CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076802

Name: Glimepiride Tablets
1 mg, 2 mg, 4 mg

Sponsor: TEVA Pharmaceuticals USA

Approval Date: October 6, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

APPROVAL LETTER

ANDA 76-802

OCT 6 2005

TEVA Pharmaceuticals USA
Attention: Philip Erickson
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 21, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Glimepiride Tablets, 1 mg, 2 mg, and 4 mg.

Reference is made to the tentative approval letter issued by this office on July 27, 2005, and to your amendments dated June 25, 2004; and August 17, 2005.

The listed drug product (RLD) referenced in your application, Amaryl Tablets of Aventis Pharmaceuticals Inc., has been subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 4,379,785 (the '785 patent) expired on October 6, 2005 (with pediatric extension).

With the expiration of the '785 patent, we have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Glimepiride Tablets, 1 mg, 2 mg, and 4 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Amaryl Tablets, 1 mg, 2 mg, and 4 mg, respectively, of Aventis Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications,
5901-B Ammendale Road
Beltsville, MD 20705-1266

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 10/6/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-802
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

Approved Electronic Labeling Located at:
\\Cdsesubogd1\n76802\N_000\2005-03-16\iss12-2004.pdf

Endorsements:
HFD-630/M.Shaikh/ 10/3/05
HFD-635/S.Liu/ S.H.Liu 10/3/05
HFD-617/L.Kwok/ 10/3/05
HFD-613/A.Payne/
HFD-613/J.Grace/

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TEVA

APPROVAL

cmc satisfactory.
10/4/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

TENTATIVE APPROVAL LETTER

ANDA 76-802

JUN 27 2005

TEVA Pharmaceuticals USA
Attention: Philip Erickson
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 21, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Glimepiride Tablets, 1 mg, 2 mg, and 4 mg.

Reference is also made to your amendments dated December 28, 2004; and February 3, March 16, May 11, and June 8, 2005.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of the exclusivity issue noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Amaryl Tablets of Aventis Pharmaceuticals Inc. (Aventis), has been subject to a period of patent protection. In the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 4,379,785 (the '785 patent) is listed with an expiration date of April 6, 2005. Your ANDA contains a paragraph III certification to the '785 patent under section 505(j)(2) (A)(vii)(III) of the Act stating that you will

not market this drug product prior to the expiration of this patent.

However, section 505A of the Act entitles the sponsor of the RLD to an additional six months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of section 505A, the sponsor of the RLD submits data previously requested by the agency relating to the use of the drug in the pediatric population. Prior to the expiration of the '785 patent, Aventis submitted data to the agency relating to the use of Amaryl Tablets in the pediatric population, and the agency has determined that these data meet the requirements of section 505A. The expiration of the '785 patent has, therefore, been effectively extended until October 6, 2005, and the agency may not issue a final approval letter to your application pursuant to section 505(j)(5)(B)(ii) of the Act prior to that date.

To reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to the OGD policy in effect at the time of receipt. The submission of multiple amendments

prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Orange Book." If you believe there are grounds for issuing the final approval letter prior to October 6, 2005, you should amend your application accordingly.

For further information on the status of this application or upon submitting an amendment to the application, please contact Peter Chen, R.Ph., Project Manager, at 301-827-5848.

Sincerely yours,

Robert Lumpkin for 6/21/2005

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-802
Division File
Field Copy
HFD-610/R. West
HFD-205

Endorsements:
HFD-620/M.Shaikh/ 6/25/05

HFD-625/M.Smela/ 6/27/05

HFD-617/P.Chen/ 4/22/05, 6/23/05

HFD-613/A.Payne/ } See attached

HFD-613/J.Grace/

6/27/2005

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RCLsted 6/27/05

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

LABELING

NDC 0093-7254-01

GLIMEPIRIDE Tablets
1 mg
ONCE A DAY

1 mg

Each tablet contains: glimepiride

℞ only

TEVA

Dosage and Administration: See package insert for full prescribing information.

Pharmacist: Dispense in a tight, light-resistant container as defined in USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

Store at 25° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

APPROVED
OCT - 6 2005

WARNING: KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Ins. 12/2004

Manufactured in Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7254-01

N 3 0

NDC 0093-7255-01

GLIMEPIRIDE Tablets
2 mg
ONCE A DAY

2 mg

Each tablet contains: glimepiride

℞ only

TEVA

Dosage and Administration: See package insert for full prescribing information.

Pharmacist: Dispense in a tight, light-resistant container as defined in USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

Store at 25° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

APPROVED
OCT - 6 2005

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Jerusalem, 91010, Israel
Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7255-01

N 3 7

NDC 0093-7256-01

GLIMEPIRIDE Tablets
4 mg
ONCE A DAY

4 mg

Each tablet contains: glimepiride

℞ only

TEVA

Dosage and Administration: See package insert for full prescribing information.

Pharmacist: Dispense in a tight, light-resistant container as defined in USP, with a child-resistant closure (as required).

Important: This package is not child resistant.

Store at 25° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

APPROVED
OCT - 6 2005

WARNING: KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Ins. 12/2004

Manufactured in Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7256-01

N 3 4

NDC 0093-7254-10

GLIMEPIRIDE
Tablets
1 mg
ONCE A DAY

Each tablet contains:
glimepiride 1 mg

℞ only

100 TABLETS

TEVA

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7254-10

NDC 0093-7255-10

GLIMEPIRIDE
Tablets
2 mg
ONCE A DAY

Each tablet contains:
glimepiride 2 mg

℞ only

100 TABLETS

TEVA

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7255-10

NDC 0093-7256-10

GLIMEPIRIDE
Tablets
4 mg
ONCE A DAY

Each tablet contains:
glimepiride 4 mg

℞ only

100 TABLETS

TEVA

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

0093-7256-10

GLIMEPIRIDE TABLETS

℞ only

7254
7255
7256

Iss. 12/2004

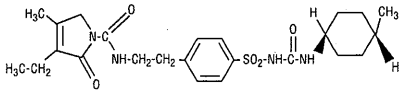
DESCRIPTION

Glimepiride tablets are an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder formulated into tablets of 1 mg, 2 mg, and 4 mg strengths for oral administration. Glimepiride tablets contain the active ingredient glimepiride and the following inactive ingredients: lactose monohydrous, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. In addition, glimepiride 1 mg tablets contain Ferric Oxide Red, glimepiride 2 mg tablets contain Ferric Oxide Yellow and FD&C Blue #2 Aluminum Lake, and glimepiride 4 mg tablets contain FD&C Blue #2 Aluminum Lake.

Chemically, glimepiride is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl) urea.

The CAS Registry Number is 93479-97-1

The structural formula is:



$C_{24}H_{34}N_4O_5S$ M.W. 490.62

Glimepiride is practically insoluble in water.

CLINICAL PHARMACOLOGY

Mechanism of Action

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Glimepiride is effective as initial drug therapy. In patients where monotherapy with glimepiride or metformin has not produced adequate glycemic control, the combination of glimepiride and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different primary mechanisms of action. This complementary effect has been observed with metformin and other sulfonylureas, in multiple studies.

Pharmacodynamics

A mild glucose-lowering effect first appeared following single oral doses as low as 0.5 to 0.6 mg in healthy subjects. The time required to reach the maximum effect (i.e., minimum blood glucose level [T_{min}]) was about 2 to 3 hours. In noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) patients, both fasting and 2 hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours.

In larger dose-ranging studies, blood glucose and HbA_{1c} were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of glimepiride. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of glimepiride up to 8 mg once daily. No difference in response was found when glimepiride was administered once or twice daily.

In two 14 week, placebo-controlled studies in 720 subjects, the average net reduction in HbA_{1c} for glimepiride tablet patients treated with 8 mg once daily was 2.0% in absolute units compared with placebo-treated patients. In a long-term, randomized, placebo-controlled study of NIDDM patients unresponsive to dietary management, glimepiride therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA_{1c}. Efficacy results were not affected by age, gender, weight, or race.

In long-term extension trials with previously-treated patients, no meaningful deterioration in mean fasting blood glucose (FBG) or HbA_{1c} levels was seen after 2½ years of glimepiride therapy.

Combination therapy with glimepiride and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body weight was > 130% of their ideal body weight. Initially, 5 to 10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FPG levels but the glimepiride/insulin therapy group used approximately 38% less insulin.

Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

Pharmacokinetics

Absorption

After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with NIDDM have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2 to 3 hours. When glimepiride was given with meals, the mean T_{max} (time to reach C_{max}) was slightly increased (12%) and the mean C_{max} and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Distribution

After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

Excretion

When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80 to 90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Pharmacokinetic Parameters

The pharmacokinetic parameters of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dose-proportionality (4 and 8 mg) study in patients with NIDDM are summarized below:

	Volunteers	Patients with NIDDM	
	Single Dose Mean ± SD	Single Dose (Day 1) Mean ± SD	Multiple Dose (Day 10) Mean ± SD
C_{max} (ng/mL)			
1 mg	103 ± 34 (12)	—	—
2 mg	177 ± 44 (12)	—	—
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	551 ± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
T_{max} (h)	2.4 ± 0.8 (48)	2.5 ± 1.2 (26)	2.8 ± 2.2 (23)
CL/f (mL/min)	52.1 ± 16.0 (48)	48.5 ± 29.3 (26)	52.7 ± 40.3 (23)
Vd/f (L)	21.8 ± 13.9 (48)	19.8 ± 12.7 (26)	37.1 ± 18.2 (23)
T½ (h)	5.3 ± 4.1 (48)	5.0 ± 2.5 (26)	9.2 ± 3.6 (23)

( ) = No. of subjects
CL/f = Total body clearance after oral dosing
Vd/f = Volume of distribution calculated after oral dosing

These data indicate that glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride were not different in healthy volunteers and in NIDDM patients. Oral clearance of glimepiride did not change over the 1 to 8 mg dose range, indicating linear pharmacokinetics.

Variability

In normal healthy volunteers, the intra-individual variabilities of C_{max}, AUC, and CL/f for glimepiride were 23%, 17%, and 15%, respectively, and the inter-individual variabilities were 25%, 29%, and 24%, respectively.

Special Populations

Geriatric

Comparison of glimepiride pharmacokinetics in NIDDM patients ≤ 65 years and those > 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Pediatric

No studies were performed in pediatric patients.

Gender

There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Race

No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of glimepiride tablets in patients with NIDDM, the antihyperglycemic effect was comparable in whites (n = 536), blacks (n = 63), and Hispanics (n = 63).

Renal Insufficiency

A single-dose, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLcr); (Group I, CLcr = 77.7 mL/min, n = 5), (Group II, CLcr = 27.7 mL/min, n = 3), and (Group III, CLcr = 9.4 mL/min, n = 7). Glimepiride was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{½}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).

A multiple-dose titration study was also conducted in 16 NIDDM patients with renal impairment using doses ranging from 1 to 8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CLcr less than 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg glimepiride may be given to NIDDM patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels.

Hepatic Insufficiency

No studies were performed in patients with hepatic insufficiency.

Other Populations

There were no important differences in glimepiride metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine.

The pharmacokinetics of glimepiride in morbidly obese patients were similar to those in the normal weight group, except for a lower C_{max} and AUC. However, since neither C_{max} nor AUC values were normalized for body surface area, the lower values of C_{max} and AUC for the obese patients were likely the result of their excess weight and not due to a difference in the kinetics of glimepiride.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

Coadministration of aspirin (1 g tid) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H2-receptor antagonists.

Concomitant administration of propranolol (40 mg tid) and glimepiride significantly increased C_{max}, AUC, and $T_{½}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of glimepiride tablets (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (e.g., fluconazole) and inducers (e.g., rifampicin) of cytochrome P450 2C9.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE

Glimepiride tablets are indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. Glimepiride may be used concomitantly with metformin when diet, exercise, and glimepiride or metformin alone do not result in adequate glycemic control.

Glimepiride tablets are also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

In initiating treatment for noninsulin-dependent diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, 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 an oral sulfonylurea or insulin should be considered. Use of glimepiride must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as a substitute for diet and exercise or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of glimepiride.

During maintenance programs, glimepiride monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations. Secondary failures to glimepiride monotherapy can be treated with glimepiride-insulin combination therapy.

In considering the use of glimepiride in asymptomatic patients, it should be recognized that blood glucose control in NIDDM has not definitely been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes. However, the Diabetes Control and Complications Trial (DCCT) demonstrated that control of HbA_{1c} and glucose was associated with a decrease in retinopathy, neuropathy, and nephropathy for insulin-dependent diabetic (IDDM) patients.

CONTRAINDICATIONS

Glimepiride tablets are contraindicated in patients with

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic 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 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. 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 advantages of glimepiride tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

General

Hypoglycemia

All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of glimepiride. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Combined use of glimepiride with insulin or metformin may increase the potential for hypoglycemia.

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 loss of control may occur. At such times, it may be necessary to add insulin in combination with glimepiride or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including glimepiride, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with glimepiride or metformin monotherapy, combined therapy with glimepiride and metformin or glimepiride and insulin may result in a response. Should secondary failure occur with combined glimepiride/metformin therapy, it may be necessary to initiate insulin therapy.

Information for Patients
Patients should be informed of the potential risks and advantages of glimepiride 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.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.

Laboratory Tests
Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Drug Interactions
(See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (> 1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Pregnancy
Teratogenic Effects
Pregnancy category C
Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, glimepiride tablets should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nonteratogenic Effects
In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers
In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, glimepiride should be discontinued in nursing mothers. If glimepiride is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above **Pregnancy,** Nonteratogenic Effects.)

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
In U.S. clinical studies of glimepiride, 608 of 1986 patients were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Comparison of glimepiride pharmacokinetics in NIDDM patients ≤ 65 years (n = 49) and those > 65 years (n = 42) was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups (see **CLINICAL PHARMACOLOGY, Special Populations,** Geriatric).

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal and hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents (see **CLINICAL PHARMACOLOGY, Special Populations,** Renal Insufficiency; **PRECAUTIONS, General;** and **DOSING AND ADMINISTRATION, Special Patient Population**).

ADVERSE REACTIONS
The incidence of hypoglycemia with glimepiride, as documented by blood glucose values < 60 mg/dL, ranged from 0.9 to 1.7% in two large, well-controlled, 1 year studies. (See **WARNINGS** and **PRECAUTIONS.**)

Glimepiride has been evaluated for safety in 2,013 patients in U.S. controlled trials, and in 1,551 patients in foreign controlled trials. More than 1,650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with glimepiride are shown below.

Adverse Events Occurring in > 1% Glimepiride Patients

	Glimepiride		Placebo	
	No.	%	No.	%
Total Treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Gastrointestinal Reactions
Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including glimepiride.

Dermatologic Reactions
Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas.

Hematologic Reactions
Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions
Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with glimepiride tablets. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions
Changes in accommodation and/or blurred vision may occur with the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 0.7%, and glimepiride, 0.4%.

OVERDOSAGE
Overdosage of sulfonylureas, including glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION
There is no fixed dosage regimen for the management of diabetes mellitus with glimepiride or any other hypoglycemic agent. The patient's fasting blood glucose and HbA_{1c} must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

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

Usual Starting Dose
The usual starting dose of glimepiride tablets as initial therapy is 1 to 2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See **PRECAUTIONS** Section for patients at increased risk.)

No exact dosage relationship exists between glimepiride and the other oral hypoglycemic agents. The maximum starting dose of glimepiride tablets should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Usual Maintenance Dose
The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1 to 2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA_{1c} levels, for example, every 3 to 6 months.

Glimepiride-Metformin Combination Therapy
If patients do not respond adequately to the maximal dose of glimepiride tablets monotherapy, addition of metformin may be considered. Published clinical information exists for the use of other sulfonylureas including glyburide, glipizide, chlorpropamide, and tolbutamide in combination with metformin.

With concomitant glimepiride tablets and metformin 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 glimepiride tablets and metformin therapy, the risk of hypoglycemia associated with glimepiride tablets therapy continues and may be increased. Appropriate precautions should be taken.

Glimepiride-Insulin Combination Therapy
Combination therapy with glimepiride tablets and insulin may also be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of > 150 mg/dL in plasma or serum depending on the patient. The recommended glimepiride tablets dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA_{1c} levels.

Specific Patient Populations
Glimepiride tablets are not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **CLINICAL PHARMACOLOGY, Special Populations** and **PRECAUTIONS, General**).

Patients Receiving Other Oral Hypoglycemic Agents
As with other sulfonylurea hypoglycemic agents, no transition period is necessary when transferring patients to glimepiride tablets. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to glimepiride tablets due to potential overlapping of drug effect.

HOW SUPPLIED
Glimepiride tablets are available in the following strengths and package sizes:
1 mg (Mottled Pink, round tablet, bisected on both sides. One side of the tablet debossed with "9" on one side of score and "3" on the other. The other side of the tablet debossed with "72" on one side of score and "54" on the other.)
Bottles of 100 and 1000.

2 mg (Mottled Green, round tablet, bisected on both sides. One side of the tablet debossed with "9" on one side of score and "3" on the other. The other side of the tablet debossed with "72" on one side of score and "55" on the other.)
Bottles of 100 and 1000.

4 mg (Mottled light Blue, round tablet, bisected on both sides. One side of the tablet debossed with "9" on one side of score and "3" on the other. The other side of the tablet debossed with "72" on one side of score and "56" on the other.)
Bottles of 100 and 1000.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

ANIMAL TOXICOLOGY
Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to 320 mg glimepiride/kg/day for 12 months (approximately 1,000 times the recommended human dose based on surface area). No evidence of tumor formation was observed in any organ. One female and one male dog developed bilateral subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture.

HUMAN OPHTHALMOLOGY DATA
Ophthalmic examinations were carried out in over 500 subjects during long-term studies using the methodology of Taylor and West and Laties et al. No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intra-ocular tension, or in any of the five lens-related variables examined.

Ophthalmic examinations were carried out during long-term studies using the method of Chylack et al. No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination.

Manufactured in Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-802** Dates of Submission: July 21, 2003 (original)

Applicant's Name: Teva Pharmaceutical Company

Established Name: Glimepiride tab, 1 mg, 2mg and 4 mg

Labeling COMMENTS:

1. **CONTAINER** (1 mg, 2mg and 4 mg): 100s and 1000s - Satisfactory in draft. However, before full approval please ensure the following changes are made:

   a. Revise storage temperature statement to read "Store between 20 and 25C (68-77F). [See USP Controlled Room Temperature]".

   b. Please ensure that your product strengths are differentiated by the use of boxing, contrasting colors or some other means.

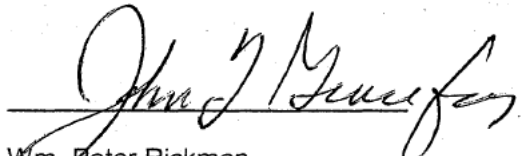
2. **INSERT:** Satisfactory in draft - See comment 1a under Container.

Please revise your labels and labeling, as instructed above, and submit in final print container labels and labels and labeling at a later time, closer to the time that you anticipated full approval. Your labels and labeling are satisfactory in draft.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-802
Date of Submission	July 21, 2003
Applicant	Teva
Drug Name	Glimepride tab
Strength(s)	1 mg, 2 mg, 4 mg

Draft Approval Summary

Container Labels		**Submitted**
1 mg, 2 mg, and 4 mg	100s, 1000s	Jul 21, 2003 vol1.1 red
Package Insert Labeling	#iss.4/2003.	Jul 21, 2003 vol 1.1 red

BASIS OF APPROVAL:

Patent Data For NDA 20-496

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4379785	Apr 6, 2005	U-118	METHOD OF LOWERING BLOOD SUGAR LEVEL	PIII	Same As

Exclusivity Data For NDA 20-496

Code/sup	Expiration	Description	*Labeling impact*
None			

Reference Listed Drug

RLD on the 356(h) form	Amaryl
NDA Number	20-496
RLD established name	Glimepride tab
Firm	Aventis
Currently approved PI	S-007
AP Date	4/15/02

Note: Firm just need to relocate "CRT" so that it appears at the end of the storage statement. Ver y minor. Ensure that strengths are differentiated. FPL required before full approval. Called 215-591-3000.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling Amaryl, NDA 20-496/s-007; Approved 4/15/03; Revised July

2001

2. PATENTS/EXCLUSIVITIES: See above
[Vol. A1.1 pg. 10-12]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM Teva , Jerusalem for teva in Sellersville PA

[Vol. A1.2]

4. CONTAINER/CLOSURE and PACKAGING CONFIGURATIONS

RLD: 1 mg, 2 mg and 4 mg, 100s and unit dose for 2 mg and 4 mg. Both side bisected (double bisect).
ANDA: 100s, 1000s bisected, HOPE, CRC

[Vol. A1.4 pg. 3440-3468] cap 3486-3504

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.2 p2850-2856]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP:
RLD: Store between 59-86.
ANDA: (b) (4).

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Dispense in well closed containers with safety closures
ANDA (*Insert*): Dispense in tight, light-resistant and child-resistant containers as defined in the USP.

9. BIOAVAILABILITY/BIOEQUIVALENCE: pending

10. OTHER

Date of Review: 9/6/03 Date of Submission: July 21, 2003

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cc:

ANDA: 76-802
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76802TAP.lab.doc
Review

John J. Grace 10/20/2003
John J. Grace 9/16/03

APPROVAL SUMMARY #1
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-802
Date of Submission	March 16, 2005
Applicant	Teva
Drug Name	Glimepiride Tablets
Strength(s)	1 mg, 2 mg, and 4 mg

Approval Summary

Container Labels		**Submitted e-FPL**
1 mg, 2 mg, and 4 mg	100s, 1000s	Mar. 16, 2005, vol. 4.1
Package Insert Labeling	#iss 12/2004.	\\Cdsesubogd1\n76802\N_000\2005-03-16\iss12-2004.pdf

BASIS OF APPROVAL:

Patent Data For NDA 20-496

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4379785	Apr 6, 2005	U-118	METHOD OF LOWERING BLOOD SUGAR LEVEL	PIII	Same As

Exclusivity Data For NDA 20-496

Code/sup	Expiration	Description	*Labeling impact*
None			

Reference Listed Drug

RLD on the 356(h) form	Amaryl
NDA Number	20-496
RLD established name	Glimepiride tab
Firm	Aventis
Currently approved PI	S-013
AP Date	8/16/04

Note:

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTE TO CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling Amaryl, NDA 20-496/s-007; Approved 4/15/03; Revised July

2001

2. PATENTS/EXCLUSIVITIES: See above
   [Vol. A1.1 pg. 10-12]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM Teva , Jerusalem for teva in Sellersville PA

   [Vol. A1.2]

4. CONTAINER/CLOSURE and PACKAGING CONFIGURATIONS

   RLD: 1 mg, 2 mg and 4 mg, 100s and unit dose for 2 mg and 4 mg. Both side bisected (double bisect).
   ANDA: 100s, 1000s bisected, HDPE, with CRC and screw.

   [Vol. A1.4 pg. 3440-3468] CRC cap 3486-3504

5. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.2 p2850-2856]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP:
   RLD: Store between 59-86.
   ANDA: [redacted] (b) (4) changed to store between 20-25C(68-77F)[See USP CRT]

8. DISPENSING STATEMENTS COMPARISON

   USP: None
   RLD: Dispense in well closed containers with safety closures
   ANDA (*Insert*): Dispense in tight, light-resistant and child-resistant containers as defined in the USP.

9. BIOAVAILABILITY/BIOEQUIVALENCE: pending

Date of Review: 4/9/05 Date of Submission: March 16, 2005

---

cc:

ANDA: 76-802
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76802AP1.lab.doc
Review
Digital signature: Apayne 4/9/05
EDR- FPL insert only and hard copies container labels
\\Cdsesubogd1\n76802\N_000\2005-03-16\iss12-2004.pdf

4/9/05
4/15/2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

CHEMISTRY REVIEWS

#1

ANDA 76-802

Glimepiride Tablets
1 mg, 2 mg, 4 mg

Teva Pharmaceuticals USA

Mujahid L. Shaikh

Division of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **76-802**

2. REVIEW #: 1

3. REVIEW DATE: December 8, 2003 (Revised on December 22, 2003)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	July 21, 2003
Amendment (To inform DMF number for (b) (4))	August 12, 2003

Note: This ANDA is accepted for filing on July 22, 2003 and Acknowledgement letter is issued to the firm on August 25, 2003.

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road, P. O. Box 1090, North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	215-591-3141

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None used
b) Non-Proprietary Name (USAN): Glimepiride Tablets

9. LEGAL BASIS FOR SUBMISSION:
The reference listed drug Amaryl® Tablets, manufactured by Aventis Pharmaceuticals Inc. (NDA 20-496) .

The drug is covered under U.S. Patent No. 4,379,785 and it expires on April 6, 2005.

11. PHARMACOL. CATEGORY: To lower glucose in Type II diabetes alone or in combination with Metformin.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1 mg, 2 mg , 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

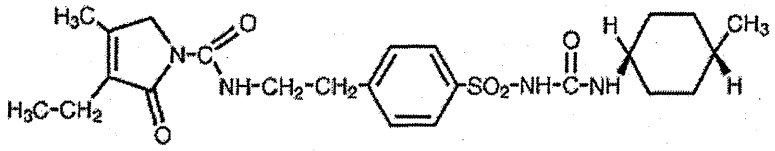
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Glimepiride: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.
Molecular Formula: $C_{24}H_{34}N_4O_5S$
Molecular Weight: 490.62
CAS Registry Number is 93479-97-1
The structural formula is:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code [1]	Status [2]	Date Review Completed	Comments
[redacted] (b) (4)				1	Deficient	12-8-03	
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	9-15-03	J.D. Ambrogio
Methods Validation	Not ready		
Labeling	Deficient	10-10-03	A. Payne/John Grace
Bioequivalence	Pending Review		
EA	Adequate	12-8-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-802

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NA (Minor) letter

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product: The proposed drug product is Glimepiride Tablets, 1mg, 2 mg, and 4 mg. The Reference Listed Drug is Amaryl® Tablets, 1 mg, 2 mg, and 4 mg and is approved for Aventis Pharmaceuticals Inc.

Drug Substance: The active ingredient in this drug product is Glimepiride

B. Description of How the Drug Product is Intended to be Used

The drug product is used as an adjunct to diet and excise to lower blood glucose in patients with non-insulin dependent (Type II) diabetes mellitus alone or in combination with metformin. Also, as an adjunct to diet, exercise, and insulin to lower blood sugar in hyperglycemic patients.

C. Basis for Approvability or Not-Approval Recommendation

In this CMC review for the ANDA, a not approvable letter is being sent to the firm including deficiencies identified in referenced DMF for the drug substance and in release and stability specifications for Glimepiride Tablets.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

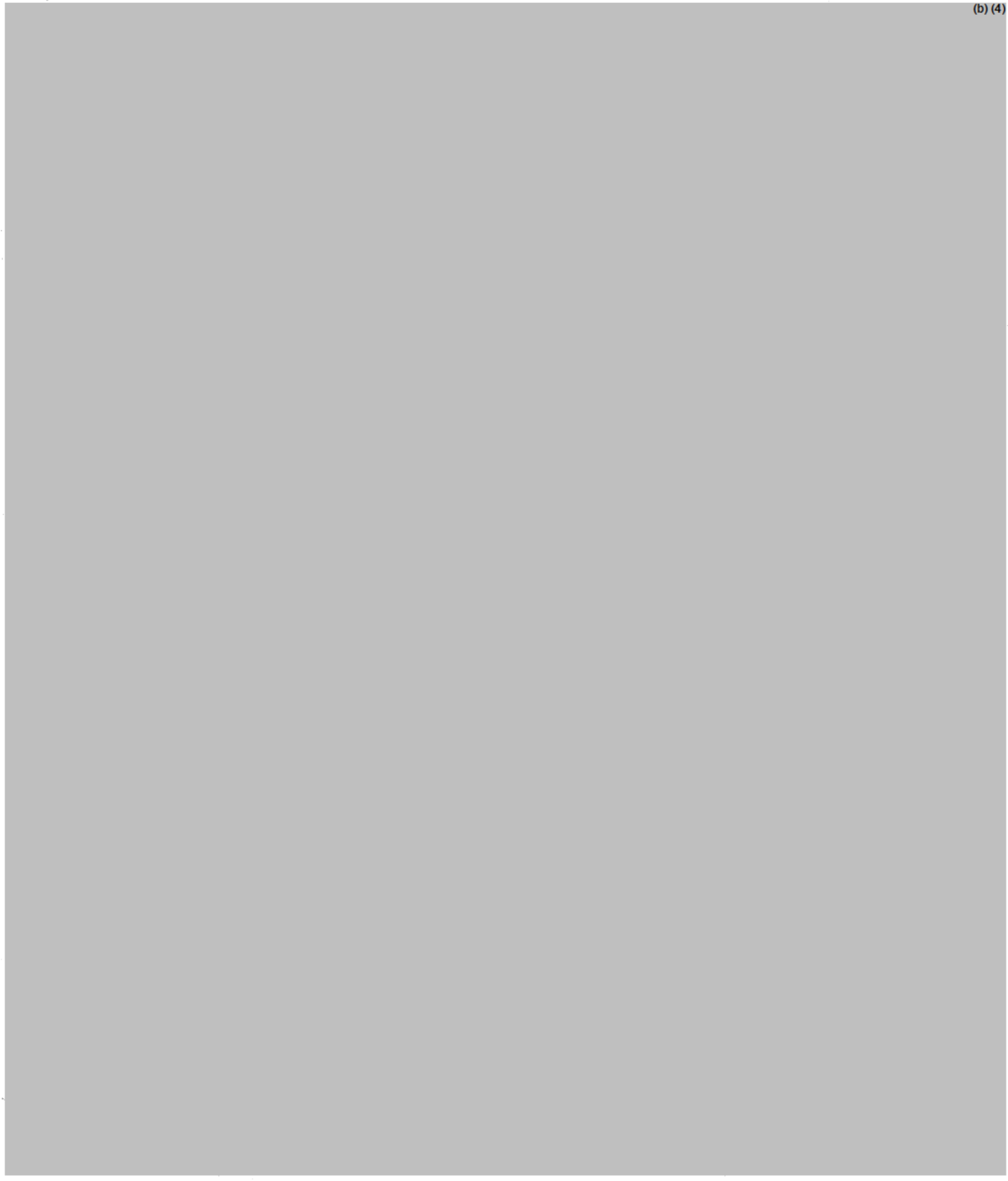
HFD-625/MShaikh/12/22/03 mujahid shaikh 12/31/03
HFD-625/MSmela/12/23/03
HFD-617/PChen/12/29/03

V:/Firmsnz/Teva/ltrs&rev/76802.R01.doc

C. CC: **ANDA 76-802**
Division File
DUP Jacket
Field Copy

Chemistry Assessment

(b) (4)



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cc: ANDA: 76-802
ANDA DUP
Division File
Field Copy

Endorsements :

HFD-625 /M. Shaikh /12/22/03 Mujahid Shaikh 12/30/03
HFD-6 25 /M. Smela /12/23/03 M Smela 1/2/04
HFD-6 17 / PChen /12/29/03 Peter Chen 12/30/03

F/t by: ard/12/29/03

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NOT APPROVABLE – MINOR

#2

ANDA 76-802

Glimepiride Tablets
1 mg, 2 mg, 4 mg

Teva Pharmaceuticals USA

Mujahid L. Shaikh

Division of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **76-802**

2. REVIEW #: 2

3. REVIEW DATE: June 22, 2005

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	July 21, 2003
Amendment (To inform DMF number for (b) (4) [redacted])	August 12, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed*	Document Date
*Bio Amendment (Response to April 7, 2004 letter)	June 25, 2004
*Minor Amendment	December 28, 2004
*Telephone amendment	February 3, 2005
Labeling	March 16, 2005
*Telephone Amendment	May 11, 2005
*Telephone Amendment	June 8, 2005

Note: This ANDA was accepted for filing on July 22, 2003 and Acknowledgement letter was issued to the firm on August 25, 2003.

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road, P. O. Box 1090, North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	215-591-3141

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None used
b) Non-Proprietary Name (USAN): Glimepiride Tablets

9. LEGAL BASIS FOR SUBMISSION:
The reference listed drug Amaryl® Tablets, manufactured by Aventis Pharmaceuticals Inc. (NDA 20-496) .

The drug is covered under U.S. Patent No. 4,379,785 and it expires on April 6, 2005.

11. PHARMACOL. CATEGORY: To lower glucose in Type II diabetes alone or in combination with Metformin.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1 mg, 2 mg , 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

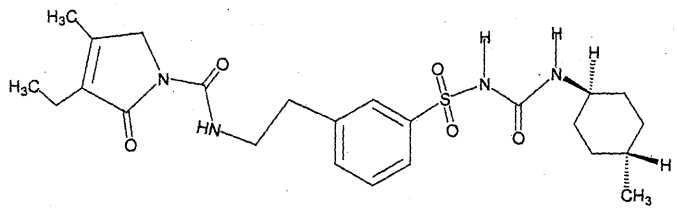
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Glimepiride: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.
Molecular Formula: $C_{24}H_{34}N_4O_5S$
Molecular Weight: 490.62
CAS Registry Number is 93479-97-1
The structural formula is:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code [1]	Status[2]	Date Review Completed	Comments
[redacted] (b) (4)				3	Adequate	10-7-04	CR # 4 by Joe Wetzel
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	9-15-03	J.D. Ambrogio
Methods Validation	Pending	1-18-05	M. Shaikh
Labeling	Acceptable	4-15-05	A. Payne/John Grace
Bioequivalence	Acceptable	7-19-04	M. Makary/K.Dhariwal/D.Conner
EA	Adequate	12-8-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

Minor Amendment

The Chemistry Review for ANDA 76-802

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: Approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

Teva has submitted commitment on page 3898 of the original submission to fully cooperate with FDA district laboratories and the OGD towards resolving any deficiencies or issues that may be brought forth during the review and validation of the test methods contained in this ANDA.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product: The proposed drug product is Glimepiride Tablets, 1mg, 2 mg, and 4 mg. The Reference Listed Drug is Amaryl® Tablets, 1 mg, 2 mg, and 4 mg and is approved for Aventis Pharmaceuticals Inc.

Drug Substance: The active ingredient in this drug product is Glimepiride

B. Description of How the Drug Product is Intended to be Used

The drug product is used as an adjunct to diet and excise to lower blood glucose in patients with non-insulin dependent (Type II) diabetes mellitus alone or in combination with metformin. Also, as an adjunct to diet, exercise, and insulin to lower blood sugar in hyperglycemic patients. The maximum recommended dose is 8 mg once daily.

C. Basis for Approvability or Not-Approval Recommendation

In this CMC review for the ANDA, acceptance specifications for Glimepiride USP, release and stability specification for the drug product including the revised dissolution specification became acceptable. Bio, EER and the labeling have acceptable status.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-630/MShaikh/ 6/22/05 mujahid shaikh 6/27/05

HFD-625/MSmela/6/23/05 M Smela 6/27/05

HFD-617/PChen/

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C. CC: **ANDA 76-802**
Division File
DUP Jacket
Field Copy

Chemistry Assessment

(b) (4)

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APPEARS THIS WAY ON ORIGINAL

#3

ANDA 76-802

Glimepiride Tablets
1 mg, 2 mg, 4 mg

Teva Pharmaceuticals USA

Mujahid L. Shaikh

Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **76-802**

2. REVIEW #: 3

3. REVIEW DATE: September 28, 2005

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	July 21, 2003
Amendment (To inform DMF number for (b) (4))	August 12, 2003
*Bio Amendment (Response to April 7, 2004 letter)	June 25, 2004
*Minor Amendment	December 28, 2004
*Telephone amendment	February 3, 2005
Labeling	March 16, 2005
*Telephone Amendment	May 11, 2005
*Telephone Amendment	June 8, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed*	Document Date
Minor Amendment	August 17, 2005

Note: This ANDA was accepted for filing on July 22, 2003 and Acknowledgement letter was issued to the firm on August 25, 2003.

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road, P. O. Box 1090, North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	215-591-3141

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None used
b) Non-Proprietary Name (USAN): Glimepiride Tablets

9. LEGAL BASIS FOR SUBMISSION:
The reference listed drug Amaryl® Tablets, manufactured by Aventis Pharmaceuticals Inc. (NDA 20-496) .

The drug is covered under U.S. Patent No. 4,379,785 and it expires on April 6, 2005.

11. PHARMACOL. CATEGORY: To lower glucose in Type II diabetes alone or in combination with Metformin.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1 mg, 2 mg , 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

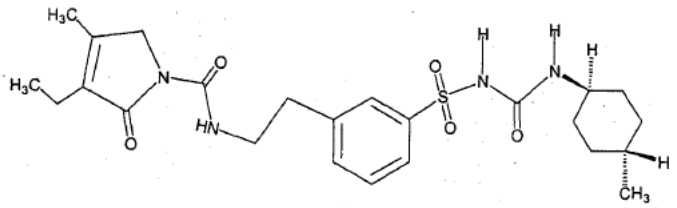
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Glimepiride: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.
Molecular Formula: $C_{24}H_{34}N_4O_5S$
Molecular Weight: 490.62
CAS Registry Number is 93479-97-1
The structural formula is:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code [1]	Status[2]	Date Review Completed	Comments
[redacted]			(b) (4)	3	Adequate	9-2-05	CR # 5 by N. Nashed
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	9-15-03	J.D. Ambrogio
Methods Validation	Pending	1-18-05	M. Shaikh
Labeling	Acceptable	4-15-05	A. Payne/John Grace
Bioequivalence	Acceptable	7-19-04	M. Makary/K.Dhariwal/D.Conner
EA	Adequate	12-8-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor Amendment

The Chemistry Review for ANDA 76-802

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: Tentatively approved on June 27, 2005. Now it is ready for final approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
Teva has submitted commitment on page 3898 of the original submission to fully cooperate with FDA district laboratories and the OGD towards resolving any deficiencies or issues that may be brought forth during the review and validation of the test methods contained in this ANDA.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product: The proposed drug product is Glimepiride Tablets, 1mg, 2 mg, and 4 mg. The Reference Listed Drug is Amaryl® Tablets, 1 mg, 2 mg, and 4 mg and is approved for Aventis Pharmaceuticals Inc.

Drug Substance: The active ingredient in this drug product is Glimepiride

B. Description of How the Drug Product is Intended to be Used

The drug product is used as an adjunct to diet and excise to lower blood glucose in patients with non-insulin dependent (Type II) diabetes mellitus alone or in combination with metformin. Also, as an adjunct to diet, exercise, and insulin to lower blood sugar in hyperglycemic patients. The maximum recommended dose is 8 mg once daily.

C. Basis for Approvability or Not-Approval Recommendation

Thos ANDA was tentatively approved on June 27, 2005. **It is acceptable for final approved.**

Acceptance specifications for Glimepiride USP, release and stability specification for the drug product including the revised dissolution specification were acceptable in tentative approved. Similarly, Bio, EER and the labeling have acceptable status at the time of tentative approval.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-630/MShaikh/ mujahid Shaikh 9/28/05

HFD-625/Shing Liu, Ph.D./ S. H. Liu 9/28/05

9/29/05

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C. CC: **ANDA 76-802**
Division File
DUP Jacket
Field Copy

Chemistry Assessment

(b) (4)

[redacted]

8 Pages have been Withheld as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-802
Drug Product Name	Glimepiride Tablets
Strength	1 mg, 2 mg and 4 mg
Applicant Name	Teva Pharmaceuticals USA
Address	North Wales, PA
Submission Date(s)	July 21, 2003
Amendment Date(s)	N/A
Reviewer	Moheb H. Makary
First Generic	Yes
File Location	V:\FIRMSNZ\TEVA\LTRS&REV\76802N0703.doc

I. Executive Summary

This submission consisted of two bioequivalence studies, one under fasting and the other nonfasting conditions and dissolution data on all strengths of the test and reference products. The studies conducted on the 4 mg tablets comparing them with Amaryl^R tablets, 4 mg, of Aventis Pharmaceuticals Inc. The study design for each of the BE studies is a two-way, crossover study in normal male and female subjects (n=30 and n=31 for the fasting and nonfasting studies, respectively). Statistical analyses of the plasma concentration data for glimepiride demonstrate bioequivalence in both studies.

For the fasting BE study, glimepiride results (point estimate, 90% CI) are: LAUC$_t$ of 102, 98.7-105%; LAUC$_i$ of 98.5, 94-103% and LCmax of 101, 92.2-111%. For the nonfasting BE study, glimepiride results (point estimate, 90% CI) are: LAUC$_t$ of 103, 99.3-106%; LAUC$_i$ of 101, 96.8-105% and LCmax of 102, 92.1-112%.

The firm also conducted dissolution testing on its glimepiride tablets, 1 mg, 2 mg and 4 mg. The dissolution testing is incomplete due to the deficiency stated below.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Glimepiride Tablets
Reference Product	Amaryl^{R} Tablets
RLD Manufacturer	Aventis Pharmaceuticals Inc.
NDA No.	20496
RLD Approval Date	November 30, 1995
Indication	AMARYL is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

B. PK/PD Information

Bioavailability	After oral administration, glimepiride is completely (100%) absorbed from the GI tract.
Food Effect	When glimepiride was given with meals, the mean T_{max} (time to reach C_{max}) was slightly increased (12%) and the mean C_{max} and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).
Tmax	2-3 hours
Metabolism	Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.
Excretion	When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces.
Half-life	5-6 hours
Relevant OGD or DBE History	The Division File contains the reviews of the following relevant documents: A.Protocol #01-034 submitted 6/6/01 B.Control #01-547 submitted 4/29/01.
Agency Guidance	BA/BE General Guidance
Drug Specific Issues (if any)	The DBE recommends that ANDA sponsors for glimepiride tablets, to conduct the following: 1. Because of the potential for hypoglycemia from glimepiride Tablet, 4 mg dose, the firm should conduct fasting and fed bioequivalence studies using the <u>1 mg dose</u>. 2. The 2 mg and 4 mg Glimepiride Tablets may be eligible for waivers of bioequivalence study requirements based on (1) acceptable biostudies on the 1 mg strength (2) acceptable dissolution testing for the 1 mg, 2 mg and 4 mg strengths (3) proportional

similarity for the 4 mg and 2 mg formulations relative to the 1 mg formulation.

The firm stated that they had not received the January 2003 Supplement of the Orange Book until April 2003. Therefore, the studies were conducted on 4 mg tablets.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Glimepiride
Internal Standard	(b) (4)
Method description	LC/MS/MS
QC range	5 00 to 380 ng/mL
Standard curve range	2.00 to 500 ng/mL
Limit of quantitation	2.00 ng/mL
Average recovery of Drug (%)	87.8%
Average Recovery of Int. Std (%)	85.9%
QC Intraday precision range (%)	2.5% to 8.8%
QC Intraday accuracy range (%)	92.5% to 108%
QC Interday precision range (%)	6.8% to 7.9%
QC Interday accuracy range (%)	97.6% to 103%
Bench-top stability (hrs)	(b) (4)
Stock stability (hrs)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	(b) (4) fold,
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chrom	Serial

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	B036501
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	32
No. of subjects completing	30
No. of subjects analyzed	30
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 23 Female: 9
Test product	Glimepiride Tablet
Reference product	Amaryl^{R} Tablet
Strength tested	4 mg
Dose	1x4 mg tablet

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	102%	98.7-105%
AUC∞	98.5%	94.0-103%
Cmax	101%	92.2-111%

Reanalysis of Study Samples Additional information in Appendix, Table 6 and Table 17				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Actual number	**% of total assays**	**Actual number**	**% of total assays**
Low IS	2	0.16	Same	
Low limit of quantitation	2	0.16	Same	
Values above the quantifiable limit	2	0.16	Same	
High IS	1	0.08	Same	
Total	7	0.56	Same	

Did use of recalculated plasma concentration data change study outcome? No

2. Single-dose Fed Bioequivalence Study

Study No.	B036502
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	32
No. of subjects completing	31
No. of subjects analyzed	31
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 16 Female 16
Test product	Glimepiride Tablet
Reference product	Amaryl^{R} Tablet
Strength tested	4 mg
Dose	1x4 mg tablet

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	103%	99.3-106%
AUC∞	101%	96.8-105%
Cmax	102%	92.1-112%

Reanalysis of Study Samples Additional information in Appendix, Table 6 and Table 17				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Actual number	**% of total assays**	**Actual number**	**% of total assays**
Unknown processing error	6	0.46	Same	
Low limit of quantitation	2	0.15	Same	
Values above the quantifiable limit	7	0.54	Same	
High IS	1	0.08	Same	
Total	16	1.23	Same	

F. Formulation

Location in appendix	SectionIV.B, Page 24
Are inactive ingredients within IIG limits?	Yes
If yes, list ingredients outside of limits	
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	All
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	Phosphate buffer pH 7.8
Volume (mL)	900
USP Apparatus type	2
Rotation (rpm)	(b) (4)
Firm's proposed specifications	NLT (b) (4) % (Q) in 30 minute
F2 metric calculated?	N/A
If no, reason why F2 not calculated	Rapid dissolved product
Is method acceptable?	No
If not then why?	The firm's dissolution method is not the same as the FDA-recommended method
Source of Method	FDA
Medium	Phosphate buffer pH 7.8
Volume (mL)	900
USP Apparatus type	2
Rotation (rpm)	**75**
FDA-recommended specifications	NLT (b) (4) % (Q) in (b) (4) minutes

H. Waiver Request(s)

Strengths for which waivers are requested	1 mg and 2 mg tablets
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	

I. Deficiency Comment

The dissolution method used by the firm is not acceptable. The firm should submit comparative dissolution testing in 900 mL of phosphate buffer pH 7.8, at 37°C using apparatus II (paddle) at **75** rpm. The test product should meet the following specification: NLT (b)(4) **% (Q) in** (b)(4) **minutes**

J. Recommendations

1. The fasting and nonfasting bioequivalence studies conducted by Teva Pharmaceuticals USA on its Glimepiride Tablet, 4 mg, lot # K-31127, comparing it to Aventis Pharmaceuticals Inc.'s Amaryl® Tablet, 4 mg, have been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Teva Pharmaceuticals USA on its , Glimepiride Tablets, 4 mg, 2 mg and 1 mg, lots #K-31127, K-31151 and K-31150, respectively, is incomplete for the reason given in deficiency comment.

3. The waiver of *in vivo* bioequivalence requirements for the firm's Glimepiride tablets, 1 mg and 2 mg, cannot be granted at present pending acceptable dissolution testing.

The firm should be informed of the deficiency comment and recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

GJP Singh, Ph.D
Division of Bioequivalence
Team Leader Review Branch III

4/5/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	B036501
Study Title	A Relative Bioavailability Study of Glimepiride 4 mg Tablets Under Fasting Conditions
Clinical Site	Novum Pharmaceutical Services
Principal Investigator	Solomon G. Ghide, M.D.
Study/Dosing Dates	Period I February 22, 2003 Period II March 01, 2003
Analytical Site	(b) (4)
Analytical Director	
Analysis Dates	March 08-23, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	30

Treatment ID	**Test**	**Reference**
Test or Reference	T	R
Product Name	Glimepiride Tablets	Amaryl® Tablets
Manufacturer	Teva Pharmaceuticals USA	Aventis Pharmaceuticals Inc.
Batch/Lot No.	K-31127	1050541
Manufacture Date	January 27, 2003	N/A
Expiration Date	N/A	June, 2004
Strength	4 mg	4 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	97.9%	97.5%
Formulation	See Appendix Section B	
Dose Administered	1x4 mg Tablet	1x4 mg Tablet
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	One week
Randomization Scheme	AB for subjects #3, 4, 5, 10, 12, 13, 15, 16, 19, 21, 24, 25, 26, 27, 29, 30 and BA for the rest of subjects.
Blood Sampling Times	Prior to dosing and at 0.50,1.0,1.50,2.0,2.50, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0 and 24.0 after dosing
Blood Volume Collected/Sample	1x10 mL
Blood Sample Processing/Storage	Blood samples were centrifuged at high speed for about 15 minutes. The resulting plasma was transferred to appropriately labeled tubes and frozen at -20^{O}C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours pre-dose and 4 hours post-dose.
Length of Confinement	From at least 11 hours pre-dose to 24 hours post-dose.
Safety Monitoring	Blood pressure and heart rate were measured prior to dosing in both periods. All subjects received 60 mL of 20% glucose solution at approximately 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, and 8 hours after dosing in each period. The subjects were monitored for symptoms of hypoglycemia.

Comments on Study Design:

All doses (1 tablet) were administered with 240 mL of 20% glucose solution. The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	9.4
Mean	28	Mean	70.9	18-40	84.4	Male	71.9	Afr. Amer.	37.5
SD	9.4	SD	11.0	41-64	15.6	Female	28.1	Hispanic	50.0
Range	18-51	Range	48.6-89	65-75				Asian	0
				>75				Others	3.1

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
04	Subject #04 was discontinued from further study participation by the investigator on 2/28/03 due adverse event of rash.	1	No
30	Subject #30 voluntarily withdrew from study participation on 02/28/03 due to personal reasons.	1	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Nausea	1	0
Rash	1	0
Decreased blood pressure	1	1
Low blood sugar	4	4
Headache	2	2
Shaky	2	2
Dizzy	0	1
Feel "funny"	0	1
Hungry	1	0
Burning sensation, left forearm	1	0
Total:	13	11

Table 4 Protocol Deviations

No deviations from the protocol were reported.

Comments on Dropouts/Adverse Events/Protocol Deviations:

The adverse events occurred approximately with similar frequency for both treatments.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent									
QC Conc. (ng/mL)	5	40	380							
Inter day Precision (%CV)	12.8	8.1	4.8							
Inter day Accuracy (%)	98	94.8	105							
Cal. Standards Conc. (ng/mL)	2	4	10	20	50	100	200	400	500	
Inter day Precision (%CV)	2.2	5.6	6.5	3.6	4.7	5.4	4.7	4.6	2.4	
Inter day Accuracy (%)	102	97	103	94	96	99.5	101	105	104	
Linearity Range (range of R^2 values)	0.998									

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
L200.107	June 20, 2001	Sample Analysis (Chromatographic)

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The total number of re-assays represented 0.56% of the overall number of samples analyzed. There were no pharmacokinetic repeats. Analytical method and data are acceptable

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	hr-ng/mL	1479.96	35.44	1469.35	37.35	1.01
AUC∞	hr-ng/mL	1613.84	34.29	1660.08	38.40	0.97
Cmax	ng/mL	231.70	41.99	226.89	38.79	1.02
Tmax	hr	4.48		4.42		
T1/2	hr	6.1		0.118		
Kel	1/hr	0.132		7.47		

Table 9 Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	1380.4	1355.34	102	98.7-105
AUC∞	1503.8	1527.34	98.5	94.0-107
Cmax	213.96	211.46	101	92.2-111

Table 10 Additional Study Information

Root mean square error, AUC	0.071
Root mean square error, Cmax	0210
Ke and AUCi determined for how many subjects?	29
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	N/A

Comments on Pharmacokinetic Analysis:

The 90% confidence intervals for AUCt, AUCi and Cmax are within the acceptable limits of 80-125% for glimepiride.

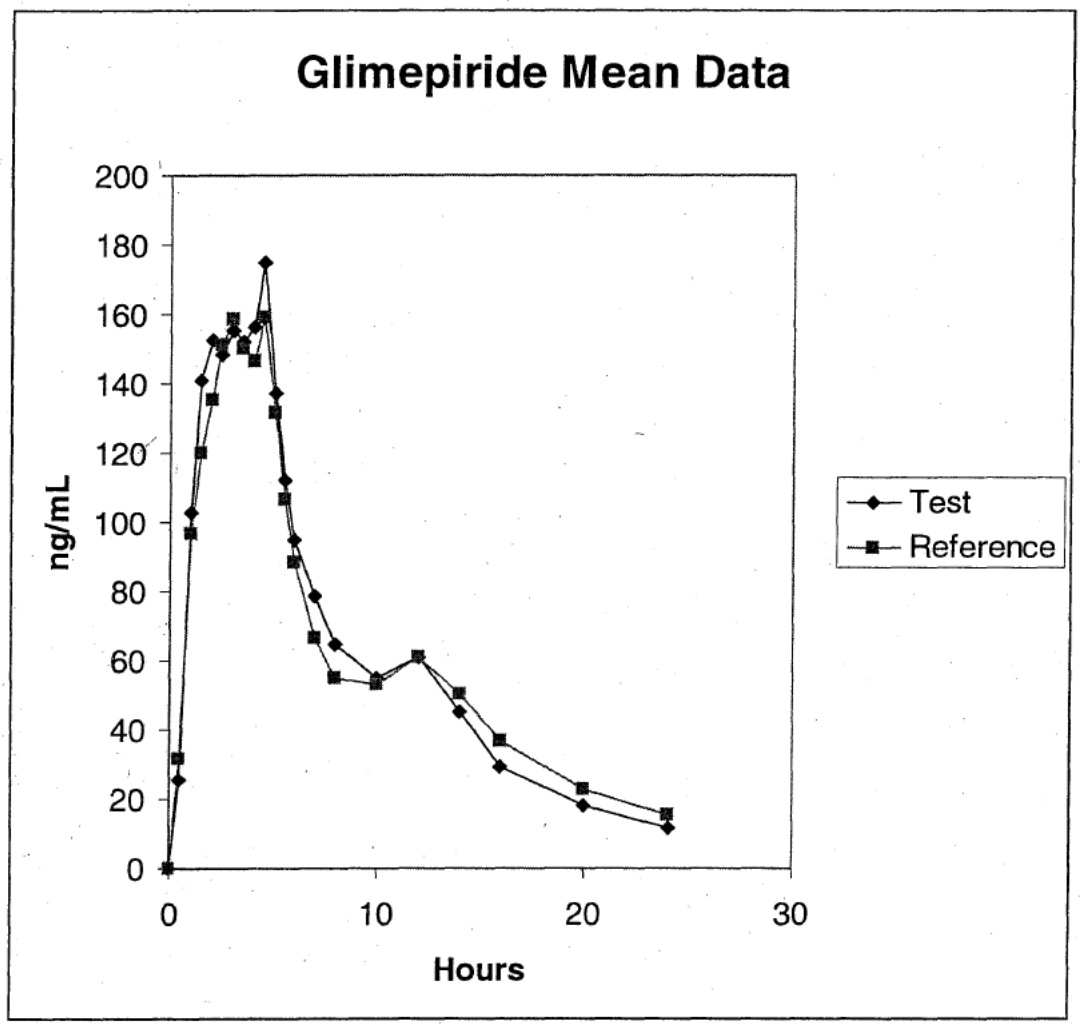
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is acceptable.

Table 11 Mean Glimepiride Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time (hr)	Test (n=30)		Reference (n=30)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.5	25.66	86.48	31.56	83.01	0.81
1	102.67	63.77	96.91	62.09	1.06
1.5	140.88	67.37	120.22	58.24	1.17
2	152.75	70.75	135.41	68.90	1.13
2.5	148.20	69.07	151.12	67.34	0.98
3	155.31	63.24	158.58	67.63	0.98
3.5	152.22	52.73	150.36	62.61	1.01
4	156.33	51.76	146.51	60.16	1.07
4.5	174.96	43.05	159.23	45.89	1.10
5	137.35	42.79	131.49	41.47	1.04
5.5	112.03	48.89	106.31	45.01	1.05
6	94.72	53.63	88.25	47.93	1.07
7	78.38	66.71	66.67	46.20	1.18
8	64.45	61.91	54.97	49.63	1.17
10	55.09	57.70	53.14	64.27	1.04
12	60.87	83.41	61.11	85.58	1.00
14	44.93	84.73	50.16	79.51	0.90
16	29.20	70.90	36.53	86.88	0.80
20	18.12	82.01	22.80	81.98	0.79
24	11.41	71.33	15.31	79.90	0.75

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	B036502
Study Title	A Relative Bioavailability Study of Glimepiride 4 mg Tablets Under Non-Fasting Conditions
Clinical Site	Novum Pharmaceutical Services
Principal Investigator	Solomon G. Ghide, M.D.
Study/Dosing Dates	Period I March 01, 2003 Period II March 08, 2003
Analytical Site	(b) (4)
Analytical Director	
Analysis Dates	March 15, 2003 - April 01, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	30

Treatment ID	**Test Product**	**Reference Product**
Test or Reference	T	R
Product Name	Glimepiride Tablets	Amaryl® Tablets
Manufacturer	Teva Pharmaceuticals USA	Aventis Pharmaceuticals Inc.
Batch/Lot No.	K-31127	1050541
Manufacture Date	January 27, 2003	N/A
Expiration Date	N/A	June, 2004
Strength	4 mg	4 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency		(b) (4)
Content Uniformity	97.9%	97.5%
Formulation	See Appendix Section B	
Dose Administered	1x4 mg Tablet	1x4 mg Tablet
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	One week
Randomization Scheme	AB for subjects #1, 3, 4, 7, 8, 9, 10, 13, 14, 16, 17, 23, 26, 27, 29, 32 and BA for the rest of subjects.
Blood Sampling Times	Same as fasting study
Blood Volume Collected/Sample	Same as fasting study
Blood Sample Processing/Storage	Same as fasting study
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 12
Length of Fasting before Meal	10 hours pre-dose until 30 minutes prior to dosing when a standard breakfast (same as the one recommended by the DBE) was given.
Length of Confinement	Same as fasting study
Safety Monitoring	Same as fasting study
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	

Comments on Study Design:

All doses (1 tablet) were administered with 240 mL of 20% glucose solution. The study design is acceptable.

Clinical Results

Table 12 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	28.1
Mean	32	Mean	73.3	18-40	84.38	Male	50	Afr. Amer.	53.1
SD	11.3	SD	10.6	41-64	15.62	Female	50	Hispanic	15.62
Range	18-56	Range	53-101	65-75	0			Asian	0
				>75	0			Others	3.1

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
11	Subject #11 was discontinued from further study participation by the investigator at period II check-in on 03/07/03 due a positive drug screen.	II	No

Table 14 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Diarrhea	1	2
Headache	0	1
Dizzy	0	1
Elevated pulse	0	1
Total:	1	5

Table 15 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Subject #29 checked into period II at 2300, approximately 8.5 hours before dosing. The protocol states the period of confinement is to be at least 10.5 hours before dosing until after the 24-hour blood collection each period. The subject stated he last ate at 1700, approximately 15 hours before dosing. The investigator reviewed the deviation and approved the subject for dosing since the subject met the requirement that he fast 10.5 hours prior to dosing and his late arrival presented no medical contraindication to continued study participation.		#29

Comments on Adverse Events/Protocol Deviations:

The adverse events reported in study probably resulted from hypoglycemia. Headache, dizziness and nausea have been seen in clinical studies on Amaryl^{R}.

b) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Parent									
QC Conc. (ng/mL)	5	40	380							
Inter day Precision (%CV)	8.7	6.7	5.5							
Inter day Accuracy (%)	103	93.5	102							
Cal. Standards Conc. (ng/mL)	2	4	10	20	50	100	200	400	500	
Inter day Precision (%CV)	3.1	5.6	5.7	5.6	2.9	3.1	3.3	3.8	3.5	
Inter day Accuracy (%)	99	105	98	95	96	102	99	105	103	
Linearity Range (range of R^2 values)	0.998									

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
L200.107	June 20, 2001	Sample Analysis (Chromatographic)

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The total number of re-assays represented 1.23% of the overall number of samples analyzed. There were no pharmacokinetic repeats. Analytical method and data are acceptable

c) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	hr-ng/mL	1639.08	51.65	1632.30	59.42	1.00
AUC∞	hr-ng/mL	1751.42	61.16	1824.74	73.79	0.96
Cmax	ng/mL	267.63	37.79	266.71	40.47	1.00
Tmax	Hr	3.57		3.58		
T1/2	Hr	5.75		5.49		
Kel	1/hr	0.131		0.136		

Table 20 Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	1479.6	1440.53	103	99.3-106
AUC∞	1539.3	1527.6	101	96.8-105
Cmax	247.8	243.7	102	92.1-112

Table 21 Additional Study Information

Root mean square error, AUC	0.078
Root mean square error, Cmax	0.229
Ke and AUCi determined for how many subjects?	28
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	N/A

Comments on Pharmacokinetic Analysis:

The 90% confidence intervals for AUCt, AUCi and Cmax are within the acceptable limits of 80-125% for glimepiride.

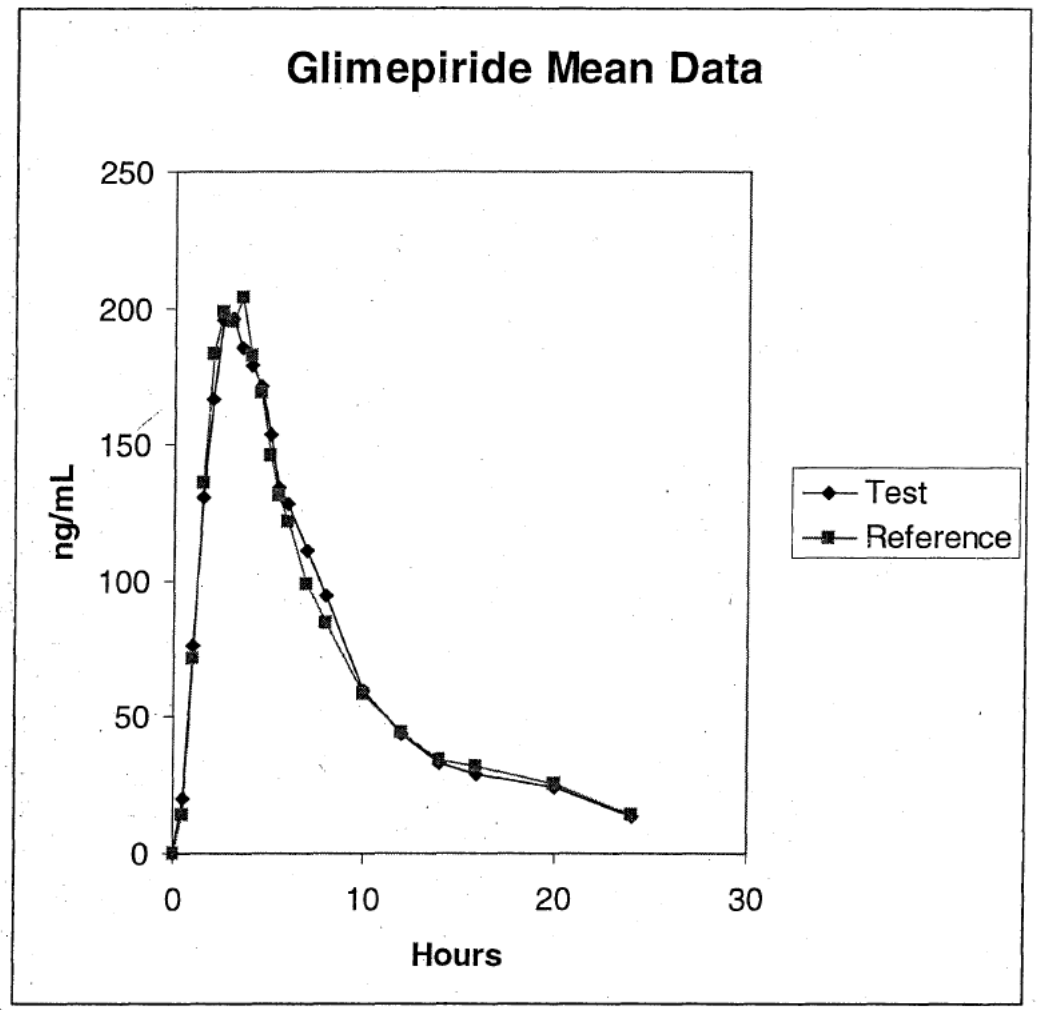
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is acceptable.

Table 22 Mean Glimepiride Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study

Time (hr)	Test (n=31)		Reference (n=31)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.5	20.15	156.36	14.36	113.78	1.40
1	76.14	119.14	71.38	90.39	1.07
1.5	130.41	86.36	135.76	75.89	0.96
2	166.55	67.67	183.21	68.21	0.91
2.5	195.67	55.48	198.34	59.88	0.99
3	196.09	48.73	195.11	43.40	1.01
3.5	185.31	47.52	204.11	47.57	0.91
4	178.93	53.89	182.85	46.09	0.98
4.5	171.45	55.12	168.91	51.85	1.02
5	153.38	51.94	146.00	55.49	1.05
5.5	134.33	54.90	130.97	63.38	1.03
6	128.03	63.48	121.76	69.19	1.05
7	110.95	74.38	98.76	73.99	1.12
8	94.55	86.27	84.71	81.72	1.12
10	59.49	102.82	58.36	94.59	1.02
12	43.65	112.96	44.44	112.41	0.98
14	33.22	119.68	34.09	129.71	0.97
16	29.05	117.75	32.15	135.38	0.90
20	24.44	127.58	25.43	148.76	0.96
24	13.73	147.83	14.16	168.97	0.97

Figure 2 Mean Glimepiride Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Quantitative Composition for Glimepiride Tablets, 1 mg, 2 mg and 4 mg:

Ingredient	Amount (mg)Tablet 1 mg strength	Amount (mg)Tablet 2 mg strength	Amount (mg) Tablet 4 mg strength
Glimepiride	1.0	2.0	4.0
Lactose Monohydrate NF (b) (4)	(b) (4)		
Sodium Starch Glycolate NF			
Povidone USP (b) (4)			
Microcrystalline Cellulose NF (b) (4)			
Color Ferric Oxide Red NF			
Color Ferric Oxide Yellow NF			
Color FD&C Blue No. 2 Aluminum Lake (b) (4)			
Magnesium Stearate NF			
(b) (4)			
Total			

(b) (4)

Percentage Composition for Glimepiride Tablets, 1 mg, 2 mg and 4 mg:

Ingredient	Amount (%)/ Tablets 1 mg strength	Amount (%) /Tablet 2 mg strength	Amount (%)/Tablet 4 mg strength
Glimepiride	(b) (4)		
Lactose Monohydrate NF (b) (4)			
Sodium Starch Glycolate NF			
Povidone USP (b) (4)			
Microcrystalline Cellulose NF (b) (4))			
Color Ferric Oxide Red NF			
Color Ferric Oxide Yellow NF			
Color FD&C Blue No. 2 Aluminum Lake (b) (4)			
Magnesium Stearate NF			
(b) (4)			
Total			

(b) (4)

C. Dissolution Data

Table 1

Sampling Time (min)	Test Product, Glimepiride Tablets Strength 1 mg Lot No.K-31150			Reference Product, Amaryl Tablets Strength 1 mg Lot No. 1048978		
	Mean	%CV	Range	Mean	%CV	Range
10	93	2.9	88-97	93	1.1	90-94
15	95	1.8	91-97	92	1.4	90-94
30	95	1.3	93-98	92	1.6	90-95
Sampling Time (min)	**Test Product, Glimepiride Tablets Strength 2 mg Lot No.K-31151**			**Reference Product, Amaryl Tablets Strength 2 mg Lot No. 1049949**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
10	95	2.1	89-97	89	4.4	83-94
15	97	1.8	93-98	95	2.6	90-99
30	96	1.3	95-99	95	2.8	91-100
Sampling Time (min)	**Test Product, Glimepiride Tablets Strength 4 mg Lot No.K-31127**			**Reference Product, Amaryl Tablets Strength 4 mg Lot No. 1050541**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
10	87	6.1	80-94	89	1.3	87-91
15	95	1.3	93-97	90	1.2	89-91
30	95	1.7	91-97	92	1.2	89-93

D. SAS Output

Study	Data	SAS Code	SAS Output
Fasting Study	glimfast.prn	glimcod.txt	glimfastingoutput.txt
Fed Study	glimfed.prn	glimcod.txt	glimfedoutput.txt

E. Additional Attachments

-----Original Message-----
From: Tran, Nhan L
Sent: Wednesday, March 24, 2004 9:29 AM
To: Makary, Moheb H
Cc: Singh, Gur J P
Subject: RE: Dissolution method for Glimepiride tablets

Moheb:

Per latest NDA review (Biopharm AND Chemistry reviews), following is the dissolution method to be recommended to firms for glimepiride tablets:

900 mL pH 7.8 Phosphate Buffer
USP Paddle, 75 rpm
NLT (b)(4)%, (b)(4) min

Thanks,

-----Original Message-----
From: Makary, Moheb H
Sent: Tuesday, March 23, 2004 2:53 PM
To: Tran, Nhan L
Cc: Makary, Moheb H
Subject: Dissolution method for Glimepiride tablets

Dr. Tran,

The dissolution method for Glimepiride tablets in our dissolution data base is:

900 mL pH 7.5 Phosphate Buffer
USP Paddle, **75 rpm**
NLT (b)(4)%, 15 min

However, in a letter to (b)(4) dated 1/8/02, the Agency recommends the following dissolution method:

900 mL pH 7.5 Phosphate Buffer
USP Paddle, **50 rpm**

Which dissolution method is recommended by the Agency for Glimepiride tablets ?

Thanks,

Moheb

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-802 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Glimepiride Tablets, 1 mg, 2 mg and 4 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution method you submitted is not acceptable. Please submit comparative dissolution testing in 900 mL of phosphate buffer pH 7.8, at 37°C using apparatus II (paddle) at **75** rpm. The test product should meet the following specification:

> Not less than (b)(4)% (Q) of the labeled amount of glimepiride in the dosage form is dissolved in (b)(4) minutes

With your response to the above deficiency, please indicate if you accept the above dissolution method and specification.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-802
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

V:\FIRMSNZ\TEVA\LTRS&REV\76802N0703.doc
Printed in final on 4/5/04

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MM for 4-5-04
HFD-658/ Bio team Leader G. Singh GSingh
HFD-650/ D. Conner 4/5/04

BIOEQUIVALENCE - DEFICIENCIES — Submission Date: 7/21/2003

1. Fating Study — Strength: 4 mg
   Clinical: Novum Pharmaceutical Services — Outcome: IC
   Analytical: (b) (4)

2. Fed Study — Strength: 4 mg
   Clinical: Novum Pharmaceutical Services — Outcome: IC
   Analytical: (b) (4)

3. Dissolution Waiver — Strength: 2 mg
   Outcome: IC

4. Dissolution Waiver — Strength: 1 mg
   Outcome: IC

Outcome Decisions:
IC - Incomplete

Glimepiride Tablets
1 mg, 2 mg and 4 mg
ANDA #76-802
Reviewer: Moheb H. Makary
W. 76802A0504.doc

Teva Pharmaceuticals USA
North Wales, PA
Submission Date:
June 25, 2004

Review of an Amendment

Executive Summary

The firm has submitted its response to the comment made by the Division of Bioequivalence (DBE) in its letter of April 07, 2004. In this amendment, Teva submitted comparative dissolution data for its Glimepiride Tablets, 1 mg, 2 mg and 4 mg versus the RLD, Amaryl^{R} Tablets, 1 mg, 2 mg and 4 mg, respectively, using the FDA' s recommended dissolution method. The dissolution data for the firm's Glimepiride Tablets, 1 mg, 2 mg and 4 mg, were found acceptable. The response is acceptable. The application is now acceptable with no deficiencies.

Background

On July 21, 2003, the firm submitted two bioequivalence studies on its Glimepiride 4 mg tablet and dissolution data on all strengths of the test and reference products. The studies were found acceptable. The dissolution testing was found incomplete.

DBE Comment

The dissolution method you submitted is not acceptable. Please submit comparative dissolution testing in 900 mL of phosphate buffer pH 7.8, at 37^{O}C using apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> *Not less than (b)(4)% (Q) of the labeled amount of glimepiride in the dosage form is dissolved in (b)(4) minutes*

With your response to the above deficiency, please indicate if you accept the above dissolution method and specification.

Firm's Response

The firm has submitted comparative dissolution results using the FDA's recommended dissolution method. The dissolution testing is acceptable. The firm also has acknowledged the recommended dissolution specification.

In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	Phosphate buffer pH 7.8
Volume (mL)	900
USP Apparatus type	2
Rotation (rpm)	75
Firm's proposed specifications	NLT (b)(4)% (Q) in (b)(4) minutes
F2 metric calculated?	N/A
If no, reason why F2 not calculated	Rapid dissolved product

Dissolution Results

Sampling Time (min)	**Test Product, Glimepiride Tablets Strength 1 mg Lot No.K-31150**			**Reference Product, Amaryl Tablets Strength 1 mg Lot No. 1072165**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
10	94	2.5	89-96	93	3.4	86-97
15	95	1.8	94-99	92	2.1	87-95
30	96	1.6	93-99	90	1.6	89-93
Sampling Time (min)	**Test Product, Glimepiride Tablets Strength 2 mg Lot No.K-31151**			**Reference Product, Amaryl Tablets Strength 2 mg Lot No. 1073702**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
10	95	2.1	92-98	97	1.9	94-101
15	96	1.4	93-98	95	1.2	94-96
30	96	1.8	93-99	96	2.3	93-101
Sampling Time (min)	**Test Product, Glimepiride Tablets Strength 4 mg Lot No.K-31127**			**Reference Product, Amaryl Tablets Strength 4 mg Lot No. 1074073**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
10	92	1.6	90-95	92	1.5	90-93
15	93	2.0	91-97	93	2.0	90-97
30	94	1.7	92-97	93	1.9	91-97

The firm's reply to the comment is acceptable.

Recommendations

1. The fasting and nonfasting bioequivalence studies conducted by Teva Pharmaceuticals USA on its Glimepiride Tablet, 4 mg, lot # K-31127, comparing it to Aventis Pharmaceuticals Inc.'s Amaryl® Tablet, 4 mg, have been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Teva Pharmaceuticals USA on its , Glimepiride Tablets, 4 mg, 2 mg and 1 mg, lots #K-31127, K-31151 and K-31150, respectively, is acceptable. The formulations for the 1 mg and 2 mg are proportionally similar to the 4 mg tablet, which underwent bioequivalence testing. The waivers of the in vivo bioequivalence study requirements for 1 mg and 2 mg tablets of the test product are granted. Teva's 1 mg and 2 mg tablets are therefore deemed bioequivalent to Amaryl® Tablets, 1 mg and 2 mg, respectively, manufactured by Aventis Pharmaceuticals Inc.

3. The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.8, at 37°C using apparatus II (paddle) at 75 rpm. The test products should meet the following specification:

> Not less than (b)(4)% (Q) of the labeled amount of glimepiride in the dosage form is dissolved in (b)(4)minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Review Branch IV
Division of Bioequivalence

Dhariwal. 7/19/04

Kuldeep R. Dhariwal, Ph.D.
Team Leader, Review Branch IV
Division of Bioequivalence

for Barbara M. Davit 7/19/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-802 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Glimepiride Tablets, 1 mg, 2 mg and 4 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.8, at 37°C using apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than (b)(4)% (Q) of the labeled amount of glimepiride in the dosage form is dissolved in (b)(4) minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara McNamara for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-802
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

V:\FIRMSNZ\TEVA\LTRS&REV\76802A0504.DOC
Printed in final on 7/19/04

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader K. Dhariwal 7/19/04
HFD-650/ D. Conner 7/19/04

BIOEQUIVALENCE - ACCEPTABLE

Submission Date: 06/25/2004

1. STUDY AMENDMENT (STA)

Strengths: 1, 2 and 4 mg
Outcome: AC

Outcome Decisions:
AC - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-802 SPONSOR : Teva Pharmaceuticals USA
DRUG AND DOSAGE FORM : Glimepiride Tablets
STRENGTH(S) : 4 mg, 2 mg and 1 mg
TYPES OF STUDIES : Fasting and Fed
CLINICAL STUDY SITE(S) : Novum Pharmaceutical Services
ANALYTICAL SITE(S) : (b) (4)

STUDY SUMMARY : Both studies are found acceptable.
DISSOLUTION : Acceptable. Waivers are granted for the 1 mg and 2 mg strengths

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __No_ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable
Yes_____ No_____X_
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)
DBE Dissolution Method and Spec acknowledged by firm: Yes _____
PROJECT MANAGER: _____ DATE:_____

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH: IV

INITIAL : MHM DATE : 7/19/04

TEAM LEADER : Kuldeep R. Dhariwal, Ph.D. BRANCH: IV

INITIAL : KRD DATE : 7/19/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 7/19/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076802

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

TEVA

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

July 21, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Glimepiride Tablets, 1 mg, 2 mg, and 4 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: *Organization of an ANDA (OGD #1, Rev. 1)*. These copies are presented in a total of **23** volumes; **11** for the archival copy and **12** for the review copy.

Please refer to Section 6 for a reviewer's note regarding the change of the reference listed drug. The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Glimepiride Tablets, 4 mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Amaryl® Tablets, 4 mg under both fasting and post-prandial conditions.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jb
Enclosures

RECEIVED
JUL 22 2003
OGD/CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

76-802

NEW CORRESP
NEW CORRESPONDENCE
NC

August 12, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
NEW CORRESPONDENCE TO JULY 21, 2003 ANDA

Dear Mr. Buehler:

We submit herewith a New Correspondence to the above-referenced July 21, 2003 ANDA for the purpose of providing additional information. At the time of submission of the original application, a Drug Master File number for Glimepiride was not available. Please be informed that DMF No. (b) (4) has now been assigned to (b) (4). Enclosed, please find an updated DMF authorization letter from (b) (4).

A copy of this notification is being provided to the District Office. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosure

RECEIVED
AUG 2 0 2003
OGD/CDER

ANDA 76-802

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

AUG 25 2003

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Glimepiride Tablets, 1 mg, 2 mg and 4 mg

DATE OF APPLICATION: July 21, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 22, 2003

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-802
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 22 Aug 2003
HFD-615/S. Middleton, CSO _____ date 8/21/03
Word File
V:\FIRMSNZ\TEVA\LTRS&REV\76802.ACK
F/T StM 8/20/03
ANDA Acknowledgment Letter!

Verified 6/27/05 Rev Set

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 76802/000
Org Code : 600
Priority :

Sponsor: TEVA PHARMS
1090 HORSHAM RD
NORTH WALES, PA 19454

Stamp Date : 22-JUL-2003
PDUFA Date :
Action Goal :
District Goal: 22-JUN-2004

Brand Name :
Estab. Name: GLIMEPIRIDE
Generic Name:
Dosage Form: (TABLET)
Strength : 1 MG, 2 MG, 4 MG

FDA Contacts: P. CHEN Project Manager (HFD-617) 301-827-5773
M. SMELA JR Team Leader (HFD-625) 301-827-5775

Overall Recommendation: ACCEPTABLE on 15-SEP-2003by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : 2517175 FEI : 2517175
TEVA NEUROSCIENCE, INC
650 CATHILL RD
SELLERSVILLE, PA 189601512

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-AUG-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-AUG-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: (b) (4)

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-AUG-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

June 25, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AB

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
BIOEQUIVALENCY AMENDMENT – RESPONSE TO APRIL 7, 2004 COMMENTS

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced pending ANDA in response to an April 7, 2004 review letter. For ease of review, please find a copy of this letter in **Attachment 1**.

Per your request, comparative dissolution testing was conducted using the following recommended dissolution parameters:

Dissolution Medium:	900 mL Phosphate Buffer, pH 7.8
Temperature:	37°C ± 0.5°C
Apparatus:	Apparatus II (paddle)
Paddle Speed:	75 rpm

Specifically, the paddle speed has been changed from (b)(4) rpm to the recommended 75 rpm. Comparative dissolution profiles conducted on 12 tablets each of the Teva lot and the innovator lot for the 1 mg, 2 mg, and 4 mg strengths are provided in **Attachment 2**. Please refer to **Attachment 3** for the revised Dissolution Method (SI-17285, Ed. No. 03), which incorporates the change in paddle speed. Please note that the innovator lots for the 1 mg and 2 mg strengths submitted in the original application expired in October 2003 and May 2004, respectively. The 4 mg innovator lot submitted in the original application will expire in June 2004. As such, the comparative dissolution profiles, provided in Attachment 2, were conducted on three new lots of innovator product.

In addition, per your request, the dissolution specification has been revised to *Not less than* (b)(4)% *(Q) of the labeled amount is dissolved in* (b)(4) *minutes*. Updated Release Specifications and Finished Product Stability Protocols reflecting the aforementioned specification are included in **Attachment 4**.

This information is submitted for your review and approval. If there are any questions, or if additional information is needed, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/sa
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

December 28, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

RECEIVED
DEC 2 9 2004
OGD / CDER

ORIG AMENDMENT
N/am

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
MINOR AMENDMENT – RESPONSE TO JANUARY 5, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA in response to a review letter from the Office of Generic Drugs, Division of Chemistry I dated January 5, 2004. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments contained in the letter are addressed in the order in which they were presented.

A. Deficiencies

1. In accord with the Agency's request, Teva has confirmed that [redacted] (b) (4), the holder of DMF [redacted] (b) (4), responded to their deficiencies. A copy of the cover letter to their submission, dated December 31, 2003, is provided in **Attachment 2**.

2. Drug Substance

   a. As requested, the limits for Related Substances have been revised to be in agreement with the limits set forth in the deficiency response by [redacted] (b) (4). The revised limits are as follows:

Related Substance	Specification	
	Original Application	Proposed (in agreement with [redacted] (b) (4))
[redacted] (b) (4)	NMT [redacted] (b) (4) %	NMT [redacted] (b) (4) %
	NMT [redacted] %	
	NMT [redacted] %	NMT [redacted] %
	NMT [redacted] %	
	-	NMT [redacted] %
	NMT [redacted] (b) (4) %	NMT [redacted] %
	N/A	NMT [redacted] %

4 Pages have been Withheld as b4 (CCI/TS) immediately following this page

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA #76-802

GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg

MINOR AMENDMENT – RESPONSE TO JANUARY 5, 2004 REVIEW LETTER

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and is provided to the Office of Generic Drugs to be forwarded as appropriate.

Philip Erickson

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

December 28, 2004
Date

RECORD OF TELEPHONE CONVERSATION

DATE: 1-25-05

PRODUCT NAME: Glimepiride Tablets, 1 mg, 2 mg and 4 mg

ANDA NUMBER: 76-802

FIRM NAME: Teva Pharmaceuticals

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD: Philip Erickson

PARTICIPANT(S) TELEPHONE: 215-591-3000

MINUTES OF CONVERSATION:

Telecon:
Mike Smela and M. Shaikh called the firm to address the remaining issues to be resolved identified during Chemistry Review # 2.

M. Shaikh told him the following issue which needs to be addressed in telephone amendment:

As the dissolution method and specification has been revised by the DBE, please test the retained samples from accelerated stability for dissolution to demonstrate that the products meet the dissolution specifications recommended by DBE. This should be done for all three executed batches. Alternatively, you may test the LT stability samples and reduce the proposed expiration dating to match the available data.

M. Shaikh also informed Philip Erickson that method validation has been requested.

Mike Smela clarified to Philip Erickson that the accelerated stability data of the RLD, as submitted in the amendment, are not acceptable to justify the impurities. Mike told him that we have accepted the proposed impurities limits.

Mike gave the fax number so that she can fax the telephone amendment to Mujahid Shaikh attention.

Mujahid Shaikh 1/25/05

NAME OF OGD REPRESENTATIVE: Mike Smela/M. Shaikh

V:\firmsnz\Teva\telecons\76802.TC1 M Smela 1/25/05

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

February 3, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/Am

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
TELEPHONE AMENDMENT – RESPONSE TO JANUARY 25, 2005 COMMUNICATION

Dear Mr. Buehler:

We submit herewith a Telephone Amendment to the above-referenced pending ANDA in response to a telephone request made by Mike Smela and Mujahid Shaikh of the Office of Generic Drugs on January 25, 2005.

Specifically, Mr. Smela and Mr. Shaikh requested the submission of actual stability data, which include the revised dissolution specification and revised dissolution parameters. Reference is made to a response submitted by Teva to the Division of Bioequivalence via a Bioequivalency Amendment on June 25, 2004. The referenced Bioequivalency Amendment incorporated the Agency's recommendations of a revised dissolution specification of *Not less than* (b)(4)*% (Q) of the labeled amount of Glimepride in the dosage form is dissolved in* (b)(4) *minutes* and revised dissolution parameters.

As requested, please find enclosed 24-month controlled room temperature stability data, which include the revised dissolution specification and parameters. Based on the data submitted herein, Teva requests a 24-month expiry for all strengths of the finished drug product.

This information is submitted in anticipation of your approval of this pending ANDA. Should there be any questions, or if additional information is needed, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/sa
Enclosure

RECEIVED
FEB 04 2005
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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philip.erickson@tevausa.com

March 16, 2005

ORIG AMENDMENT
N/RF

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
LABELING AMENDMENT – RESPONSE TO OCTOBER 15, 2003 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced pending ANDA in response to a review letter from the Office of Generic Drugs, Division of Labeling and Program Support dated October 15, 2003. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments contained in the letter are addressed in the order in which they were presented.

1. CONTAINER
   a. As requested, the storage statement has been revised to read 'Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]'.
   b. As per Teva's standard practice, the differentiation of product strengths is incorporated into our final printed labels.
2. INSERT
   a. As per your letter, our package insert was satisfactory in draft. Please note, however, that we have revised our insert to be in accordance with the labeling of the reference listed drug, Amaryl® Tablets, approved August 16, 2004.

In accord with the above-mentioned revisions we provide the following: 12 copies of final print container labels for each strength as well as comparisons of the container labels to those last submitted (**Attachment 2**) and a CD containing an electronic version of our final printed insert in Word and PDF format along with a comparison between the revised insert and our last submitted version in PDF format (**Attachment 3**). Please note the submission of the electronic labeling is in accord with 21 CFR 314.94(d) requiring mandatory electronic submission of labeling effective June 8, 2004.

This information is submitted for your continued review and approval of this ANDA. Should there be any questions, or if additional information is needed, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/cj
Enclosures

RECEIVED
MAR 17 2005
OGD / CDER

RECORD OF TELEPHONE CONVERSATION

Teva was contacted to provide the following information as a telephone amendment:

Since a monograph for the drug substance became official in USP on April 1, 2005, please evaluate your analytical methods for comparability and your specifications for compliance. Please confirm if you will use the impurity methods proposed in the ANDA or the USP methods. If the USP method is used, it must be demonstrated to be suitable for all the impurities identified in the ANDA. If the ANDA method is used, it must be demonstrated to be suitable for all the impurities in the USP monograph. Alternatively, both methods and limits may be used for drug substance acceptance.

Please provide a Certificate of Analysis for the drug substance tested by the methods in the USP monograph to document compliance.

DATE May 2, 2005

ANDA NUMBER 76-802

TELECON

INITIATED BY

SPONSOR

FDA X

PRODUCT NAME
Glimepiride Tablets, 1 mg, 2 mg, and 4 mg

FIRM NAME
Teva Pharmaceuticals USA

NAME OF PERSON WITH WHOM CONVERSATION WAS HELD
Philip Erickson

TELEPHONE NUMBER
215-591-3141

SIGNATURE

P. Chen 5/2/05

V:\FIRMSNZ\TEVA\TELECONS\76802-2May2005-tc.doc
CC: ANDA 76-802
Chem Div I, T-con Notebook

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
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Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

May 11, 2005

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AM

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
TELEPHONE AMENDMENT – RESPONSE TO MAY 2, 2005 COMMUNICATION

Dear Mr. Buehler:

We submit herewith a Telephone Amendment to the above-referenced pending ANDA in response to a telephone request made by Mr. Peter Chen of the Office of Generic Drugs on May 2, 2005. Specifically, Mr. Chen requested that we evaluate our drug substance methods and specifications for compliance with the new USP monograph for Glimepiride which became official on April 1, 2005. It was further requested that we confirm whether we intend to use the impurities methods presented in our ANDA or those now contained in USP.

Please note that we are unable to conduct a thorough evaluation at this time due to the unavailability of reference standards for Compounds (b) (4). We have been in contact with Mr. Robert Tyler of USP, via email dated March 10, 2005, who has agreed to contact Teva once the reference standards have been released. He also provided the following quote from General Notices: USP Reference Standards: "The requirements for any new USP or NF standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available. The availability of new USP Reference Standards and the official dates of the USP or NF standards, tests, or assays requiring their use are announced via Supplements or Interim Revision Announcements."

We commit to respond to the above requests in full as soon as we can obtain the reference standards, either from USP or other means, that are needed to perform the evaluation and demonstrate compliance to USP.

This information is submitted for your continued review of this pending ANDA. Should there be any questions, or if additional information is needed, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/cj

RECEIVED
MAY 12 2005
OGD / CDER

N:\GENERICS\PENN\FDACORE\Glimepiride\corres\T-Amend May 2005\cover.doc

RECORD OF TELEPHONE CONVERSATION

Reference is made to Teva's telephone amendment dated May 11, 2005.

We contacted Teva to provide additional information as a telephone amendment.

We informed Teva that would like adequate information for the DS to indicate that it conforms to USP or if not what the issue is. This information is required before approval. Since some USP reference standards are not currently available, we informed Teva they may use house standards.

Even if all USP impurity reference standards are not available, a house standard for the [redacted] (b) (4) should be.

For the [redacted] (b) (4) impurity, using the house standard or a standard provided by the API supplier, if the RRT matches the USP monograph, then we will consider it adequate information to ensure performance of the method.

DATE May 12, 2005

ANDA NUMBER 76-802

TELECON

INITIATED BY

SPONSOR

FDA X

PRODUCT NAME
Glimepiride Tablets, 1 mg, 2 mg, and 4 mg

FIRM NAME
Teva Pharmaceuticals USA

NAME OF PERSON WITH WHOM CONVERSATION WAS HELD
Philip Erickson

TELEPHONE NUMBER
215-591-3141

SIGNATURE
M.Smela M Smela 5/13/05

P.Chen Patricia Chen 5/12/05

V:\FIRMSNZ\TEVA\TELECONS\76802-12May2005-tc.doc
CC: ANDA 76-802
Chem Div I, T-con Notebook

Administrative Offices:
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Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
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June 8, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AM

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
TELEPHONE AMENDMENT – RESPONSE TO MAY 13, 2005 COMMUNICATION

Dear Mr. Buehler:

We submit herewith a Telephone Amendment to the above-referenced pending ANDA in response to a telephone request made by Mr. Peter Chen of the Office of Generic Drugs on May 13, 2005. Specifically, Mr. Chen requested that we provide documentation to illustrate our compliance with the new USP monograph for Glimepiride which became official on April 1, 2005.

Teva's analytical method for Glimepiride, RM-0429, Ed. 04, has been revised according to the current USP monograph. The Glimepiride related compounds USP method has been applied and the detection of related compound (b) (4) ((b) (4)) confirmed by using an alternate standard from the supplier, (b) (4).

Please find attached the following documents in support of this revision:

- Teva's revised Summary of Raw Material Specifications for Glimepiride (**Attachment 1**)
- Teva's revised analytical method for Glimepiride, RM-0429, Ed. 04 (**Attachment 2**)

This information is submitted for your continued review of this pending ANDA. Should there be any questions, or if additional information is needed, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/cj
Enclosures

RECEIVED
JUN 09 2005
OGD / CDER

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-802 Applicant Teva Pharmaceuticals USA
Drug Glimepiride Tablets Strength(s) 1 mg, 2 mg and 4 mg

APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 15 Feb 2005 Initials MMS	Date Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA#
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Date of latest Labeling Review/Approval Summary pending
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: PII → '785 ∴ Eligible for TA only
Comments:
~~Eligible for Full Approval~~

2. Project Manager, Peter Chen Team 2 Review Support Branch	Date 2/14/05 Initials PC	Date 2/14/05 Initials PC

Original Rec'd date 7/22/03
Date Acceptable for Filing 7/22/03
Patent Certification (type) III
Date Patent/Exclus.expires 4/6/05
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
Pediatric Study submitted
Waiver Pending as of 4/14/05.
Acceptable Bio reviews tabbed Yes ☑ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 9/15/03
Date of Office Bio Review 7/19/04
Date of Labeling Approv. Sum 10/10/03; 4/15/05
Labeling Acceptable Email Rec'd Yes ☑ No ☐
Labeling Acceptable Email filed Yes ☑ No ☐
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☑ No ☐
Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐

3. David Read ~~(PP IVs Only) Pre-MMA~~ Language included ☐ OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments: See revised version. DO NOT ISSUE UNTIL AFTER DECISION OF PED. EX BD (MAY 24).		Date 4/15/05 Initials DTR
4. Div. Dir./~~Deputy Dir.~~ Chemistry Div. I ~~II OR~~ III Comments: The conclusion is satisfactory.		Date 6/27/05 Initials RR

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)
N/A. Refer to Andex's ANDA 76-995 for this drug product - T/A'ed on 1/19/05.

6. Vacant RLD = Amaryl Tablets 1mg, 2mg, 4mg Date _____
Deputy Dir., DLPS Initials _____
Aventis Pharmaceuticals, Inc. NDA 20-496 (001, 002, 003)

7. Peter Rickman Date 6/27/05
Director, DLPS Initials _____ for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 9/15/04 (Verified 6/27/05). No O.H.I. alerts noted. Bioequivalence studies (fasting and non-fasting) on the 4mg strength found acceptable 4/5/05. Dissolution studies for all 3 strengths found acceptable 2/19/04. Waivers granted to 1mg and 2mg strengths under 21 CFR 320.22(d)(2). Bio study test sites have acceptable OSI/FDA inspection histories. Office level bio endorsed 7/19/04. Labeling found acceptable 4/15/05. CMC found acceptable 6/21/05. Methods validation was requested and is pending. Commitment has been received from TEVA.

8. Robert L. West Date 6/27/2005
Deputy Director, OGD Initials _____ for RLW
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: TEVA made a paragraph III certification to the 1998 patent due to expire on 10/6/05 (with pediatric extension). There are no other unexpired patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for tentative approval.

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

10. Project Manager, Team 2 Peter Chen Date 6/27/05
Review Support Branch Initials _____
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
3:45 Time notified of approval by phone 3:46 Time approval letter faxed
FDA Notification:
6/27 3:55 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
6/27 _____ Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
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Direct Dial: (215) 591-3141
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philip.erickson@tevausa.com

August 17, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT -
FINAL APPROVAL REQUESTED

AM

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

We submit herewith a minor amendment to the above referenced Abbreviated New Drug Application in accord with a letter from the Office of Generic Drugs dated June 27, 2005 which granted tentative approval of this file. The letter noted that Teva would be eligible for final approval of ANDA #76-802 upon the expiration of pediatric exclusivity associated with U.S. Patent # 4,379,785 on October 6, 2005, the only patent listed for the RLD Amaryl® Tablets. As such, TEVA is respectfully requesting final approval of Glimepiride Tablets, 1 mg, 2 mg, and 4 mg on October 6, 2005.

As requested in the June 27, 2005 tentative approval letter, we include herein documents that have been revised since they were last provided to the Agency in either our original ANDA or subsequent amendments.

1. Updated patent certification which reflects the issuance of pediatric exclusivity to Aventis Pharmaceuticals, the holder of NDA #20-496 for Amaryl® Tablets. The updated patent certification along with the printout of the reference-listed drug's patent and exclusivity listings in the electronic *Approved Drug Products With Therapeutic Equivalence Evaluations* (Electronic Orange Book) are provided in **Attachment 1**. Please note that acknowledgment of pediatric exclusivity is the only change to our original certification.

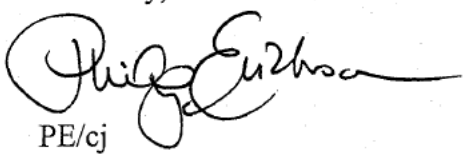
2. Revised manufacturing procedures for Glimepiride Tablets. Revisions include formatting and compendial name changes as well as the utilization of a (b) (4) tabletting machine in place of a (b) (4) for Glimepiride Tablets, 2 mg and 4 mg. These tablet presses are within the same class and subclass as defined in the SUPAC-IR/MR Manufacturing Equipment Addendum,

section (VI)(B)(1) and thus are of the same design and operating principles as defined in SUPAC-IR (VI)(A)(1). As such, the change in tablet (b) (4) is not expected to have an effect on the identity, strength, quality, purity, or potency of the drug product.

Please note that the final print container labeling, an electronic version of our final print package insert, and comparisons to our last submitted versions were provided to the Agency in a labeling Amendment dated March 16, 2005.

This information is submitted toward the final approval of ANDA #76-802 for Glimepiride Tablets, 1 mg, 2 mg, and 4 mg. Should there be any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/cj
Enclosures

Administrative Offices:
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Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
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Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

September 27, 2005

ORIG AMENDMENT
N /AF

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-802
GLIMEPIRIDE TABLETS, 1 mg, 2 mg, and 4 mg
LABELING AMENDMENT – PACKAGE INSERT REVISION

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced tentatively approved ANDA in response to the reference listed drug's package insert revision approved on September 19, 2005. Please find enclosed a CD containing the electronic version of our final printed insert in both Word and PDF format along with a comparison between the revised insert and our last submitted version in PDF format in **Attachment 1**.

Please note that Teva is eligible for final approval of ANDA #76-802 on October 6, 2005 in accord with the expiration of pediatric exclusivity associated with U.S. Patent # 4,379,785.

This information is submitted for your continued review and final approval of this ANDA. Should there be any questions, or if additional information is needed, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/ct

PE/ct
Enclosures

RECEIVED
SEP 28 2005
OGD/CDER

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-802 Applicant Teva Pharmaceuticals USA
Drug Glimepiride Tablets Strength(s) 1mg, 2mg and 4mg

APPROVAL ☑ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 9/29/05 Initials [illegible] Date 10/5/05 Initials [illegible] for

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 20-496 Previously granted
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☐
Type of Letter:
Comments: PIII to 1785 PED exp. 10/6/05 - okay for full AP 10/6/05.

2. Project Manager, Lisa Kwok Team II
Review Support Branch
Date 9/29/05 Initials [illegible] Date 10/3/05 Initials [illegible]

Original Rec'd date 7/21/03
Date Acceptable for Filing 7/22/05
Patent Certification (type) PIII
Date Patent/Exclus.expires 10/6/05
Citizens' Petition/Legal Case Yes☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status
Date of Office Bio Review 7/19/04
Date of Labeling Approv. Sum 4/15/05
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☑
Suitability Petition/Pediatric Waiver
Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☑ Date 7/27/05
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials
Comments:
NA.

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Date 10/4/05 Initials [illegible]
Comments:
cmc satisfactory.

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

(b) (4)

[redacted]

6. Vacant RLD= Amaryl Tablets 1mg, 2mg, 4mg
Deputy Dir., DLPS Aventis Pharmaceuticals, Inc. NDA 20-496 (001, 002, 003) Date_____
Initials_____

7. Peter Rickman Date 10/5/05
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: This ANDA was tentatively approved on 6/27/05. Refer to the administrative sign-off form completed at that time. On 8/17/05 TEVA submitted a minor amendment providing for minor CMC updates and requesting final approval effective 10/6/05. FPI remains acceptable for approval (via e-mail, Grace et al). CMC is acceptable for approval 9/28/05. Methods validation was requested and is pending - the standard commitment has been received from TEVA. EES is acceptable - see e-mail dated 9/15/05 in package.

OR

8. Robert L. West Date 10/5/2005
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: TEVA made a paragraph 3 certification to the '785 patent expiring on 10/6/05 (pediatric extension). There are no other unexpired patents or exclusivity listed on the current "Orange Book" for this drug product. This ANDA is recommended for final approval on October 6, 2005.

9. Gary Buehler Date 10/6/05
Director, OGD Initials GB
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team Lisa Kwok Date 10/6/05
Review Support Branch Initials LK
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
9:10 AM Time notified of approval by phone 9:16 AM Time approval letter faxed
FDA Notification:
10/6/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
10/6/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Approval Letter Faxed to Orange Book Staff @ 301-827-7337: Date/Time: _____

File V:/division/dlps/approvrou9.doc