMATON WAS REQUESTED.

6. Relevant tests/laboratory data

LDH INCREASED

7. Other relevant history, including preexisting medical conditions: CAUCASIAN

NI

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS

#2. MEVACOR (CONTINUED)

2. Dose, frequency & route used

#1. ORAL

#2. 20 MG BID ORAL

3. Therapy dates

#1. UNK CONTINUING 2 YEARS

#2. UNK-06/00/97

4. Diagnosis for use

#1. DIABETES MELLITUS

#2. HYPERLIPIDEMIA

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #

#1. NI

#2. NI

7. Exp.date

#1. NI

#2. NI

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [X] doesn't apply

#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

UNK

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 12/10/97

5. (A)NDA # 20-357

IND # ____

PLA # ____

pre-1938 [ ] yes

OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)

LDH INC

9. Mfr.report number

M074497

E. Initial reporter

1. Name, address & phone number

2. Health professional? [X] yes [ ] no

3. Occupation: PHYSICIAN

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074497

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name: #3. GLYNASE
2. Dose, frequency & route used: #3. 3 MG QD ORAL
3. Therapy dates: #3. NI
4. Diagnosis for use: #3. DIABETES MELLITUS
5. Event abated after use stopped or dose reduced
   - #3 ☐ yes ☐ no ☒ doesn't apply
   - ☐ yes ☐ no ☐ doesn't apply
6. Lot #: #3. NI
7. Exp.date: #3. NI
8. Event reappeared after reintroduction
   - ☐ yes ☐ no ☒ doesn't apply
   - #3 ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074512

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A NURSE PRACTITIONER REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE THAT A FEMALE PATIENT (AGE NOT PROVIDED) DEVELOPED HYPOGLYCEMIC EPISODES WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID. THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT'S MEDICAL HISTORY INCLUDED CONGESTIVE HEART FAILURE. AFTER SHE STARTED TAKING GLUCOPHAGE, SHE DEVELOPED THE HYPOGLYCEMIC EPISODES AND GLUCOPHAGE WAS STOPPED. AFTER GLUCOPHAGE THERAPY WAS DISCONTINUED, THE PATIENT DEVELOPED EDEMA OF HER LEGS. SHE WAS PLACED BACK ON GLUCOPHAGE AT 500 MG QD, AND THE EDEMA ABATED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
SERUM GLUCOSE DECREASED

7. Other relevant history, including preexisting medical conditions
CONGESTIVE HEART FAILURE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/26/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
HYPOGLYCEM
UNEXPECTED BENEFIT

9. Mfr.report number
M074512

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
NURSE PRACTITIONER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074514

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: NI ☐ female ☐ male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN'S ASSISTANT REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT TWO PATIENTS DEVELOPED PROFOUND FATIGUE WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THIS FILE REPRESENTS PATIENT #1 OF 2. THERAPY DATES WERE NOT PROVIDED; THE PATIENT WAS TAKING "THE MAXIMUM DOSE." IT WAS REPORTED THAT THE PATIENT (AGE AND GENDER NOT SPECIFIED) BECAME SO FATIGUED THAT IT "WAS HARD TO GET OUT OF BED." GLUCOPHAGE THERAPY WAS STOPPED; THE PATIENT'S OUTCOME WAS NOT REPORTED. ADDITIONAL INFORMATION WAS REQUESTED. CROSS REFERENCE CARES FILE #M074585.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNINGB.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
12/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
ASTHENIA

9. Mfr.report number
M074514

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN'S ASSISTANT

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074523

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)

- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 11/10/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 53-YEAR-OLD FEMALE PATIENT DEVELOPED LEUKOPENIA AND THROMBOCYTOPENIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF DIABETES MELLITUS TYPE II. IN 1994, HER WHITE BLOOD CELL COUNT WAS NORMAL. ON NOVEMBER 10, 1997, LABORATORY TESTING REVEALED THE FOLLOWING: WBC 2.05 K/MM3 (N=4.80-10.80 K/MM3), PLATELET COUNT 82 K/MM3 (N=150-450 K/MM3), HEMOGLOBIN 12.9 M/MM3 (N=10.0-16.0 M/MM3) AND HEMATOCRIT 38.7 % (N=37.0-47.0%). ON NOVEMBER 13, 1997, REPEAT TESTING SHOWED WBC 2.41, PLATELET COUNT 85 AND CONTINUED NORMAL HEMOGLOBIN AND HEMATOCRIT. BY NOVEMBER 21, 1997 HER WBC WAS 2.08 AND PLATELET COUNT WAS FURTHER DECREASED AT 81. THE PATIENT IS CURRENTLY BEING MAINTAINED ON GLUCOPHAGE THERAPY. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

WBC NORMAL
00/00/94
WBC 2.05 K/CU MM
11/10/97
WBC 2.41 K/CU MM
11/13/97
WBC 2.08 K/CU MM
11/21/97
PLATELET COUNT 82 K/CU MM
11/10/97
PLATELET COUNT 85 K/CU MM
11/13/97

(CONTINUED)

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS

2. Dose, frequency & route used: #1. ORAL

3. Therapy dates: #1. NI

4. Diagnosis for use: #1. DIABETES MELLITUS TYPE II

5. Event abated after use stopped or dose reduced: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: UNK

G. All manufacturers

1. Contact office - name/address:
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 12/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
LEUKOPENIA
THROMBOCYTOPENIA

9. Mfr.report number: M074523

E. Initial reporter

1. Name, address & phone number

2. Health professional? [X] yes [ ] no

3. Occupation: PHYSICIAN

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074523

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data

```
PLATELET COUNT 81 K/CU MM
   11/21/97
HEMOGLOBIN 12.9 G/DL
   11/10/97
HEMOGLOBIN NORMAL
   11/13/97
HEMATOCRIT 38.7 %
   11/10/97
HEMATOCRIT NORMAL
   11/13/97
```

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074532

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 70 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHARMACIST REPORTED THAT A 70-YEAR-OLD MALE PATIENT DEVELOPED AN EXACERBATION OF HYPERGLYCEMIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT WAS TAKING GLUCOPHAGE FOR AN UNSPECIFIED TIME, AND WAS USING INSULIN THE LAST FOUR YEARS. HIS NORMAL BEDTIME GLUCOSE LEVELS RANGE FROM 130 TO 140; HE DID A "GLUCOSE STICK" AND THEN NOTED AN INCREASE TO 200. HE REPORTEDLY HAD BEEN TAKING GLUCOPHAGE "FOR SOME TIME" WITHOUT DOING A GLUCOSE CHECK. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

SERUM GLUCOSE 130-140

SERUM GLUCOSE 200

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 500 MG

#2. INSULIN

2. Dose, frequency & route used

#1. 500 MG BID ORAL

#2. SQ

3. Therapy dates

#1. NI

#2. UNK 4 YEARS

4. Diagnosis for use

#1. NON-INSULIN-DEPENDENT DIABETES

#2. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot #

#1. NI

#2. NI

7. Exp.date

#1. NI

#2. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

UNK

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.

BRISTOL-MYERS SQUIBB

WORLDWIDE SAFETY & SURVEILLANCE

MAIL LOCATION D23-07

P.O.BOX 4000

PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/15/97

5. (A)NDA # 20-357

IND # ____

PLA # ____

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

☐ 5-day ☐ 15-day

☐ 10-day ☒ periodic

☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

HYPERGLYCEM

REACT AGGRAV

9. Mfr.report number: M074532

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: PHARMACIST

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074533

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex NI ☐ female ☐ male

4. Weight ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A PATIENT (AGE AND GENDER NOT PROVIDED) DEVELOPED BURNING OF THE MOUTH WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 1.5 WEEKS. PRIOR TO GLUCOPHAGE, THE PATIENT WAS TAKING A SULFONLYUREA, WHICH FAILED TO PROVIDE ADEQUATE DIABETIC CONTROL. AFTER 1.5 WEEKS ON GLUCOPHAGE, HE DEVELOPED THE ABOVE EVENTS; HE WAS REFERRED TO A DENTIST, WHO STATED THAT "ALL IS FINE WITH THE ORAL CAVITY." GLUCOPHAGE THERAPY WAS STOPPED; THE PATIENT'S OUTCOME WAS NOT REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
1.5 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/15/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
STOMATITIS

9. Mfr.report number
M074533

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074534

UF/Dist report # NA

FDA Use Only

A. Patient information

1 Patient Identifier — In confidence

2. Age at time of event: or 64 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 64-YEAR-OLD MALE PATIENT DEVELOPED PORPHYRIA AFTER TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG QD FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT WAS INITIALLY TAKING REZULIN (TROGLITAZONE) AND REQUESTED THAT IT BE DISCONTINUED. GLUCOPHAGE 850 MG QD WAS PRESCRIBED IN ITS PLACE, AND THE PATIENT THEN BEGAN EXPERIENCING GASTROINTESTINAL SYMPTOMS INCLUDING ABDOMINAL PAIN. HE WAS SWITCHED TO AMARYL (GLIMERPIRIDE), AND SUBSEQUENTLY COMPLAINED OF BROWN URINE IN ADDITION TO ABDOMINAL PAIN. HE WAS DIAGNOSED WITH PORPHYRIA, WHICH THE PHYSICIAN CONSIDERED CAUSALLY RELATED TO AMARYL AND NOT GLUCOPHAGE THERAPY. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG
#2. AMARYL

2. Dose, frequency & route used
#1. 850 MG QD ORAL
#2. ORAL

3. Therapy dates
#1. NI
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
12/15/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
PORPHYRIA

9. Mfr.report number
M074534

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074536

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT SHE DEVELOPED LEG CRAMPS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QID. SHE WAS ALSO TAKING REZULIN (TROGLITAZONE) AND AMARYL (GLIMERPIRIDE). TOTAL DURATION OF GLUCOPHAGE THERAPY WAS TWO MONTHS. THE PATIENT REFUSED TO PROVIDE ANY FURTHER INFORMATION.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QID ORAL

3. Therapy dates
#1. UNK
2 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
REZULIN

AMARYL

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/16/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
CRAMPS LEG

9. Mfr.report number
M074536

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074560

UF/Dist report # NA

FDA Use Only

A. Patient information

1. [illegible]fier: In confidence

2. Age at time of event: or 52 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 08/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A CONSUMER REPORTED THAT HIS 52-YEAR-OLD WIFE DEVELOPED TACHYCARDIA, HEARTBURN AND DIZZINESS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN AUGUST, 1997; SINCE THAT TIME SHE HAS BEEN EXPERIENCING THE ABOVE EVENTS. SHE HAS BEEN TO THE EMERGENCY ROOM TWO TIMES FOR THESE SYMPTOMS; THE PHYSICIAN DIAGNOSED ANXIETY AND DOES NOT CONSIDER THE EVENTS RELATED TO GLUCOPHAGE THERAPY. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
HEART RATE INCREASED
08/00/97

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 08/00/97-UNK

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
MICRONASE
LOVASTATIN
VERAPAMIL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/16/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
TACHYCARDIA
DYSPEPSIA
DIZZINESS
ANXIETY

9. Mfr.report number
M074560

E. Initial reporter

1. Name, address & phone number
USA

2. Health professional?
[ ] yes [X] no

3. Occupation
PATIENT'S HUSBAND

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074585

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex NI ☐ female ☐ male

4. Weight ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN'S ASSISTANT REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT TWO PATIENTS DEVELOPED PROFOUND FATIGUE WHILE TAKING GLUCOPHAGE (METFORMIN HCL). THIS FILE REPRESENTS PATIENT #2 OF 2. THERAPY DATES WERE NOT PROVIDED; THE PATIENT WAS TAKING "THE MAXIMUM DOSE." IT WAS REPORTED THAT THE PATIENT (AGE AND GENDER NOT SPECIFIED) BECAME SO FATIGUED THAT IT "WAS HARD TO GET OUT OF BED." GLUCOPHAGE THERAPY WAS STOPPED; THE PATIENT'S OUTCOME WAS NOT REPORTED. ADDITIONAL INFORMATION WAS REQUESTED. CROSS REFERENCE CARES FILE #M074514.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS

2. Dose, frequency & route used
#1. ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNINGB.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ initial ☐ follow-up# ____

8. Adverse event term(s)
ASTHENIA

9. Mfr.report number
M074585

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN'S ASSISTANT

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074596

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 72 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or 64.9 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 12/10/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 72-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED AN ELEVATION IN BLOOD SUGAR WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON APPROXIMATELY DECEMBER 10, 1997. AS SOON AS HE STARTED THE DRUG, HIS BLOOD SUGAR INCREASED TO THE RANGE OF 250 TO 317 MG/DL. HE WAS CONCOMITANTLY TAKING AN ANTIBIOTIC (UNSPECIFIED). AS OF DECEMBER 17, 1997, THE EVENT IS UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data

FASTING BLOOD SUGAR 250-317 MG/DL
12/10/97

7. Other relevant history, including preexisting medical conditions

NONE

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG TID ORAL

3. Therapy dates: #1. 12/10/97-UNK 1 WEEKS

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced: #1 ☐ yes ☐ no ☒ doesn't apply; ☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction: #1 ☐ yes ☐ no ☒ doesn't apply; ☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: ANTIBIOTIC

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/17/97

5. (A)NDA # 20-357; IND # ____; PLA # ____; pre-1938 ☐ yes; OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

HYPERGLYCEM
REACT AGGRAV

9. Mfr.report number: M074596

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074603

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 62 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 12/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 62-YEAR-OLD MALE CONSUMER REPORTED THAT HIS "SKIN SMELLED BAD, LIKE THE TABLETS" WHILE TAKING GLUCOPHAGE (METFORMIN HCL) FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT HAS BEEN TAKING GLUCOPHAGE FOR APPROXIMATELY ONE YEAR; DAILY DOSE WAS NOT PROVIDED. IN MID-DECEMBER, 1997 (FOR THE PAST 2 TO 3 DAYS), THE PATIENT NOTED THE ABOVE SYMPTOMS. AS OF DECEMBER 18, 1997, THE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS

2. Dose, frequency & route used

#1. ORAL

3. Therapy dates

#1. UNK
1 YEARS

4. Diagnosis for use

#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

TOLAZAMIDE

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/18/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ initial ☐ follow-up# ____

8. Adverse event term(s)

BODY ODOR

9. Mfr.report number

M074603

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074617

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence
2. Age at time of event: or 29 YRS; Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: 11/15/97
4. Date of this report: 01/21/98
5. Describe event or problem

A 29-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED HAIR LOSS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS TWO MONTHS. ON NOVEMBER 15, 1997, THE PATIENT INITIALLY NOTICED THE HAIR LOSS; HE NOTED THERE IS NO PARTICULAR PATTERN (EQUAL AMOUNT OF LOSS FROM CHEST AND HEAD). HE STATED THAT HE HAD NO DIETARY OR MEDICATION CHANGES (NOT TAKING ANY CONCOMITANT DRUGS). AS OF DECEMBER 17, 1997, THE EVENT IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG
2. Dose, frequency & route used: #1. 500 MG BID ORAL
3. Therapy dates: #1. 00/00/97-UNK 2 MONTHS
4. Diagnosis for use: #1. DIABETES MELLITUS
5. Event abated after use stopped or dose reduced: #1 ☐ yes ☐ no ☒ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction: #1 ☐ yes ☐ no ☒ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #: NOT REPORTED
10. Concomitant medical products: NONE

G. All manufacturers

1. Contact office - name/address:
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☒ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:

4. Date received by manufacturer: 12/17/97
5. (A)NDA # 20-357; IND # ____; PLA # ____; pre-1938 ☐ yes; OTC product ☐ yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☒ periodic
   - ☒ initial ☐ follow-up# ____
8. Adverse event term(s): ALOPECIA
9. Mfr.report number: M074617

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no
3. Occupation: CONSUMER
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074620

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier: In confidence
2. Age at time of event: or 53 YRS; Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death ____
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A 53-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED BREAST ENGORGEMENT AND VAGINAL SPOTTING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE (EXACT DATE UNKNOWN) AND AFTER 3 TO 4 DAYS, SHE EXPERIENCED BREAST ENGORGEMENT (ALSO AFFECTING HER NIPPLES WHICH WERE "FIRM"). SHE STOPPED GLUCOPHAGE FOR APPROXIMATELY ONE WEEK, AND THE SYMPTOM RESOLVED. SHE RESTARTED GLUCOPHAGE, AND THEN DEVELOPED VAGINAL SPOTTING. SHE CONTACTED HER PHYSICIAN, WHO ADVISED HER THAT THE EVENT WAS PROBABLY "IDIOSYNCRATIC" AND HE ADVISED HER TO CONTINUE GLUCOPHAGE AT A LOWER DOSE (500 MG QD). NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data: UNK
7. Other relevant history, including preexisting medical conditions: UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG
2. Dose, frequency & route used: #1. 500 MG BID ORAL
3. Therapy dates: #1. UNK CONTINUING 3-4 DAYS
4. Diagnosis for use: #1. DIABETES MELLITUS
5. Event abated after use stopped or dose reduced: #1 [X] yes [ ] no [ ] doesn't apply; [ ] yes [ ] no [ ] doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction: [ ] yes [ ] no [X] doesn't apply; #1 [ ] yes [ ] no [ ] doesn't apply
9. NDC #: NOT REPORTED
10. Concomitant medical products: UNK

G. All manufacturers

1. Contact office - name/address:
   HEIDE CUNNING, B.S.
   BRISTOL-MYERS SQUIBB
   WORLDWIDE SAFETY & SURVEILLANCE
   MAIL LOCATION D23-07
   P.O.BOX 4000
   PRINCETON, NEW JERSEY 08543-4000
2. Phone number: 609-252-3737
3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [X] consumer
   - [ ] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:
4. Date received by manufacturer: 12/18/97
5. (A)NDA # 20-357; IND # ____; PLA # ____; pre-1938 [ ] yes; OTC product [ ] yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - [ ] 5-day [ ] 15-day
   - [ ] 10-day [X] periodic
   - [X] Initial [ ] follow-up# ____
8. Adverse event term(s): BREAST ENGORGE; METRORRHAGIA
9. Mfr.report number: M074620

E. Initial reporter

1. Name, address & phone number
2. Health professional? [ ] yes [X] no
3. Occupation: CONSUMER
4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074623

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or 75 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 07/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 75-YEAR-OLD FEMALE REPORTED THAT SHE DEVELOPED ALOPECIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN JUNE, 1997; SHE WAS NOT TAKING ANY CONCOMITANT DRUGS. IN JULY, 1997 SHE DEVELOPED THE ABOVE EVENT. AS OF DECEMBER 18, 1997, THE ALOPECIA IS UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. 06/00/97-UNK

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/18/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
ALOPECIA

9. Mfr.report number
M074623

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074644

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 65 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☒ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 12/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 65-YEAR-OLD MALE CONSUMER REPORTED THAT HE EXPERIENCED SLURRED SPEECH, DISORIENTATION, AND COMPLAINED THAT THE PRODUCT WAS INEFFECTIVE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE GREATER THAN ONE YEAR AGO. HE HAD BEEN RUNNING GLUCOSE LEVELS WITH GOOD CONTROL IN THE RANGE OF 75 TO 100 MG/DL. IN DECEMBER, 1997, HE NOTED THAT HE PASSED A GLUCOPHAGE TABLET WHOLE IN THE STOOL. AS HE HAS A CHEMISTRY BACKROUND, HE ATTEMPTED TO DISSOLVE THE TABLET BOTH IN AN ACID SOLUTION AND IN WATER, AND HE NOTED THAT THE TABLET DID NOT DISSOLVE. HIS GLUCOSE LEVELS BECAME ELEVATED AT 246 MG/DL. HE ALSO BECAME TRANSIENTLY DISORIENTED AND HAD SOME SLURRED SPEECH. THE LOT NUMBER FOR THIS GLUCOPHAGE PRESCRIPTION WAS UNKNOWN TO THE REPORTER. HE RETURNED THE GLUCOPHAGE TO

(CONTINUED)

6. Relevant tests/laboratory data
SERUM GLUCOSE 75-100 MG/DL
00/00/97
SERUM GLUCOSE 246 MG/DL
12/00/97
SERUM GLUCOSE 75-100 MG/DL
12/00/97

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK CONTINUING >1 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ATENOLOL
ACCUPRIL
GLUCOTROL
HYDROCHLOROTHIAZIDE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/19/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
NO DRUG EFFECT
SPEECH DIS
CONFUS

9. Mfr.report number
M074644

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074644

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

THE PHARMACY, AND WAS GIVEN A NEW PRESCIPTION. HE TESTED THE NEW TABLETS IN BOTH ACID AND WATER SOLUTIONS, AND NOTED THAT THE NEW TABLET DISSOLVED READILY. HIS GLUCOSE LEVELS HAVE ALSO RETURNED TO BASELINE AND HE HAD NO FURTHER SLURRED SPEECH OR DISORIENTATION. HIS MEDICAL HISTORY INCLUDED HYPERTENSION. ADDITIONAL INFORMATION HAS BEEN REQUESTED. CROSS REFERENCE PRODUCT COMPLAINT #23663.

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074658

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 64 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 64-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED ACHING OF THE BONES WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG QD FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT HAS BEEN TAKING GLUCOPHAGE ON AND OFF FOR THE PAST YEAR. SINCE STARTING THE DRUG, THE PATIENT HAS BEEN EXPERIENCING THE ABOVE SYMPTOM. HIS MEDICAL HISTORY INCLUDED HYPERTENSION AND IRREGULAR HEARTBEAT. WHEN HE STOPS GLUCOPHAGE THERAPY, THE BODY ACHES RESOLVE, AND WHEN HE RESUMES GLUCOPHAGE, THE SYMPTOMS REAPPEAR. AS OF DECEMBER 19, 1997, THE EVENT IS UNRESOLVED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

IRREGULAR HEARTBEAT

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG QD ORAL

3. Therapy dates
#1. UNK
1 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ATENOLOL

AMARYL

PROBANTHINE

TETRACYCLINE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/19/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
PAIN BONE

9. Mfr.report number
M074658

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074668

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 71 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 71-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG QD FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS SIX MONTHS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

UNK

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name

#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used

#1. ORAL

3. Therapy dates

#1. UNK
6 MONTHS

4. Diagnosis for use

#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

☐ yes ☐ no ☐ doesn't apply

6. Lot #

#1. NI

7. Exp.date

#1. NI

8. Event reappeared after reintroduction

☐ yes ☐ no ☒ doesn't apply

#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #

NOT REPORTED

10. Concomitant medical products

UNK

G. All manufacturers

1. Contact office - name/address

LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 12/19/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)

DIARRHEA

9. Mfr.report number

M074668

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☒ no

3. Occupation: CONSUMER

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074688

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 74 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 07/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 74-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APPROXIMATELY JULY, 1997; AFTER ONE WEEK, SHE DEVELOPED THE ABOVE SYMPTOM. HER MEDICAL HISTORY INCLUDED ALLERGY TO CODEINE. THE DIARRHEA HAS PERSISTED FOR FIVE MONTHS, AND AS OF DECEMBER 19, 1997 SHE HAS HAD NO RELIEF. SHE WAS CONCOMITANTLY TAKING GLYBURIDE. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
ALLERGY CODEINE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 07/00/97-UNK
5 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLYBURIDE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/19/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA

9. Mfr.report number
M074688

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074696

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI
4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER, AGE NOT SPECIFIED, REPORTED THAT SHE DEVELOPED MUSCLE ACHES WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 2 WEEKS. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. UNK
2 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
CAPOTEN

GLYBURIDE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/22/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
MYALGIA

9. Mfr.report number
M074696

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074773

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or 65 YRS — Date of birth:
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: 12/30/97
4. Date of this report: 01/21/98
5. Describe event or problem

A 65-YEAR-OLD MALE CONSUMER REPORTED THAT HE DEVELOPED SHORTNESS OF BREATH AND IRREGULAR HEARTBEATS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG QAM AND 500 MG IN THE AFTERNOON FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. AFTER TAKING GLUCOPHAGE FOR FOUR MONTHS, HE DEVELOPED THE ABOVE SYMPTOMS ON DECEMBER 30, 1997. THE SYMPTOMS OCCURRED EVERY 10 MINUTES. MEDICAL HISTORY INCLUDED IMPOTENCE. THE EVENTS SUBSEQUENTLY RESOLVED; THE STATUS OF GLUCOPHAGE THERAPY WAS NOT REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
IMPOTENCE

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1350 MG QD ORAL

3. Therapy dates
#1. 00/00/97-UNK
4 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NALDECON SENIOR DX

LOVASTATIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other: ____

4. Date received by manufacturer
12/31/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
DYSPNEA

PALPITAT

9. Mfr.report number
M074773

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M074869

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or NI — Date of birth:
3. Sex NI — ☐ female ☐ male
4. Weight — ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A HEALTH PROFESSIONAL REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE, THAT A PATIENT (AGE AND GENDER NOT REPORTED) DEVELOPED INCREASED LIVER ENZYMES WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG QD. THERAPY DATES WERE NOT PROVIDED. AFTER THE PATIENT'S DOSAGE WAS INCREASED FROM 500 MG QD TO 850 MG QD, THE ABOVE EVENT OCCURRED. ADDITIONAL INFORMATION WAS REQUESTED.

6. Relevant tests/laboratory data
LIVER ENZYMES INCREASED

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG QD ORAL

3. Therapy dates
#1. NI

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/20/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
LIVER FUNC ABNORM

9. Mfr.report number
M074869

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
HEALTH PROFESSIONAL

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075031

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier
In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex
[X] female
[ ] male

4. Weight
____ lbs
or
NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A FEMALE CONSUMER (AGE NOT SPECIFIED) REPORTED THAT SHE DEVELOPED FLATULENCE WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 1000 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT HAS BEEN TAKING GLUCOPHAGE FOR A DURATION OF TWO YEARS. HER MEDICAL HISTORY INCLUDED HYPERTENSION. SINCE STARTING GLUCOPHAGE THERAPY, SHE HAS BEEN EXPERIENCING THE ABOVE EVENT.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 1000 MG BID ORAL

3. Therapy dates
#1. UNK
2 YEARS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
HUMALOG
ULTRA LENTE
LEVOTHYROID
CLONIDINE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/26/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
FLATUL

9. Mfr.report number
M075031

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075032

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 12/15/97

4. Date of this report: 01/21/98

5. Describe event or problem
A FEMALE CONSUMER (AGE NOT SPECIFIED) REPORTED THAT SHE DEVELOPED A DECREASE IN THE SPEED OF HER URINE STREAM WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 250 MG BID FOR TREATMENT OF DIABETES MELLITUS. SHE STARTED TAKING GLUCOPHAGE IN NOVEMBER, 1997; THERAPY DURATION WAS FOUR WEEKS. ON APPROXIMATELY DECEMBER 15, 1997, SHE NOTED THAT HER "URINE TRICKLES BEFORE IT FLOWS REGULAR." HER MEDICAL HISTORY INCLUDED HYPERTENSION. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 11/00/97-UNK
4 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
FELODIPINE

HORMONE THERAPY

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
URIN TRACT DIS

9. Mfr.report number
M075032

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075041

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 12/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A MALE CONSUMER (AGE NOT SPECIFIED) REPORTED THAT HE DEVELOPED WORSENED HYPERGLYCEMIA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG QD FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT WAS TAKING GLUCOPHAGE FOR A DURATION OF ONE WEEK (EXACT THERAPY DATES NOT PROVIDED). IN DECEMBER, 1997 THE PATIENT HAD AN INCREASE IN FASTING BLOOD SUGAR FROM (PRIOR TO GLUCOPHAGE) 150 TO 200 (AFTER GLUCOPHAGE STARTED). HE STOPPED TAKING GLUCOPHAGE, AND HIS FASTING BLOOD SUGAR DECREASED BACK TO 150. HIS MEDICAL HISTORY INCLUDED GOUT AND HYPERTENSION. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
FASTING BLOOD SUGAR 150

FASTING BLOOD SUGAR 200
12/00/97
FASTING BLOOD SUGAR 150

7. Other relevant history, including preexisting medical conditions
GOUT

HYPERTENSION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. UNK
1 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ALLOPURINOL

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☒ Initial ☐ follow-up# ____

8. Adverse event term(s)
HYPERGLYCEM
REACT AGGRAV

9. Mfr.report number
M075041

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075046

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier: In confidence

2. Age at time of event: or 51 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
[ ] death ____
[ ] life-threatening
[ ] hospitalization-initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other:

3. Date of event: 10/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 51-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED DIARRHEA AND GAS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG TID FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APPROXIMATELY OCTOBER, 1997 AND HAS BEEN EXPERIENCING THE ABOVE EVENTS SINCE THAT TIME. AS OF DECEMBER 29, 1997, THE SYMPTOMS ARE UNRESOLVED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG TID ORAL

3. Therapy dates
#1. 10/00/97-UNK

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
[ ] yes [ ] no [X] doesn't apply
#1
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
PRINIVIL
K-DUR
TRIAMTERENE
SYNTHROID
(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
[ ] foreign
[ ] study
[ ] literature
[X] consumer
[ ] health professional
[ ] user facility
[ ] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer
12/29/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
[ ] 5-day [ ] 15-day
[ ] 10-day [X] periodic
[X] Initial [ ] follow-up# ____

8. Adverse event term(s)
DIARRHEA
FLATUL

9. Mfr.report number
M075046

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075046

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products
PREMARIN

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075059

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence
2. Age at time of event: or 64 YRS; Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI
4. Date of this report: 01/21/98

5. Describe event or problem

A 64-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE DEVELOPED GAS PAINS WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 250 MG QD FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 3.5 MONTHS. SHE "RECENTLY" DEVELOPED THE ABOVE EVENT. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 250 MG QD ORAL

3. Therapy dates
#1. UNK
3.5 MONTHS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
MICRONASE

PREMARIN

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
12/26/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] Initial [ ] follow-up# ____

8. Adverse event term(s)
PAIN ABDO

9. Mfr.report number
M075059

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M075246

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or NI
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE THAT A FEMALE PATIENT (AGE NOT SPECIFIED) DEVELOPED WORSENED RENAL FUNCTION AND GASTROINTESTINAL SIDE-EFFECTS WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED. THE PATIENT HAD A SERUM CREATININE OF 1.2; AFTER AN ACE INHIBITOR (UNSPECIFIED) WAS ADDED TO HER REGIMEN, HER RENAL FUNCTION WORSENED WITH A SERUM CREATININE OF 1.7. THE PATIENT ALSO HAD POSSIBLE GASTROINTESTINAL SIDE EFFECTS (UNCLEAR FROM THE DOCUMENTATION SUBMITTED). IT WAS ATTEMPTED TO OBTAIN ADDITIONAL INFORMATION VIA TELEPHONE WITHOUT SUCCESS. ADDITIONAL INFORMATION WILL BE REQUESTED IN WRITING.

6. Relevant tests/laboratory data

SERUM CREATININE 1.2

SERUM CREATININE 1.7

7. Other relevant history, including preexisting medical conditions

RENAL DYSFUNCTION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS
#2. ACE INHIBITOR

2. Dose, frequency & route used
#1. ORAL
#2. NI

3. Therapy dates
#1. NI
#2. NI

4. Diagnosis for use
#1. DIABETES MELLITUS
#2. UNK

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

6. Lot #
#1. NI
#2. NI

7. Exp.date
#1. NI
#2. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [X] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
UNK

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/26/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [X] initial [ ] follow-up# ____

8. Adverse event term(s)
KIDNEY FUNC ABNORM
REACT AGGRAV
GI DIS

9. Mfr.report number
M075246

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[X] yes [ ] no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Facsimile Form FDA-3500A Follow-Up Reports
Serious Expected Spontaneous Domestic Adverse Events
By Manufacturer File Number

Received October 1, 1997 to December 31, 1997

There were no follow-up reports of serious expected adverse events received during this reporting period.

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Facsimile Form FDA-3500A Follow-Up Reports
Nonserious Spontaneous Domestic Adverse Events
By Manufacturer File Number

Received October 1, 1997 to December 31, 1997

There were eleven follow-up reports of nonserious adverse events received during this reporting period.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M065521

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 45 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: NI

4. Date of this report: 01/21/98

5. Describe event or problem

A 45-YEAR-OLD FEMALE CONSUMER REPORTED THAT SHE EXPERIENCED KIDNEY PAIN WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG DAILY. GLUCOPHAGE THERAPY WAS STARTED APPROXIMATELY ONE YEAR AGO AND THE CONSUMER HAS BEEN TAKING GLUCOPHAGE "ON AND OFF" THROUGHOUT THE YEAR. THE CONSUMER ALSO STATED THAT SHE HAS A LEFT KIDNEY CYST (THE DATE OF ONSET WAS NOT REPORTED). THE CONSUMER ADDED THAT EVERY TIME SHE IS "ON" GLUCOPHAGE THERAPY HER KIDNEY HURTS AND WHEN SHE DISCONTINUES THERAPY, THE PAIN ABATES. CONCOMITANT MEDICATIONS INCLUDED AN UNSPECIFIED ANTIHYPERTENSIVE, ZANTAC (RANITIDINE HCL), AND UNSPECIFIED HORMONES.

SUPPLEMENTAL INFORMATION WAS RECEIVED ON MAY 27, 1997 FROM THE CONSUMER. SHE REPORTED THAT SHE ALSO EXPERIENCED A

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG QD ORAL

3. Therapy dates
#1. UNK-10/09/97
1.5-2 YEARS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ANTIHYPERTENSIVE
ZANTAC
HORMONES
PRILOSEC

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
10/27/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [ ] Initial [X] follow-up# 1

8. Adverse event term(s)
PAIN KIDNEY
CYST
RASH
ACNE
HEMATURIA

9. Mfr.report number
M065521

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M065521

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

RASH AND PIMPLES WHILE TAKING GLUCOPHAGE. SHE DID NOT WISH TO PROVIDE ANY FURTHER INFORMATION.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON OCTOBER 27, 1997. SHE HAD PREVIOUSLY REPORTED THAT SHE HAD DEVELOPED RENAL CYSTS WITH KIDNEY PAIN; SHE NOW STATED THAT SHE WAS EXPERIENCING BLOOD IN THE URINE AND A BURNING PAIN, ALONG WITH THE CYSTS. AFTER A TOTAL OF 1.5 TO 2 YEARS ON GLUCOPHAGE THERAPY FOR TREATMENT OF NON-INSULIN DEPENDENT DIABETES, SHE STOPPED THE DRUG ON OCTOBER 9, 1997. FOLLOWING DISCONTINUATION OF GLUCOPHAGE, THE BLEEDING HAS STOPPED; HOWEVER, THE PAIN PERSISTS (AS OF OCTOBER 27, 1997). SHE WAS CONCOMITANTLY TAKING PRILOSEC (OMEPRAZOLE) IN ADDITION TO THE PREVIOUSLY REPORTED DRUGS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068554

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 40 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or 96.7 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 04/30/97

4. Date of this report: 01/21/98

5. Describe event or problem

A CARDIOLOGIST SPONTANEOUSLY REPORTED THAT A 40 YEAR OLD MALE EXPERIENCED INCREASING ELEVATIONS OF CREATINE PHOSPHOKINASE (CPK) WHILE RECEIVING GLUCOPHAGE (METFORMIN HYDROCHLORIDE) TABLET THERAPY. GLUCOPHAGE THERAPY, 500 MG ORALLY EVERY 12 HOURS, WAS INITIATED IN APRIL 1997 FOR THE TREATMENT OF NON-INSULIN-DEPENDENT DIABETES MELLITUS. IN MAY 1997, THE PATIENT'S CPK WAS 401. ON JULY 2ND, HIS CPK WAS 632. OTHER THAN A COMPLAINT OF BACK PAIN AT HIS LAST JULY VISIT, HE WAS ASYMPTOMATIC. HIS CARDIOLOGIST AND ENDOCRINOLOGIST CONSIDERED HIM TO BE GLUCOSE-CONTROLLED. THE PATIENT'S MEDICAL HISTORY INCLUDED HYPERCHOLESTEROLEMIA, MILDLY ELEVATED SERUM CREATININE, HYPERTENSION, AND AN AORTIC VALVE REPLACEMENT. CONCOMITANT MEDICATIONS INCLUDED POTASSIUM 10 MEQ IN THE MORNING AND 20 MEQ IN THE EVENING, SLOW-MAG 400 DAILY, ZESTRIL (LISINOPRIL) 20 MG DAILY, PROCARDIA (NIFEDIPINE)60 MG DAILY, COUMADIN

(CONTINUED)

6. Relevant tests/laboratory data

CPK 546
04/30/97
CPK 670
05/07/97
CPK 401
05/22/97
CPK 642
07/02/97
HEMOGLOBIN A1C 5.4

SERUM CREATININE MILD ELEV.

(CONTINUED)

7. Other relevant history, including preexisting medical conditions

HYPERCHOLESTEROLEMIA

HYPERTENSION

AORTIC VALVE REPLACEMENT

CREATININE ELEVATED

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG QD PO

3. Therapy dates: #1. 02/18/97-08/08/97 6 MONTHS

4. Diagnosis for use: #1. NON-INSULIN-DEPENDENT DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☒ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. D7J113A

7. Exp.date: #1. 12/99

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products

MICRONASE
CONTINUES
PROCARDIA XL
CONTINUES
ZESTRIL
CONTINUES
SLOW-MAG

(CONTINUED)

G. All manufacturers

1. Contact office - name/address

HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other:

4. Date received by manufacturer: 10/01/97

5. (A)NDA # 20-357 IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day ☐ 10-day ☒ periodic ☐ Initial ☒ follow-up# 1

8. Adverse event term(s)
CREATINE PK INC
PAIN BACK

9. Mfr.report number: M068554

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: ENDOCRINOLOGIST

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068554

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event

4. Date of this report

5. Describe event or problem

(WARFARIN SODIUM)2.5-5MG DAILY, AND MICRONASE (GLYBURIDE) 2.5 MG DAILY. THE PHYSICIAN ALSO REPORTED THAT THE PATIENT HAD A HEMOGLOBIN A1C RESULT OF 5.4 (DATE OF TEST WAS NOT REPORTED). THE PATIENT HAD A "SULFA ALLERGY."

SUPPLEMENTAL INFORMATION RECEIVED AUGUST 6, 1997, FROM THE PATIENT'S ENDOCRINOLOGIST INDICATED THAT THE PATIENT'S CPK WAS NOTED TO BE INCREASED ON APRIL 30, 1997, WITH A REPORTED VALUE OF 546. ON MAY 7TH, HIS CPK REACHED A HIGH OF 670. ON MAY 22ND, IT DROPPED TO 401. ON JULY 2ND, IT ROSE AGAIN TO 642. IN RESPONSE TO THE EVENT, GLUCOPHAGE THERAPY WAS DECREASED ON JULY 24TH (DOSAGE AND FREQUENCY WERE NOT REPORTED) AND A DETERMINATION OF THE IMPACT OF THE DECREASE ON THE CPK ELEVATION HAD NOT BEEN MADE AT THE TIME OF REPORTING. CONCOMITANT MEDICATIONS INCLUDED

(CONTINUED)

6. Relevant tests/laboratory data

CPK 312
08/08/97
CPK 499
00/00/97

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name

2. Dose, frequency & route used

3. Therapy dates

4. Diagnosis for use

5. Event abated after use stopped or dose reduced
☐ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #

7. Exp.date

8. Event reappeared after reintroduction
☐ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #

10. Concomitant medical products

K-DUR
CONTINUES
COUMADIN
CONTINUES
VITAMIN C
CONTINUES
VITAMIN E
CONTINUES

G. All manufacturers

1. Contact office - name/address

2. Phone number

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other: ____

4. Date received by manufacturer

5. (A)NDA # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☐ follow-up# ____

8. Adverse event term(s)

9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068554

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

K-DUR (POTASSIUM CHLORIDE), PROCARDIA XL (NIFEDIPINE EXTENDED-RELEASE), MICRONASE (GLYBURIDE), COUMADIN (WARFARIN SODIUM), ZESTRIL (LISINOPRIL), AND VITAMINS E AND C.

SUPPLEMENTAL INFORMATION RECEIVED FROM THE PATIENT'S ENDOCRINOLOGIST INDICATED THAT GLUCOPHAGE THERAPY DATES WERE FEBRUARY 18-AUGUST 8, 1997. CPK RESULTS OBTAINED ON AUGUST 8TH WERE 312. THE PATIENT WAS SCHEDULED FOR A REPEAT CPK AT THE END OF AUGUST WHILE OFF GLUCOPHAGE THERAPY. THE PHYSICIAN WAS NOT SURE WHETHER THE PATIENT'S BACK PAIN HAD RESOLVED. THE PATIENT WAS NOT TREATED FOR FOR EITHER EVENT.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING

(CONTINUED)

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply
   ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068554

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

PHYSICIAN ON OCTOBER 1, 1997. IT WAS REPORTED THAT A FOLLOW-UP CPK LEVEL WAS 499 (DATE NOT SPECIFIED) AFTER GLUCOPHAGE THERAPY WAS STOPPED. HE NOTED THAT THE CPK LEVEL HAS "NEVER RETURNED TO NORMAL" AND THAT THE RELATIONSHIP TO GLUCOPHAGE IS UNCLEAR. HE DID NOT CONSIDER ANY CONCOMITANT DRUGS SUSPECT REGARDING THE EVENT. HE ADDED THAT THE PATIENT HAS NO SYMPTOMS. THE LOT NUMBER FOR HIS GLUCOPHAGE PRESCRIPTION WAS D7J113A, EXPIRATION DECEMBER, 1999. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068637

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 40 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or 102.6 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 07/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED THAT A 40-YEAR-OLD FEMALE CONSUMER DEVELOPED A DECREASE IN BICARBONATE WHILE TAKING GLUCOPHAGE (METFORMIN HCL). DAILY DOSAGE AND EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS APPROXIMATELY THREE TO FOUR MONTHS. THE PATIENT STARTED TAKING GLUCOPHAGE IN APRIL, 1997; HER BASELINE SERUM CREATININE WAS 1.0 AND "GLUCOSE WAS ELEVATED" PRIOR TO STARTING GLUCOPHAGE THERAPY. AT A JUNE, 1997 OFFICE VISIT, THE PATIENT'S BICARBONATE WAS 17 AND LACTATE WAS 19 MG/DL. AT A SUBSEQUENT JULY, 1997 OFFICE VISIT, HER BICARBONATE WAS DECREASED (VALUE UNKNOWN) AND LACTATE WAS "THE SAME". HER MEDICAL HISTORY INCLUDED NON-INSULIN DEPENDENT DIABETES MELLITUS, HYPERTENSION AND HYPERLIPIDEMIA. CONCOMITANT MEDICATIONS INCLUDED GLUCOTROL (GLIPIZIDE) 15 MG QD AND PRINIVIL (LISINOPRIL) 5 MG QD. THE REPORTER PLANS TO DISCONTINUE GLUCOPHAGE AND LATER RECHALLENGE THE PATIENT TO

(CONTINUED)

6. Relevant tests/laboratory data

BICARBONATE 17
06/10/97
LACTATE 19 MG/DL
06/00/97
BICARBONATE 17
06/25/97
LACTATE 19 MG/DL
07/11/97
SERUM GLUCOSE 143
04/11/97
SERUM CREATININE 1.0

(CONTINUED)

7. Other relevant history, including preexisting medical conditions

HYPERTENSION

HYPERLIPIDEMIA

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS

2. Dose, frequency & route used: #1. 500 MG BID ORAL

3. Therapy dates: #1. 04/00/97-00/00/97 3-4 MONTHS

4. Diagnosis for use: #1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #: #1. UNKNOWN

7. Exp.date: #1. UNKNOWN

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products
GLUCOTROL

PRINIVIL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer: 10/08/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [ ] Initial [X] follow-up# 1

8. Adverse event term(s)
ACIDOSIS

LAB TEST ABNORM

9. Mfr.report number: M068637

E. Initial reporter

1. Name, address & phone number

2. Health professional? [X] yes [ ] no

3. Occupation: PHYSICIAN

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068637

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

OBSERVE THE "CHANGES IN BICARBONATE LEVELS." ADDITIONAL INFORMATION WAS REQUESTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN VIA HIS OFFICE NURSE ON JULY 21, 1997. IT WAS REPORTED THAT THE PATIENT'S LACTATE LEVEL OF 19 MG/DL WAS CONSIDERED ELEVATED (REFERENCE RANGE =9-16 MG/DL). THE PATIENT WAS NOT CONSIDERED TO HAVE LACTIC ACIDOSIS, AND WAS NOT ADMITTED TO A HOSPITAL. HIS TOTAL DAILY GLUCOPHAGE DOSAGE WAS 500 MG BID. NO FURTHER DETAILS WERE PROVIDED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN ON OCTOBER 8, 1997. GLUCOPHAGE THERAPY WAS STOPPED (DATE NOT SPECIFIED). THE REPORTER STATED THAT

(CONTINUED)

6. Relevant tests/laboratory data

SERUM GLUCOSE 141
06/25/97
BICARBONATE DECREASED
07/00/97
URINALYSIS NORMAL
04/25/97

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M068637

UF/Dist report # N.A.

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

IT WAS "UNKNOWN" IF THE EVENTS ABATED FOLLOWING DISCONTINUATION OF GLUCOPHAGE THERAPY. THE PATIENT'S WEIGHT WAS NOTED TO BE 226 POUNDS. WITH REGARD TO LABORATORY RESULTS, THE REFERENCE RANGES AND CONFIRMED DATES WERE AS FOLLOWS: APRIL 11, 1997: SERUM GLUCOSE 143 MG/DL (N=70-115 MG/DL), URINALYSIS-NORMAL; JUNE 10, 1997:SERUM GLUCOSE 158 MG/DL, BICARBONATE 17 (N= 20-32 MEQ/L), JUNE 25, 1997: SERUM GLUCOSE 141 MG/DL, BICARBONATE 17 MEQ/L AND JULY 11, 1997: LACTIC ACID 19 MG/DL (NORMAL AS ABOVE). LOT NUMBER AND EXPIRATION DATE FOR THE PATIENT'S GLUCOPHAGE PRESCRIPTION WAS UNKNOWN. THE REPORTER STATED THAT THERE WAS "NO SEQUELAE RESULTING FROM THE EVENTS. PLEASE NOTE: THE ABOVE REFERENCE RANGES WERE PROVIDED BY THE TESTING LABORATORY.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070042

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier: In confidence
2. Age at time of event: or Date of birth:
3. Sex: [X] female [ ] male
4. Weight: ____ lbs or 78.9 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death
   - [ ] life-threatening
   - [ ] hospitalization-initial or prolonged
   - [ ] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event: NI
4. Date of this report: 01/21/98
5. Describe event or problem

A PHARMACIST SPONTANEOUSLY REPORTED THAT A 70 YEAR OLD FEMALE STATED TO THE PARMACIST THAT GLUCOPHAGE THERAPY "MADE HER SICK." THE CONSUMER WAS TAKING GLUCOPHAGE 500 MG TABLETS (THE DATES OF THERAPY, FREQUENCY, AND INDICATION FOR USE WERE NOT REPORTED). ADDITIONAL INFORMATION WAS REQUESTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE REPORTING PHARMACIST ON OCTOBER 31, 1997. SHE STATED THAT THE PATIENT, A 174 POUND FEMALE, HAD INITIALLY OBTAINED SAMPLES OF GLUCOPHAGE FROM HER PHYSICIAN, AND DID NOT HAVE ANY ADVERSE EFFECTS (OLD FORMULATION WITHOUT NDC NUMBER IMPRINTED ON TABLETS). SHE THEN OBTAINED A PRESCRIPTION FOR THE GLUCOPHAGE TABLETS (WITH THE NDC NUMBER IMPRINTED ON THE SURFACE), LOT NUMBER NOT

(CONTINUED)

6. Relevant tests/laboratory data: UNK
7. Other relevant history, including preexisting medical conditions: HYPERTENSION; CANCER; GASTROINTESTINAL TUMOR

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG
2. Dose, frequency & route used: #1. 500 MG PO
3. Therapy dates: #1. NI
4. Diagnosis for use: #1. NI
5. Event abated after use stopped or dose reduced: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply
6. Lot #: #1. NI
7. Exp.date: #1. NI
8. Event reappeared after reintroduction: #1 [ ] yes [ ] no [X] doesn't apply; [ ] yes [ ] no [ ] doesn't apply
9. NDC #: 0087-6060-05
10. Concomitant medical products: UNK

G. All manufacturers

1. Contact office - name/address:
   LOUISE LOVAS, B.S.N., R.N.
   BRISTOL-MYERS SQUIBB
   WORLDWIDE SAFETY & SURVEILLANCE
   MAIL LOCATION D23-07
   P.O.BOX 4000
   PRINCETON,NEW JERSEY 08543-4000
2. Phone number: 609-252-3737
3. Report source (check all that apply)
   - [ ] foreign
   - [ ] study
   - [ ] literature
   - [ ] consumer
   - [X] health professional
   - [ ] user facility
   - [ ] company representative
   - [ ] distributor
   - [ ] other:
4. Date received by manufacturer: 10/31/97
5. (A)NDA # 20-357; IND # ____; PLA # ____; pre-1938 [ ] yes; OTC product [ ] yes
6. If IND, protocol #: NA
7. Type of report (check all that apply)
   - [ ] 5-day [ ] 15-day
   - [ ] 10-day [X] periodic
   - [ ] Initial [X] follow-up# 1
8. Adverse event term(s):
   MALAISE
   DYSPEPSIA
   DIARRHEA
   PAIN
   TASTE PERVERS
9. Mfr.report number: M070042

E. Initial reporter

1. Name, address & phone number
2. Health professional? [X] yes [ ] no
3. Occupation: PHARMACIST
4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070042

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

PROVIDED, AND SUBSEQUENTLY DEVELOPED UPSET STOMACH, DIARRHEA, "DISCOMFORT" AND A BAD TASTE. HER MEDICAL HISTORY INCLUDED HIGH BLOOD PRESSURE, CANCER ("CANCER SURVIVOR") AND DUODENAL TUMOR. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA — ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070759

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 54 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 00/00/97

4. Date of this report: 01/21/98

5. Describe event or problem
A 54-YEAR-OLD MALE PATIENT DEVELOPED DIARRHEA WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 850 MG TID FOR TREATMENT OF DIABETES MELLITUS. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS SIX MONTHS. THE PATIENT'S MEDICAL HISTORY INCLUDED ARTHRITIS; HIS DIABETES IS NON-INSULIN DEPENDENT. AS OF SEPTEMBER 3, 1997, THE DIARRHEA IS UNRESOLVED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN ON NOVEMBER 4, 1997. IT WAS REPORTED THAT THE PATIENT WAS LAST SEEN IN THE PHYSICIAN'S OFFICE ON JUNE 13, 1997. AT THAT TIME, HE WAS DESCRIBED AS "TOLERATING MEDICATION." NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
ARTHRITIS

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG TID ORAL

3. Therapy dates
#1. UNK 6 MONTHS

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
INDOMETHACIN

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
11/04/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☐ initial ☒ follow-up# 1

8. Adverse event term(s)
DIARRHEA

9. Mfr.report number
M070759

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070925

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 75 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 00/00/96

4. Date of this report: 01/21/98

5. Describe event or problem

A 76 YEAR OLD MALE SPONTANEOUSLY REPORTED THAT HE EXPERIENCED FACIAL EDEMA WHILE TAKING GLUCOPHAGE (METFORMIN HYDROCHLORIDE) TABLET THERAPY. GLUCOPHAGE THERAPY, 500 MG ORALLY TWICE PER DAY, WAS INITIATED APPROXIMATELY 1 1/2 YEARS PRIOR TO THE TIME OF REPORTING FOR THE TREATMENT OF NON-INSULIN-DEPENDENT DIABETES MELLITUS. SHORTLY AFTER THE INITIATION OF THERAPY, THE CONSUMER BEGAN EXPERIENCING SLIGHT PERIORBITAL EDEMA WHICH WAS ONGOING. FOUR MONTHS AGO, HE BEGAN TO EXPERIENCE FULL FACIAL EDEMA WHICH IS ONGOING. HE WAS PRESCRIBED ALLEGRA (FEXOFENADINE HYDROCHLORIDE) TO TREAT THE SWELLING. HE DENIED TAKING ANY MEDICATIONS CONCOMITANTLY. HE REPORTED HAVING "SOME REACTION TO PENICILLIN."

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER

(CONTINUED)

6. Relevant tests/laboratory data
SERUM GLUCOSE GOOD CTRL

7. Other relevant history, including preexisting medical conditions
DRUG REACTION

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID PO

3. Therapy dates
#1. 08/00/96-06/30/97 CONTINUING

4. Diagnosis for use
#1. NON-INSULIN-DEPENDENT DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N., R.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
10/22/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☐ Initial ☒ follow-up# 1

8. Adverse event term(s)
EDEMA FACE
EDEMA
HYPER GUM

9. Mfr.report number
M070925

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070925

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

ON SEPTEMBER 24, 1997. HE REPORTED THAT MORE SPECIFICALLY, THE FACIAL SWELLING HAS INCLUDED HIS EYELIDS, GUMS AND JAW. HE HAS ALSO HAD SWELLING OF THE LEFT ARM. HIS RIGHT EYE ON SEPTEMBER 7TH (YEAR NOT SPECIFIED) WAS COMPLETELY SWOLLEN SHUT. HE HAS CONSULTED THREE PHYSICIANS, AND A DIAGNOSIS HAS NOT BEEN RENDERED REGARDING THESE SYMPTOMS. LABORATORY TESTS ALSO FAILED TO REVEAL AN ETIOLOGY. NO FURTHER DETAILS WERE REPORTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN ON OCTOBER 22, 1997. HE REPORTED THAT THE PATIENT STARTED TAKING GLUCOPHAGE IN AUGUST, 1996, AND THAT THE DRUG PROVIDED EXCELLENT GLYCEMIC CONTROL FOR THE PATIENT. FOLLOWING THE PATIENT'S PROGRESSIVE EDEMA AS NOTED ABOVE, THE PHYSICIAN DISCONTINUED THE

(CONTINUED)

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070925

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

PATIENT'S GLUCOPHAGE THERAPY ON JUNE 30, 1997. AFTER DISCONTINUATION OF THE DRUG, ALL OF THE SYMPTOMS IMPROVED. IT WAS NOT NOTED IF THERE WAS COMPLETE RESOLUTION OF SYMPTOMS. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070966

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 73 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or 73.5 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 03/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

THE WIFE OF A 73 YEAR OLD MALE SPONTANEOUSLY REPORTED THAT HE EXPERIENCED STOMACH CRAMPS AND FLATULENCE WHILE TAKING GLUCOPAHGE (METFORMIN HYDROCHLORIDE) TABLET THERAPY. GLUCOPHAGE THERAPY, 850 MG ORALLY THREE TIMES PER DAY, WAS INITIATED 6 MONTHS PRIOR TO THE TIME OF REPORTING. THE EVENTS WERE ONGOING THROUGHOUT THERAPY. CONCOMITANT MEDICATIONS INCLUDED ATENOLOL, MEVACOR (LOVASTATIN), TRIAMTERENE, MICRONASE (GLYBURIDE), HYTRIN (TERAZOSIN HYDROCHLORIDE), ASCRIPTIN (ASPIRIN, MAGNESIUM HYDROXIDE, ALUMINUM HYDROXIDE, AND CALCIUM CARBONATE), AND LORAZEPAM. ADDITIONAL INFORMATION WAS REQUESTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON OCTOBER 8, 1997. HE REPORTED THAT HIS GLUCOPHAGE PRESCRIPTION WAS FROM LOT NUMBER MK054, EXPIRATION DATE

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
UNK

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 850 MG

2. Dose, frequency & route used
#1. 850 MG TID PO

3. Therapy dates
#1. 03/00/97-00/00/97 CONTINUING

4. Diagnosis for use
#1. DIABETES MELLITUS TYPE II

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. MK054

7. Exp.date
#1. 10/99

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
ATENOLOL
MICRONASE
MEVACOR
TRIAMTERENE

(CONTINUED)

G. All manufacturers

1. Contact office - name/address
LOUISE LOVAS, B.S.N., R.N.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON, NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
12/09/97

5. (A)NDA # 20-357
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☐ Initial ☒ follow-up# 1

8. Adverse event term(s)
PAIN ABDO
FLATUL

9. Mfr.report number
M070966

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
ENDOCRINOLOGIST

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

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APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M070966

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

OCTOBER, 1999. HE COMPLAINED THAT HE WAS EXPERIENCING THE GAS "24 HOURS A DAY" WITH INTERMITTENT STOMACH CRAMPS. NO FURTHER DETAILS WERE PROVIDED.

SUPPLEMENTAL INFORMATION WAS RECIEVED FROM THE TREATING PHYSICIAN ON DECEMBER 9, 1997. IT WAS REPORTED THAT THE SYMPTOMS STARTED WITH ABDOMINAL CRAMPS (WITH DISCOMFORT) WHICH HAVE GRADUALLY DECREASED AFTER THE GLUCOPHAGE DOSAGE WAS LOWERED TO 850 MG BID FROM TID. THE INDICATION FOR THE GLUCOPHAGE THERAPY WAS DIABETES MELLITUS TYPE II. NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

HYTRIN

ASCRIPTIN

LORAZEPAM

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071254

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 73 YRS
Date of birth:

3. Sex: [X] female [ ] male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [ ] hospitalization-initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event: 09/01/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 73 Y/O FEMALE CONSUMER REPORTED THAT SHE DEVELOPED BELCHING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES. EXACT THERAPY DATES FOR GLUCOPHAGE WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 3 TO 4 WEEKS. ON APPROXIMATELY SEPTEMBER 1, 1997, SHE BEGAN EXPERIENCING THE ABOVE SYMPTOM. HER MEDICAL HISTORY INCLUDED HYPERCHOLESTEROLEMIA AND "ULCERS." CONCOMITANT DRUGS INCLUDED INSULIN, MEVACOR (LOVASTATIN) AND CIMETIDINE. NO FURTHER DETAILS WERE REPORTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON NOVEMBER 18, 1997. IT WAS REPORTED THAT IN ADDITION TO BELCHING, SHE WAS ALSO EXPERIENCING HEADACHES AND "GAS." SHE STATED THAT THE SYMPTOMS HAVE "EASED UP." THE STATUS OF GLUCOPHAGE THERAPY WAS NOT REPORTED. SHE REMAINS

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
HYPERCHOLESTEROLEMIA

ULCERS

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 00/00/97-UNK
3-4 WEEKS

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
[ ] yes [ ] no [ ] doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
INSULIN
CONTINUES
MEVACOR

CIMETIDINE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer
11/18/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [ ] Initial [X] follow-up# 1

8. Adverse event term(s)
ERUCTAT

HEADACHE

FLATUL

9. Mfr.report number
M071254

E. Initial reporter

1. Name, address & phone number

2. Health professional?
[ ] yes [X] no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [X] unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071254

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

ON INSULIN. NO FURTHER DETAILS WERE REPORTED.

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071402

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or Date of birth

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or 97.6 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 08/00/97

4. Date of this report: 01/21/98

5. Describe event or problem

A PHYSICIAN REPORTED VIA A BRISTOL-MYERS SQUIBB SALES REPRESENTATIVE THAT A PATIENT (AGE AND GENDER NOT SPECIFIED) DEVELOPED EYE SENSITIVITY TO LIGHT WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID. EXACT THERAPY DATES WERE NOT PROVIDED; THERAPY DURATION WAS REPORTED AS 4 TO 6 WEEKS. ADDITIONAL INFORMATION WAS REQUESTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN ON OCTOBER 15, 1997. IT WAS REPORTED THAT THE PATIENT, A 49-YEAR-OLD MALE WEIGHING 215 POUNDS, STARTED TAKING GLUCOPHAGE ON JULY 24, 1997. PRIOR TO GLUCOPHAGE THERAPY, HE WAS TAKING GLYBURIDE 5 MG BID. HE DID NOT EXPERIENCE "ANY PROBLEMS" DURING GLYBURIDE THERAPY. GLUCOPHAGE WAS ADDED, AND THREE TO FOUR WEEKS LATER, HE COMPLAINED OF SENSITIVITY TO LIGHT AND VISUAL PROBLEMS.

(CONTINUED)

6. Relevant tests/laboratory data

VISUAL ACUITY 20/25
00/00/97
SERUM GLUCOSE 184
00/00/97
SERUM GLUCOSE 113
00/00/97

7. Other relevant history, including preexisting medical conditions

UNK

C. Suspect medication(s)

1. Name: #1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used: #1. 500 MG BID ORAL

3. Therapy dates: #1. 07/24/97-08/00/97 4-6 WEEKS

4. Diagnosis for use: #1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #: #1. NI

7. Exp.date: #1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #: NOT REPORTED

10. Concomitant medical products: GLYBURIDE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number: 609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 10/15/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☐ initial ☒ follow-up# 1

8. Adverse event term(s)
PHOTOPHOBIA
VISION ABNORM
RETINAL DIS

9. Mfr.report number: M071402

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☒ yes ☐ no

3. Occupation: PHYSICIAN

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071402

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

HE UNDERWENT EVALUATION BY OPTOMETRY, AND "CHANGES IN THE RETINA" (UNSPECIFIED) WERE NOTED. THE PATIENT STOPPED GLUCOPHAGE IN LATE AUGUST, 1997. FOLLOWING DISCONTINUATION OF THE DRUG, HE NOTED IMPROVEMENT IN HIS VISION, IMPROVEMENT IN THE SYMPTOMS OF PHOTOPHOBIA AND HIS RETINAL EXAMINATION SHOWED IMPROVEMENT. FOLLOW-UP VISUAL ACUITY TEST WAS 20/25 (BASELINE NOT REPORTED). A RANDOM SERUM GLUCOSE LEVEL PRIOR TO GLUCOPHAGE THERAPY WAS 184; FOLLOWING DISCONTINUATION OF THE DRUG, A RANDOM LEVEL WAS 113. THE PATIENT IS DESCRIBED AS CURRENTLY "DOING WELL." GLUCOPHAGE THERAPY HAS NOT BEEN REINTRODUCED.NO FURTHER DETAILS WERE REPORTED.

6. Relevant tests/laboratory data
7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA
Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071563

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 75 YRS
Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 09/13/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 75 Y/O MALE CONSUMER REPORTED THAT HE DEVELOPED DIARRHEA AND BLOOD IN THE STOOL WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE IN SEPTEMBER, 1997; AFTER A TOTAL OF SIX DOSES, HE NOTED THE ABOVE SYMPTOMS. HE STOPPED TAKING GLUCOPHAGE AND THE BLOOD DID NOT REAPPEAR. HE WAS NOT TAKING ANY CONCOMITANT DRUGS AND HAD NO RELEVANT MEDICAL CONDITIONS OR ALLERGIES.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE TREATING PHYSICIAN ON NOVEMBER 11, 1997. HE REPORTED THAT THE PATIENT HAD A HISTORY OF RECTAL BLEEDING IN APRIL, 1997, WHICH RESULTED IN THE REMOVAL OF POLYPS. THE EVENTS OF DIARRHEA WITH BLOOD IN THE STOOL OCCURRED INITIALLY (WHILE ON

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
RECTAL POLYPECTOMY
RECTAL BLEEDING
RECTAL POLYPS

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 09/00/97-09/00/97
6 DOSES

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
NONE

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer
11/11/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☐ initial ☒ follow-up# 1

8. Adverse event term(s)
MELENA
DIARRHEA

9. Mfr.report number
M071563

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☒ yes ☐ no

3. Occupation
PHYSICIAN

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

APPEARS THIS WAY ON ORIGINAL

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071563

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event
4. Date of this report
5. Describe event or problem

GLUCOPHAGE THERAPY) ON SEPTEMBER 13, 1997. NO FURTHER DETAILS WERE PROVIDED.

APPEARS THIS WAY ON ORIGINAL

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction — ☐ yes ☐ no ☐ doesn't apply; ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ____
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

APPEARS THIS WAY ON ORIGINAL

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071910

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence

2. Age at time of event: or 79 YRS — Date of birth:

3. Sex: ☐ female ☒ male

4. Weight: ____ lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

☐ death ____
☐ life-threatening
☐ hospitalization-initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 08/01/97

4. Date of this report: 01/21/98

5. Describe event or problem

A 79 Y/O MALE CONSUMER REPORTED THAT HE DEVELOPED A FEELING OF WARMTH AND ITCHING WHILE TAKING GLUCOPHAGE (METFORMIN HCL) 500 MG BID FOR TREATMENT OF DIABETES MELLITUS. THE PATIENT STARTED TAKING GLUCOPHAGE ON AUGUST 1, 1997; SINCE THAT TIME HE HAS BEEN EXPERIENCING THE ABOVE SYMPTOMS. CONCOMITANT DRUGS INCLUDED GLUCOTROL (GLIPIZIDE) FOR A FOUR MONTH DURATION. AS OF SEPTEMBER 30, 1997 THE EVENTS ARE UNRESOLVED. NO FURTHER DETAILS WERE REPORTED.

SUPPLEMENTAL INFORMATION WAS RECEIVED FROM THE CONSUMER ON OCTOBER 22, 1997. HE REPORTED THAT "HE DID NOT AND HAS NOT EXPERIENCED ANY REACTION TO GLUCOPHAGE MEDICATION." THE PATIENT DID NOT, HOWEVER, PROVIDE ANOTHER EXPLANATION OR CAUSE FOR THE EVENT.

(CONTINUED)

6. Relevant tests/laboratory data
UNK

7. Other relevant history, including preexisting medical conditions
NI

C. Suspect medication(s)

1. Name
#1. GLUCOPHAGE TABS 500 MG

2. Dose, frequency & route used
#1. 500 MG BID ORAL

3. Therapy dates
#1. 08/01/97-UNK CONTINUING

4. Diagnosis for use
#1. DIABETES MELLITUS

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
☐ yes ☐ no ☐ doesn't apply

6. Lot #
#1. NI

7. Exp.date
#1. NI

8. Event reappeared after reintroduction
☐ yes ☐ no ☒ doesn't apply
#1 ☐ yes ☐ no ☐ doesn't apply

9. NDC #
NOT REPORTED

10. Concomitant medical products
GLUCOTROL

G. All manufacturers

1. Contact office - name/address
HEIDE CUNNING, B.S.
BRISTOL-MYERS SQUIBB
WORLDWIDE SAFETY & SURVEILLANCE
MAIL LOCATION D23-07
P.O.BOX 4000
PRINCETON,NEW JERSEY 08543-4000

2. Phone number
609-252-3737

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other:

4. Date received by manufacturer
10/22/97

5. (A)NDA # 20-357
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #
NA

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☐ Initial ☒ follow-up# 1

8. Adverse event term(s)
VASODILAT
PRURITUS

9. Mfr.report number
M071910

E. Initial reporter

1. Name, address & phone number

2. Health professional?
☐ yes ☒ no

3. Occupation
CONSUMER

4. Initial reporter also sent report to FDA
☐ yes ☐ no ☒ unk

FDA
Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Approved by FDA: 11/01/93

Mfr report # M071910

UF/Dist report # NA

FDA Use Only

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization-initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:

3. Date of event
4. Date of this report

5. Describe event or problem

NO FURTHER DETAILS WERE PROVIDED.

6. Relevant tests/laboratory data

7. Other relevant history, including preexisting medical conditions

C. Suspect medication(s)

1. Name
2. Dose, frequency & route used
3. Therapy dates
4. Diagnosis for use
5. Event abated after use stopped or dose reduced: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
6. Lot #
7. Exp.date
8. Event reappeared after reintroduction: ☐ yes ☐ no ☐ doesn't apply / ☐ yes ☐ no ☐ doesn't apply
9. NDC #
10. Concomitant medical products

G. All manufacturers

1. Contact office - name/address
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up# ____
8. Adverse event term(s)
9. Mfr.report number

E. Initial reporter

1. Name, address & phone number

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Bristol-Myers Squibb Company

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M074209	ACCIDENTAL OVERDOSE	ACCIDENTAL OVERDOSE	INITIAL
	LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL	

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M065521	CYST	LEFT RENAL CYST	FOLLOW-UP
	ACNE	PIMPLES	
	HEMATURIA	HEMATURIA	
	KIDNEY PAIN	KIDNEY PAIN	
	RASH	RASH	
M068554	BACK PAIN	PAIN IN BACK	FOLLOW-UP
	CREATINE PHOSPHOKINASE INCREASED	RISING CPK	
M068637	ACIDOSIS	DECREASED BICARBONATE	FOLLOW-UP
	LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL	
M070042	MALAISE	FEELING SICK	FOLLOW-UP
	PAIN	DISCOMFORT	
	DYSPEPSIA	UPSET STOMACH	
	DIARRHEA	DIARRHEA	
	TASTE PERVERSION	BAD TASTE	
M070759	DIARRHEA	DIARRHEA	FOLLOW-UP
M070925	FACE EDEMA	EDEMA FACE EYES	FOLLOW-UP
	GUM HYPERPLASIA	SWOLLEN GUMS	
	EDEMA	EDEMA ARM	
M070966	ABDOMINAL PAIN	STOMACH CRAMPS	FOLLOW-UP
	FLATULENCE	FLATULENCE	
M071254	HEADACHE	HEADACHE	FOLLOW-UP
	ERUCTATION	BELCHING	
	FLATULENCE	GAS	

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M071402	ABNORMAL VISION PHOTOPHOBIA RETINAL DISORDER	VISUAL PROBLEMS EYE SENSITIVE TO LIGHT RETINAL CHANGES	FOLLOW-UP
M071563	DIARRHEA MELENA	DIARRHEA BLOOD IN STOOL	FOLLOW-UP
M071910	VASODILATATION PRURITUS	FEELING OF WARMTH ITCHING	FOLLOW-UP
M071924	DYSPEPSIA	UPSET STOMACH	INITIAL
M071941	SOMNOLENCE	DROWSY	INITIAL
M071962	ABDOMINAL PAIN	PAIN RIB ABDOMEN	INITIAL
M071968	URINARY FREQUENCY	URINARY FREQUENCY	INITIAL
M072013	ASTHENIA	FATIGUE	INITIAL
M072037	ASTHENIA SEDIMENTATION RATE INCREASED LAB TEST ABNORMAL	WEAKNESS FATIGUE SEDIMENTATION RATE INCREASED INCREASED LACTIC ACID LEVEL	INITIAL
M072068	NAUSEA	SICK TO STOMACH	INITIAL
M072101	CHEST PAIN DYSPNEA	CHEST PAIN SHORTNESS OF BREATH	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M072103	LIVER FUNCTION TESTS ABNORMAL	INCREASED LIVER FUNCTION TESTS	INITIAL
	LIVER FATTY DEPOSIT	FATTY LIVER	
M072116	HYPERTENSION	ELEVATED BLOOD PRESSURE	INITIAL
	TACHYCARDIA	RAPID PULSE	
	DYSPEPSIA	HEARTBURN	
	DEPRESSION	DEPRESSION	
M072313	FLATULENCE	FLATULENCE	INITIAL
M072322	LAB TEST ABNORMAL	VITAMIN B12 INCREASED	INITIAL
M072323	AGGRAVATION REACTION	HYPERGLYCEMIA EXACERBATED	INITIAL
	HYPERGLYCEMIA	HYPERGLYCEMIA	
M072336	DYSPEPSIA	HEARTBURN	INITIAL
	DIARRHEA	DIARRHEA	
M072363	LIVER FUNCTION TESTS ABNORMAL	ELEVATED LIVER FUNCTION TESTS	INITIAL
	BILIRUBINEMIA	BILIRUBIN INCREASED	
	LACTIC DEHYDROGENASE INCREASED	LDH ELEVATED	
M072386	PAIN	CRAMPS	INITIAL
	FLATULENCE	GAS	
	TASTE PERVERSION	BAD TASTE IN MOUTH	
M072393	PRURITUS	ITCHING	INITIAL
	RASH	SKIN REDNESS	

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M072394	CHEST PAIN	CHEST PAIN	INITIAL
	PAIN	MUSCULOSKELETAL PAIN	
	DIZZINESS	LIGHTHEADEDNESS	
	DIARRHEA	DIARRHEA	
M072451	INCREASED APPETITE	HUNGER	INITIAL
	MYASTHENIA	MUSCLE WEAKNESS	
	SWEATING	SWEATING	
M072473	DYSPEPSIA	GASTROINTESTINAL UPSET	INITIAL
M072474	BACK PAIN	LOW BACK PAIN	INITIAL
M072513	ASTHENIA	WEAKNESS	INITIAL
	CHILLS	CHILLS	
	DIARRHEA	DIARRHEA	
	NAUSEA	NAUSEA	
M072622	PRURITUS	ITCHING	INITIAL
	RASH	RASH	
M072623	NAUSEA	NAUSEA	INITIAL
M072653	SWEATING	PERSPIRATION	INITIAL
M072654	LIVER FUNCTION TESTS ABNORMAL	ELEVATED LIVER FUNCTION TESTS	INITIAL
M072697	HYPOGLYCEMIA	HYPOGLYCEMIA	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M072698	DIARRHEA	DIARRHEA	INITIAL
M072703	DRUG INTERACTION HYPOGLYCEMIA	DRUG INTERACTION ERYTHROMYCIN HYPOGLYCEMIA	INITIAL
M072737	DYSPEPSIA NAUSEA VOMITING	STOMACH UPSET NAUSEA VOMITING	INITIAL
M072748	TASTE PERVERSION	SALTY TASTE	INITIAL
M072754	BODY ODOR	SKIN ODOR ABNORMAL	INITIAL
M072755	DIARRHEA FLATULENCE	DIARRHEA GAS	INITIAL
M072780	LAB TEST ABNORMAL MALAISE	FLUCTUATING GLUCOSE LEVELS FEELING BAD	INITIAL
M072824	TWITCHING	FACIAL TWITCHING	INITIAL
M072832	MYALGIA DYSPNEA LAB TEST ABNORMAL	MUSCLE ACHES SHORTNESS OF BREATH INCREASED LACTIC ACID LEVEL	INITIAL
M072844	ASTHENIA WEIGHT LOSS	WEAKNESS FATIGUE WEIGHT LOSS	INITIAL
M072853	ABDOMINAL PAIN SWEATING	STOMACH CRAMPS SWEATING	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M072894	PAIN	CRAMPS	INITIAL
	DYSPEPSIA	STOMACHACHE	
	DIARRHEA	DIARRHEA	
M072905	PALLOR	LOOKS GRAY	INITIAL
	EDEMA	SWELLING	
	HYPERTONIA	TIGHT MUSCLE	
M072988	INSOMNIA	INSOMNIA	INITIAL
M073028	DIARRHEA	DIARRHEA	INITIAL
M073072	PAIN	CRAMPING	INITIAL
	MELENA	BLOODY STOOL	
	DIARRHEA	DIARRHEA	
M073080	DIARRHEA	DIARRHEA	INITIAL
M073082	URINE ABNORMALITY	ODOR IN URINE	INITIAL
M073087	BACK PAIN	PAIN BACK	INITIAL
	NEUROPATHY	NERVE DAMAGE	
M073092	ANOREXIA	LOSS OF APPETITE	INITIAL
M073159	ABNORMAL STOOLS	SOFT STOOLS	INITIAL
	ALBUMINURIA	PROTEIN IN URINE	
	FLATULENCE	BLOATING	

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M073188	FLATULENCE	FLATULENCE	INITIAL
M073213	HYPOGLYCEMIA	HYPOGLYCEMIA	INITIAL
M073216	ABNORMAL VISION	BLURRY VISION	INITIAL
M073238	FLATULENCE	BLOATING	INITIAL
M073255	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M073262	SWEATING DECREASED	SWEATING DECREASED	INITIAL
M073267	RASH	ECZEMATOUS RASH	INITIAL
M073298	PALPITATION DIZZINESS NAUSEA	HEART PALPITATIONS DIZZINESS NAUSEA	INITIAL
M073363	CIRCUMORAL PARESTHESIA	NUMBNESS TINGLING AROUND MOUTH	INITIAL
M073366	AGGRAVATION REACTION HYPERGLYCEMIA	HYPERGLYCEMIA EXACERBATED HYPERGLYCEMIA	INITIAL
M073372	DIARRHEA FLATULENCE	DIARRHEA BLOATING	INITIAL
M073399	MYALGIA DYSPNEA LAB TEST ABNORMAL	MUSCLE ACHES SHORTNESS OF BREATH INCREASED LACTIC ACID LEVEL	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M073400	MYALGIA	MUSCLE ACHES	INITIAL
	DYSPNEA	SHORTNESS OF BREATH	
	LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL	
M073401	MYALGIA	MUSCLE ACHES	INITIAL
	DYSPNEA	SHORTNESS OF BREATH	
	LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL	
M073404	HEADACHE	HEAD PRESSURE	INITIAL
	WEIGHT LOSS	WEIGHT LOSS	
M073421	ALOPECIA	HAIR LOSS	INITIAL
	HAIR DISORDER	DRY HAIR	
M073473	TASTE PERVERSION	METALLIC TASTE	INITIAL
M073480	ABDOMINAL PAIN	STOMACH CRAMPS	INITIAL
	BACK PAIN	PAIN BACK	
	PAIN	LEG PAIN	
	DIZZINESS	DIZZINESS LIGHTHEADEDNESS	
	ANOREXIA	DECREASED APPETITE	
	DIARRHEA	DIARRHEA	
M073490	ABDOMINAL PAIN	STOMACH PAIN	INITIAL
	DIARRHEA	DIARRHEA	
M073515	DYSPEPSIA	STOMACH PROBLEMS	INITIAL
M073519	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M073525	CHEST PAIN	EXERTIONAL CHEST PAIN	INITIAL
M073526	ANOREXIA	LOSS OF APPETITE	INITIAL
M073530	TASTE PERVERSION	METALLIC TASTE	INITIAL
M073549	DIARRHEA TASTE PERVERSION	DIARRHEA METALLIC TASTE	INITIAL
M073571	DYSPEPSIA EYE DISORDER KIDNEY FUNCTION ABNORMAL ANOREXIA DIARRHEA	STOMACH UPSET FLOATERS EYE RENAL DYSFUNCTION LOSS OF APPETITE DIARRHEA	INITIAL
M073582	ALLERGIC REACTION	ALLERGIC REACTION	INITIAL
M073680	DIZZINESS DYSPNEA	LIGHTHEADEDNESS DIFFICULTY BREATHING	INITIAL
M073682	CONSTIPATION	CONSTIPATION	INITIAL
M073692	LIVER FUNCTION TESTS ABNORMAL BASOPHILIA WBC ABNORMAL HYPERGLYCEMIA HYPONATREMIA	INCREASED LIVER ENZYMES BASOPHILIA INCREASED WBC INCREASED GLUCOSE DECREASED SODIUM	INITIAL
M073829	MALAISE	ILL FEELING	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M073839	PRURITUS	ITCHING	INITIAL
M073863	HEPATITIS LIVER FUNCTION TESTS ABNORMAL	LIVER INFLAMMATION INCREASED LIVER FUNCTION TESTS	INITIAL
M073924	DIARRHEA DEHYDRATION	DIARRHEA DEHYDRATION	INITIAL
M073947	TACHYCARDIA INSOMNIA DIARRHEA	INCREASED HEART RATE INSOMNIA DIARRHEA	INITIAL
M073951	DIARRHEA	DIARRHEA	INITIAL
M073962	EDEMA	FLUID RETENTION	INITIAL
M073983	URINARY INCONTINENCE DIARRHEA	INCONTINENCE SEVERE DIARRHEA	INITIAL
M073990	DRUG INTERACTION HYPERGLYCEMIA	MULTIPLE DRUG INTERACTION INCREASED SERUM GLUCOSE	INITIAL
M073993	HYPERTENSION	HYPERTENSION	INITIAL
M073994	HEADACHE SKIN DISCOLORATION	HEADACHE REDDISH PURPLE AREA CHEEKS	INITIAL
M074001	DIZZINESS NAUSEA	DIZZINESS NAUSEA	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M074008	ALLERGIC REACTION	ALLERGIC RASH	INITIAL
M074052	INSOMNIA	INSOMNIA	INITIAL
M074117	MALAISE KIDNEY PAIN URINE ABNORMALITY	SICK FEELING KIDNEY PAIN URINE DISCOLORATION	INITIAL
M074208	HYPOGLYCEMIA	HYPOGLYCEMIA	INITIAL
M074212	AGGRAVATION REACTION RASH	RASH EXACERBATED RASH ON FACE & SCALP	INITIAL
M074218	ARTHRALGIA DRY SKIN DIARRHEA	JOINT PAIN DRY SKIN DIARRHEA	INITIAL
M074219	ABDOMINAL PAIN BACK PAIN	PAIN RIB ABDOMEN PAIN BACK	INITIAL
M074231	ABDOMINAL PAIN MYALGIA	ABDOMINAL GAS PAIN MUSCLE ACHES	INITIAL
M074256	LAB TEST ABNORMAL NERVOUSNESS	FLUCTUATING GLUCOSE LEVELS SHAKY FEELING	INITIAL
M074274	STUPOR VASODILATATION	DRUNK FEELING FLUSHING	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M074283	ERYTHROCYTES ABNORMAL LEUKOPENIA THROMBOCYTOPENIA	DECREASED RED BLOOD CELLS DECREASED WBC DECREASED PLATELETS	INITIAL
M074286	PERIPHERAL EDEMA	SWELLING FEET	INITIAL
M074311	HEMORRHAGE DIARRHEA	BLEEDING PENIS DIARRHEA	INITIAL
M074322	PAIN	SEVERE CRAMPS	INITIAL
M074323	DYSPEPSIA DYSURIA URINARY RETENTION	STOMACH DISTRESS DIFFICULTY URINATING INABILITY TO EMPTY BLADDER	INITIAL
M074325	PARESTHESIA TASTE PERVERSION	NUMBNESS TONGUE METALLIC TASTE	INITIAL
M074336	DYSPEPSIA TASTE PERVERSION DIARRHEA	UPSET STOMACH BAD TASTE DIARRHEA	INITIAL
M074348	MYALGIA	MUSCLE PAIN	INITIAL
M074446	ABDOMINAL PAIN DIARRHEA NAUSEA	ABDOMINAL PAIN DIARRHEA NAUSEA	INITIAL
M074448	INCREASED APPETITE WEIGHT GAIN	APPETITE INCREASED WEIGHT GAIN	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M074464	DYSPEPSIA DIARRHEA NAUSEA	STOMACHACHE DIARRHEA NAUSEA	INITIAL
M074469	LEUKOCYTOSIS LYMPHOCYTOSIS	LEUKOCYTOSIS LYMPHOCYTOSIS	INITIAL
M074478	MYALGIA	LEG MUSCLE PAIN	INITIAL
M074480	DRUG LEVEL INCREASED	INCREASED ALCOHOL BLOOD LEVEL	INITIAL
M074497	LACTIC DEHYDROGENASE INCREASED	LDH INCREASED	INITIAL
M074512	UNEXPECTED BENEFIT HYPOGLYCEMIA	UNEXPECTED BENEFIT HYPOGLYCEMIA	INITIAL
M074514	ASTHENIA	EXTREME FATIGUE	INITIAL
M074523	LEUKOPENIA THROMBOCYTOPENIA	LEUKOPENIA THROMBOCYTOPENIA	INITIAL
M074532	AGGRAVATION REACTION HYPERGLYCEMIA	HYPERGLYCEMIA EXACERBATED HYPERGLYCEMIA	INITIAL
M074533	STOMATITIS	BURNING MOUTH	INITIAL
M074534	PORPHYRIA	PORPHYRIA	INITIAL
M074536	LEG CRAMPS	CRAMPS LEGS	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M074560	TACHYCARDIA DYSPEPSIA ANXIETY DIZZINESS	TACHYCARDIA HEARTBURN ANXIETY DIZZINESS	INITIAL
M074585	ASTHENIA	EXTREME FATIGUE	INITIAL
M074596	AGGRAVATION REACTION HYPERGLYCEMIA	HYPERGLYCEMIA EXACERBATED HYPERGLYCEMIA	INITIAL
M074603	BODY ODOR	ODOR SKIN	INITIAL
M074617	ALOPECIA	HAIR LOSS	INITIAL
M074620	BREAST ENGORGEMENT METRORRHAGIA	BREAST ENGORGEMENT VAGINAL SPOTTING	INITIAL
M074623	ALOPECIA	ALOPECIA	INITIAL
M074644	CONFUSION LACK OF DRUG EFFECT SPEECH DISORDER	DISORIENTED LACK OF EFFECT SLURRED SPEECH	INITIAL
M074658	BONE PAIN	BONE PAIN	INITIAL
M074668	DIARRHEA	DIARRHEA	INITIAL
M074688	DIARRHEA	DIARRHEA	INITIAL

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MFR(CTU) FILE NO.	EXPANDED COSTART TERM	REPORTED TERM	REPORT TYPE
M074696	MYALGIA	MUSCLE ACHES	INITIAL
M074773	PALPITATION DYSPNEA	IRREGULAR HEARTBEAT SHORTNESS OF BREATH	INITIAL
M074869	LIVER FUNCTION TESTS ABNORMAL	INCREASED LIVER FUNCTION TESTS	INITIAL
M075031	FLATULENCE	FLATULENCE	INITIAL
M075032	URINARY TRACT DISORDER	URINE FLOW SLOW	INITIAL
M075041	AGGRAVATION REACTION HYPERGLYCEMIA	HYPERGLYCEMIA EXACERBATED HYPERGLYCEMIA	INITIAL
M075046	DIARRHEA FLATULENCE	DIARRHEA GAS	INITIAL
M075059	ABDOMINAL PAIN	GAS PAIN	INITIAL
M075246	AGGRAVATION REACTION GASTROINTESTINAL DISORDER KIDNEY FUNCTION ABNORMAL	RENAL DYSFUNCTION AGGRAVATED GASTROINTESTINAL DISTURBANCE RENAL DYSFUNCTION	INITIAL

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Index of Suspected Interacting Drugs
From Spontaneous, Literature, and Drug Related Phase IV Study Sources
By Manufacturer File Number

Included in this Periodic Adverse Drug Experience Report

Manufacturer File Number	Source (spontaneous, literature or clinical study)	Country	Adverse Drug Experience(s) (Expanded COSTART term(s))	Suspected Interacting Drug(s)
M072703	Spontaneous	USA	Hypoglycemia, Drug Interaction	Erythromycin
M073990	Spontaneous	USA	Hyperglycemia, Drug Interaction	Aspirin, Unspecified Anti-Inflammatory

Unless otherwise indicated these files are contained in other sections of this report.
* This adverse drug experience report did not qualify for inclusion in other sections of this submission.
** This adverse drug experience report was reported unnder another NDA, ANDA, ADA, or AADA (see Section IIIG)

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Narrative Summary and Analysis of Information in this Report

October 1, 1997 to December 31, 1997

FDA MEDWATCH PROGRAM

There were five reports associated with the FDA MedWatch Program during this reporting period. These reports are identified in the indices and tabulations by a central triage unit (CTU) number which appears in parentheses.

No reports were received through the FDA MedWatch program which were classified as non-serious.

FREEDOM OF INFORMATION ACT

There was one report received directly form the FDA via the Freedom Of Information Act during this reporting period. The report is file number M073452 which is listed in the 15-day tables of this report. These reports are identified in the indices and tabulations by a FOI reference number [FOI] which appears in brackets.

NONSERIOUS

There are one hundred forty two initial and eleven follow-up nonserious adverse drug experience reports included in this submission.

SERIOUS EXPECTED

There was one initial and no follow-up serious expected adverse drug experience reports included in this submission.

SERIOUS UNEXPECTED

There were forty four initial and forty seven follow-up 15-Day Alert reports submitted by Bristol-Myers Squibb during this reporting period. Many of these 15-Day Reports cited lactic acidosis and/or death related to lactic acidosis which normally would have been considered serious *but not unexpected*, because lactic acidosis is labeled in the package insert. However, in accordance with a prior agreement with the FDA (as of September 12, 1995) Bristol-Myers Squibb Worldwide Safety and Surveillance forwards all post-marketing reports pertaining to lactic acidosis as 15-Day Alert Reports. The following events, selected on the basis of possible clinical significance, have been chosen for comment. If all cases under a particular heading are not accounted for, this indicates that the information available to us was either inadequate or of little clinical significance.

NARRATIVE SUMMARY and ANALYSIS of 15-DAY REPORTS

The following reports of serious, unexpected adverse drug experiences (plus reports of lactic acidosis) have been selected for presentation in the narrative summary on the basis of their potential significance to the safety profile of metformin hydrochloride therapy for diabetes mellitus. The cases are organized according to their respective body system, and consequently, cases with multiple events may be referenced more than once.

BODY AS A WHOLE

Aggravation Reaction

During this reporting period, there were eight respective reports of aggravation reactions during therapy with metformin hydrochloride. A causal relationship with metformin is difficult to establish in each case, considering that these events reflect pre-existing, usually progressive, medical conditions, most of which are not uncommon in diabetic patients:

File #M055721: Acute renal failure exacerbated.
File #M073270: Chronic renal insufficiency exacerbated. **(Reference CTU# 72212E)**
File #M074636: Congestive heart failure exacerbated.
File #B034888: Diabetes mellitus exacerbated.
File #M070857: Heart failure exacerbated.
File #M070533: Hyperglycemia exacerbated.
File #M071098: Peripheral vascular disease exacerbated. **(Reference CTU# 70394E)**
File #B035006: Renal failure exacerbated.

Allergic Reactions

Allergic Drug Reaction

File #B034888: A 61-year-old diabetic female developed toxic epidermal necrolysis during therapy with metformin hydrochloride, triamterene, hydrochlorothiazide, Marcumar® (phenprocoumon), Diblocin® (doxazosin mesylate). (Other than

metformin, the indications for the other medications were not stated). The patient was admitted to a hospital and systemic steroid therapy was administered. Outcome was not reported. Medical history included hypertension, goiter, angioplasty and stent placement for coronary artery disease, and allergy to pyrazolone. The dermatologist considered the event to be drug-induced with a possible relationship to metformin hydrochloride. Initial and follow-up reports of German origin, via Groupe Lipha, France.

Allergic Rash
File #M071551: A diabetic male patient of unspecified age developed skin ulceration and a rash while taking metformin hydrochloride, Tolinase® (tolazamide hydrochloride), insulin (regular and NPH), and lovastatin. A skin biopsy reportedly indicated a medication allergy. The events resolved after discontinuation of metformin therapy. Medical history included hypercholesterolemia and gangrene of a foot leading to amputation. Follow-up report of U.S. origin.

Allergic Reaction
File #M070533: Hyperglycemia exacerbated, fever, malaise, weight loss, arthralgia, allergic reaction, and lactic acidosis were reported in a 65-year-old diabetic female with a history of colitis, hyperglycemia, and hysterectomy. The allergic reaction was not described, but was evidenced by an elevated eosinophil count. Concomitant medications included NPH insulin, calcium, Metamucil® Premarin®, and amoxicillin. Medical history included hyperglycemia, colitis, and a hysterectomy. The events resolved following medical treatment and discontinuation of metformin. Follow-up report of U.S. origin.

Death (Including Sudden Death) Reported with Lactic Acidosis

Reports of Lactic Acidosis and Death Originating from within the U.S.A.

Three of the 22 case reports of lactic acidosis originating from U.S. sources during this reporting period also reported the death of the patient. The corresponding case numbers, listed below, are also described in the Lactic Acidosis section of the body system category *Metabolic and Nutritional Disorders*. The cause of death is indicated if it was reported:

File #M055721: Renal failure; lactic acidosis.
File #M070857: End-stage heart failure and lactic acidosis due to end-stage heart failure.
File #M072169: (Specific cause of death was not provided)

Reports of Lactic Acidosis and Death Originating from outside of the U.S.A.

Four of the eleven cases of lactic acidosis originating from non-U.S. sources during this reporting period were associated with a fatal outcome. The corresponding case numbers, listed below, are also described in the Lactic Acidosis section of the body system category *Metabolic and Nutritional Disorders*. The causes of death are indicated as reported:

File #B030650: Lactic acidosis and cardiovascular distress.
File #B034381: Multisystem organ failure.
File #B035293: Bronchopulmonary infection, septic shock, renal insufficiency, major metabolic acidosis, acute foot ischemia.
File #B035974: Multiple organ failure.

Death (Including Sudden Death) Not Associated with Reports of Lactic Acidosis

File#B034346: A 76-year-old diabetic female treated with metformin hydrochloride and glibenclamide underwent surgery for aortic valve replacement. The oral diabetic agents were discontinued 24 hours prior to surgery and insulin was administered for glycemic control. Within 24 hours post-operatively, she developed acute renal failure and metabolic acidosis which led to death six hours later. Medical history included coronary artery disease, aortic stenosis, and hypertension. Renal function was normal prior to and immediately following surgery. The cause of death was reported to be metabolic acidosis, anuria, and heart rate disorders. Follow-up report from Groupe Lipha, France.

File #B035192: Following 6 days of therapy with Fucidine® (fusidic acid) (indication not stated), and one day of therapy with each of the following medications: metformin hydrochloride, Daflon® (diosmin), furosemide, and potassium chloride, an 80-year-old male developed jaundice and fever and died.

Medical history and detailed clinical information were not provided, except for elevated serum bilirubin and hepatic transaminase levels, and evidence of old hepatitis A and B. Septic shock was reported to have been considered as a cause of death. Initial report via Groupe Lipha, France.

File #M072121: A 74-year-old diabetic female patient developed diarrhea, urticaria, confusion, weakness which progressed to an obtunded then comatose state, thrombotic thrombocytopenic purpura, and death while taking metformin hydrochloride, ticlopidine hydrochloride, and atorvastatin. Medical history included atherosclerotic cardiovascular disease, coronary artery stent placement, coronary artery bypass graft, hyperlipidemia, and colon cancer. The reporting physician considered all of the above drugs as potential suspect regarding the etilolgy of thrombotic thrombocytic purpura. Initial report of U.S. origin.

File #M072835: A 74-year-old diabetic female patient with a history of hypertension and chronic alcohol abuse was admitted to a hospital with severe metabolic acidosis while taking metformin hydrochloride and acetaminophen. The patient also developed hepatic failure and died as a result of E. coli sepsis. Serum lactate was elevated and blood metformin assay was within a therapeutic range. The reporting physician did not relate the cause of death to metformin therapy. Initial and follow-up reports of U.S. origin.

File #M073011: A 71-year-old diabetic female developed severe metabolic acidosis, cardiac arrest, was declared brain dead, and expired following the withdrawal of mechanical ventilation. Medical therapy included metformin hydrochloride, lisinopril, glyburide, gemfibrozil, calcium, aspirin, and colestipol. There was not a history of renal dysfunction. Initial report of U.S. origin. **(Reference CTU# 71903E)**

File #M073290: A 72-year-old diabetic male developed a myocardial infarction, pulmonary edema, cardiac arrest, and died while taking metformin hydrochloride. The patient had continued metformin therapy up until the time of an elective myelogram with an unspecified contrast agent, and the above events occurred following the procedure. It was not reported whether the patient received a dose of metformin after the myelogram. (Minimal information was provided). The reporting physician did not consider the patient's death to be attributed to metformin therapy. Initial report of U.S. origin.

File #M073865: A 55-year-old diabetic male experienced a fatal myocardial infarction during therapy with metformin hydrochloride, synthroid, and an unspecified diuretic. Medical history included hypertension. (Minimal information was provided). Initial report of U.S. origin.

Comment on the Reports of Death (Including Sudden Death)

Of the 14 reports of death during this reporting period, a total of seven (21.2%) of the 33 reports citing lactic acidosis, received from all sources worldwide, included death. The incidence of death reported with lactic acidosis was well-within the expected rate of up to 50% as is stated in the U.S. package insert for Glucophage®. Although death was reported as an outcome in these cases of lactic acidosis, virtually all of the patients described had other serious medical conditions such as renal failure, sepsis, shock, cardiopulmonary failure, etc., which contributed significantly to the causes of death.

Seven of the 14 reports of death were not associated with the diagnosis of lactic acidosis. The etiologies of these deaths, when reported, do not appear to be unusual for this population of diabetic patients, who are known to have had a variety of significant acute and chronic medical conditions.

Intentional Overdose/Suicide Attempt

File #B034409: A 24-year-old non-diabetic male was admitted to hospital following an intentional overdose of 12.5 grams of metformin hydrochloride, plus alcohol ingestion, presenting with acute renal failure. The patient recovered following treatment. Medical history was not provided. Follow-up report from the United Kingdom, via Groupe Lipha, France.

File #B033973: A 29-year-old non-diabetic male developed hypoglycemia, abnormal renal function, lactic acidosis and coma following an intentional overdose of metformin hydrochloride, glibenclamide, and nabumetone (quantities not reported). Medical history was negative for renal disorders, but was otherwise not specified. The patient recovered. Follow-up report from Groupe Lipha, France.

File #B035720: A 40-year-old diabetic female was admitted to hospital following an intentional overdose of metformin hydrochloride (sixty 850 mg tablets) with diarrhea, hepatic cytolysis, and lactic acidosis. Medical history included a previous suicide attempt, depression, alcoholism, delirium, and psoriasis. The patient recovered. Initial and follow-up reports from Groupe Lipha, France.

File #B029180: A 58-year-old diabetic male attempted suicide by ingesting ninety 850 mg tablets of metformin hydrochloride and subsequently developed acute renal failure, diabetic ketoacidosis, lactic acidosis, and a bronchial obstruction. Blood metformin assay levels were significantly elevated. Medical history included depression, epilepsy, and alcohol and tobacco abuse. The patient recovered. Follow-up report from Groupe Lipha, France.

Accidental Overdose

File #M074053: A diabetic female patient of unspecified age confused her metformin hydrochloride tablets with aspirin and instead of taking one 500 mg tablet of metformin daily, she occasionally took 2 or more tablets a day. During this unspecified period, she experienced muscle pain and weakness which resolved following the complete withdrawal of metformin. Medical history included multiple allergies. Initial report of U.S. origin.

Laboratory Test Abnormality
Decreased Serum pH; Increased Creatine Phosphokinase; Increased Liver Function Tests; and Increased Serum Lactate

File #M069502: A 71-year-old diabetic female developed acute renal failure, increased liver function tests, decreased serum pH, increased creatine phosphokinase, elevated serum lactate, and shortness of breath during therapy with metformin hydrochloride. The laboratory abnormalities resolved following dialysis and supportive therapy. There were no concomitant medications reported and medical history included ischemic cardiomyopathy, no known allergies, and no alcohol or tobacco use. A definitive diagnosis was not reported. Follow-up report of U.S. origin. **(Reference CTU# 67742E)**

Increased Serum Lactic Acid (Lactic Acidosis was not reported)

File #M072851: A 72-year-old diabetic male developed metabolic acidosis with "overcompensated respiratory alkalosis," and transiently elevated serum lactate, during metformin hydrochloride therapy. Renal function was stated to have been normal and, blood metformin level was within the normal therapeutic range. The etiology of the metabolic imbalance was not reported and the patient was improving at the time of the report. Initial and follow-up reports of U.S. origin.

File #M074011: A 45-year-old diabetic male patient developed acute dehydration, renal insufficiency, and an elevated serum lactic acid level while taking metformin hydrochloride. Metformin blood levels are pending. A specific diagnosis was not reported. (Minimal information was provided). Initial report of U.S. origin.

Sepsis

There were four reports of sepsis during this period: **File #M053275 (CTU# 36235E) - bacteremia; File #M074470 - unspecified sepsis; File #M072835 - E. coli sepsis; and File #M071127 - urinary sepsis.** The first two cases were associated with lactic acidosis and the latter two cases were associated with metabolic acidosis.

Septic Shock

File #B035293: Heart failure, respiratory infection, septic shock, anuria, respiratory failure, impaired renal function, metabolic acidosis, elevated blood metformin level, lactic acidosis and death were reported in a 75-year-old diabetic male. Medical history included arterial disease, leg amputation, appendectomy, glaucoma, cataract surgery, urinary lithiasis, and pneumonia. Initial and follow-up reports from Groupe Lipha, France.

CARDIOVASCULAR SYSTEM

Arteriosclerosis

Renal Artery Stenosis

File #B033584: Renal artery stenosis, acute renal failure, lactic acidosis, and elevated plasma and erythrocyte metformin levels in an 85-year-old diabetic female, with a

history of renal failure. Following treatment, a "favorable" outcome of the acute events was reported. Follow-up report from Groupe Lipha, France.

Bradycardia

Bradycardia or decreased heart rate was reported in three cases during metformin hydrochloride therapy **(File #s: M064948; M074613; and M071270)**. Each of the patients had underlying acute and chronic medical conditions which may have possibly been associated with the etiology of the event.

Cardiogenic shock

File #M055721: Acute renal failure exacerbated, hypoglycemia, cardiogenic shock, lactic acidosis, and death resulting from sepsis and metabolic imbalance were reported in a 90-year-old diabetic female. Medical history included renal insufficiency, hypertension, obesity, pancreatitis, organic brain syndrome with dementia, and bilateral below-the knee amputations. Follow-up report of U.S. origin.

Cardiac Arrest

Cardiac arrest or cardiopulmonary arrest was reported in 6 of the cases during this reporting period: **File #s: B029179; M071270; M073088; M073370; M073011 (CTU# 71903E); and M073290**. The outcome was fatal in the latter two cases. Cardiac arrest is not an uncommon event in diabetic patients of middle age and older in the presence of other acute and chronic medical conditions.

Heart Failure

Seven cases during this reporting period included reports of heart failure - **File #s: B035293; M064948; M070857; M071957 (CTU# 70554E); M073459; M073739; and M074636**. Five of the patients were 71-years-of-age or greater and five patients were reported to have had a history of cardiovascular disease. Two patients had a fatal outcome: A 72-year-old male **(File #M070857)** died as a result of "end-stage heart failure and lactic acidosis due to end-stage heart failure; and a 71-year-old male **(File #B035293)** died following metabolic acidosis, a pulmonary infection, renal failure, acute ischemia of a foot, and septic shock.

Myocardial Infarction

There were three reports of acute myocardial infarctions during this reporting period - **File #s: M072321; M073290; and M073865**. The latter two cases had a fatal outcome. (All of the cases were initial reports of U.S. origin and limited information was available at the time of this report).

Syncope

Four cases included reports of syncope during this period. Three of the events were most likely associated with intercurrent medical conditions, and One case did not describe other acute medical problems, but related a history of previous cardiovascular disorders in the patient's medical history:

File #M070109: Ventricular tachycardia
File #M070241: Metabolic acidosis **(Reference CTU# 68380E)**
File #B035783: Hypoglycemia
File #M072637: History of hypertension and cerebrovascular accident.

DIGESTIVE SYSTEM

Cholestatic Jaundice

File #B035192: Following 6 days of therapy with Fucidine® (fusidic acid) (indication not stated), and one day of therapy with each of the following medications: metformin hydrochloride, Daflon® (diosmin), furosemide, and potassium chloride, an 80-year-old male developed jaundice and fever and died. Medical history and detailed clinical information were not provided, except for elevated serum bilirubin and hepatic transaminase levels, and evidence of old hepatitis A and B. Septic shock was reported to have been considered as a cause of death. Initial report via Groupe Lipha, France.

File #M071132: A 64-year-old diabetic male was admitted to a hospital for progressive painless jaundice over a 5-week period accompanied by dark urine, anorexia, fatigue, and weight loss. Medical history included hypertension, coronary artery disease, myocardial infarctions, spinal stenosis, and bipolar disorder. A liver biopsy revealed cholestasis, portal edema, acute inflammation and ductular proliferation. The jaundice slowly resolved over a two-month period following the discontinuation of metformin hydrochloride. A follow-up literature report from a U.S. publication.

Hepatic Cirrhosis
File #B035021: A 63-year-old diabetic female developed cirrhosis of the liver resulting in hepatic failure during therapy with metformin hydrochloride. There was not a history of jaundice, hepatitis, alcohol abuse or blood transfusion. No other medication was taken by the patient prior to the event. Outcome was not reported. The reporting physician considered the events "possibly" related to metformin therapy. Initial report from Groupe Lipha, France.

Duodenitis
File #M069284: Hyperglycemia, hepatic function abnormalities, renal function abnormalities, dehydration, cholelithiasis, gastroesophageal reflux, splenomegaly, duodenitis, and lactic acidosis were reported in a 69-year-old diabetic male. Biopsies of esophageal inflammatory mucosa and small bowel mucosa revealed benign lesions. Medical history included rheumatoid arthritis, degenerative joint disease, bilateral cataract surgery, retinal detachment, hypertension, depression, leukoplakia, tobacco and alcohol use, tinnitus, erectile dysfunction, paresthesia, and impaired vision. Follow-up report of U.S. origin.

Hepatitis
File #M071444: Acute renal failure, hepatitis, dehydration, hyperglycemia, rhabdomyolysis, pancreatitis, thrombocytopenia, and lactic acidosis were reported in a 58-year-old diabetic male with a history of alcohol abuse, alcoholic cardiomyopathy, alcoholic liver disease, congestive heart failure, and hypertension. Metformin blood levels were below the lower limit of quantitation. The patient's history ao alcololism was considered as an etiologic factor regarding hepatitis. His condition was improving at the time of the last report. Follow-up reports of U.S. origin.

Ischemic Colitis
File #B034381: Hypoglycemic coma, diarrhea, dehydration, leukocytosis, ischemic colitis (for which surgery was performed), multisystem organ failure, elevated blood metformin level, lactic acidosis, and death were reported in a 71-year-old diabetic male. Death was attributed to multisystem organ failure. Medical history included cardiac arrhythmia and end stage renal disease. Follow-up report from Groupe Lipha, France.

Hepatic Cytolysis

File #B034262: A 60-year-old diabetic male developed "hepatic cytolysis" and jaundice during therapy with metformin hydrochloride. Viral tests for hepatitis A, B, and C were negative as was serology for cytomegalovirus, mononucleosis, and herpes virus. Ultrasound of the liver was normal. There were no concomitant medications. Medical history included cholelithiasis and unspecified hepatic "problems." The events resolved following the discontinuation of metformin. The physician reported that the event was possibly related to metformin therapy. Follow-up report from Groupe Lipha, France.

File #B035720: Intentional overdose of metformin hydrochloride, suicide attempt, diarrhea, hepatic cytolysis, and lactic acidosis were reported in a 40-year-old diabetic female with history of depression , alcoholism, delirium, previous suicide attempt, and psoriasis. The patient recovered following treatment. Details pertaining to "hepatic cytolysis" were not provided. Initial and follow-up reports from Groupe Lipha, France.

Hepatic Failure

File #B035021: A 63-year-old diabetic female developed cirrhosis of the liver resulting in hepatic failure during therapy with metformin hydrochloride. There was not a history of jaundice, hepatitis, alcohol abuse or blood transfusion. No other medication was taken by the patient prior to the event. Outcome was not reported. The reporting physician considered the events "possibly" related to metformin therapy. Initial report from Groupe Lipha, France.

File #M072835: A 74-year-old diabetic female patient with a history of hypertension and chronic alcohol abuse was admitted to a hospital with severe metabolic acidosis, while taking metformin hydrochloride and acetaminophen. The patient also developed hepatic failure and died as a result of E. coli sepsis. Serum lactate was elevated and blood metformin assay was within a therapeutic range. The reporting physician did not judge the cause of death to be related to metformin therapy. Initial and follow-up reports of U.S. origin.

File #M064948: Hyperglycemia, sinus infection, bradycardia, liver failure, congestive heart failure, inability to urinate, and lactic acidosis were reported in a 78-year-old diabetic female with a history of coronary artery disease, hyperlipidemia, and polymyalgia rheumatica. The liver failure was reported to have been transient, and additional information was not provided. Follow-up report of U.S. origin.

Liver Function Test Abnormalities

Seven cases, during this period, included reported abnormalities of liver function tests without a diagnosis of liver disease - **File #s; M068571 (CTU# 66477E); M073459; M069502 (CTU# 67742E); M074443; M074636; M072233; and M069284**. Three of the cases reported a resolution of the abnormalities and one case was improved at the time this report. Three cases included lactic acidosis and five included renal dysfunction. The etiology was discussed for two of the patients: one series of liver function abnormalities was attributed to methotxerate and the other was "possibly" attributed to metformin hydrochloride.

Hepatitis

File #M071444: Acute renal failure, hepatitis, dehydration, hyperglycemia, rhabdomyolysis, pancreatitis, thrombocytopenia, and lactic acidosis were reported in a 58-year-old diabetic male with a history of alcohol abuse, alcoholic cardiomyopathy, congestive heart failure, and hypertension. The pancreatitis was judged to be a "chemical" pancreatitis, rather than inflammatory in etiology. Following treatment, serum amylase and lipase levels returned to normal. Follow-up reports of U.S. origin.

Peptic Ulcer

File #M074613: A 45-year-old developed a hernia (presumed to be hiatal), peptic ulcer, hypochromic anemia, bradycardia, weakness, chills, and general malaise during therapy with metformin hydrochloride and glynase. Medical history was not provided. The "hernia" and peptic ulcer were diagnosed with endoscopy. There reportedly were no signs of gastrointestinal bleeding or colitis. (Minimal information was provided) Initial report from a U.S. consumer.

ENDOCRINE SYSTEM

Hypothyroidism

File #M053275: Bacteremia, fungal infection, depression, hypothyroidism, coronary artery disease, respiratory insufficiency, autonomic neuropathy, vocal cord ulcers, laryngeal edema, hypotension, and lactic acidosis were reported in a 60-year-old female with a history of insulin-dependent diabetes, and continuous peritoneal dialysis for chronic renal failure. Medical history also included obesity, diabetic retinopathy, hypertension, drug allergies, leg ulcer and gangrene, and angioplasty. Levothyroxine sodium therapy was initiated for the treatment of hypothyroidism. Follow-up report of U.S. origin. **(Reference CTU# 36235E)**

HEMATOLOGIC AND LYMPHATIC SYSTEM

Anemia (Unspecified)

File #B029179: Acute renal failure, dehydration, gastroenteritis, respiratory failure, cardiorespiratory arrest, coma, anemia, thrombocytopenia, and lactic acidosis were reported in a female diabetic patient stated to be in her 70s. The etiologies of the anemia and thrombocytopenia were not elucidated at the time of this report. Follow-up report from Groupe Lipha, France.

Hypochromic Anemia

File #M074613: A 45-year-old developed a hernia (presumed to be hiatal), peptic ulcer, hypochromic anemia, bradycardia, weakness, chills, and general malaise during therapy with metformin hydrochloride and glynase. Medical history was not provided. The "hernia" and peptic ulcer were diagnosed with endoscopy. There reportedly were no signs of gastrointestinal bleeding or colitis. Additional details regarding the anemia were not reported. (Minimal information was provided). Initial report from a U.S. consumer.

Pancytopenia

File #M068571: A 29-year-old diabetic female developed pancytopenia, epistaxis, ear pain, pharyngitis, fever, and liver function abnormalities during metformin therapy. Concomitant medications were methotrexate, acetaminophen, oxaprozin, and

Darvocet-N®. Medical history included rheumatoid arthritis and bone marrow depression. A bone marrow biopsy was reported to have been normal. All of the medications were withdrawn and the pancytopenia subsequently resolved, but reoccurred following a re-challenge with metformin. The reporting pharmacist indicated that methotrexate, oxaprozin, acetaminophen, and metformin were considered to be suspect drugs in the etiology of pancytopenia. Follow-up report of U.S. origin. **(Reference CTU# 66477E).**

Thrombocytopenia

File #B029179: Acute renal failure, dehydration, gastroenteritis, respiratory failure, cardiorespiratory arrest, coma, anemia, thrombocytopenia, and lactic acidosis were reported in a female diabetic stated to be in her 70s. Medical history included hypertension, asthma, obesity, chronic respiratory failure, and ischemic cardiomyopathy. An etiology for the thrombocytopenia was not reported. The most recent report stated further investigation of thrombocytopenia and anemia were planned. Follow-up report from Groupe Lipha, France.

File #B035191: A 74-year-old diabetic female was admitted to a hospital with thrombocytopenia during therapy with metformin hydrochloride, glyburide, Odrik® (trandolapril), and aspirin. Medical history included hypertension. Further details, including outcome, were not provided. Initial and follow-up reports from Groupe Lipha, France.

File #M071444: Acute renal failure, hepatitis, dehydration, hyperglycemia, rhabdomyolysis, pancreatitis, thrombocytopenia, and lactic acidosis were reported in a 58-year-old diabetic male with a history of alcoholic cardiomyopathy, congestive heart failure, and hypertension. Details pertaining to the outcome and etiology of the thrombocytopenia were not provided. Follow-reports of U.S. origin.

Thrombocytopenia, Decreased Red Blood Cells, and Leukopenia

File #B033099: A 62-year-old diabetic male was reported to have developed a decrease in red blood cell count, leukopenia, thrombocytopenia, nausea, vomiting, and diarrhea during therapy with oxacillin sodium, spironolactone, metformin hydrochloride, zolpidem hemitartrate, pefloxacin mesylate, and metoclopramide hydrochloride. The antibiotics were administered for

treatment of a foot lesion. Medical history included alcoholism, ascites, splenomegaly, and portal hypertension. The thrombocytopenia, decreased red blood cells, and leukopenia resolved upon discontinuation of perflacine. The reporter judged a causal relationship between metformin and the hematologic abnormalities as "remote." Initial report from Groupe Lipha, France.

Thrombocytopenic Purpura

File #B034380: A 61-year-old male patient was treated in a hospital for thrombocytopenic purpura, a conjunctival hemorrhage, and an unspecified hematoma. The etiology of thrombocytopenic purpura was undetermined. The patient recovered without sequelae. Medical history included hypertension and varicose veins. In addition to metformin hydrochloride, the following drugs were considered by the treating physician to be possibly related to the event: troxerution, Coversyl® (perindopril), Fonzylane (buflomedil hydrochloride), insulin, and Tilcotil® (tenoxicam). Details pertaining to the outcome of the events were not provided. The physician considered a "possible" causal relationship between tenoxicam and thrombocytopenia. Follow-up report from Groupe Lipha, France.

Thrombotic Thrombocytopenic Purpura

File #M072121: A 74-year-old diabetic female patient developed diarrhea, urticaria, confusion, and weakness which progressed to an obtunded then comatose state, thrombotic thrombocytopenic purpura, and death while taking metformin hydrochloride, ticlopidine hydrochloride, and atorvastatin. Plasma phoresis was not successful in the treatment of thrombotic thrombocytopenic purpura. Medical history included atherosclerotic cardiovascular disease, coronary artery stent placement, coronary artery bypass graft, hyperlipidemia, and colon cancer. The reporting physician considered all of the above drugs as potential suspect regarding the etilolgy of thrombotic thrombocytic purpura. Initial report of U.S. origin.

METABOLIC AND NUTRITIONAL DISORDERS

Acidosis
Metabolic Acidosis

During this reporting period, eleven cases included reports of metabolic acidosis **[File #s: B034346; B035293; M070241 (CTU# 68380E); M071127; M072321; M072835; M072851; M073011 (CTU# 71903E); M073460; (CTU# 72531E); M073784; and M073459.]** Serum lactic acid was elevated in three of the four cases that reported lactate assays **[File #s: B035293; M072835; and M072851.]** One case, **File #B035293**, reported both metabolic acidosis and lactic acidosis and is also discussed in the lactic acidosis section. All of the eleven case reports included acute and/or chronic medical conditions which may have been related to the etiology of metabolic disturbances.

Lactic Acidosis

Reports of Lactic Acidosis Originating from within the U.S.A.

File #M053275: Bacteremia, fungal infection, depression, hypothyroidism, coronary artery disease, respiratory insufficiency, autonomic neuropathy, vocal cord ulcers, laryngeal edema, hypotension, and lactic acidosis were reported in a 60-year-old female with a history of insulin-dependent diabetes, and continuous peritoneal dialysis fotr the treatment of chronic renal failure. Medical history also included obesity, diabetic retinopathy, hypertension, drug allergies, leg ulcer and gangrene, and angioplasty. Follow-up report. **(Reference CTU# 36235E)**

File #M055721: Acute renal failure exacerbated, hypoglycemia, cardiogenic shock, lactic acidosis, and death resulting from sepsis and metabolic imbalance were reported in a 90-year-old diabetic female. Medical history included renal insufficiency, hypertension, obesity, pancreatitis, organic brain syndrome with dementia, and bilateral below-the-knee amputations. Follow-up report.

File #M064948: Hyperglycemia, sinus infection, bradycardia, liver failure, congestive heart failure, inability to urinate, and lactic acidosis were reported in a 78-year-old diabetic female with a history of coronary artery disease, hyperlipidemia, and polymyalgia rheumatica. Follow-up report.

File #M069284: Hyperglycemia, abnormal hepatic function, abnormal renal function, dehydration, cholelithiasis, gastroesophageal reflux, splenomegaly, duodenitis, and lactic acidosis were reported in a 69-year-old diabetic male. Medical history included rheumatoid arthritis, degenerative joint disease, bilateral cataract surgery, retinal detachment, hypertension, depression, leukoplakia, tobacco and alcohol use, tinnitus, erectile dysfunction, paresthesia, and impaired vision. Follow-up report.

File #M069519: Lactic acidosis in a 45-year-old diabetic female with a history of breast cancer, and hypothyroidism. Follow-up report.

File #M070533: Hyperglycemia (exacerbated), fever, malaise, weight loss, arthralgia, allergic reaction, and lactic acidosis in a 65-year-old diabetic female with a history of colitis, hyperglycemia, and hysterectomy. Follow-up report.

File #M070857: Heart failure (exacerbated), elevated serum creatinine, lactic acidosis, and death in a 72-year-old diabetic male with a history of heart failure and coronary artery disease. Follow-up report.

File #M071098: Digitalis intoxication, uremia, dehydration, peripheral vascular disease exacerbated, decubitus ulcer, peripheral gangrene, urinary tract infection, and lactic acidosis in an 80-year-old female. Medical history included hypertension, hyponatremia, congestive heart failure, atrial fibrillation, glaucoma, pulmonary hypertension, peptic ulcer disease, angioplasty, fungal infection, cholelithiasis, diabetic retinopathy, atrial septal defect, and penicillin allergy. Follow-up reports. **(Reference CTU# 70394E)**

File #M071444: Acute renal failure, hepatitis, dehydration, hyperglycemia, rhabdomyolysis, pancreatitis, thrombocytopenia, and lactic acidosis in a 58-year-old diabetic male with a history of alcohol abuse, alcoholic cardiomyopathy, congestive heart failure, and hypertension. Follow-up reports.

File #M071958: Lactic acidosis in a female diabetic patient of unspecified age with a history of hypertension. Initial report.

File #M072169: Acute renal failure, dehydration, lactic acidosis and death in an 80-year-old diabetic female. (Minimal information was provided). Initial report.

File #M072233: Renal insufficiency, liver function abnormalities, and lactic acidosis in a 65-year-old diabetic male with a history of hypertension and obesity. Initial report.

File #M072800: Proteinuria, increased serum creatinine, encephalopathy, and lactic acidosis in a 60-year-old female. (Minimal information was provided). Initial report.

File #M073088: Acute renal failure, heart block, cardiac arrest, respiratory failure, elevated metformin in blood level, and lactic acidosis were reported in a 94-year-old female with a history of abnormal renal function. Initial and follow-up reports.

File #M073270: Chronic renal insufficiency (exacerbated) and lactic acidosis were reported in a 75-year-old diabetic female with a history of renal dysfunction. Initial report. **(Reference CTU# 72212E)**

File #M073370: Cardiorespiratory arrest, urinary tract infection, pneumonia, and lactic acidosis were reported in a 58-year-old diabetic female with a history of chronic renal failure and cardiomegaly. Initial report.

File #M073423: Multisystem organ failure and lactic acidosis were reported in an 85-year-old diabetic female. (Minimal information was provided). Initial report. **(Reference CTU #72367E)**

File #M073452: Renal dysfunction and lactic acidosis were reported in a 75-year-old diabetic female with a history of acute renal failure and heart failure. Initial report. **(Reference Freedom of Information #s 1726085 and 1751721).**

File #M074470: Sepsis and lactic acidosis were reported in a 67-year-old diabetic female with a history of chronic renal insufficiency, hypertension, and congestive heart failure. Initial report.

File #M074636: Renal impairment, congestive heart failure exacerbated, elevated liver function tests, angina, and lactic acidosis were reported in a 75-year-old female with a history of congestive heart failure, hyperlipidemia, coronary bypass graft surgery, and paroxysmal atrial fibrillation. Initial report.

File #M074645: Lactic acidosis was reported in a 72-year-old diabetic female with a history of hypertension, hypertriglyceridemia, proteinuria, leg weakness, and cardiovascular disease. Initial report.

File #M074671: Renal function abnormality, hypotension, elevated white blood cell count, and lactic acidosis were reported in a 60-year-old diabetic male. Initial report.

Comment on the Reports of Lactic Acidosis Originating from within this U.S.A.

Twenty-two cases reporting "lactic acidosis" are included in this Periodic Adverse Drug Experience Report. There were 12 reports containing initial information only; 1 report containing both initial and follow-up information; and 9 reports containing follow-up information only. (Two of the initial reports and two of the follow-up reports were received by the Sponsor via the FDA MedWatch Program. One of the initial reports was received by the Sponsor via the FDA Freedom of Information Office).

As stated in the current U.S. package insert for Glucophage®, lactic acidosis is characterized by elevated blood lactate level (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate / pyruvate ratio.

In accordance with the criteria employed by the FDA, and from other analyses of lactic acidosis, a lactate value of 5.0 mmol/L or greater establishes a presumptive diagnosis of lactic acidosis. Of the 14 cases that included actual lactic acid values with the respective units of measure either specified or apparent, 9 cases reported lactate levels that were equal to or greater than 5.0 mmol/L. Tables I and II, at the end of this narrative summary, highlight important clinical findings regarding these patients. (The conversion factor employed when lactate values were expressed in mg/dL is: 1.0 mmol/L = 9.0 mg/dL. When multiple lactate levels had been reported, attempt has been made to select the value closest to the time of diagnosis.)

In total, 13 of the 22 cases were evaluable, as the following nine reports did not provide sufficient clinical information for analysis and comment: **File #s: M069284; M069519; M070533; M071958; M072169; M072233; M072800; M073423 (CTU#72367E); and M074645.**

In 9 (69.2%) of the 13 evaluable cases of lactic acidosis, the initiation of metformin hydrochloride therapy was either definitely or likely not in accordance with at least one aspect of the current U.S. package insert for Glucophage® pertaining to *Indications and Use, Contraindications, Warnings, or Precautions:*

File #M053275: History of chronic renal failure treated with peritoneal dialysis; insulin-dependent diabetes mellitus. **(Reference CTU# 36235E).**
File #M055721: History of renal insufficiency.
File #M070857: History of significant heart failure.
File #M071444: History of congestive heart failure; severe dilated cardiomyopathy; alcohol abuse; alcoholic liver disease.
File #M073088: History of renal impairment.
File #M073270: History of chronic renal insufficiency **(Reference CTU# 72212E).**
File #M073370: History of chronic renal failure and cardiomegaly.
File #M073452: History of renal impairment and congestive heart failure. **(FOI #s: 1726085 and 1751721).**
File #M074470: History of chronic renal insufficiency and congestive heart failure.

Three of the 13 evaluable cases of lactic acidosis (23.1%) did not convey ostensible elements of inappropriate patient selection for metformin hydrochloride therapy, but each of these patients, however, developed at least one subsequent illness or condition which may have been a predisposing factor in the etiology of lactic acidosis:

File #M064948: Poor glycemic control; congestive heart failure; infection; transient liver failure;
File #M071098: Dehydration **(Reference CTU #70394E)**
File #M074636: Acute renal failure possible related to intravascular contrast agent, exacerbation of heart failure.

In summary, 11 (50%) of the total of 22 cases reported as "lactic acidosis" from U.S. sources included blood lactate values of a magnitude (≥5.0 mmol/L) that would support this diagnosis.

Nine (69.2%) of the 13 evaluable cases of lactic acidosis reported from U.S. sources occurred in patients who were apparently initiated on Glucophage® (metformin hydrochloride) therapy for diabetes mellitus not in full accordance with the prescribing information in the current U.S. package insert. Chronic renal failure and congestive heart failure were the predominant factors.

Three (23.1%) of the evaluable cases of lactic acidosis may have had a causal relationship to the development of an illness or condition predisposing to lactic acidosis following initiation of metformin hydrochloride therapy. Acute renal failure, dehydration, heart failure, infection, and liver failure were identified in this group.

Three (13.6%) of the 22 reports of lactic acidosis originating from within the U.S.A. reported a fatal outcome

Reports of Lactic Acidosis Originating from outside of the U.S.A.

File #B029179: Acute renal failure, dehydration, gastroenteritis, respiratory failure, cardiorespiratory arrest, coma, anemia, thrombocytopenia, and lactic acidosis were reported in a female diabetic patient stated to be in her 70s. Medical history included hypertension, asthma, obesity, chronic respiratory failure, and ischemic cardiomyopathy. Follow-up report from Groupe Lipha, France.

File #B029180: Diabetic ketoacidosis, acute renal failure, bronchial obstruction, suicide attempt, elevated blood metformin level, and lactic acidosis were reported in a 58-year-old diabetic male with a history of depression, epilepsy, and alcohol and tobacco use. Follow-up report from Groupe Lipha, France.

File #B030650: Sciatica, diarrhea, lactic acidosis, and death were reported in a 66-year-old diabetic female with a history rheumatoid arthritis, chronic pancreatitis, asthma, and HIV infection. Follow-up reports from Groupe Lipha, France.

File #B032549: Multisystem organ failure, shock, elevated blood metformin level, and lactic acidosis were reported in a 47-year-old male with a history of peripheral arterial obstruction, and alcohol and tobacco use. Follow-up reports from Groupe Lipha, France.

File #B033584: Acute renal failure, renal artery stenosis, elevated blood metformin level, and lactic acidosis were reported in an 85-year-old diabetic female. Follow-up report from Groupe Lipha, France.

File #B033973: Hypoglycemia, intentional overdose of metformin hydrochloride, abnormal renal function, coma, and lactic acidosis were reported in a 29-year-old non-diabetic male. Follow-up report from Groupe Lipha, France.

File #B034381: Hypoglycemic coma, diarrhea, dehydration, leukocytosis, ischemic colitis, multisystem organ failure, elevated blood metformin level, lactic acidosis and death were reported in a 71-year-old diabetic male. Medical history included cardiac arrhythmia and end stage renal disease. Follow-up report from Groupe Lipha, France.

File #B035006: Acute renal failure, pneumopathy, respiratory failure, elevated blood metformin level, and lactic acidosis were reported in a 67-year-old diabetic female with a history of chronic renal failure. Initial and follow-up reports from Groupe Lipha, France.

File #B035293: Heart failure, respiratory infection, septic shock, anuria, respiratory failure, impaired renal function, metabolic acidosis, elevated blood metformin level, lactic acidosis and death were reported in a 75-year-old diabetic male. Medical history included arterial disease, leg amputation, appendectomy, glaucoma, cataract surgery, urinary lithiasis, and pneumonia. Initial and follow-up reports from Groupe Lipha, France.

File #B035720: Intentional overdose of metformin hydrochloride, suicide attempt, diarrhea, hepatic cytolysis, and lactic acidosis were reported in a 40-year-old diabetic female with a history of depression, alcoholism, delirium, previous suicide attempt, and psoriasis. Initial and follow-up reports from Groupe Lipha, France.

File #B035974: Hyperglycemia, pneumonia, multisystem organ failure, lactic acidosis, and death were reported in a 66-year-old male with a history of surgery for a hernia. A literature report from Germany received via Groupe Lipha, France.

Comment on the Reports of Lactic Acidosis Originating from outside of the U.S.A.

Eleven cases from non-U.S. sources included the diagnosis of lactic acidosis. One report contained initial information only; three reports included both initial and follow-up information; seven reports contained follow-up information only.

Of the nine cases that included lactic acid values with the respective units of measure specified, eight cases reported lactate levels that were equal to or greater than 5.0 mmol/L.

There were ten evaluable cases, as one case, **File #B032549** did not provide sufficient clinical information for analysis and comment.

In 5 (50%) of the ten evaluable cases of lactic acidosis, the initiation of metformin hydrochloride therapy was not in accordance with at least one aspect of the current U.S. package insert for Glucophage® pertaining to *Indications and Use, Contraindications, Warnings, or Precautions:*

File #B029179: History of renal insufficiency and congestive heart failure.
File #B033584: History of renal failure and inadequate management of metformin hydrochloride therapy.
File #B033973: Intentional overdose of metformin plus glibenclamide and nabumetone by a *non-diabetic* patient.
File #B035006: History of chronic renal failure and inadequate management of metformin therapy.
File #B035293: History of renal failure and congestive heart failure.

Five (50%) of the ten evaluable cases of lactic acidosis did not convey ostensible elements of inappropriate initiation of therapy with metformin hydrochloride, but each of these patients, however, developed at least one subsequent illness or condition which may have been a predisposing factor in the etiology of lactic acidosis:

File #B029180: Attempted suicide with an overdose of metformin hydrochloride, by a diabetic patient; dehydration; acute renal failure; diabetic ketoacidosis.
File #B030650: Gastrointestinal disturbance; profuse diarrhea.
File #B034381: Ischemic colitis; diarrhea.

File #B035720: Attempted suicide with overdose of metformin hydrochloride by a diabetic patient.

File #B035974: Post-operative complications of hernia repair; pneumonia; hypoalimentation.

In summary, eight of the total of eleven cases reported as "lactic acidosis" from sources outside of the U.S. provided blood lactate values of a magnitude (≥5.0 mM/L) that would support this diagnosis.

Five (50%) of the ten evaluable cases of lactic acidosis reported from sources outside of the U.S. occurred in patients that were apparently initiated on Glucophage® (metformin hydrochloride) therapy for diabetes mellitus not in full accordance with the prescribing information in the current package insert.

Five (50%) of the evaluable cases of lactic acidosis may have had a causal relationship to the development of an illness or condition predisposing to lactic acidosis subsequent to the initiation of metformin hydrochloride therapy.

Four (36.4%) of the eleven reports of lactic acidosis originating from outside of the U.S.A. reported a fatal outcome.

Hyperglycemia

Five reports during this period listed hyperglycemia as an adverse event **[File #s: B035974; M064948; M069284; M070533; and M071444].** Each of these reports also included the diagnosis of lactic acidosis. Inadequate glycemic control, and the effects of the acute and chronic medical conditions of these patients must be considered in the etiology of these reports of hyperglycemia.

Hypoglycemia

Seven reports during this period included the diagnosis of hypoglycemia **[File #s: B033973; B034462; B035190; B035194; B035783; M055721; and M074365.]** It is unlikely that metformin therapy is associated with the etiology of hypoglycemia because clinical research to date has not demonstrated such a relationship with therapeutic doses of metformin hydrochloride in the treatment of type II diabetic patients.

Hypoglycemic Coma

File #B034381: Hypoglycemic coma, diarrhea, dehydration, leukocytosis, ischemic colitis, multisystem organ failure, elevated blood metformin level, lactic acidosis and death in a 71-year-old diabetic male. Medical history included cardiac arrhythmia and end stage renal disease. Follow-up report from Groupe Lipha, France.

Ketoacidosis

File #B029180: A 58-year-old diabetic male developed diabetic ketoacidosis, acute renal failure, bronchial obstruction, elevated blood metformin level, and lactic acidosis following a suicide attempt with an overdose of metformin hydrochloride. Medical history includes depression, epilepsy, and alcohol and tobacco use. The patient recovered. Follow-up report from Groupe Lipha, France.

Respiratory Alkalosis

File #M072851: A 72-year-old diabetic male developed metabolic acidosis with "overcompensated respiratory alkalosis," and transiently elevated serum lactate, during metformin hydrochloride therapy. Renal function was stated to have been normal and, blood metformin level was within the normal therapeutic range. The etiology of the metabolic imbalance was not reported and the patient was improving at the time of the report. Initial and follow-up reports of U.S. origin.

MUSCULOSKELETAL SYSTEM

Muscle Weakness

File #M070367: A consumer reported that her 59-year-old husband developed generalized weakness, muscle weakness, blurred vision, weight loss, confusion, memory impairment, and a kidney infection while taking metformin hydrochloride, lovastatin, diltiazem, and lisinopril / hydrochlorothiazide. Follow-up information from the physician stated that a diagnosis had not been rendered for the events; the patient continues to take metformin resulting in good glycemic control; and the patient has refused to come into the physicians office. Follow-up report of U.S. origin.

File #M074443: A male diabetic patient in his 70s developed increased liver function tests, muscle weakness, and fell while taking metformin hydrochloride. Creatine kinase was within normal limits. The patient was changed to insulin therapy and was discharged from the hospital fully recovered. Medical history includes hemolytic anemia during glyburide therapy. Initial report of U.S. origin.

Rhabdomyolysis

File #M071444: Acute renal failure, hepatitis, dehydration, hyperglycemia, rhabdomyolysis, pancreatitis, thrombocytopenia, and lactic acidosis were reported in a 58-year-old diabetic male with a history of alcohol abuse, alcoholic cardiomyopathy, congestive heart failure, and hypertension. At the time of discharge from hospital, the rhabdomyolysis had resolved as evidenced by normal serum creatine kinase. Follow-up reports of U.S. origin.

NERVOUS SYSTEM

Cerebral Hemorrhage / Cerebrovascular Accident

File #M073459: A 55-year-old diabetic male enrolled in a clinical trial developed renal insufficiency, non-anion gap metabolic acidosis, elevated liver function tests, heart failure, transient ischemic attack, and accidental injury resulting in cerebral hemorrhage. The patient recovered with unspecified sequelae, and was discharged from the hospital. The investigator attributed renal insufficiency, metabolic acidosis, and elevated liver function tests as possibly related to metformin therapy. Initial report of U.S. origin.

Choreiform Movements

File #M074365: A nurse practitioner reported that an 80-year-old female developed choreiform movements of the face, and upper and lower extremities with difficulty speaking and swallowing during treatment with metformin hydrochloride and glipizide for recently-diagnosed diabetes mellitus. Her symptoms have improved following the discontinuation of metformin hydrochloride. Additional information was not provided. Initial report of U.S. origin.

Depersonalization and Sleep Disturbance

File #M072637: Following an initial dose of metformin hydrochloride, a female patient in her 70s experienced a depersonalization reaction, syncope, somnolence, and urinary incontinence. The events did not recur when changed to glynase and troglitozone for glycemic control. Medical history included hypertension and a cerebrovascular accident. Concomitant medication included chlorpropamide which was discontinued following the event. Initial report of U.S. origin.

Encephalopathy

File #M072800: Proteinuria, increased serum creatinine, encephalopathy, and lactic acidosis was reported in a 60-year-old female. She was stated to have had unspecified co-existing medical conditions, and was described as "brain dead" at the time of the report. (Minimal information was provided). Initial report of U.S. origin.

File #M073011: A 71-year-old diabetic female developed severe metabolic acidosis, cardiac arrest, was declared brain dead, and expired following the withdrawal of mechanical ventilation. Medical therapy included metformin hydrochloride, lisinopril, glyburide, gemfibrozil, calcium, aspirin, and colestipol. There was not a history of renal dysfunction. Initial report of U.S. origin. **(Reference CTU# 71903E)**

Myoclonus

File #B035194: A 69-year-old diabetic female was admitted to hospital for spastic myoclonia and comatose condition resulting from hypoglycemia during therapy with metformin hydrochloride, glyburide, and morphine sulfate (for lumber pain). Medical history included hypertension, lumber radiculopathy, diabetic retinopathy, diabetic nephropathy, and vascular disease. Outcome was favorable with residual psychomotor retardation after the above medications were withdrawn. Initial report from Groupe Lipha, France.

Autonomic Neuropathy

File #M053275: Bacteremia, fungal infection, depression, hypothyroidism, coronary artery disease, respiratory insufficiency, autonomic neuropathy, vocal cord ulcers and laryngeal edema, (due to intubation), hypotension, and lactic acidosis were reported in a 60-year-old female with a history of insulin-dependent

diabetes for chronic renal failure. Medical history also included obesity, diabetic retinopathy, hypertension, drug allergies, leg ulcer and gangrene, and angioplasty. The neuropathy was attributed to diabetes mellitus. Follow-up report of U.S. origin. **(Reference CTU# 36235E)**

RESPIRATORY SYSTEM

Respiratory Failure

Six cases during this period included reports of respiratory failure occurring in conjunction with severe acute and chronic medical conditions, as indicated below:

File #B029179: Lactic acidosis, acute renal failure, cardiac arrests, shock, anemia, and a history of chronic respiratory failure, asthma, and cardiomyopathy.

File #B035006: Lactic acidosis, end-stage chronic renal failure, and a history of anemia and hypertension.

File #B035293: Lactic acidosis, heart failure, septic shock, anuria, vascular disease, abnormal kidney function, death, and a history of pneumonia.

File #M069502: Acute renal failure, liver function abnormality, elevated creatine kinase, and a history of cardiomyopathy. **(CTU# 67742E)**

File #M073011: Metabolic acidosis, cardiac arrest, encephalopathy, and death. **(CTU# 71903E)**

File #M073088: Lactic acidosis, heart block, cardiac arrest, and acute and chronic kidney failure.

Pneumonia

File #B035974: Hyperglycemia, pneumonia, multisystem organ failure, lactic acidosis, and death were reported in a 66-year-old male with a history of surgery for a hernia. The pneumonia occurred during the post-operative period and was not attributed to metformin therapy by the physician. A literature report from Germany received via Groupe Lipha, France.

File #M073370: Cardiorespiratory arrest, urinary tract infection pneumonia, urinary tract infection, and lactic acidosis were reported in a 58-year-old diabetic female with a history of chronic renal failure and cardiomegaly. Sputum culture was positive for Klebsiella. Additional details regarding the pneumonia were not provided. Initial report of U.S. origin.

Respiratory Disorder

File #M053275: Bacteremia, fungal infection, depression, hypothyroidism, coronary artery disease, respiratory insufficiency, autonomic neuropathy, vocal cord ulcers and laryngeal edema, hypotension, and lactic acidosis were reported in a 60-year-old female with a history of insulin-dependent diabetes for chronic renal failure. Medical history also included obesity, diabetic retinopathy, hypertension, drug allergies, leg ulcer and gangrene, and angioplasty. Additional details regarding respiratory insufficiency were not reported, apart from treatment with intubation and ventilation. Follow-up report of U.S. origin. **(Reference CTU# 36235E)**

SKIN AND APPENDAGES

Epidermal Necrolysis

File #B034888: A 61-year-old diabetic female developed toxic epidermal necrolysis during therapy with metformin hydrochloride, triamterene, hydrochlorothiazide, Marcumar® (phenprocoumon), Dublocin® (doxazosin). (Other than metformin, the indications for the other medications were not stated). The patient was admitted to a hospital and systemic steroid therapy was administered. Outcome was not reported. Medical history include hypertension, goiter, angioplasty, and stent placement for coronary artery disease, and allergy to pyrazolone. The dermatologist considered the event to be drug-induces with a possible relationship to metformin hydrochloride. Initial and follow-up reports of German origin, via Groupe Lipha, France.

Erythema Multiforme

File #B036086: A 67-year-old diabetic male developed erythema multiforme after having taking metformin hydrochloride for approximately 10 weeks. Concomitant therapy included miglitol. Both medications were discontinued and the lesions healed with prednisone therapy. (Minimal information was provided). Initial report from Canada via Groupe Lipha, France.

Urticaria

File #B032901: A 54-year-old diabetic male developed diarrhea and "giant generalized urticaria with edema of the extremities." There was no laryngeal or facial edema. Treatment included oral cortisone and antihysamine. Medical history included obesity, tobacco use, hypercholesterolism, rheumatism and was negative for allergies. Follow-up report from Groupe Lipha, France.

File #M072121: A 74-year-old diabetic female patient developed diarrhea, urticaria, confusion, and weakness which progressed to an obtunded then comatose state, thrombotic thrombocytopenic purpura, and death while taking metformin hydrochloride, ticlopidine hydrochloride, and atorvastatin. Plasma phoresis was not successful in the treatment of thrombotic thrombocytopenic purpura. Medical history included atherosclerotic cardiovascular disease, coronary artery stent placement, coronary artery bypass graft, hyperlipidemia, and colon cancer. The reporting physician considered all of the above drugs as potential suspect regarding the etilolgy of thrombotic thrombocytic purpura. Details pertaining to the urticaria were not provided. Initial report of U.S. origin.

SPECIAL SENSES

Blurred Vision

File #M070367: A consumer reported that her 59-year-old husband developed generalized weakness, muscle weakness, blurred vision, weight loss, confusion, memory impairment, and a kidney infection while taking metformin hydrochloride, lovastatin, diltiazem, and lisinopril / hydrochlorothiazide. Follow-up information from the physician stated that a diagnosis had not been rendered for the events, the patient continues to take metformin resulting in good glycemic control; and the patient has refused to come into the physicians office. Follow-up report of U.S. origin.

Ear Pain

File #M068571: A 29-year-old diabetic female developed pancytopenia, epistaxis, ear pain, pharyngitis, fever, and liver function abnormalities during metformin therapy. Concomitant medications were methotrexate, acetaminophen, oxaprozin, and Darvocet-N®. Medical history included rheumatoid arthritis and bone

marrow depression. A bone marrow biopsy was reported to have been normal. All of the medications were withdrawn and the pancytopenia subsequently resolved, but reoccurred following a re-challenge with metformin. The reporting pharmacist indicated that methotrexate, oxaprozin, acetaminophen, and metformin were considered to be suspect drugs in the etiology of pancytopenia. The etiology of the ear pain was not specified. Follow-up report of U.S. origin. **(Reference CTU# 66477E).**

UROGENITAL SYSTEM

Renal Dysfunction

(The following events are listed according to COSTART terminology). There were 13 reports of acute kidney failure during this period **[File #s: B029179; B033584; B034346; B034409; B035006; M055721; M069502 (CTU# 67742E); M071444; M072169; M072652; M073088; M071127; and B029180]**. There were 11 reports of abnormal kidney function **[File #s: M073270 (CTU# 72212E); M069284; B035293; M073452: B033973; M074671: M074636; M070241 (CTU# 68380E); M072233; M073459; and M074011]**; one case of albuminuria, **File #M072800**; one case of anuria, **File #B035293**; one case of kidney failure, **File #M070824**; one case of nephrosclerosis and kidney tubular necrosis, **File #M073784**; and one case of uremia, **File #M071098 (CTU# 70394E)**. Renal dysfunction is a condition associated with diabetes mellitus, and has not been demonstrated to have had a causal relationship with metformin hydrochloride therapy in controlled clinical investigations.

Breast Cancer

File #M071969: A pharmacist reported that a 68-year-old diabetic female was diagnosed with breast cancer after approximately 6 months of metformin hydrochloride therapy. Concomitant medications included progesterone and Estratest®. She is scheduled to undergo a lumpectomy. Initial report of U.S. origin.

CONCLUSION

The clinical information presented in this Periodic Adverse Drug Experience Report of Glucophage® (metformin hydrochloride) represents the following classifications and numbers of adverse drug experience reports received by Bristol-Myers Squibb from 1 October 1997 through 31 December 1997: *Nonserious Adverse Drug Experiences* -- 142 initial, and 11 follow-up reports; *Serious, Expected Adverse Drug Experiences* --1 initial, and no follow-up reports. Five reports were received directly via the FDA MedWatch Program., and one report was received from the FDA via the Freedom of Information Act. Forty-four initial, and 47 follow-up reports were submitted to the Food and Drug Administration during this period as 15-Day Alert Reports, representing *Serious, Unexpected Adverse Drug Experiences.* Of the total 15-Day Alert Reports submitted to the FDA during this period, a significant number of the reports (33 in total) were cases reported as lactic acidosis, (22 of U.S. origin, 11 of non-U.S. origin) which although were considered expected, were sent as 15-Day Alert Reports in accordance with a prior agreement with the FDA.

Eleven (50%) of the 22 case reports citing "lactic acidosis" of U. S. Origin reported blood lactate values of a magnitude that would support a presumptive diagnosis of the condition. Sixty-nine percent of the evaluable cases of lactic acidosis of U.S. origin appeared to represent inappropriate patient selection for metformin hydrochloride therapy of diabetes mellitus. The most frequently observed contraindication in this group of cases was pre-existing renal dysfunction. Twenty-three percent of the evaluable cases of lactic acidosis did not convey ostensible elements of inappropriate initiation of therapy with metformin hydrochloride, but each of these patients, however, developed at least one subsequent illness or condition which may have been a predisposing factor in the etiology of lactic acidosis. A total of seven (21.2%) of the 33 reports citing lactic acidosis, received from all sources worldwide, included death. The incidence of death reported with lactic acidosis was well-within the expected rate of up to 50% as is stated in the U.S. package insert for Glucophage®.

Bristol-Myers Squibb continues to conduct a variety of professional educational programs throughout the United States for the purpose of enhancing the awareness of physicians and other healthcare providers of the appropriate patient selection and management criteria for Glucophage® therapy, as currently described in the product monograph.

In conclusion, there were no unusual or new trends of safety findings identified during the review of the reports for this submission.

PERIODIC ADVERSE DRUG EXPERIENCE REPORT
Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

1 October 1997 through 31 December 1997

TABEL I
REPORTS OF LACTIC ACIDOSIS of U.S. ORIGIN WITH LACTATE ≥ 5 mmol/L IN PATIENTS OF *ALL* AGES AT TIME OF ONSET

	DEATH REPORTED	DEATH NOT REPORTED
Number (male/female)	0	9 (3/6)
Mean Age[1]	--	66.4 (62.3/68.8)
Creatinine >1.5 mg/dL[2]	--	6
Creatinine ≤1.5 mg/dL[2]	--	2
Furosemide - Yes[3]	--	1
Furosemide - No[3]	--	8
Digoxin - Yes[3]	--	2
Digoxin - No[3]	--	7
Furosemide + Digoxin - Yes[3]	--	0
CHF (Hx and/or AE)	--	2
Renal Impairment (Hx and/or AE)	--	5

[1] Age was not reported for one patient (female). The patients' ages ranged from 58-84 years of age. One patient (female, age 94) was over the age of 80.

[2] Blood creatinine level was not reported in one of the cases.

[3] Patients for whom concomitant medications were specified.

PERIODIC ADVERSE DRUG EXPERIENCE REPORT
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(metformin hydrochloride)
NDA 20-357

1 October 1997 through 31 December 1997

TABLE II
REPORTS OF LACTIC ACIDOSIS of U.S. ORIGIN WITH LACTATE ≥ 5 mmol/L IN PATIENTS ≥ 80 YEARS OF AGE AT TIME OF ONSET

	DEATH REPORTED	DEATH NOT REPORTED
Number (male/female)	0	1 (Female)
Mean Age	--	94
Creatinine >1.5 mg/dL[4]	--	yes
Creatinine ≤ 1.5 mg/dL[1]	--	--
Furosemide	--	no
Digoxin	--	yes
CHF (Hx and/or AE)	--	yes
Renal Impairment (Hx and/or AE)	--	not reported

[4] Four of the 9 cases did not report blood creatinine values.

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B029179	SHOCK	SHOCK	FOLLOW-UP	11/06/97
	HEART ARREST	CARDIORESPIRATORY ARREST		
	GASTROENTERITIS	GASTROENTERITIS		
	THROMBOCYTOPENIA	THROMBOCYTOPENIA		
	ANEMIA	ANEMIA		
	DEHYDRATION	DEHYDRATION		
	COMA	COMA		
	APNEA	RESPIRATORY FAILURE		
	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B029180	SUICIDE ATTEMPT	SUICIDE ATTEMPT	FOLLOW-UP	11/10/97
	KETOSIS	KETOACIDOSIS		
	LUNG DISORDER	BRONCHIAL OBSTRUCTION		
	ACUTE KIDNEY FAILURE	RENAL FAILURE ACUTE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B030650	NEURALGIA	SCIATICA	FOLLOW-UP	11/05/97
	DEATH	DEATH	"	11/20/97
	DIARRHEA	DIARRHEA		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B032549	MULTISYSTEM ORGAN FAILURE	MULTISYSTEM ORGAN FAILURE	FOLLOW-UP	11/20/97
	SHOCK	CARDIOVASCULAR COLLAPSE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B032901	PERIPHERAL EDEMA	PERIPHERAL EDEMA	FOLLOW-UP	11/03/97
	ANGIOEDEMA	GIANT URTICARIA		
	DIARRHEA	DIARRHEA		

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B033099	THROMBOCYTOPENIA	THROMBOCYTOPENIA	INITIAL	10/01/97
	LEUKOPENIA	LEUKOPENIA		
	ERYTHROCYTES ABNORMAL	DECREASED RED BLOOD CELLS		
	VOMITING	VOMITING		
	NAUSEA	NAUSEA		
	DIARRHEA	DIARRHEA		
B033584	ARTERIOSCLEROSIS	RENAL ARTERY STENOSIS	FOLLOW-UP	10/02/97
	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B033973	COMA	COMA	FOLLOW-UP	12/15/97
	KIDNEY FUNCTION ABNORMAL	RENAL FUNCTION ABNORMAL		
	INTENTIONAL OVERDOSE	OVERDOSE METFORMIN INTENTIONAL		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
	HYPOGLYCEMIA	HYPOGLYCEMIA		
B034262	LIVER DAMAGE	HEPATIC CYTOLYSIS	FOLLOW-UP	10/15/97
B034346	DEATH	DEATH	FOLLOW-UP	10/31/97
	ARRHYTHMIA	HEART RATE IRREGULAR		
	AORTIC STENOSIS	AORTIC VALVE DISORDER		
	ACIDOSIS	ACIDOSIS METABOLIC		
	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE		
	DIARRHEA	DIARRHEA		
B034380	HEMORRHAGE	HEMATOMA	FOLLOW-UP	11/05/97
	THROMBOCYTOPENIC PURPURA	THROMBOCYTOPENIC PURPURA		
	EYE HEMORRHAGE	CONJUNCTIVAL HEMORRHAGE		

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B034381	MULTISYSTEM ORGAN FAILURE	MULTISYSTEM ORGAN FAILURE	FOLLOW-UP	11/06/97
	DEATH	DEATH		
	INTESTINAL NECROSIS	ISCHEMIC COLITIS		
	LEUKOCYTOSIS	LEUKOCYTOSIS		
	HYPOGLYCEMIC REACTION	HYPOGLYCEMIC COMA		
	DIARRHEA	DIARRHEA		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
	DEHYDRATION	DEHYDRATION		
B034409	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE	FOLLOW-UP	10/29/97
	INTENTIONAL OVERDOSE	INTENTIONAL OVERDOSE		
B034462	CONFUSION	CONFUSION	FOLLOW-UP	11/20/97
	VOMITING	VOMITING		
	DIARRHEA	DIARRHEA		
	HYPOGLYCEMIA	HYPOGLYCEMIA		
B034502	HYPONATREMIA	HYPONATREMIA	FOLLOW-UP	12/15/97
	HYPERKALEMIA	HYPERKALEMIA		
B034722	SKIN NECROSIS	SKIN LESION	INITIAL	10/01/97
B034888	AGGRAVATION REACTION	DIABETES MELLITUS EXACERBATED	INITIAL	10/08/97
	ALLERGIC REACTION	ALLERGIC DRUG REACTION	FOLLOW-UP	11/24/97
	DIABETES MELLITUS	DIABETES MELLITUS		
	EPIDERMAL NECROLYSIS	DRUG INDUCED TOXIC EPIDERMAL NECROLYSIS		
B035006	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE	INITIAL	10/15/97
	AGGRAVATION REACTION	RENAL FAILURE EXACERBATED	FOLLOW-UP	10/29/97
	LUNG DISORDER	PNEUMOPATHY		
	APNEA	RESPIRATORY FAILURE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		

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B035021	LIVER FAILURE	HEPATIC FAILURE	INITIAL	10/17/97
	CIRRHOSIS OF LIVER	CIRRHOSIS HEPATIC		
B035190	HYPOGLYCEMIA	HYPOGLYCEMIA	INITIAL	10/27/97
	DYSARTHRIA	DYSARTHRIA		
B035191	THROMBOCYTOPENIA	THROMBOCYTOPENIA	INITIAL	10/27/97
			FOLLOW-UP	11/20/97
B035192	DEATH	DEATH	INITIAL	10/28/97
	CHOLESTATIC JAUNDICE	CHOLESTATIC HEPATITIS		
B035194	MYOCLONUS	MYOCLONUS	INITIAL	10/28/97
	COMA	METABOLIC COMA		
	HYPOGLYCEMIA	HYPOGLYCEMIA		
B035293	ACIDOSIS	ACIDOSIS METABOLIC	INITIAL	11/05/97
	ANURIA	ANURIA	FOLLOW-UP	11/20/97
	APNEA	RESPIRATORY FAILURE	"	12/02/97
	SEPTIC SHOCK	SEPTIC SHOCK	"	12/08/97
	INFECTION	RESPIRATORY INFECTION		
	DEATH	DEATH		
	VASCULAR DISORDER	ISCHEMIA OF FOOT		
	LEFT HEART FAILURE	LEFT VENTRICULAR FAILURE		
	LUNG EDEMA	ACUTE PULMONARY EDEMA		
	LUNG DISORDER	PNEUMOPATHY		
	KIDNEY FUNCTION ABNORMAL	IMPAIRED RENAL FUNCTION		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B035720	HOSTILITY	AGGRESSIVE BEHAVIOR	INITIAL	12/03/97
	SUICIDE ATTEMPT	SUICIDE ATTEMPT	FOLLOW-UP	12/15/97
	LIVER DAMAGE	HEPATIC CYTOLYSIS		
	INTENTIONAL OVERDOSE	OVERDOSE METFORMIN INTENTIONAL		
	DIARRHEA	DIARRHEA		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		

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B035783	INJURY ACCIDENTAL	HEAD TRAUMA	INITIAL	12/11/97
	SYNCOPE	LOSS OF CONSCIOUSNESS		
	HYPOGLYCEMIA	HYPOGLYCEMIA		
B035974	MULTISYSTEM ORGAN FAILURE	MULTISYSTEM ORGAN FAILURE	INITIAL	12/19/97
	DEATH	DEATH		
	SHOCK	CIRCULATORY SHOCK		
	HYPERGLYCEMIA	HYPERGLYCEMIA		
	PNEUMONIA	PNEUMONIA		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
B036086	ERYTHEMA MULTIFORME	ERYTHEMA MULTIFORME	INITIAL	12/24/97
M053275 (36235E)	SEPSIS	BACTEREMIA	FOLLOW-UP	10/16/97
	INFECTION FUNGAL	FUNGAL INFECTION		
	HYPOTENSION	HYPOTENSIVE		
	CARDIOVASCULAR DISORDER	CARDIAC DISORDER		
	HYPOTHYROIDISM	HYPOTHYROIDISM		
	NEUROPATHY	AUTONOMIC NEUROPATHY		
	DEPRESSION	DEPRESSION		
	RESPIRATORY DISORDER	RESPIRATORY INSUFFICIENCY		
	LARYNX EDEMA	LARYNX EDEMA		
	LARYNGITIS	VOCAL CORD ULCERS		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M055721	DEATH	DEATH	FOLLOW-UP	11/14/97
	AGGRAVATION REACTION	ACUTE RENAL FAILURE EXACERBATED		
	CARDIOGENIC SHOCK	CARDIOGENIC SHOCK		
	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
	HYPOGLYCEMIA	HYPOGLYCEMIA		

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M064948	HEART FAILURE	CONGESTIVE HEART FAILURE	FOLLOW-UP	10/21/97
	BRADYCARDIA	BRADYCARDIA		
	LIVER FAILURE	LIVER FAILURE		
	HYPERGLYCEMIA	HYPERGLYCEMIA		
	SINUSITIS	SINUS INFECTION		
	URINATION IMPAIRED	INABILITY TO URINATE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M068571 (66477E)	FEVER	FEVER	FOLLOW-UP	10/14/97
	LIVER FUNCTION TESTS ABNORMAL	ELEVATED LIVER FUNCTION TEST		
	PANCYTOPENIA	PANCYTOPENIA		
	PHARYNGITIS	SORE THROAT		
	EPISTAXIS	NOSEBLEED		
	EAR PAIN	EARACHE		
M069284	LIVER FUNCTION TESTS ABNORMAL	TRANSAMINASES ELEVATED	FOLLOW-UP	10/16/97
	GASTROINTESTINAL DISORDER	GASTROESOPHAGEAL REFLUX		
	DUODENITIS	DUODENITIS		
	CHOLELITHIASIS	CHOLELITHIASIS		
	SPLENOMEGALY	SPLENOMEGALY		
	HYPERGLYCEMIA	HYPERGLYCEMIA		
	KIDNEY FUNCTION ABNORMAL	ELEVATED RENAL FUNCTION TESTS		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
	DEHYDRATION	DEHYDRATION		
M069502 (67742E)	LAB TEST ABNORMAL	DECREASED SERUM PH	FOLLOW-UP	10/08/97
	LIVER FUNCTION TESTS ABNORMAL	INCREASED LIVER FUNCTION TESTS		
	CREATINE PHOSPHOKINASE INCREASED	CREATINE KINASE INCREASED		
	APNEA	RESPIRATORY FAILURE		
	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE		

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M069519	LACTIC ACIDOSIS	LACTIC ACIDOSIS	FOLLOW-UP	10/10/97
M070109	VENTRICULAR TACHYCARDIA SYNCOPE	SUSTAINED VENTRICULAR TACHYCARDIA BLACKOUTS	FOLLOW-UP	10/17/97
M070241 (68380E)	SYNCOPE ACIDOSIS KIDNEY FUNCTION ABNORMAL VOMITING	SYNCOPE ACIDOSIS METABOLIC RENAL INSUFFICIENCY VOMITING	FOLLOW-UP	10/07/97
M070367	INFECTION ASTHENIA WEIGHT LOSS MYASTHENIA CONFUSION AMNESIA AMBLYOPIA VOMITING	INFECTION KIDNEY GENERALIZED WEAKNESS WEIGHT LOSS MUSCLE WEAKNESS CONFUSION MEMORY IMPAIRMENT BLURRED VISION VOMITING	FOLLOW-UP	10/08/97
M070533	MALAISE FEVER ALLERGIC REACTION AGGRAVATION REACTION WEIGHT LOSS HYPERGLYCEMIA ARTHRALGIA LACTIC ACIDOSIS	MALAISE FEVER ALLERGIC REACTION HYPERGLYCEMIA EXACERBATED WEIGHT LOSS HYPERGLYCEMIA JOINT PAIN LACTIC ACIDOSIS	FOLLOW-UP	11/10/97
M070824	KIDNEY FAILURE CONSTIPATION	RENAL FAILURE CONSTIPATION	FOLLOW-UP	11/06/97

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M070857	DEATH	DEATH	FOLLOW-UP	11/11/97
	AGGRAVATION REACTION	HEART FAILURE EXACERBATED		
	HEART FAILURE	HEART FAILURE		
	CREATININE INCREASED	SERUM CREATININE INCREASED		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M071098 (70394E)	AGGRAVATION REACTION	PERIPHERAL VASCULAR DISEASE EXACERBATED	FOLLOW-UP	10/08/97
	PERIPHERAL VASCULAR DISORDER	PERIPHERAL VASCULAR DISEASE	"	10/16/97
	PERIPHERAL GANGRENE	GANGRENE PERIPH		
	DIGITALIS INTOXICATION	DIGITALIS INTOXICATION		
	DEHYDRATION	DEHYDRATION		
	SKIN ULCER	DECUBITUS ULCER		
	URINARY TRACT INFECTION	URINARY TRACT INFECTION		
	UREMIA	AZOTEMIA RENAL		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M071127	SEPSIS	URINARY SEPSIS	FOLLOW-UP	11/06/97
	DEHYDRATION	DEHYDRATION		
	ACIDOSIS	ACIDOSIS METABOLIC		
	ACUTE KIDNEY FAILURE	ACUTE RENAL INSUFFICIENCY		
	VOMITING	VOMITING		
M071132	CHOLESTATIC JAUNDICE	CHOLESTATIC JAUNDICE	FOLLOW-UP	10/17/97
M071270	HEART ARREST	CARDIAC ARREST	FOLLOW-UP	10/15/97
	BRADYCARDIA	DECREASED HEART RATE		
M071444	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE	FOLLOW-UP	10/23/97
	PANCREATITIS	PANCREATITIS	"	11/10/97
	HEPATITIS	HEPATITIS		
	THROMBOCYTOPENIA	THROMBOCYTOPENIA		
	HYPERGLYCEMIA	HYPERGLYCEMIA		
	DEHYDRATION	DEHYDRATION		
	RHABDOMYOLYSIS	RHABDOMYOLYSIS		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		

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M071551	ALLERGIC REACTION SKIN ULCER	ALLERGIC RASH SKIN ULCERATION	FOLLOW-UP	10/22/97
M071833	ASTHENIA ABDOMINAL PAIN DIZZINESS	FATIGUE ABDOMINAL PAIN DIZZINESS LIGHTHEADEDNESS	INITIAL	10/02/97
M071957 (70554E)	HEART FAILURE CORONARY ARTERY DISORDER	CONGESTIVE HEART FAILURE CORONARY ARTERY DISEASE	INITIAL	10/02/97
M071958	LACTIC ACIDOSIS	LACTIC ACIDOSIS	INITIAL	10/07/97
M071969	BREAST CARCINOMA	BREAST CANCER	INITIAL	10/08/97
M072121	MULTISYSTEM ORGAN FAILURE DEATH ASTHENIA THROMBOTIC THROMBOCYTOPENIC PURPURA COMA URTICARIA DIARRHEA	MULTISYSTEM ORGAN FAILURE DEATH WEAKNESS THROMBOTIC THROMBOCYTOPENIC PURPURA COMA HIVES DIARRHEA	INITIAL	10/09/97
M072169	DEATH DEHYDRATION STUPOR ACUTE KIDNEY FAILURE LACTIC ACIDOSIS	DEATH DEHYDRATION UNRESPONSIVE ACUTE RENAL FAILURE LACTIC ACIDOSIS	INITIAL	10/10/97
M072233	LIVER FUNCTION TESTS ABNORMAL KIDNEY FUNCTION ABNORMAL LACTIC ACIDOSIS	LIVER FUNCTION TESTS ABNORMAL RENAL INSUFFICIENCY LACTIC ACIDOSIS	INITIAL	10/15/97

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M072321	MYOCARDIAL INFARCT	ACUTE MYOCARDIAL INFARCTION	INITIAL	10/14/97
	ACIDOSIS	ACIDOSIS METABOLIC		
M072441	INJURY ACCIDENTAL	FALL	INITIAL	10/17/97
	ASTHENIA	SEVERE WEAKNESS		
	WEIGHT LOSS	WEIGHT LOSS		
	DIZZINESS	DIZZINESS		
M072637	SYNCOPE	FAINTED	INITIAL	10/22/97
	SLEEP DISORDER	SLEEP PROLONGED		
	DEPERSONALIZATION	CRAZY		
	URINARY INCONTINENCE	INCONTINENCE URINARY		
M072652	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE	INITIAL	10/22/97
M072800	CREATININE INCREASED	INCREASED SERUM CREATININE	INITIAL	10/29/97
	ENCEPHALOPATHY	SEVERE BRAIN DAMAGE		
	ALBUMINURIA	PROTEINURIA		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M072835	ACIDOSIS	ACIDOSIS METABOLIC	INITIAL	10/30/97
	DEATH	DEATH	FOLLOW-UP	11/20/97
	SEPSIS	ESCHERICHIA COLI SEPSIS	"	11/25/97
	LIVER FAILURE	HEPATIC FAILURE		
M072851	ACIDOSIS	ACIDOSIS METABOLIC	INITIAL	11/03/97
	RESPIRATORY ALKALOSIS	RESPIRATORY ALKALOSIS	FOLLOW-UP	12/17/97
	LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL		
M073011 (71903E)	DEATH	DEATH	INITIAL	10/28/97
	HEART ARREST	CARDIAC ARREST		
	ACIDOSIS	ACIDOSIS METABOLIC		
	ENCEPHALOPATHY	SEVERE BRAIN DAMAGE		
	APNEA	RESPIRATORY FAILURE		

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M073088	ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE	INITIAL	11/03/97
	HEART BLOCK	HEART BLOCK	FOLLOW-UP	12/17/97
	HEART ARREST	CARDIAC ARREST		
	APNEA	RESPIRATORY FAILURE		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M073270 (72212E)	AGGRAVATION REACTION	CHRONIC RENAL INSUFFICIENCY EXACERBATED	INITIAL	11/04/97
	KIDNEY FUNCTION ABNORMAL	CHRONIC RENAL INSUFFICIENCY		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M073290	DEATH	DEATH	INITIAL	11/10/97
	MYOCARDIAL INFARCT	MYOCARDIAL INFARCTION		
	HEART ARREST	CARDIAC ARREST		
	LUNG EDEMA	PULMONARY EDEMA		
M073370	HEART ARREST	CARDIORESPIRATORY ARREST	INITIAL	11/12/97
	PNEUMONIA	PNEUMONIA		
	URINARY TRACT INFECTION	URINARY TRACT INFECTION		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M073423 (72367E)	MULTISYSTEM ORGAN FAILURE	MULTISYSTEM ORGAN FAILURE	INITIAL	11/07/97
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
*M073452 [FOI]	KIDNEY FUNCTION ABNORMAL	RENAL DYSFUNCTION	INITIAL	11/06/97
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M073459	INJURY ACCIDENTAL	FALL	INITIAL	11/21/97
	HEART FAILURE	CONGESTIVE HEART FAILURE		
	LIVER FUNCTION TESTS ABNORMAL	ELEVATED LIVER FUNCTION TESTS		
	ACIDOSIS	NONANION GAP METABOLIC ACIDOSIS		
	CEREBROVASCULAR ACCIDENT	STROKE		
	CEREBRAL HEMORRHAGE	INTRACEREBRAL BLEEDING		
	KIDNEY FUNCTION ABNORMAL	RENAL INSUFFICIENCY		

* = FOI NUMBERS 1726085 AND 1751721

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M073460 (72531E)	ANOREXIA	POOR ORAL INTAKE	INITIAL	11/10/97
	DEHYDRATION	PLASMA OSMOLALITY INCREASED		
	ACIDOSIS	ACIDOSIS METABOLIC		
	STUPOR	UNRESPONSIVE		
M073739	HEART FAILURE	ACUTE CONGESTIVE HEART FAILURE	INITIAL	11/21/97
M073784	ACIDOSIS	ACIDOSIS METABOLIC	INITIAL	11/25/97
	NEPHROSCLEROSIS	KIMMELSTIEL WILSON SYNDROME		
	KIDNEY TUBULAR NECROSIS	ACUTE TUBULAR NECROSIS		
M073865	DEATH	DEATH	INITIAL	12/01/97
	MYOCARDIAL INFARCT	MYOCARDIAL INFARCTION		
M074011	DEHYDRATION	ACUTE DEHYDRATION	INITIAL	12/11/97
	KIDNEY FUNCTION ABNORMAL	RENAL INSUFFICIENCY		
	LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL		
M074053	MEDICATION ERROR	MEDICATION ERROR	INITIAL	12/11/97
	ASTHENIA	WEAKNESS		
	MYALGIA	MUSCLE PAIN		
	ACCIDENTAL OVERDOSE	ACCIDENTAL OVERDOSE		
M074365	CHOREOATHETOSIS	CHOREIFORM MOVEMENTS	INITIAL	12/17/97
	HYPOGLYCEMIA	HYPOGLYCEMIA		
M074443	INJURY ACCIDENTAL	FALL	INITIAL	12/18/97
	LIVER FUNCTION TESTS ABNORMAL	INCREASED LIVER FUNCTION TESTS		
	MYASTHENIA	MUSCLE WEAKNESS		

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M074470	SEPSIS	SEPSIS	INITIAL	12/18/97
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M074602	FLU SYNDROME	FLU LIKE SYMPTOMS	INITIAL	12/23/97
	FLATULENCE	BLOATING GAS		
	DEHYDRATION	DEHYDRATION		
M074613	MALAISE	MALAISE	INITIAL	12/23/97
	HERNIA	HERNIA		
	CHILLS	COLD		
	ASTHENIA	WEAKNESS		
	BRADYCARDIA	BRADYCARDIA		
	PEPTIC ULCER	ULCER		
	HYPOCHROMIC ANEMIA	DECREASED HEMOGLOBIN		
	STUPOR	UNRESPONSIVENESS		
M074636	AGGRAVATION REACTION	CONGESTIVE HEART FAILURE EXACERBATED	INITIAL	12/23/97
	HEART FAILURE	CONGESTIVE HEART FAILURE		
	ANGINA PECTORIS	ANGINA		
	LIVER FUNCTION TESTS ABNORMAL	INCREASED LIVER FUNCTION TESTS		
	KIDNEY FUNCTION ABNORMAL	RENAL IMPAIRMENT		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		
M074645	LACTIC ACIDOSIS	LACTIC ACIDOSIS	INITIAL	12/23/97
M074671	HYPOTENSION	SEVERE HYPOTENSION	INITIAL	12/24/97
	WBC ABNORMAL	INCREASED WBC		
	KIDNEY FUNCTION ABNORMAL	RENAL FUNCTION ABNORMAL		
	LACTIC ACIDOSIS	LACTIC ACIDOSIS		

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Index of 15-Day Increased Frequency Alert Reports

Submitted October 1, 1997 to December 31, 1997

No increased frequency alert reports were submitted during this reporting period.

Note: The requirement for the submission of increased frequency reports as expedited reports for human drug and licensed biological products was revoked on July 25, 1997.

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BODY SYSTEM/ EXPANDED COSTART TERM	REPORTED TERM	MFR(CTU) FILE NO.	NO. OF FILES PER EXPANDED COSTART TERM
BODY AS A WHOLE			
ABDOMINAL PAIN	ABDOMINAL PAIN	M071833	1
ACCIDENTAL OVERDOSE	ACCIDENTAL OVERDOSE	M074053	1
AGGRAVATION REACTION	ACUTE RENAL FAILURE EXACERBATED	M055721	8
	CHRONIC RENAL INSUFFICIENCY EXACERBATED	M073270 (72212E)	
	CONGESTIVE HEART FAILURE EXACERBATED	M074636	
	DIABETES MELLITUS EXACERBATED	B034888	
	HEART FAILURE EXACERBATED	M070857	
	HYPERGLYCEMIA EXACERBATED	M070533	
	PERIPHERAL VASCULAR DISEASE EXACERBATED	M071098 (70394E)	
	RENAL FAILURE EXACERBATED	B035006	
ALLERGIC REACTION	ALLERGIC DRUG REACTION	B034888	3
	ALLERGIC RASH	M071551	
	ALLERGIC REACTION	M070533	
ASTHENIA	FATIGUE	M071833	6
	GENERALIZED WEAKNESS	M070367	
	SEVERE WEAKNESS	M072441	
	WEAKNESS	M072121	
		M074053	
		M074613	
CHILLS	COLD	"	1
DEATH	DEATH	B030650	14
		B034346	
		B034381	
		B035192	
		B035293	
		B035974	
		M055721	
		M070857	
		M072121	
		M072169	
		M072835	
		M073011 (71903E)	
		M073290	
		M073865	
FEVER	FEVER	M068571 (66477E)	2
		M070533	

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FLU SYNDROME	FLU LIKE SYMPTOMS	M074602	1
HERNIA	HERNIA	M074613	1
INFECTION	INFECTION KIDNEY	M070367	2
	RESPIRATORY INFECTION	B035293	
INFECTION FUNGAL	FUNGAL INFECTION	M053275 (36235E)	1
INJURY ACCIDENTAL	FALL	M072441	4
		M073459	
		M074443	
	HEAD TRAUMA	B035783	
INTENTIONAL OVERDOSE	INTENTIONAL OVERDOSE	B034409	3
	OVERDOSE METFORMIN INTENTIONAL	B033973	
		B035720	
LAB TEST ABNORMAL	DECREASED SERUM PH	M069502 (67742E)	3
	INCREASED LACTIC ACID LEVEL	M072851	
		M074011	
MALAISE	MALAISE	M070533	2
		M074613	
MEDICATION ERROR	MEDICATION ERROR	M074053	1
MULTISYSTEM ORGAN FAILURE	MULTISYSTEM ORGAN FAILURE	B032549	5
		B034381	
		B035974	
		M072121	
		M073423 (72367E)	
SEPSIS	BACTEREMIA	M053275 (36235E)	4
	ESCHERICHIA COLI SEPSIS	M072835	
	SEPSIS	M074470	
	URINARY SEPSIS	M071127	
SEPTIC SHOCK	SEPTIC SHOCK	B035293	1
SUICIDE ATTEMPT	SUICIDE ATTEMPT	B029180	2
		B035720	

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CARDIOVASCULAR SYSTEM			
ANGINA PECTORIS	ANGINA	M074636	1
AORTIC STENOSIS	AORTIC VALVE DISORDER	B034346	1
ARRHYTHMIA	HEART RATE IRREGULAR	"	1
ARTERIOSCLEROSIS	RENAL ARTERY STENOSIS	B033584	1
BRADYCARDIA	BRADYCARDIA	M064948	3
		M074613	
	DECREASED HEART RATE	M071270	
CARDIOGENIC SHOCK	CARDIOGENIC SHOCK	M055721	1
CARDIOVASCULAR DISORDER	CARDIAC DISORDER	M053275 (36235E)	1
CORONARY ARTERY DISORDER	CORONARY ARTERY DISEASE	M071957 (70554E)	1
DIGITALIS INTOXICATION	DIGITALIS INTOXICATION	M071098 (70394E)	1
HEART ARREST	CARDIAC ARREST	M071270	6
		M073011 (71903E)	
		M073088	
		M073290	
	CARDIORESPIRATORY ARREST	B029179	
		M073370	
HEART BLOCK	HEART BLOCK	M073088	1
HEART FAILURE	ACUTE CONGESTIVE HEART FAILURE	M073739	6
	CONGESTIVE HEART FAILURE	M064948	
		M071957 (70554E)	
		M073459	
		M074636	
	HEART FAILURE	M070857	
HEMORRHAGE	HEMATOMA	B034380	1
HYPOTENSION	HYPOTENSIVE	M053275 (36235E)	2
	SEVERE HYPOTENSION	M074671	
LEFT HEART FAILURE	LEFT VENTRICULAR FAILURE	B035293	1
MYOCARDIAL INFARCT	ACUTE MYOCARDIAL INFARCTION	M072321	3
	MYOCARDIAL INFARCTION	M073290	
		M073865	
PERIPHERAL GANGRENE	GANGRENE PERIPH	M071098 (70394E)	1
PERIPHERAL VASCULAR DISORDER	PERIPHERAL VASCULAR DISEASE	"	1
SHOCK	CARDIOVASCULAR COLLAPSE	B032549	3
	CIRCULATORY SHOCK	B035974	
	SHOCK	B029179	

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SYNCOPE	BLACKOUTS	M070109	4
	FAINTED	M072637	
	LOSS OF CONSCIOUSNESS	B035783	
	SYNCOPE	M070241 (68380E)	
VASCULAR DISORDER	ISCHEMIA OF FOOT	B035293	1
VENTRICULAR TACHYCARDIA	SUSTAINED VENTRICULAR TACHYCARDIA	M070109	1
DIGESTIVE SYSTEM			
ANOREXIA	POOR ORAL INTAKE	M073460 (72531E)	1
CHOLELITHIASIS	CHOLELITHIASIS	M069284	1
CHOLESTATIC JAUNDICE	CHOLESTATIC HEPATITIS	B035192	2
	CHOLESTATIC JAUNDICE	M071132	
CIRRHOSIS OF LIVER	CIRRHOSIS HEPATIC	B035021	1
CONSTIPATION	CONSTIPATION	M070824	1
DIARRHEA	DIARRHEA	B030650	8
		B032901	
		B033099	
		B034346	
		B034381	
		B034462	
		B035720	
		M072121	
DUODENITIS	DUODENITIS	M069284	1
FLATULENCE	BLOATING GAS	M074602	1
GASTROENTERITIS	GASTROENTERITIS	B029179	1
GASTROINTESTINAL DISORDER	GASTROESOPHAGEAL REFLUX	M069284	1
HEPATITIS	HEPATITIS	M071444	1
INTESTINAL NECROSIS	ISCHEMIC COLITIS	B034381	1
LIVER DAMAGE	HEPATIC CYTOLYSIS	B034262	2
		B035720	
LIVER FAILURE	HEPATIC FAILURE	B035021	3
		M072835	
	LIVER FAILURE	M064948	
LIVER FUNCTION TESTS ABNORMAL	ELEVATED LIVER FUNCTION TEST	M068571 (66477E)	7
	ELEVATED LIVER FUNCTION TESTS	M073459	
	INCREASED LIVER FUNCTION TESTS	M069502 (67742E)	
		M074443	
		M074636	

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BODY SYSTEM/ EXPANDED COSTART TERM	REPORTED TERM	MFR(CTU) FILE NO.	NO. OF FILES PER EXPANDED COSTART TERM
	LIVER FUNCTION TESTS ABNORMAL	M072233	
	TRANSAMINASES ELEVATED	M069284	
NAUSEA	NAUSEA	B033099	1
PANCREATITIS	PANCREATITIS	M071444	1
PEPTIC ULCER	ULCER	M074613	1
VOMITING	VOMITING	B033099	5
		B034462	
		M070241 (68380E)	
		M070367	
		M071127	
ENDOCRINE SYSTEM			
HYPOTHYROIDISM	HYPOTHYROIDISM	M053275 (36235E)	1
HEMIC AND LYMPHATIC SYSTEM			
ANEMIA	ANEMIA	B029179	1
ERYTHROCYTES ABNORMAL	DECREASED RED BLOOD CELLS	B033099	1
HYPOCHROMIC ANEMIA	DECREASED HEMOGLOBIN	M074613	1
LEUKOCYTOSIS	LEUKOCYTOSIS	B034381	1
LEUKOPENIA	LEUKOPENIA	B033099	1
PANCYTOPENIA	PANCYTOPENIA	M068571 (66477E)	1
SPLENOMEGALY	SPLENOMEGALY	M069284	1
THROMBOCYTOPENIA	THROMBOCYTOPENIA	B029179	4
		B033099	
		B035191	
		M071444	
THROMBOCYTOPENIC PURPURA	THROMBOCYTOPENIC PURPURA	B034380	1
THROMBOTIC THROMBOCYTOPENIC PURPURA	THROMBOTIC THROMBOCYTOPENIC PURPURA	M072121	1
WBC ABNORMAL	INCREASED WBC	M074671	1

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METABOLIC AND NUTRITIONAL DISORDERS			
ACIDOSIS	ACIDOSIS METABOLIC	B034346	11
		B035293	
		M070241 (68380E)	
		M071127	
		M072321	
		M072835	
		M072851	
		M073011 (71903E)	
		M073460 (72531E)	
		M073784	
	NONANION GAP METABOLIC ACIDOSIS	M073459	
CREATINE PHOSPHOKINASE INCREASED	CREATINE KINASE INCREASED	M069502 (67742E)	1
CREATININE INCREASED	INCREASED SERUM CREATININE	M072800	2
	SERUM CREATININE INCREASED	M070857	
DEHYDRATION	ACUTE DEHYDRATION	M074011	10
	DEHYDRATION	B029179	
		B034381	
		M069284	
		M071098 (70394E)	
		M071127	
		M071444	
		M072169	
		M074602	
	PLASMA OSMOLALITY INCREASED	M073460 (72531E)	
DIABETES MELLITUS	DIABETES MELLITUS	B034888	1
HYPERGLYCEMIA	HYPERGLYCEMIA	B035974	5
		M064948	
		M069284	
		M070533	
		M071444	
HYPERKALEMIA	HYPERKALEMIA	B034502	1
HYPOGLYCEMIA	HYPOGLYCEMIA	B033973	7
		B034462	
		B035190	
		B035194	
		B035783	

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		M055721	
		M074365	
HYPOGLYCEMIC REACTION	HYPOGLYCEMIC COMA	B034381	1
HYPONATREMIA	HYPONATREMIA	B034502	1
KETOSIS	KETOACIDOSIS	B029180	1
LACTIC ACIDOSIS	LACTIC ACIDOSIS	B029179	33
		B029180	
		B030650	
		B032549	
		B033584	
		B033973	
		B034381	
		B035006	
		B035293	
		B035720	
		B035974	
		M053275 (36235E)	
		M055721	
		M064948	
		M069284	
		M069519	
		M070533	
		M070857	
		M071098 (70394E)	
		M071444	
		M071958	
		M072169	
		M072233	
		M072800	
		M073088	
		M073270 (72212E)	
		M073370	
		M073423 (72367E)	
		* M073452 [FOI]	
		M074470	
		M074636	
		M074645	
		M074671	

* = FOI NUMBERS 1726085 AND 1751721

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PERIPHERAL EDEMA	PERIPHERAL EDEMA	B032901	1
RESPIRATORY ALKALOSIS	RESPIRATORY ALKALOSIS	M072851	1
WEIGHT LOSS	WEIGHT LOSS	M070367	3
		M070533	
		M072441	
MUSCULOSKELETAL SYSTEM			
ARTHRALGIA	JOINT PAIN	M070533	1
MYALGIA	MUSCLE PAIN	M074053	1
MYASTHENIA	MUSCLE WEAKNESS	M070367	2
		M074443	
RHABDOMYOLYSIS	RHABDOMYOLYSIS	M071444	1
NERVOUS SYSTEM			
AMNESIA	MEMORY IMPAIRMENT	M070367	1
CEREBRAL HEMORRHAGE	INTRACEREBRAL BLEEDING	M073459	1
CEREBROVASCULAR ACCIDENT	STROKE	"	1
CHOREOATHETOSIS	CHOREIFORM MOVEMENTS	M074365	1
COMA	COMA	B029179	4
		B033973	
		M072121	
	METABOLIC COMA	B035194	
CONFUSION	CONFUSION	B034462	2
		M070367	
DEPERSONALIZATION	CRAZY	M072637	1
DEPRESSION	DEPRESSION	M053275 (36235E)	1
DIZZINESS	DIZZINESS	M072441	2
	DIZZINESS LIGHTHEADEDNESS	M071833	
DYSARTHRIA	DYSARTHRIA	B035190	1
ENCEPHALOPATHY	SEVERE BRAIN DAMAGE	M072800	2
		M073011 (71903E)	
HOSTILITY	AGGRESSIVE BEHAVIOR	B035720	1
MYOCLONUS	MYOCLONUS	B035194	1
NEURALGIA	SCIATICA	B030650	1
NEUROPATHY	AUTONOMIC NEUROPATHY	M053275 (36235E)	1
SLEEP DISORDER	SLEEP PROLONGED	M072637	1
STUPOR	UNRESPONSIVE	M072169	3
		M073460 (72531E)	

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	UNRESPONSIVENESS	M074613	
RESPIRATORY SYSTEM			
APNEA	RESPIRATORY FAILURE	B029179	6
		B035006	
		B035293	
		M069502 (67742E)	
		M073011 (71903E)	
		M073088	
EPISTAXIS	NOSEBLEED	M068571 (66477E)	1
LARYNGITIS	VOCAL CORD ULCERS	M053275 (36235E)	1
LARYNX EDEMA	LARYNX EDEMA	"	1
LUNG DISORDER	BRONCHIAL OBSTRUCTION	B029180	3
	PNEUMOPATHY	B035006	
		B035293	
LUNG EDEMA	ACUTE PULMONARY EDEMA	"	2
	PULMONARY EDEMA	M073290	
PHARYNGITIS	SORE THROAT	M068571 (66477E)	1
PNEUMONIA	PNEUMONIA	B035974	2
		M073370	
RESPIRATORY DISORDER	RESPIRATORY INSUFFICIENCY	M053275 (36235E)	1
SINUSITIS	SINUS INFECTION	M064948	1
SKIN & APPENDAGES			
ANGIOEDEMA	GIANT URTICARIA	B032901	1
EPIDERMAL NECROLYSIS	DRUG INDUCED TOXIC EPIDERMAL NECROLYSIS	B034888	1
ERYTHEMA MULTIFORME	ERYTHEMA MULTIFORME	B036086	1
SKIN NECROSIS	SKIN LESION	B034722	1
SKIN ULCER	DECUBITUS ULCER	M071098 (70394E)	2
	SKIN ULCERATION	M071551	
URTICARIA	HIVES	M072121	1

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SPECIAL SENSES			
AMBLYOPIA	BLURRED VISION	M070367	1
EAR PAIN	EARACHE	M068571 (66477E)	1
EYE HEMORRHAGE	CONJUNCTIVAL HEMORRHAGE	B034380	1
UROGENITAL SYSTEM			
ACUTE KIDNEY FAILURE	ACUTE RENAL FAILURE	B029179	13
		B033584	
		B034346	
		B034409	
		B035006	
		M055721	
		M069502 (67742E)	
		M071444	
		M072169	
		M072652	
		M073088	
	ACUTE RENAL INSUFFICIENCY	M071127	
	RENAL FAILURE ACUTE	B029180	
ALBUMINURIA	PROTEINURIA	M072800	1
ANURIA	ANURIA	B035293	1
BREAST CARCINOMA	BREAST CANCER	M071969	1
KIDNEY FAILURE	RENAL FAILURE	M070824	1
KIDNEY FUNCTION ABNORMAL	CHRONIC RENAL INSUFFICIENCY	M073270 (72212E)	11
	ELEVATED RENAL FUNCTION TESTS	M069284	
	IMPAIRED RENAL FUNCTION	B035293	
	RENAL DYSFUNCTION	*M073452 [FOI]	
	RENAL FUNCTION ABNORMAL	B033973	
		M074671	
	RENAL IMPAIRMENT	M074636	
	RENAL INSUFFICIENCY	M070241 (68380E)	
		M072233	
		M073459	
		M074011	
KIDNEY TUBULAR NECROSIS	ACUTE TUBULAR NECROSIS	M073784	1
NEPHROSCLEROSIS	KIMMELSTIEL WILSON SYNDROME	"	1
UREMIA	AZOTEMIA RENAL	M071098 (70394E)	1

* = FOI NUMBERS 1726085 AND 1751721

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URINARY INCONTINENCE	INCONTINENCE URINARY	M072637	1
URINARY TRACT INFECTION	URINARY TRACT INFECTION	M071098 (70394E) M073370	2
URINATION IMPAIRED	INABILITY TO URINATE	M064948	1

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BODY AS A WHOLE			
ACCIDENTAL OVERDOSE	ACCIDENTAL OVERDOSE	M074209	1
LAB TEST ABNORMAL	INCREASED LACTIC ACID LEVEL	"	1

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BODY SYSTEM/ EXPANDED COSTART TERM	REPORTED TERM	MFR(CTU) FILE NO.	NO. OF FILES PER EXPANDED COSTART TERM
BODY AS A WHOLE			
ABDOMINAL PAIN	ABDOMINAL GAS PAIN	M074231	9
	ABDOMINAL PAIN	M074446	
	GAS PAIN	M075059	
	PAIN RIB ABDOMEN	M071962	
		M074219	
	STOMACH CRAMPS	M070966	
		M072853	
		M073480	
	STOMACH PAIN	M073490	
AGGRAVATION REACTION	HYPERGLYCEMIA EXACERBATED	M072323	7
		M073366	
		M074532	
		M074596	
		M075041	
	RASH EXACERBATED	M074212	
	RENAL DYSFUNCTION AGGRAVATED	M075246	
ALLERGIC REACTION	ALLERGIC RASH	M074008	2
	ALLERGIC REACTION	M073582	
ASTHENIA	EXTREME FATIGUE	M074514	6
		M074585	
	FATIGUE	M072013	
	WEAKNESS	M072513	
	WEAKNESS FATIGUE	M072037	
		M072844	
BACK PAIN	LOW BACK PAIN	M072474	5
	PAIN BACK	M073087	
		M073480	
		M074219	
	PAIN IN BACK	M068554	
BODY ODOR	ODOR SKIN	M074603	2
	SKIN ODOR ABNORMAL	M072754	
CHEST PAIN	CHEST PAIN	M072101	3
		M072394	
	EXERTIONAL CHEST PAIN	M073525	
CHILLS	CHILLS	M072513	1

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CYST	LEFT RENAL CYST	M065521	1
DRUG INTERACTION	DRUG INTERACTION ERYTHROMYCIN	M072703	2
	MULTIPLE DRUG INTERACTION	M073990	
DRUG LEVEL INCREASED	INCREASED ALCOHOL BLOOD LEVEL	M074480	1
FACE EDEMA	EDEMA FACE EYES	M070925	1
HEADACHE	HEAD PRESSURE	M073404	3
	HEADACHE	M071254	
		M073994	
LAB TEST ABNORMAL	FLUCTUATING GLUCOSE LEVELS	M072780	9
		M074256	
	INCREASED LACTIC ACID LEVEL	M068637	
		M072037	
		M072832	
		M073399	
		M073400	
		M073401	
	VITAMIN B12 INCREASED	M072322	
LACK OF DRUG EFFECT	LACK OF EFFECT	M073255	3
		M073519	
		M074644	
MALAISE	FEELING BAD	M072780	4
	FEELING SICK	M070042	
	ILL FEELING	M073829	
	SICK FEELING	M074117	
PAIN	CRAMPING	M073072	7
	CRAMPS	M072386	
		M072894	
	DISCOMFORT	M070042	
	LEG PAIN	M073480	
	MUSCULOSKELETAL PAIN	M072394	
	SEVERE CRAMPS	M074322	
UNEXPECTED BENEFIT	UNEXPECTED BENEFIT	M074512	1

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CARDIOVASCULAR SYSTEM			
HEMORRHAGE	BLEEDING PENIS	M074311	1
HYPERTENSION	ELEVATED BLOOD PRESSURE	M072116	2
	HYPERTENSION	M073993	
PALLOR	LOOKS GRAY	M072905	1
PALPITATION	HEART PALPITATIONS	M073298	2
	IRREGULAR HEARTBEAT	M074773	
TACHYCARDIA	INCREASED HEART RATE	M073947	3
	RAPID PULSE	M072116	
	TACHYCARDIA	M074560	
DIGESTIVE SYSTEM			
ABNORMAL STOOLS	SOFT STOOLS	M073159	1
ANOREXIA	DECREASED APPETITE	M073480	4
	LOSS OF APPETITE	M073092	
		M073526	
		M073571	
CONSTIPATION	CONSTIPATION	M073682	1
DIARRHEA	DIARRHEA	M070042	29
		M070759	
		M071563	
		M072336	
		M072394	
		M072513	
		M072698	
		M072755	
		M072894	
		M073028	
		M073072	
		M073080	
		M073372	
		M073480	
		M073490	
		M073549	
		M073571	
		M073924	

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		M073947	
		M073951	
		M074218	
		M074311	
		M074336	
		M074446	
		M074464	
		M074668	
		M074688	
		M075046	
	SEVERE DIARRHEA	M073983	
DYSPEPSIA	GASTROINTESTINAL UPSET	M072473	13
	HEARTBURN	M072116	
		M072336	
		M074560	
	STOMACH DISTRESS	M074323	
	STOMACH PROBLEMS	M073515	
	STOMACH UPSET	M072737	
		M073571	
	STOMACHACHE	M072894	
		M074464	
	UPSET STOMACH	M070042	
		M071924	
		M074336	
ERUCTATION	BELCHING	M071254	1
FLATULENCE	BLOATING	M073159	11
		M073238	
		M073372	
	FLATULENCE	M070966	
		M072313	
		M073188	
		M075031	
	GAS	M071254	
		M072386	
		M072755	
		M075046	
GASTROINTESTINAL DISORDER	GASTROINTESTINAL DISTURBANCE	M075246	1

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GUM HYPERPLASIA	SWOLLEN GUMS	M070925	1
HEPATITIS	LIVER INFLAMMATION	M073863	1
INCREASED APPETITE	APPETITE INCREASED	M074448	2
	HUNGER	M072451	
LIVER FUNCTION TESTS ABNORMAL	ELEVATED LIVER FUNCTION TESTS	M072363	6
		M072654	
	INCREASED LIVER ENZYMES	M073692	
	INCREASED LIVER FUNCTION TESTS	M072103	
		M073863	
		M074869	
MELENA	BLOOD IN STOOL	M071563	2
	BLOODY STOOL	M073072	
NAUSEA	NAUSEA	M072513	8
		M072623	
		M072737	
		M073298	
		M074001	
		M074446	
		M074464	
	SICK TO STOMACH	M072068	
STOMATITIS	BURNING MOUTH	M074533	1
VOMITING	VOMITING	M072737	1
HEMIC AND LYMPHATIC SYSTEM			
BASOPHILIA	BASOPHILIA	M073692	1
ERYTHROCYTES ABNORMAL	DECREASED RED BLOOD CELLS	M074283	1
LEUKOCYTOSIS	LEUKOCYTOSIS	M074469	1
LEUKOPENIA	DECREASED WBC	M074283	2
	LEUKOPENIA	M074523	
LYMPHOCYTOSIS	LYMPHOCYTOSIS	M074469	1
SEDIMENTATION RATE INCREASED	SEDIMENTATION RATE INCREASED	M072037	1
THROMBOCYTOPENIA	DECREASED PLATELETS	M074283	2
	THROMBOCYTOPENIA	M074523	
WBC ABNORMAL	INCREASED WBC	M073692	1

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METABOLIC AND NUTRITIONAL DISORDERS			
ACIDOSIS	DECREASED BICARBONATE	M068637	1
BILIRUBINEMIA	BILIRUBIN INCREASED	M072363	1
CREATINE PHOSPHOKINASE INCREASED	RISING CPK	M068554	1
DEHYDRATION	DEHYDRATION	M073924	1
EDEMA	EDEMA ARM	M070925	3
	FLUID RETENTION	M073962	
	SWELLING	M072905	
HYPERGLYCEMIA	HYPERGLYCEMIA	M072323	7
		M073366	
		M074532	
		M074596	
		M075041	
	INCREASED GLUCOSE	M073692	
	INCREASED SERUM GLUCOSE	M073990	
HYPOGLYCEMIA	HYPOGLYCEMIA	M072697	5
		M072703	
		M073213	
		M074208	
		M074512	
HYPONATREMIA	DECREASED SODIUM	M073692	1
LACTIC DEHYDROGENASE INCREASED	LDH ELEVATED	M072363	2
	LDH INCREASED	M074497	
LIVER FATTY DEPOSIT	FATTY LIVER	M072103	1
PERIPHERAL EDEMA	SWELLING FEET	M074286	1
PORPHYRIA	PORPHYRIA	M074534	1
WEIGHT GAIN	WEIGHT GAIN	M074448	1
WEIGHT LOSS	WEIGHT LOSS	M072844	2
		M073404	

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MUSCULOSKELETAL SYSTEM			
ARTHRALGIA	JOINT PAIN	M074218	1
BONE PAIN	BONE PAIN	M074658	1
LEG CRAMPS	CRAMPS LEGS	M074536	1
MYALGIA	LEG MUSCLE PAIN	M074478	8
	MUSCLE ACHES	M072832	
		M073399	
		M073400	
		M073401	
		M074231	
		M074696	
	MUSCLE PAIN	M074348	
MYASTHENIA	MUSCLE WEAKNESS	M072451	1
NERVOUS SYSTEM			
ANXIETY	ANXIETY	M074560	1
CIRCUMORAL PARESTHESIA	NUMBNESS TINGLING AROUND MOUTH	M073363	1
CONFUSION	DISORIENTED	M074644	1
DEPRESSION	DEPRESSION	M072116	1
DIZZINESS	DIZZINESS	M073298	6
		M074001	
		M074560	
	DIZZINESS LIGHTHEADEDNESS	M073480	
	LIGHTHEADEDNESS	M072394	
		M073680	
HYPERTONIA	TIGHT MUSCLE	M072905	1
INSOMNIA	INSOMNIA	M072988	3
		M073947	
		M074052	
NERVOUSNESS	SHAKY FEELING	M074256	1
NEUROPATHY	NERVE DAMAGE	M073087	1
PARESTHESIA	NUMBNESS TONGUE	M074325	1
SOMNOLENCE	DROWSY	M071941	1
SPEECH DISORDER	SLURRED SPEECH	M074644	1
STUPOR	DRUNK FEELING	M074274	1
TWITCHING	FACIAL TWITCHING	M072824	1

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VASODILATATION	FEELING OF WARMTH	M071910	2
	FLUSHING	M074274	
RESPIRATORY SYSTEM			
DYSPNEA	DIFFICULTY BREATHING	M073680	7
	SHORTNESS OF BREATH	M072101	
		M072832	
		M073399	
		M073400	
		M073401	
		M074773	
SKIN & APPENDAGES			
ACNE	PIMPLES	M065521	1
ALOPECIA	ALOPECIA	M074623	3
	HAIR LOSS	M073421	
		M074617	
DRY SKIN	DRY SKIN	M074218	1
HAIR DISORDER	DRY HAIR	M073421	1
PRURITUS	ITCHING	M071910	4
		M072393	
		M072622	
		M073839	
RASH	ECZEMATOUS RASH	M073267	5
	RASH	M065521	
		M072622	
	RASH ON FACE & SCALP	M074212	
	SKIN REDNESS	M072393	
SKIN DISCOLORATION	REDDISH PURPLE AREA CHEEKS	M073994	1
SWEATING	PERSPIRATION	M072653	3
	SWEATING	M072451	
		M072853	
SWEATING DECREASED	SWEATING DECREASED	M073262	1

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SPECIAL SENSES			
ABNORMAL VISION	BLURRY VISION	M073216	2
	VISUAL PROBLEMS	M071402	
EYE DISORDER	FLOATERS EYE	M073571	1
PHOTOPHOBIA	EYE SENSITIVE TO LIGHT	M071402	1
RETINAL DISORDER	RETINAL CHANGES	"	1
TASTE PERVERSION	BAD TASTE	M070042	8
		M074336	
	BAD TASTE IN MOUTH	M072386	
	METALLIC TASTE	M073473	
		M073530	
		M073549	
		M074325	
	SALTY TASTE	M072748	
UROGENITAL SYSTEM			
ALBUMINURIA	PROTEIN IN URINE	M073159	1
BREAST ENGORGEMENT	BREAST ENGORGEMENT	M074620	1
DYSURIA	DIFFICULTY URINATING	M074323	1
HEMATURIA	HEMATURIA	M065521	1
KIDNEY FUNCTION ABNORMAL	RENAL DYSFUNCTION	M073571	2
		M075246	
KIDNEY PAIN	KIDNEY PAIN	M065521	2
		M074117	
METRORRHAGIA	VAGINAL SPOTTING	M074620	1
URINARY FREQUENCY	URINARY FREQUENCY	M071968	1
URINARY INCONTINENCE	INCONTINENCE	M073983	1
URINARY RETENTION	INABILITY TO EMPTY BLADDER	M074323	1
URINARY TRACT DISORDER	URINE FLOW SLOW	M075032	1
URINE ABNORMALITY	ODOR IN URINE	M073082	2
	URINE DISCOLORATION	M074117	

BRISTOL-MYERS SQUIBB COMPANY
PERIODIC ADVERSE DRUG EXPERIENCE REPORT
GLUCOPHAGE TABS
(METFORMIN HCL)
NDA 20-357

INDEX OF ADVERSE DRUG EVENTS REPORTED UNDER ANOTHER B-MS NDA, ANDA, ADA OR AADA

SUBMITTED BETWEEN 10/01/97 AND 12/31/97

NO DATA TO REPORT

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Current Prescribing Information

October 1, 1997 to December 31, 1997

The current package insert number and revision date are P6369-01, October, 1997.

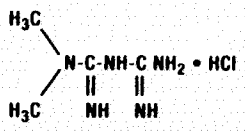
Bristol-Myers Squibb Company

P6369-01

CAUTION: Federal law prohibits dispensing without prescription.

GLUCOPHAGE® (metformin hydrochloride tablets)
500 mg and 850 mg

DESCRIPTION
GLUCOPHAGE (metformin hydrochloride tablets) is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to the oral sulfonylureas. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg and 850 mg of metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate and hydroxypropyl methylcellulose (hypromellose) coating.

CLINICAL PHARMACOLOGY:
Antidiabetic Activity
GLUCOPHAGE is an antihyperglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from those of sulfonylureas. GLUCOPHAGE decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, GLUCOPHAGE does not produce hypoglycemia in either diabetic or nondiabetic subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese NIDDM patients whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with GLUCOPHAGE (up to 2.55 g/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and HbA_{1c} of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to placebo group (see Table 1).

Table 1. GLUCOPHAGE vs Placebo
Summary of Mean Changes from Baseline* in Plasma Glucose, HbA_{1c} and Body Weight, at Final Visit (29-week study)

	GLUCOPHAGE (n = 141)	Placebo (n = 145)	P-Value
FPG (mg/dL)			
Baseline	241.5	237.7	NS
Change at FINAL VISIT	−53.0	6.3	0.001**
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS
Change at FINAL VISIT	−1.4	0.4	0.001**
Body Weight (lbs)			
Baseline	201.0	206.0	NS
Change at FINAL VISIT	−1.4	−2.4	NS

*All patients on diet therapy at Baseline **Statistically significant

Monotherapy with GLUCOPHAGE may be effective in patients who have not responded to sulfonylureas or who have only a partial response to sulfonylureas or who have ceased to respond to sulfonylureas. In such patients, if adequate glycemic control is not attained with GLUCOPHAGE monotherapy, the combination of GLUCOPHAGE and a sulfonylurea may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

A 29-week, double-blind, placebo-controlled study of GLUCOPHAGE and glyburide, alone and in combination, was conducted in obese NIDDM patients who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see Table 2). Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG and HbA_{1c} of 14 mg/dL, 3 mg/dL and 0.2%, respectively. In contrast, those randomized to GLUCOPHAGE (metformin hydrochloride tablets) (up to 2.5 g/day) did not experience a deterioration in glycemic control, but rather a slight improvement, with mean reductions in FPG, PPG and HbA_{1c} of 1 mg/dL, 6 mg/dL and 0.4%, respectively. The combination of GLUCOPHAGE and glyburide was synergistic in reducing FPG, PPG and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Compared to results of glyburide treatment alone, the net differences with combination treatment were −77 mg/dL, −68 mg/dL and −1.9%, respectively (see Table 2).

Table 2. Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or Glycophage (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Plasma Glucose, HbA_{1c} and Body Weight, at Final Visit (29-week study)

	Comb (n = 213)	Glyb (n = 208)	GLU (n = 216)	P-values Glyb vs Comb	GLU vs Comb	GLU vs Glyb
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS	NS	NS
Change at FINAL VISIT	−63.5	13.7	−0.9	0.001**	0.001**	0.025**
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS	NS	0.007**
Change at FINAL VISIT	−1.7	0.2	−0.4	0.001**	0.001**	0.001**
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS	NS	NS
Change at FINAL VISIT	0.9	−0.7	−8.4	0.011**	0.001**	0.001**

*All patients on glyburide, 20 mg/day, at Baseline **Statistically significant

The magnitude of the decline in fasting blood glucose concentration following the institution of GLUCOPHAGE (metformin hydrochloride tablets) therapy is proportional to the level of fasting hyperglycemia. Non-insulin-dependent diabetics with higher fasting glucose concentrations will experience greater declines in plasma glucose and glycosylated hemoglobin.

GLUCOPHAGE has a modest favorable effect on serum lipids, which are often abnormal in NIDDM patients. In clinical studies, particularly when baseline levels were abnormally elevated, GLUCOPHAGE, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol and LDL cholesterol levels and had no adverse effects on other lipid levels (see Table 3).

Table 3. Summary of Mean Percent Reduction of Major Serum Lipid Variables at Final Visit (29-week study)

	Glycophage vs. Placebo (% Change from Baseline)		Combined Glycophage/Glyburide vs. Monotherapy (% Change from Baseline)		
	Glycophage (n = 141)	Placebo (n = 145)	Glycophage (n = 216)	Glycophage/Glyburide (n = 213)	Glyburide (n = 208)
Total Cholesterol	−5%*	1%	−2%	−4%**	1%
Total Triglycerides	−16%	1%	−3%**	−8%**	4%
LDL-Cholesterol	−8%*	1%	−4%**	−6%**	3%
HDL-Cholesterol	2%	−1%	5%	3%	1%

*P < 0.05 vs. Placebo **P < 0.05 vs. Glyburide

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tends to remain stable or may even decrease somewhat (see Tables 1 and 2).

In summary, metformin-treated patients showed significant improvement in all parameters of glycemic control (FPG, PPG and HbA_{1c}), stabilization or decrease in body weight, and a tendency to improvement in the lipid profile, particularly when baseline values are abnormally elevated.

Pharmacokinetics
Absorption and Bioavailability:
The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:
The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE (metformin hydrochloride tablets), steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Elimination:
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 4) is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours in blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations:
NIDDM Subjects:
In the presence of normal renal function, there are no differences between single or multiple dose pharmacokinetics of metformin between diabetics and nondiabetics (see Table 4), nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency:
In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see Table 4).

Hepatic Insufficiency:
No pharmacokinetic studies have been conducted in subjects with hepatic insufficiency.

Geriatrics:
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Table 4).

Table 4. Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE

Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	C_{max}[b] (µg/mL)	t_{max}[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg SD[d] (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg SD (74)[e]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg t.i.d. for 19 doses[f] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with NIDDM:			
850 mg SD (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg t.i.d. for 19 doses[f] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[g], healthy nondiabetic adults:			
850 mg SD (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-Impaired adults: 850 mg SD			
Mild (CL_{cr}[h] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a]-All doses given fasting except the first 18 doses of the multiple dose studies;
[b]-Peak plasma concentration;
[c]-Time to peak plasma concentration;
[d]-SD = single dose;
[e]-Combined results (average means) of five studies: mean age 32 years (range 23-59 yrs).
[f]-Kinetic study done following dose 19, given fasting.
[g]-Elderly subjects, mean age 71 years (range 65-81 years).
[h]-CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2.

Pediatrics:
No pharmacokinetic studies have been conducted in pediatric subjects.

Gender:
Metformin pharmacokinetic parameters did not differ significantly in diabetic and nondiabetic subjects when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with NIDDM, the antihyperglycemic effect of GLUCOPHAGE was comparable in males and females.

Race:
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of GLUCOPHAGE in patients with NIDDM, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51) and hispanics (n=24).

INDICATIONS AND USE
GLUCOPHAGE (metformin hydrochloride tablets), as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia cannot be satisfactorily managed on diet alone.

GLUCOPHAGE may be used concomitantly with a sulfonylurea when diet and GLUCOPHAGE or a sulfonylurea alone do not result in adequate glycemic control.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. Loss of blood glucose control in diet-managed patients may be transient, thus requiring only short-term pharmacologic therapy. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of GLUCOPHAGE alone or GLUCOPHAGE plus a sulfonylurea should be considered.

If, after a suitable trial of such treatments, glucose control still has not been achieved, consideration should be given to the use of insulin. Judgments should be based on regular clinical and laboratory evaluations.

CONTRAINDICATIONS:
GLUCOPHAGE is contraindicated in patients with:
1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS** and **PRECAUTIONS**).
2. Congestive heart failure requiring pharmacologic treatment.
3. GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also **PRECAUTIONS**).
4. Known hypersensitivity to metformin hydrochloride.
5. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS

Lactic Acidosis:
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY:
The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 1027 patients who were randomly assigned to one of five treatment groups (*Diabetes*, 19 (Suppl.2):747-830, 1970; *Diabetes*, 24 (Suppl.1):65-184, 1975).

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) or diet plus a fixed dose of phenformin (100 mg per day), had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone, resulting in discontinuation of both these treatments in the UGDP study. Total mortality was increased in both the tolbutamide- and phenformin-treated groups and this increase was statistically significant in the phenformin-treated group. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of GLUCOPHAGE and alternative modes of therapy.

Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other related oral antidiabetic drugs, in view of the similarities in mode of action and chemical structure among the drugs in each category.

PRECAUTIONS
General:
Monitoring of renal function—GLUCOPHAGE (metformin hydrochloride tablets) is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function in elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see **DOSAGE AND ADMINISTRATION**). For patients ≥80 years of age, see **WARNINGS**.

Before initiation of GLUCOPHAGE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition—Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (See **Drug Interactions**), should be used with caution.

Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and acute with contrast materials)—Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states—Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued.

Surgical procedures—GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure (except minor procedures not

associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake—Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE.

Impaired Hepatic Function—Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels—A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see **Laboratory Tests**).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of previously controlled diabetic—A diabetic patient previously well controlled on GLUCOPHAGE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Hypoglycemia—Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose—When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE (metformin hydrochloride tablets) and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

Information for Patients:
Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE.

GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

(See Patient Labeling Printed Below)

Laboratory Tests:
Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also **DOSAGE AND ADMINISTRATION**).

Initial and periodic monitoring of hematologic parameters (*e.g.*, hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE (metformin hydrochloride tablets) therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Drug Interactions:
Glyburide: In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see **DOSAGE AND ADMINISTRATION**, Concomitant Glucophage and Oral Sulfonylurea Therapy).
Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.
Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.
Cationic Drugs: Cationic drugs (*e.g.*, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.
Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in-vivo* micronuclei formation test (mouse bone marrow).

Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis.

Pregnancy:
Teratogenic effects:
Pregnancy Category B. Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers:
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted.

Geriatric Use:
Controlled clinical studies of GLUCOPHAGE did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see **CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics**). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see also **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS
Lactic Acidosis: See **WARNINGS, PRECAUTIONS** and **OVERDOSAGE** Sections.
Gastrointestinal Reactions: Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE (metformin hydrochloride tablets) with meals (see **DOSAGE AND ADMINISTRATION**).

Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, GLUCOPHAGE should be temporarily discontinued.

For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: During initiation of GLUCOPHAGE therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolves spontaneously.

Dermatologic Reactions: The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy.

Hematologic: (See also **PRECAUTIONS**). During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered.

DRUG ABUSE AND DEPENDENCE:
GLUCOPHAGE possesses no pharmacodynamic properties, either primary or secondary, which could be expected to result in abuse as a recreational drug or addiction.

OVERDOSAGE:
Hypoglycemia has not been seen even with ingestion of up to 85 grams of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION:
There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE or any other pharmacologic agent. Dosage of GLUCOPHAGE must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. GLUCOPHAGE should be given in divided doses with meals and should be started at a low dose, with gradual dose escalation, as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see below, **USUAL STARTING DOSE**), fasting plasma glucose should be used to determine the therapeutic response to GLUCOPHAGE and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLUCOPHAGE, either when used as monotherapy or in combination with sulfonylurea.

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of GLUCOPHAGE may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Usual Starting Dose:
In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

GLUCOPHAGE 500 mg Tablets:
The usual starting dose of GLUCOPHAGE 500 mg tablets is one tablet b.i.d., given with the morning and evening meals. Dosage increases should be made in increments of one tablet every week, given in divided doses, up to a maximum of 2500 mg per day. GLUCOPHAGE (metformin hydrochloride tablets) can be administered twice a day up to 2000 mg per day (e.g., 1000 mg b.i.d. with morning and evening meals) if a 2500 mg daily dose is required, it may be better tolerated given t.i.d. with meals.

GLUCOPHAGE 850 mg Tablets:
The usual starting dose of GLUCOPHAGE 850 mg tablets is one tablet daily, given with the morning meal. Dosage increases should be made in increments of one tablet every OTHER week, given in divided doses, up to a maximum of 2550 mg per day. The usual maintenance dose is 850 mg b.i.d. with the morning and evening meals. When necessary, patients may be given 850 mg t.i.d. with meals.

Transfer from Other Antidiabetic Therapy:
When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to GLUCOPHAGE, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged

retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant GLUCOPHAGE and Oral Sulfonylurea Therapy:
If patients have not responded to four weeks of the maximum dose of GLUCOPHAGE monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing GLUCOPHAGE at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide). Published clinical information exists for the use of metformin with either chlorpropamide, tolbutamide or glipizide. No published clinical information exists regarding concomitant use of metformin with acetohexamide or tolazamide.

With concomitant GLUCOPHAGE and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant GLUCOPHAGE and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea).

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUCOPHAGE and the maximum dose of an oral sulfonylurea, institution of insulin therapy and discontinuation of these oral agents should be considered.

Specific Patient Populations:
GLUCOPHAGE is not recommended for use in pregnancy or for use in pediatric patients.

The initial and maintenance dosing of GLUCOPHAGE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See **WARNINGS**.)

In debilitated or malnourished patients, the dosing should also be conservative and based on a careful assessment of renal function.

HOW SUPPLIED
GLUCOPHAGE® (brand of metformin hydrochloride tablets) is supplied as round, white to off-white, film-coated tablets, available in the following strengths:

500 mg	Bottles of 100	NDC 0087-6060-05
850 mg	Bottles of 100	NDC 0087-6070-05

GLUCOPHAGE 500 mg tablets are debossed with BMS 6060 around the periphery of the tablet on one side and 500 across the face of the other side.

GLUCOPHAGE 850 mg tablets are debossed with BMS 6070 around the periphery of the tablet on one side and 850 across the face of the other side.

Storage
Store between 15°–30° C (59°–86° F).
Dispense in light resistant container.

PATIENT INFORMATION ABOUT
GLUCOPHAGE® (metformin hydrochloride tablets)

WARNING: A small number of people who have taken Glucophage have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take Glucophage. (See Question Nos. 7-11)

Q1. Why do I need to take GLUCOPHAGE?
Your doctor has prescribed GLUCOPHAGE (GLUE-coe-fahj) to treat your type II diabetes. This is also known as non-insulin-dependent diabetes mellitus (NIDDM).

Q2. What is type II diabetes?
People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

Q3. How is type II diabetes usually controlled?
High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Before taking GLUCOPHAGE you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOPHAGE, you should still exercise and follow the diet recommended for your diabetes.

Q4. Does GLUCOPHAGE work differently from other glucose-control medications?
Yes it does. Until GLUCOPHAGE was introduced, all the available oral glucose-control medications were from the same chemical group called sulfonylureas. These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. GLUCOPHAGE lowers the amount of sugar in your blood by helping your body respond better to its own insulin. GLUCOPHAGE does not cause your body to produce more insulin. Therefore, GLUCOPHAGE rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

Q5. What happens if my blood sugar is still too high?
When blood sugar cannot be lowered enough by either GLUCOPHAGE or a sulfonylurea, the two medications may be effective taken together. However, if you are unable to maintain your blood sugar with diet, exercise and glucose-control medication taken orally, then your doctor may prescribe injectable insulin to control your diabetes.

Q6. Can GLUCOPHAGE cause side effects?
GLUCOPHAGE, like all blood-sugar lowering medications, can cause side effects in some patients. Most of these side effects are minor and will go away after you've taken GLUCOPHAGE for a while. However, there are also serious, but rare side effects related to GLUCOPHAGE (see below).

Q7. What kind of side effects can GLUCOPHAGE cause?
If side effects occur, they usually occur during the first few weeks of therapy. They are normally minor ones such as diarrhea, nausea and upset stomach. Taking your GLUCOPHAGE with meals can help reduce these side effects.

Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their dose lowered or stop taking GLUCOPHAGE, either temporarily or permanently. Although these problems occur in up to one-third of patients when they first start taking GLUCOPHAGE, you should tell your doctor if the problems come back or start later on during the therapy.

About three out of one hundred people report having a temporary unpleasant or metallic taste when they start taking GLUCOPHAGE.

Q8. Are there any serious side effects that GLUCOPHAGE can cause?
GLUCOPHAGE rarely causes serious side effects. The most serious side effect that GLUCOPHAGE can cause is called lactic acidosis.

Q9. What is lactic acidosis and can it happen to me?
Lactic acidosis is caused by a buildup of lactic acid in the blood. Lactic acidosis associated with GLUCOPHAGE is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking GLUCOPHAGE over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the cases.

It's also important for your liver to be working normally when you take GLUCOPHAGE. Your liver helps remove lactic acid from your bloodstream.

Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally.

There is no evidence that GLUCOPHAGE causes harm to the kidneys or liver.

Q10. Are there other risk factors for lactic acidosis?
Your risk of developing lactic acidosis from taking GLUCOPHAGE is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should discuss your risk with your physician. You should not take GLUCOPHAGE if:

- You have chronic kidney or liver problems
- You have congestive heart failure which is treated with medications, e.g., digoxin (Lanoxin®) or furosemide (Lasix®)
- You drink alcohol excessively (all the time or short-term "binge" drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have certain x-ray procedures with injectable contrast agents
- You are going to have surgery
- You develop a serious condition such as a heart attack, severe infection, or a stroke.
- You are ≥80 years of age and have NOT had your kidney function tested.

Q11. What are the symptoms of lactic acidosis?
Some of the symptoms include: feeling very weak, tired or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or suddenly developing a slow or irregular heartbeat.

If you notice these symptoms, or if your medical condition has suddenly changed, stop taking GLUCOPHAGE (metformin hydrochloride tablets) and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q12. What does my doctor need to know to decrease my risk of lactic acidosis?
Tell your doctor if you have an illness that results in severe vomiting, diarrhea and/or fever, or if your intake of fluids is significantly reduced. These situations can lead to severe dehydration, and it may be necessary to stop taking GLUCOPHAGE temporarily.

You should let your doctor know if you are going to have any surgery or specialized x-ray procedures that require injection of contrast agents. GLUCOPHAGE therapy will need to be stopped temporarily in such instances.

Q13. Can I take GLUCOPHAGE with other medications?
Remind your doctor that you are taking GLUCOPHAGE when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOPHAGE may interfere with the way some drugs work and some drugs may interfere with the action of GLUCOPHAGE.

Q14. What if I become pregnant while taking GLUCOPHAGE?
Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take GLUCOPHAGE during pregnancy.

Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of GLUCOPHAGE if you are nursing a child.

Q15. Are there other risks associated with GLUCOPHAGE?
There is some evidence that any oral diabetes drug may increase the risk of heart problems. Experts are not sure what the real risk is for heart problems, if any, from taking oral diabetes medicine.

Q16. How do I take GLUCOPHAGE?
Your doctor will tell you how many GLUCOPHAGE tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of GLUCOPHAGE and your dosage will be increased gradually until your blood sugar is controlled.

Q17. Where can I get more information about GLUCOPHAGE?
This leaflet is a summary of the most important information about GLUCOPHAGE. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type II diabetes as well as GLUCOPHAGE and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.

Distributed by
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

P6369-01

Revised October 1997

PATIENT INFORMATION

Bristol-Myers Squibb Company P6389-01

CAUTION: Federal law prohibits dispensing without prescription.

Patient Information About

GLUCOPHAGE®

(metformin hydrochloride tablets)
500 mg and 850 mg

WARNING: A small number of people who have taken Glucophage have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take Glucophage. (See Question Nos. 7-11)

Q1. Why do I need to take GLUCOPHAGE?

Your doctor has prescribed GLUCOPHAGE (GLUE-coe-fahj) to treat your type II diabetes. This is also known as non-insulin-dependent diabetes mellitus (NIDDM).

Q2. What is type II diabetes?

People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

Q3. How is type II diabetes usually controlled?

High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Before taking GLUCOPHAGE you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOPHAGE, you should still exercise and follow the diet recommended for your diabetes.

Q4. Does GLUCOPHAGE work differently from other glucose-control medications?

Yes it does. Until GLUCOPHAGE was introduced, all the available oral glucose-control medications were from the same chemical group called sulfonylureas. These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. GLUCOPHAGE lowers the amount of sugar in your blood by helping your body respond better to its own insulin. GLUCOPHAGE does not cause your body to produce more insulin. Therefore, GLUCOPHAGE rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

Q5. What happens if my blood sugar is still too high?

When blood sugar cannot be lowered enough by either GLUCOPHAGE or a sulfonylurea, the two medications may be effective taken together. However, if you are unable to maintain your blood sugar with diet, exercise and glucose-control medication taken orally, then your doctor may prescribe injectable insulin to control your diabetes.

Q6. Can GLUCOPHAGE cause side effects?

GLUCOPHAGE, like all blood-sugar lowering medications, can cause side effects in some patients. Most of these side effects are minor and will go away after you've taken GLUCOPHAGE for a while. However, there are also serious, but rare side effects related to GLUCOPHAGE (see below).

Q7. What kind of side effects can GLUCOPHAGE cause?

If side effects occur, they usually occur during the first few weeks of therapy. They are normally minor ones such as diarrhea, nausea and upset stomach. Taking your GLUCOPHAGE with meals can help reduce these side effects.

Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their dose lowered or stop taking GLUCOPHAGE, either temporarily or permanently. Although these problems occur in up to one-third of patients when they first start taking GLUCOPHAGE, you should tell your doctor if the problems come back or start later on during the therapy.

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- You have chronic kidney or liver problems
- You have congestive heart failure which is treated with medications, e.g., digoxin (Lanoxine) or furosemide (Lasix®)
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- You are going to have certain x-ray procedures with injectable contrast agents
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- You are ≥80 years of age and have NOT had your kidney function tested.

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Distributed by
Bristol-Myers Squibb
Company
Princeton, NJ 08543 USA

Revised October 1997 P6369-01

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Description of Prescribing Changes since the Previous Reporting Period

October 1, 1997 to December 31, 1997

The current package insert (approved and released) has been changed since the previous reporting period. These changes are described on the following pages.

10 pages

DRAFT

LABELING.

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Index of Company Sponsored Studies

October 1, 1997 to December 31, 1997

No Bristol-Myers Squibb sponsored studies were approved for initiation during this reporting period. The following Lipha sponsored studies were initiated during this reporting period.

Country	Protocol Number	Protocol Title
United Kingdom	MET/UK/97.02	Multi centre, double-blind, randomized study to assess the synergistic action of metformin and two fibrates (bezafibrate or fenofibrate) co-administered in hyperlipaemic NIDDM patients.
France	MET/F/97.03	Pilot pharmacokinetic study to assess the effect of Zinc and metformin associated in solution on the bioavailability of two solutions of metformin (500mg and 850 mg). Open, randomized, five-way cross-over, single dose study under fasting conditions in 9 healthy volunteers.

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

Summary of Non-U.S.A. Product Safety Actions

October 1, 1997 to December 31, 1997

We are unaware of any non-U.S.A. product safety actions taken during this reporting period.

Bristol-Myers Squibb Company

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

New Safety Information

October 1, 1997 to December 31, 1997

Refer to the attached "Dear Colleague" letter which was sent to approximately 140,000 health care professionals on November 14, 1997.

U.S. EXPERIENCE SUPPORTS THE SAFETY PROFILE OF GLUCOPHAGE

Dear Colleague:

GLUCOPHAGE® (metformin hydrochloride tablets) was introduced in the United States over two and one-half years ago, and, to date, over 3 million patients have been treated with GLUCOPHAGE.[1]

This rapid uptake has allowed us to continue to assess the safety profile of GLUCOPHAGE. In fact, the ongoing GLUCOPHAGE safety surveillance analysis in the U.S. indicates that the GLUCOPHAGE safety profile is consistent with that of the worldwide experience.

Read on to find out how we've revised the GLUCOPHAGE package insert to further improve your ability to appropriately select patients and continue to prescribe GLUCOPHAGE with confidence.

Appropriate patient selection is always key

As you know, patients with type 2 diabetes can be safely and effectively treated with GLUCOPHAGE; however, there are certain patients who should not be treated with this medication since they are at risk of developing lactic acidosis.

The risk of lactic acidosis, a rare but serious and potentially life-threatening condition (up to half the cases may be fatal), can be reduced by continuing to avoid the use of GLUCOPHAGE in patients:

- at increased risk for significant drug accumulation (e.g., renal impairment), or
- with an impaired ability to clear lactate (e.g., conditions associated with tissue hypoperfusion or hypoxic states, or substantial liver impairment).

Bristol-Myers Squibb is committed to helping you better define patients with type 2 diabetes who are appropriate for GLUCOPHAGE therapy. In a continued effort to help minimize the risk of lactic acidosis in these patients, the safety experience of GLUCOPHAGE in the United States has been carefully monitored since its introduction in May 1995. The surveillance analysis indicates that:

- The U.S. safety experience is consistent with the worldwide experience.
- The reported worldwide incidence of lactic acidosis associated with GLUCOPHAGE is approximately 0.03 cases per 1,000 patient-years exposure.
- Reported cases of lactic acidosis occurred primarily in patients with renal insufficiency and/or other concomitant medical conditions, reinforcing the importance of appropriate patient selection.

New revisions improve appropriate patient selection

Although the incidence of lactic acidosis is rare and is consistent with the worldwide experience, a thorough review of all reported cases indicates that there is an opportunity to increase your ability to more appropriately select patients and help minimize the risk of lactic acidosis. Therefore, the following revisions to the GLUCOPHAGE package insert are being made. These revisions are intended to help you better define appropriate patients for GLUCOPHAGE therapy.

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** enclosed.

Patients ≥ 80 years of age

Renal function is an important consideration in selecting appropriate patients for GLUCOPHAGE® (metformin hydrochloride tablets). Because aging is generally associated with a decline in renal function, it is now recommended that a creatinine clearance rate assessment be obtained in patients ≥80 years of age prior to the initiation of GLUCOPHAGE therapy. GLUCOPHAGE treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not impaired.

Patients with congestive heart failure (CHF)

The existence of CHF in a patient with type 2 diabetes increases the risk for hypoperfusion, hypoxia, and possible renal insufficiency. This is particularly true in patients with severe heart failure. Since any of these conditions may increase the risk of lactic acidosis, it is prudent to contraindicate the use of GLUCOPHAGE in all patients with CHF who require pharmacologic treatment.

As you know, GLUCOPHAGE should also be avoided in patients with impaired hepatic function or excessive alcohol intake (acute or chronic), or acute or chronic metabolic acidosis, including diabetic ketoacidosis. Temporarily withhold in patients receiving parenteral iodinated contrast materials. GLUCOPHAGE is not recommended for pediatric patients or pregnant women. (**Please see CONTRAINDICATIONS, boxed WARNING and PRECAUTIONS in complete prescribing information enclosed.** As with all sulfonylureas and biguanides, GLUCOPHAGE labeling includes a Special Warning on Increased Risk of Cardiovascular Mortality based on the UGDP study.)

As an adjunct to diet, *only* GLUCOPHAGE delivers all of these benefits:

- GLUCOPHAGE is as effective as sulfonylureas but without the risk of hypoglycemia (when used alone and under normal circumstances).[2-6]
- GLUCOPHAGE lowers blood glucose levels by decreasing insulin resistance,[7] a major underlying cause of type 2 diabetes. Therefore, GLUCOPHAGE lowers or maintains fasting plasma insulin levels.[8]
- GLUCOPHAGE decreases or stabilizes body weight,[3] and favorably affects lipids, particularly when elevated.[9,10]

Your selection of appropriate patients for treatment with GLUCOPHAGE has resulted in an excellent U.S. safety record. The revisions to the package insert will help ensure more appropriate patient selection and continued success with GLUCOPHAGE.

Sincerely,

Douglas A. Young, PhD
Medical Director, Metabolism

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** enclosed.

References: 1. Based on the Walsh America/PMSI Oral Anti-Diabetic Patient Tracking Analysis, June 1997. 2. Hermann LS, Scherstén B, Bitzén P-O, et al: Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: a double-blind controlled study. *Diabetes Care* 17(10):1100-1109, 1994. 3. Campbell IW, Menzies DG, Chalmers J, et al: One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. *Diabetes Metab* 21(4):394-400, 1994. 4. Clarke BF, Campbell IW: Comparison of metformin and chlorpropamide in non-obese, maturity-onset diabetics uncontrolled by diet. *BMJ* 2:1576-1578, December 17, 1977. 5. Collier A, Watson HHK, Patrick AW, et al: Effect of glycaemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non-insulin-dependent) diabetic patients. *Diabetes Metab* 15(6):420-425, 1989. 6. Turner R, Cull C, Holman R, for the United Kingdom Prospective Diabetes Study Group: United Kingdom prospective diabetes study (UKPDS) 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 124 (1, pt 2):136-145, 1996. 7. Nagi DK, Yudkin JS: Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. *Diabetes Care* 16(4):621-629, 1993. 8. United Kingdom Prospective Diabetes Study Group: United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. *BMJ* 310:83-88, January 14, 1995. 9. Pentikäinen PJ, Voutilainen E, Aro A, et al: Cholesterol lowering effect of metformin in combined hyperlipidemia: placebo controlled double blind trial. *Ann Med* 22:307-312, 1990. 10. DeFronzo RA, Goodman AM, and the Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333(9):541-549, 1995.

MEDWatch 1-800-332-1088 available to report serious adverse events for any drug.

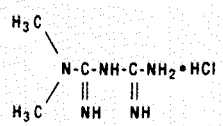
 F5-B013 Issued: November 1997 Printed in USA Printed on recyclable paper

CAUTION: Federal law prohibits dispensing without prescription.

GLUCOPHAGE® (metformin hydrochloride tablets) 500 mg and 850 mg

DESCRIPTION

GLUCOPHAGE (metformin hydrochloride tablets) is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to the oral sulfonylureas. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg and 850 mg of metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate and hydroxypropyl methylcellulose (hypromellose) coating.

CLINICAL PHARMACOLOGY:

Antidiabetic Activity

GLUCOPHAGE is an antihyperglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from those of sulfonylureas. GLUCOPHAGE decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, GLUCOPHAGE does not produce hypoglycemia in either diabetic or nondiabetic subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese NIDDM patients whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with GLUCOPHAGE (up to 2.55 g/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and HbA_{1c} of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to placebo group (see Table 1).

Table 1. GLUCOPHAGE vs Placebo
Summary of Mean Changes from Baseline* in Plasma Glucose HbA_{1c} and Body Weight, at Final Visit (29-week study)

	GLUCOPHAGE (n = 141)	Placebo (n = 145)	P-Value
FPG (mg/dL)			
Baseline	241.5	237.7	NS
Change at FINAL VISIT	−53.0	6.3	0.001**
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS
Change at FINAL VISIT	−1.4	0.4	0.001**
Body Weight (lbs)			
Baseline	201.0	206.0	NS
Change at FINAL VISIT	−1.4	−2.4	NS

*All patients on diet therapy at Baseline
**Statistically significant

Monotherapy with GLUCOPHAGE may be effective in patients who have not responded to sulfonylureas or who have only a partial response to sulfonylureas or who have ceased to respond to sulfonylureas. In such patients, if adequate glycemic control is not attained with GLUCOPHAGE monotherapy, the combination of GLUCOPHAGE and a sulfonylurea may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

A 29-week, double-blind, placebo-controlled study of GLUCOPHAGE and glyburide, alone and in combination, was conducted in obese NIDDM patients who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see Table 2). Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG and HbA_{1c} of 14 mg/dL, 3 mg/dL and 0.2%, respectively. In contrast, those randomized to GLUCOPHAGE (metformin hydrochloride tablets) (up to 2.5 g/day) did not experience a deterioration in glycemic control, but rather a slight improvement, with mean reductions in FPG, PPG and HbA_{1c} of 1 mg/dL, 6 mg/dL and 0.4%, respectively. The combination of GLUCOPHAGE and glyburide was synergistic in reducing FPG, PPG and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Compared to results of glyburide treatment alone, the net differences with combination treatment were −77 mg/dL, −68 mg/dL and −1.9%, respectively (see Table 2).

Table 2. Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or Glucophage (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Plasma Glucose, HbA_{1c} and Body Weight, at Final Visit (29-week study)

	Comb (n = 213)	Glyb (n = 209)	GLU (n = 210)	P-values Glyb vs Comb	GLU vs Comb	GLU vs Glyb
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS	NS	NS
Change at FINAL VISIT	−63.5	13.7	−0.9	0.001**	0.001**	0.025**
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS	NS	0.007**
Change at FINAL VISIT	−1.7	0.2	−0.4	0.001**	0.001**	0.001**
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS	NS	NS
Change at FINAL VISIT	0.9	−0.7	−8.4	0.011**	0.001**	0.001**

*All patients on glyburide, 20 mg/day, at Baseline
**Statistically significant

The magnitude of the decline in fasting blood glucose concentration following the institution of GLUCOPHAGE (metformin hydrochloride tablets) therapy is proportional to the level of fasting hyperglycemia. Non-insulin-dependent diabetics with higher fasting glucose concentrations will experience greater declines in plasma glucose and glycosylated hemoglobin.

GLUCOPHAGE has a modest favorable effect on serum lipids, which are often abnormal in NIDDM patients. In clinical studies, particularly when baseline levels were abnormally elevated, GLUCOPHAGE, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol and LDL cholesterol levels and had no adverse effects on other lipid levels (see Table 3).

Table 3. Summary of Mean Percent Reduction of Major Serum Lipid Variables at Final Visit (29-week study)

	Glucophage vs. Placebo (% Change from Baseline)		Combined Glucophage/Glyburide vs. Monotherapy (% Change from Baseline)		
	Glucophage (n = 141)	Placebo (n = 145)	Glucophage (n = 210)	Glucophage/ Glyburide (n = 213)	Glyburide (n = 209)
Total Cholesterol	−5%*	1%	−2%	−4%**	1%
Total Triglycerides	−16%	1%	−3%**	−8%**	4%
LDL-Cholesterol	−8%*	1%	−4%**	−6%**	3%
HDL-Cholesterol	2%	−1%	5%	3%	1%

*$P < 0.05$ vs. Placebo
**$P < 0.05$ vs. Glyburide

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tends to remain stable or may even decrease somewhat (see Tables 1 and 2).

In summary, metformin-treated patients showed significant improvement in all parameters of glycemic control (FPG, PPG and HbA_{1c}), stabilization or decrease in body weight, and a tendency to improvement in the lipid profile, particularly when baseline values are abnormally elevated.

Pharmacokinetics

Absorption and Bioavailability:
The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:
The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE (metformin hydrochloride tablets), steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 μg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Elimination:
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 4) is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations:
NIDDM Subjects:
In the presence of normal renal function, there are no differences between single or multiple dose pharmacokinetics of metformin between diabetics and nondiabetics (see Table 4), nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency:
In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see Table 4).

Hepatic Insufficiency:
No pharmacokinetic studies have been conducted in subjects with hepatic insufficiency.

Geriatrics:
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Table 4).

Table 4. Select Mean (± S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE

Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	C_{max}[b] (μg/mL)	t_{max}[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg SD[d] (24)	1.03 (± 0.33)	2.75 (± 0.81)	600 (± 132)
850 mg SD (74)[e]	1.60 (± 0.38)	2.64 (± 0.82)	552 (± 139)
850 mg t.i.d. for 19 doses[f] (9)	2.01 (± 0.42)	1.79 (± 0.94)	642 (± 173)
Adults with NIDDM:			
850 mg SD (23)	1.48 (± 0.5)	3.32 (± 1.08)	491 (± 138)
850 mg t.i.d. for 19 doses[f] (9)	1.90 (±0.62)	2.01 (± 1.22)	550 (± 160)
Elderly[g], healthy nondiabetic adults:			
850 mg SD (12)	2.45 (± 0.70)	2.71 (± 1.05)	412 (± 98)
Renal-impaired adults: 850 mg SD			
Mild (CL_{cr}[h] 61-90 mL/min) (5)	1.86 (± 0.52)	3.20 (± 0.45)	384 (± 122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (± 1.83)	3.75 (± 0.50)	108 (± 57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (± 0.92)	4.01 (± 1.10)	130 (± 90)

[a]–All doses given fasting except the first 18 doses of the multiple dose studies;
[b]–Peak plasma concentration;
[c]–Time to peak plasma concentration;
[d]–SD = single dose;
[e]–Combined results (average means) of five studies: mean age 32 years (range 23-59 yrs).
[f]–Kinetic study done following dose 19, given fasting.
[g]–Elderly subjects, mean age 71 years (range 65-81 years).
[h]–CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2.

Pediatrics:
No pharmacokinetic studies have been conducted in pediatric subjects.

Gender:
Metformin pharmacokinetic parameters did not differ significantly in diabetic and nondiabetic subjects when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with NIDDM, the antihyperglycemic effect of GLUCOPHAGE (metformin hydrochloride tablets) was comparable in males and females.

Race:
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of GLUCOPHAGE in patients with NIDDM, the antihyperglycemic effect was comparable in whites (n = 249), blacks (n = 51) and hispanics (n = 24).

INDICATIONS AND USE

GLUCOPHAGE (metformin hydrochloride tablets), as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia cannot be satisfactorily managed on diet alone.

GLUCOPHAGE may be used concomitantly with a sulfonylurea when diet and GLUCOPHAGE or a sulfonylurea alone do not result in adequate glycemic control.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. Loss of blood glucose control in diet-managed patients may be transient, thus requiring only short-term pharmacologic therapy. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of GLUCOPHAGE alone or GLUCOPHAGE plus a sulfonylurea should be considered.

If, after a suitable trial of such treatments, glucose control still has not been achieved, consideration should be given to the use of insulin. Judgments should be based on regular clinical and laboratory evaluations.

CONTRAINDICATIONS:

GLUCOPHAGE is contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
2. Congestive heart failure requiring pharmacologic treatment.
3. GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS).
4. Known hypersensitivity to metformin hydrochloride.
5. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUCOPHAGE treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE (metformin hydrochloride tablets), since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE (metformin hydrochloride tablets) should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY:

The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 1027 patients who were randomly assigned to one of five treatment groups (*Diabetes*, 19 (Suppl.2):747-830, 1970; *Diabetes*, 24 (Suppl.1):65-184, 1975).

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) or diet plus a fixed dose of phenformin (100 mg per day), had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone, resulting in discontinuation of both these treatments in the UGDP study. Total mortality was increased in both the tolbutamide- and phenformin-treated groups and this increase was statistically significant in the phenformin-treated group. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of GLUCOPHAGE and alternative modes of therapy.

Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other related oral antidiabetic drugs, in view of the similarities in mode of action and chemical structure among the drugs in each category.

PRECAUTIONS

General:

Monitoring of renal function — GLUCOPHAGE is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION). For patients ≥ 80 years of age, see WARNINGS.

Before initiation of GLUCOPHAGE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (See Drug Interactions), should be used with caution.

Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and scans with contrast materials) — Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states — Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued.

Surgical procedures — GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake — Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE.

Impaired hepatic function — Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels — A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE (metformin hydrochloride tablets) or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of previously controlled diabetic — A diabetic patient previously well controlled on GLUCOPHAGE (metformin hydrochloride tablets) who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia — Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose — When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

Information for Patients:

Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE.

GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

(See Patient Labeling Printed Below)

Laboratory Tests:

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Drug Interactions:

Glyburide: In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage and Oral Sulfonylurea Therapy).

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in-vivo* micronuclei formation test (mouse bone marrow).

Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis.

Pregnancy:

Teratogenic effects:

Pregnancy Category B. Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers:

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted.

Geriatric Use:

Controlled clinical studies of GLUCOPHAGE (metformin hydrochloride tablets) did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see also WARNINGS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Lactic Acidosis: See WARNINGS, PRECAUTIONS and OVERDOSAGE Sections.

Gastrointestinal Reactions: Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE with meals (see DOSAGE AND ADMINISTRATION).

Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, GLUCOPHAGE should be temporarily discontinued.

For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: During initiation of GLUCOPHAGE therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolves spontaneously.

Dermatologic Reactions: The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy.

Hematologic: (See also PRECAUTIONS). During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered.

DRUG ABUSE AND DEPENDENCE:

GLUCOPHAGE possesses no pharmacodynamic properties, either primary or secondary, which could be expected to result in abuse as a recreational drug or addiction.

OVERDOSAGE:

Hypoglycemia has not been seen even with ingestion of up to 85 grams of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION:

There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE or any other pharmacologic agent. Dosage of GLUCOPHAGE must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. GLUCOPHAGE should be given in divided doses with meals and should be started at a low dose, with gradual dose escalation, as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see below, USUAL STARTING DOSE), fasting plasma glucose should be used to determine the therapeutic response to GLUCOPHAGE and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. **The therapeutic goal should be to decrease both fast-**

ing plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLUCOPHAGE (metformin hydrochloride tablets), either when used as monotherapy or in combination with sulfonylurea.

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of GLUCOPHAGE may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Usual Starting Dose:
In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

GLUCOPHAGE 500 mg Tablets:
The usual starting dose of GLUCOPHAGE 500 mg tablets is one tablet b.i.d., given with the morning and evening meals. Dosage increases should be made in increments of one tablet every week, given in divided doses, up to a maximum of 2500 mg per day. GLUCOPHAGE can be administered twice a day up to 2000 mg per day (e.g., 1000 mg b.i.d. with morning and evening meals). If a 2500 mg daily dose is required, it may be better tolerated given t.i.d. with meals.

GLUCOPHAGE 850 mg Tablets:
The usual starting dose of GLUCOPHAGE 850 mg tablets is one tablet daily, given with the morning meal. Dosage increases should be made in increments of one tablet every OTHER week, given in divided doses, up to a maximum of 2550 mg per day. The usual maintenance dose is 850 mg b.i.d. with the morning and evening meals. When necessary, patients may be given 850 mg t.i.d. with meals.

Transfer from Other Antidiabetic Therapy:
When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to GLUCOPHAGE, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant GLUCOPHAGE and Oral Sulfonylurea Therapy:
If patients have not responded to four weeks of the maximum dose of GLUCOPHAGE monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing GLUCOPHAGE at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide). Published clinical information exists for the use of metformin with either chlorpropamide, tolbutamide or glipizide. No published clinical information exists regarding concomitant use of metformin with acetohexamide or tolazamide.

With concomitant GLUCOPHAGE and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant GLUCOPHAGE and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea).

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUCOPHAGE and the maximum dose of an oral sulfonylurea, institution of insulin therapy and discontinuation of these oral agents should be considered.

Specific Patient Populations:
GLUCOPHAGE is not recommended for use in pregnancy or for use in pediatric patients.

The initial and maintenance dosing of GLUCOPHAGE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See WARNINGS.)

In debilitated or malnourished patients, the dosing should also be conservative and based on a careful assessment of renal function.

HOW SUPPLIED
GLUCOPHAGE® (brand of metformin hydrochloride tablets) is supplied as round, white to off-white, film-coated tablets, available in the following strengths:

500 mg	Bottles of 100	NDC 0087-6060-05
850 mg	Bottles of 100	NDC 0087-6070-05

GLUCOPHAGE 500 mg tablets are debossed with BMS 6060 around the periphery of the tablet on one side and 500 across the face of the other side. GLUCOPHAGE 850 mg tablets are debossed with BMS 6070 around the periphery of the tablet on one side and 850 across the face of the other side.

Storage
Store between 15°–30° C (59°–86° F).

PATIENT INFORMATION ABOUT GLUCOPHAGE® (metformin hydrochloride tablets) 500 mg and 850 mg

WARNING: A small number of people who have taken Glucophage have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take Glucophage. (See Question Nos. 7-11)

Q1. Why do I need to take GLUCOPHAGE?
Your doctor has prescribed GLUCOPHAGE (GLUE-coe-fahj) to treat your type II diabetes. This is also known as non-insulin-dependent diabetes mellitus (NIDDM).

Q2. What is type II diabetes?
People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

Q3. How is type II diabetes usually controlled?
High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Before taking GLUCOPHAGE you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOPHAGE, you should still exercise and follow the diet recommended for your diabetes.

Q4. Does GLUCOPHAGE work differently from other glucose-control medications?
Yes it does. Until GLUCOPHAGE (metformin hydrochloride tablets) was introduced, all the available oral glucose-control medications were from the same chemical group called sulfonylureas. These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. GLUCOPHAGE lowers the amount of sugar in your blood by helping your body respond better to its own insulin. GLUCOPHAGE (metformin hydrochloride tablets) does not cause your body to produce more insulin. Therefore, GLUCOPHAGE rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

Q5. What happens if my blood sugar is still too high?
When blood sugar cannot be lowered enough by either GLUCOPHAGE or a sulfonylurea, the two medications may be effective taken together. However, if you are unable to maintain your blood sugar with diet, exercise and glucose-control medication taken orally, then your doctor may prescribe injectable insulin to control your diabetes.

Q6. Can GLUCOPHAGE cause side effects?
GLUCOPHAGE, like all blood-sugar lowering medications, can cause side effects in some patients. Most of these side effects are minor and will go away after you've taken GLUCOPHAGE for a while. However, there are also serious, but rare side effects related to GLUCOPHAGE (see below).

Q7. What kind of side effects can GLUCOPHAGE cause?
If side effects occur, they usually occur during the first few weeks of therapy. They are normally minor ones such as diarrhea, nausea and upset stomach. Taking your GLUCOPHAGE with meals can help reduce these side effects.

Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their dose lowered or stop taking GLUCOPHAGE, either temporarily or permanently. Although these problems occur in up to one-third of patients when they first start taking GLUCOPHAGE, you should tell your doctor if the problems come back or start later on during the therapy.

About three out of one hundred people report having a temporary unpleasant or metallic taste when they start taking GLUCOPHAGE.

Q8. Are there any serious side effects that GLUCOPHAGE can cause?
GLUCOPHAGE rarely causes serious side effects. The most serious side effect that GLUCOPHAGE can cause is called lactic acidosis.

Q9. What is lactic acidosis and can it happen to me?
Lactic acidosis is caused by a buildup of lactic acid in the blood. Lactic acidosis associated with GLUCOPHAGE is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking GLUCOPHAGE over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the cases.

It's also important for your liver to be working normally when you take GLUCOPHAGE. Your liver helps remove lactic acid from your bloodstream.

Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally.

There is no evidence that GLUCOPHAGE causes harm to the kidneys or liver.

Q10. Are there other risk factors for lactic acidosis?
Your risk of developing lactic acidosis from taking GLUCOPHAGE is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should discuss your risk with your physician. You should not take GLUCOPHAGE if:

- You have chronic kidney or liver problems
- You have congestive heart failure which is treated with medications, e.g., digoxin (Lanoxin®) or furosemide (Lasix®)
- You drink alcohol excessively (all the time or short-term "binge" drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have certain x-ray procedures with injectable contrast agents
- You are going to have surgery
- You develop a serious condition such as a heart attack, severe infection, or a stroke
- You are ≥ 80 years of age and have NOT had your kidney function tested.

Q11. What are the symptoms of lactic acidosis?
Some of the symptoms include: feeling very weak, tired or uncomfortable; unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or suddenly developing a slow or irregular heartbeat.

If you notice these symptoms, or if your medical condition has suddenly changed, stop taking GLUCOPHAGE and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q12. What does my doctor need to know to decrease my risk of lactic acidosis?
Tell your doctor if you have an illness that results in severe vomiting, diarrhea and/or fever, or if your intake of fluids is significantly reduced. These situations can lead to severe dehydration, and it may be necessary to stop taking GLUCOPHAGE temporarily.

You should let your doctor know if you are going to have any surgery or specialized x-ray procedures that require injection of contrast agents. GLUCOPHAGE therapy will need to be stopped temporarily in such instances.

Q13. Can I take GLUCOPHAGE with other medications?
Remind your doctor that you are taking GLUCOPHAGE when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOPHAGE may interfere with the way some drugs work and some drugs may interfere with the action of GLUCOPHAGE.

Q14. What if I become pregnant while taking GLUCOPHAGE?
Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take GLUCOPHAGE during pregnancy.

Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of GLUCOPHAGE if you are nursing a child.

Q15. Are there other risks associated with GLUCOPHAGE?
There is some evidence that any oral diabetes drug may increase the risk of heart problems. Experts are not sure what the real risk is for heart problems, if any, from taking oral diabetes medicine.

Q16. How do I take GLUCOPHAGE?
Your doctor will tell you how many GLUCOPHAGE tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of GLUCOPHAGE and your dosage will be increased gradually until your blood sugar is controlled.

Q17. Where can I get more information about GLUCOPHAGE?
This leaflet is a summary of the most important information about GLUCOPHAGE. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type II diabetes as well as GLUCOPHAGE and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.

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PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Glucophage® Tablets
(metformin hydrochloride)
NDA 20-357

October 1, 1997 to December 31, 1997

There were no spontaneous report(s) received by the sponsor pertaining to marketed formulations of metformin other than metformin hydrochloride.