CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-686

Name: Glyburide Tablets USP (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg

Sponsor: Novopharm

Approval Date: April 20, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

APPROVAL LETTER

ANDA 74-686

APR 20 1999

Novopharm NC, Inc.
Attention: Dietrich Bartel
U.S. Agent for: Novopharm Limited
4700 Novopharm Boulevard
Wilson, NC 27893

Dear Sir:

This is in reference to your abbreviated new drug application dated June 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Glyburide Tablets USP (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg.

Reference is also made to our Tentative Approval letter dated November 10, 1998, and to your amendments dated January 13, March 15, and March 24, 1999.

The listed drug product referenced in your application is subject to periods of patent protection which expire on April 5, 2005 (U.S. Patent No. 4,735,805 [the '805 patent]) and April 10, 2007 (U.S. Patent No. 4,916,163 [the '163 patent]), respectively. Your application contains certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents will not be infringed by your manufacture, use, or sale of Glyburide Tablets USP, (Micronized). Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent(s) which are the subject of the certifications before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by the patent holders. You notified the Agency that Novopharm Limited (Novopharm) complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement regarding the '805 patent was brought against Novopharm within the statutory forty-five day period. However, you notified the Agency that Pharmacia & Upjohn Company initiated a patent infringement action against you in the United States District Court for the Northern District of Illinois Eastern Division involving the '163 patent (Pharmacia & Upjohn Company v. Novopharm Limited, Civil Action No. 97 C 3992). Subsequently on March 15, 1999, you notified the Agency that the court decided in favor of Novopharm and that the decision was not appealed by the plaintiff.

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 Glyburide Tablets USP, (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Glynase® PresTab® Tablets, 1.5 mg, 3 mg, 4.5 mg, and 6 mg, respectively, of Pharmacia and Upjohn Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 4/20/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-686
Division File
FIELD COPY
HFD-610/RLWest
HFD-92
HFD-210/B.Poole
HFD-330/
HFD-205/

Endorsements:
HFD-625/M.Shaikh/3/29/99 Mujahid Shaikh 4/1/99
HFD-625/M.Smela/3/29/99 *M Smela 4/1/99
HFD-617/D.Huie (Manderson for)/3/31/99 D Huie 4/6/99
HFD-613/A.Vezza/3-31-99 A Vezza 4/6/99
HFD-613/J.Grace J Doleman for 4/6/99

V:\firmsnz\novophar\ltrs&rev\74686.apd
F/T by: bc/3-31-99

APPROVAL

Robert Lewis 4/20/99

* There is no reference in AP letter as to what the generic 4.5mg tablet is equivalent to.
Revised 4/19/99
Corrected RLW 4/20/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

TENTATIVE APPROVAL LETTER

ANDA 74-686

NOV 10 1998

Novopharm NC, Inc.
Attention: Dietrich Bartel
U.S. Agent for: Novopharm Limited
4700 Novopharm Boulevard
Wilson, NC 27893

Dear Sir:

This is in reference to your abbreviated new drug application dated June 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Glyburide Tablets USP (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg.

Reference is also made to your amendments dated September 24, 1996; January 17, and March 21, 1997; and March 2, June 30, August 27, October 27, and November 9, 1998.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. 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 of the facilities used in the manufacturing and testing of the drug product), and is therefore subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application is subject to periods of patent protection which expire on April 5, 2005, (Patent No. 4,735,805, the '805 patent) and April 10, 2007, (Patent No. 4,916,163, the '163 patent). Your application contains certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that to the best of Novopharm Limited's knowledge, the patents will not be infringed by the manufacture, use, or sale of Glyburide Tablets USP, (Micronized). Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent(s) which are the subject of the certifications before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is

received. You have notified FDA that Novopharm Limited has complied with the requirements of Section 505(j)(2)(B) of the Act by providing the required notice to each patent holder and that no action for patent infringement regarding the '805 patent was brought against Novopharm Limited within the statutory forty-five day period. However, you also notified FDA that litigation is underway in the United States District Court for the Northern District of Illinois, involving a challenge to the '163 patent (Pharmacia & Upjohn Company v. Novopharm Limited, Civil Action No. 97C/3992). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(I), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision [505(j)(5)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

   c. the '163 patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application 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 before the effective final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Denise Huie, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

D. L. Sporn 11/10/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-686
ANDA #74-686/Division file
Field Copy
HFD-92
HFD-210
HFD-330
HFD-610/J.Phillips

Endorsements:

HFD-625/MShaikh/10-2-98 Mujahid Shaikh 10/8/98
HFD-613/AVezza/ A Vezza 10-8-98
HFD-613/JGrace/ 10/8/98
HFD-625/MSmela/10-5-98 MS Smela 10/8/98
HFD-617/DHuie/ DHuie 10/5/98
X:\new\firmsnz\novophar\ltrs&rev\~~74686app.ltr.~~ 74686_TA
FT by: bc/10-5-98

TENTATIVE Approval Letter

AP letter revised to include 10/27/98 CMC amendment.
Mujahid Shaikh 10/28/98
M Smela 10/28/98

10/28/98

Robert Lewis for Jerry Phillips 11/7/98

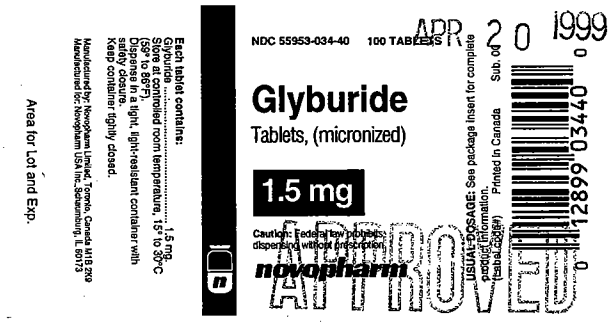
CENTER FOR DRUG EVALUATION AND RESEARCH

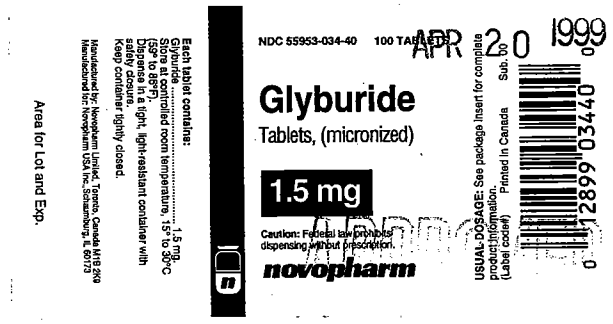
APPLICATION NUMBER:

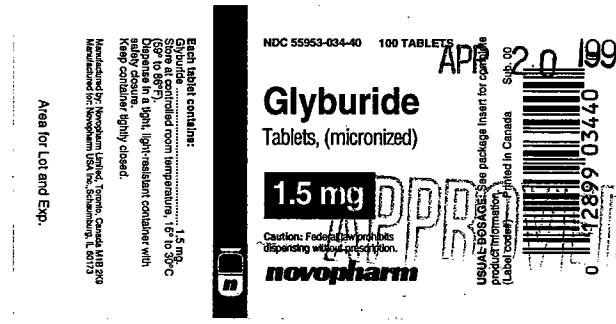
ANDA 74-686

APPROVED LABELING

Mago


NDC 55953-034-40 100 TABLETS
Glyburide
Tablets, (micronized)
1.5 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#)
Printed in Canada
Sub. 00
APR 20 1999
0 12899 03440 0
APPROVED
Each tablet contains:
Glyburide ..... 1.5 mg.
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.


NDC 55953-034-40 100 TABLETS
Glyburide
Tablets, (micronized)
1.5 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#)
Printed in Canada
Sub. 00
APR 20 1999
0 12899 03440 0
Each tablet contains:
Glyburide ..... 1.5 mg.
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.


NDC 55953-034-40 100 TABLETS
Glyburide
Tablets, (micronized)
1.5 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
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Sub. 00
APR 20 1999
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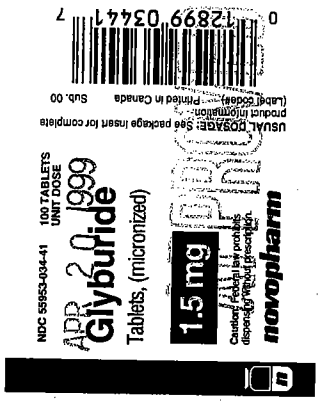
Area for Lot and Exp.



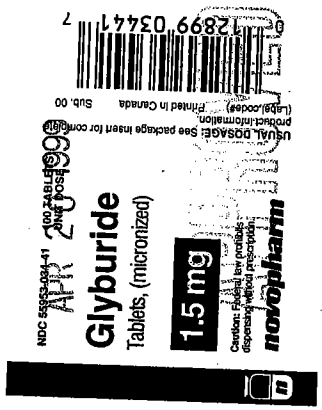
Each tablet contains:
Glyburide ..... 1.5 mg.

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.



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Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
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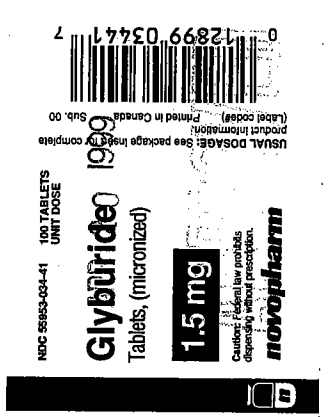
Area for Lot and Exp.



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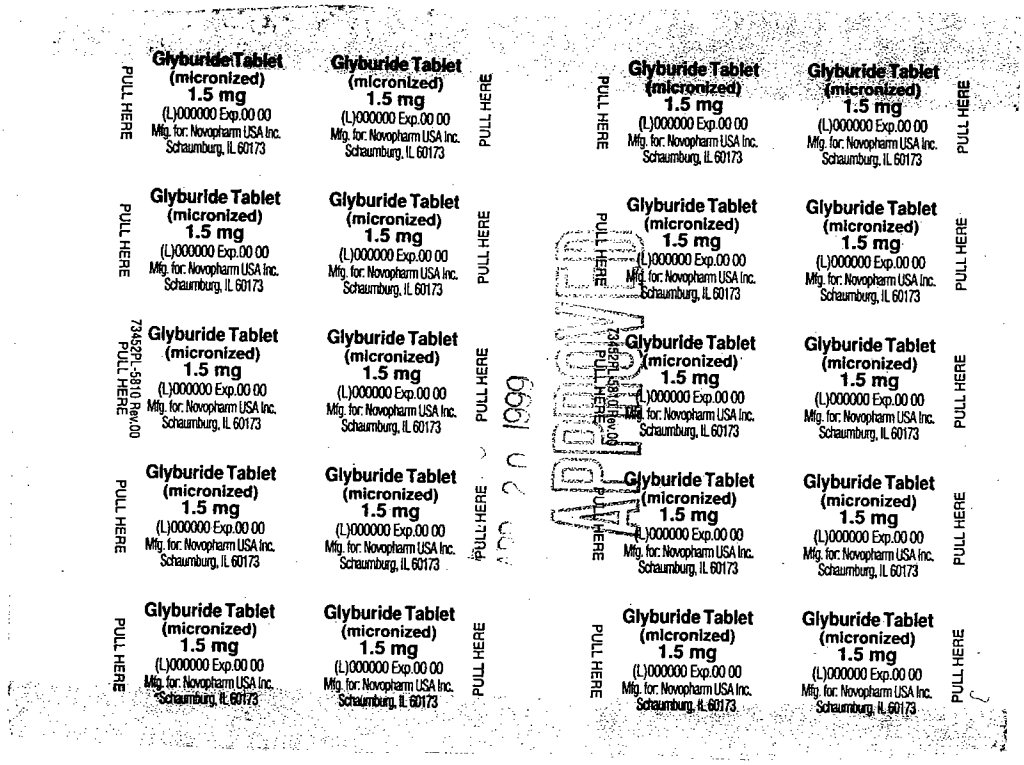
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

74686

Original



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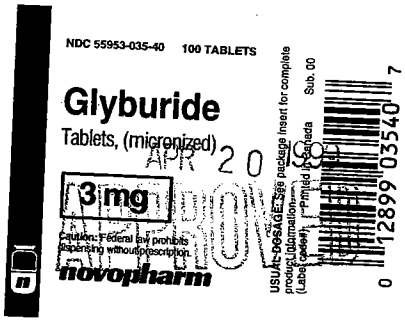
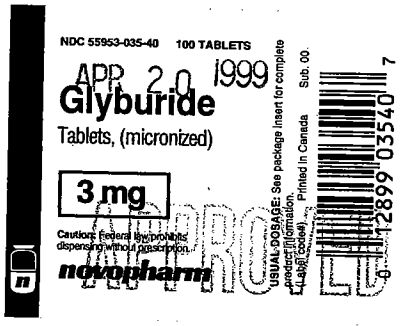

NDC 55953-035-40 100 TABLETS
Glyburide
Tablets, (micronized)
3 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#) Printed in Canada Sub. 00
0 12899 03540 7
Each tablet contains:
Glyburide ..... 3 mg
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a light, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.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APR 20 1999
Glyburide
Tablets, (micronized)
3 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#) Printed in Canada Sub. 00
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Each tablet contains:
Glyburide ..... 3 mg
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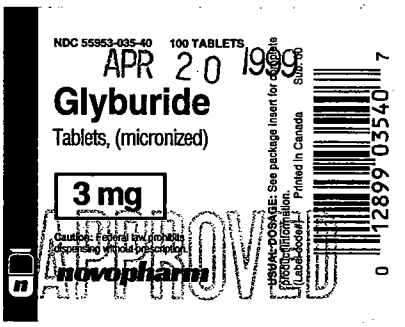
Dispense in a light, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.


NDC 55953-035-40 100 TABLETS
APR 20 1999
Glyburide
Tablets, (micronized)
3 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
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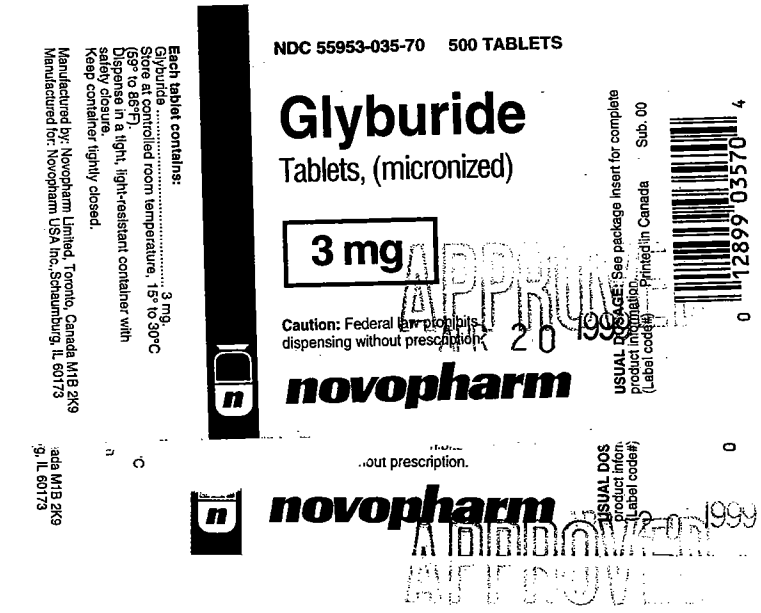
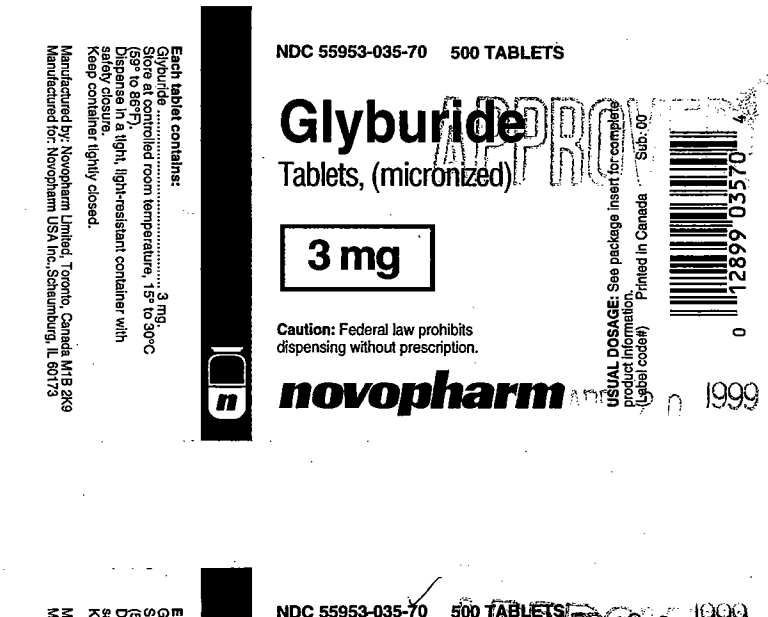
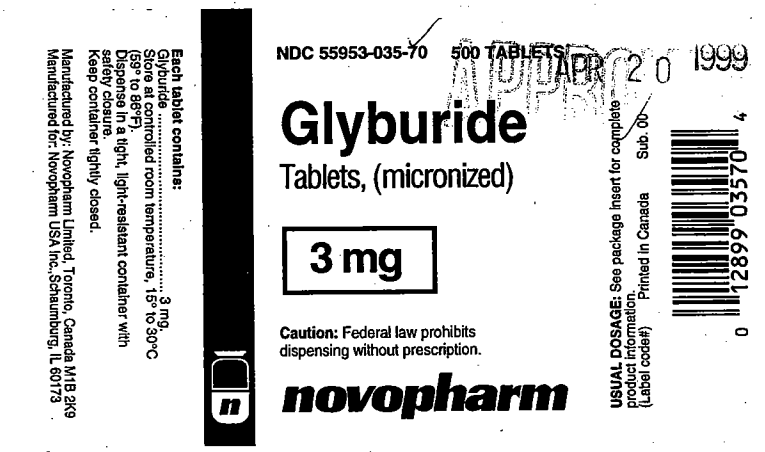
Glyburide ..... 3 mg
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a light, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.



Area for Lot and Exp.



Area for Lot and Exp.



Area for Lot and Exp.

NDC 55953-035-80 1000 TABLETS

Glyburide

Tablets, (micronized)

3 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL DOSAGE: See package insert for complete product information.

(Label code#) Printed in Canada Sub. 00

0 12899 03580 3

APR 20 1999

APPROVED

Each tablet contains:
Glyburide ..... 3 mg.
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc.,Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-035-80 1000 TABLETS

Glyburide

Tablets, (micronized)

3 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL DOSAGE: See package insert for complete product information.

(Label code#) Printed in Canada Sub. 00

0 12899 03580 3

APR 20 1999

APPROVED

Each tablet contains:
Glyburide ..... 3 mg.
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc.,Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-035-80 1000 TABLETS

Glyburide

Tablets, (micronized)

3 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL DOSAGE: See package insert for complete product information.

(Label code#) Printed in Canada Sub. 00

0 12899 03580 3

APR 20 1999

APPROVED

Each tablet contains:
Glyburide ..... 3 mg.
Store at controlled room temperature, 15° to 30°C (59° to 86°F).
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc.,Schaumburg, IL 60173

Area for Lot and Exp.

Original

NDC 55953-035-41 100 TABLETS UNIT DOSE

Glyburide

Tablets, (micronized)

3 mg

APR 20 1999

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL DOSAGE: See package insert for complete product information.

(Label code#) Printed in Canada Sub. 00

0 12899 03541 4

Each tablet contains:
Glyburide ..... 3 mg.

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-035-41 100 TABLETS UNIT DOSE

Glyburide

Tablets, (micronized)

3 mg

APR 20 1999

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL DOSAGE: See package insert for complete product information.

(Label code#) Printed in Canada Sub. 00

0 12899 03541 4

Each tablet contains:
Glyburide ..... 3 mg.

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-035-41 100 TABLETS UNIT DOSE

Glyburide

Tablets, (micronized)

3 mg

APR 20 1999

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL DOSAGE: See package insert for complete product information.

(Label code#) Printed in Canada Sub. 00

0 12899 03541 4

Each tablet contains:
Glyburide ..... 3 mg.

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

Original 1

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

73453PL-5810 Rev.00

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

73453PL-5810 Rev.00

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
PULL HERE

Glyburide Tablet
(micronized)
3 mg
(L)000000 Exp.00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
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Glyburide Tablet
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Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173
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APR 20 1999

APPROVED

03

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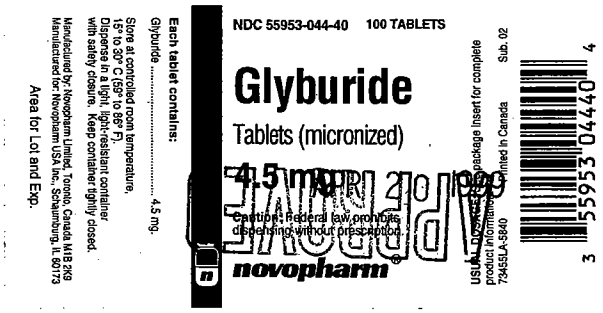
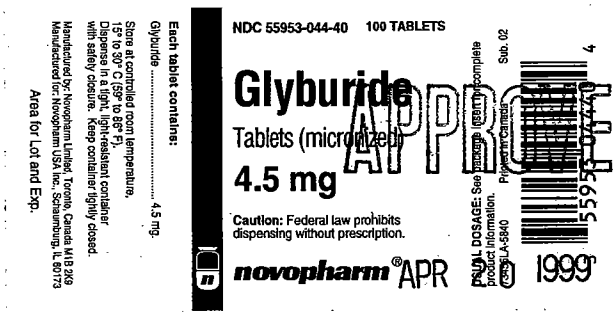

NDC 55953-044-40 100 TABLETS
Glyburide
Tablets (micronized)
4.5 mg
APR 20 1999
APPROVED
Caution: Federal law prohibits dispensing without prescription.
novopharm®
USUAL DOSAGE: See package insert for complete product information.
73455LA-5840
Printed in Canada
Sub. 02
55953 04440 4
Each tablet contains:
Glyburide ..... 4.5 mg.
Store at controlled room temperature, 15° to 30° C (59° to 86° F).
Dispense in a tight, light-resistant container with safety closure. Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.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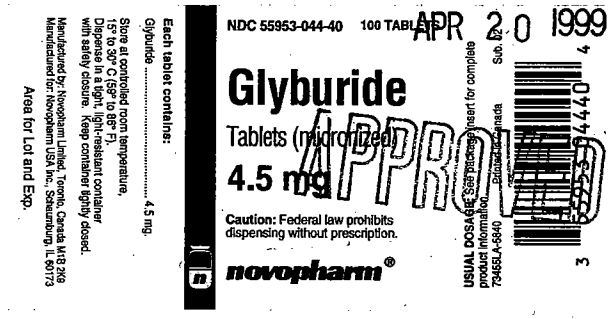
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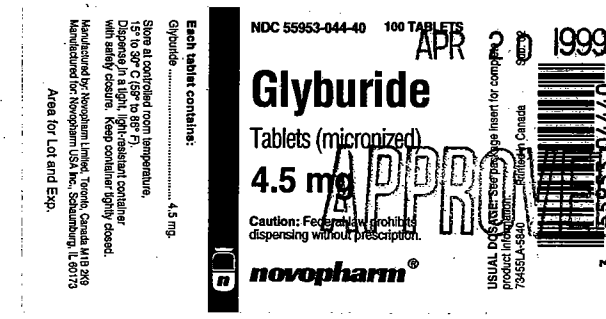
Area for Lot and Exp.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APR 20 1999
Glyburide
Tablets (micronized)
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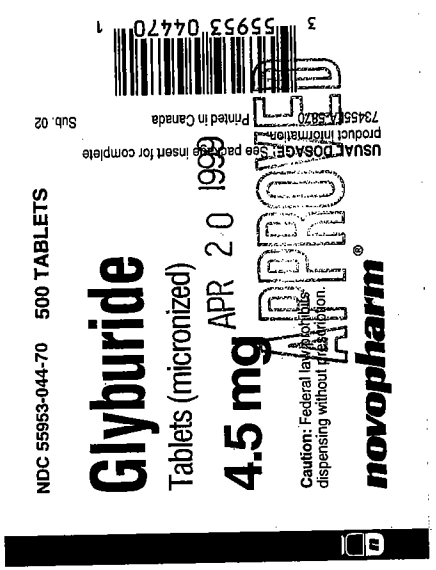

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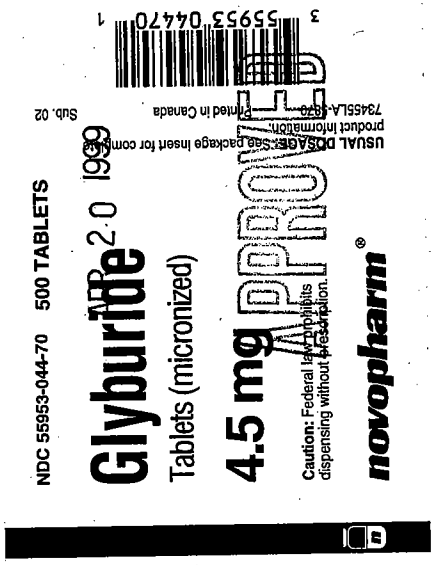
Area for Lot and Exp.



Each tablet contains:
Glyburide ..... 4.5 mg.

Store at controlled room temperature,
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Dispense in a tight, light-resistant container
with safety closure.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc.,Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-044-41 100 TABLETS UNIT DOSE

APR 20 1999

Glyburide

Tablets (micronized)

4.5 mg

Caution: Federal law prohibits dispensing without prescription.

APPROVED

novopharm®

USUAL DOSAGE: See package insert for complete product information.

Printed in Canada Sub. 02

7245SLA5941

3 55953 04441 1

Each tablet contains:
Glyburide ..... 4.5 mg.

Store at controlled room temperature, 15° to 30° C (59° to 86° F).

This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-044-41 100 TABLETS UNIT DOSE

APR 20 1999

Glyburide

Tablets (micronized)

4.5 mg

Caution: Federal law prohibits dispensing without prescription.

APPROVED

novopharm®

USUAL DOSAGE: See package insert for complete product information.

Printed in Canada Sub. 02

7245SLA5941

3 55953 04441 1

Each tablet contains:
Glyburide ..... 4.5 mg.

Store at controlled room temperature, 15° to 30° C (59° to 86° F).

This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

NDC 55953-044-41 100 TABLETS UNIT DOSE

APR 20 1999

Glyburide

Tablets (micronized)

4.5 mg

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APPROVED

novopharm®

USUAL DOSAGE: See package insert for complete product information.

Printed in Canada Sub. 02

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3 55953 04441 1

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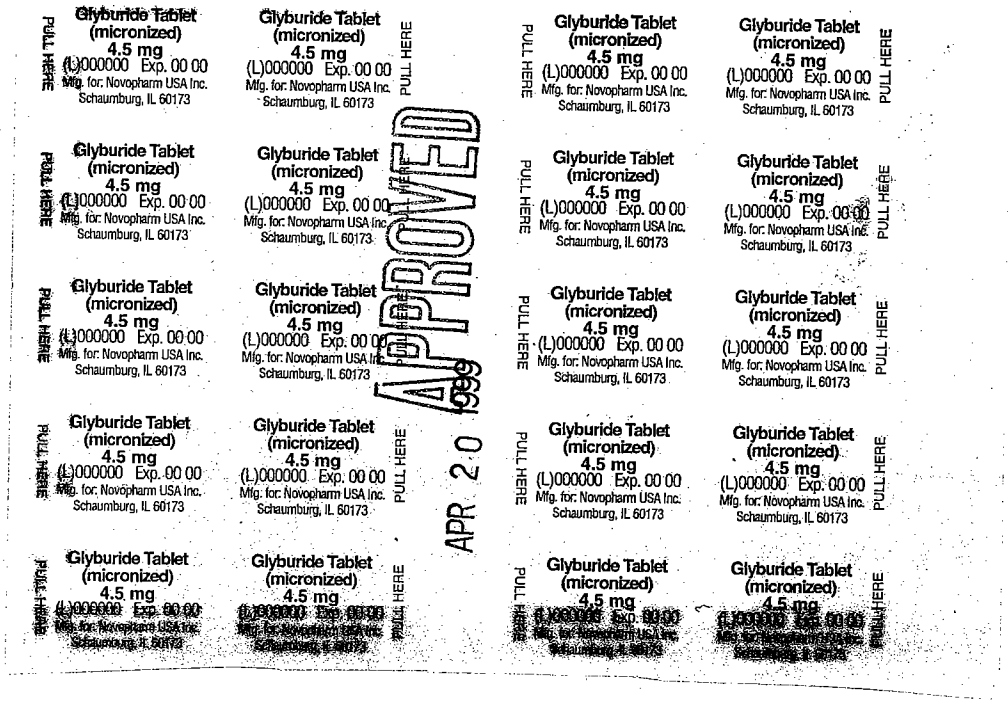
This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Area for Lot and Exp.

73455PL-5810 Rev. 00



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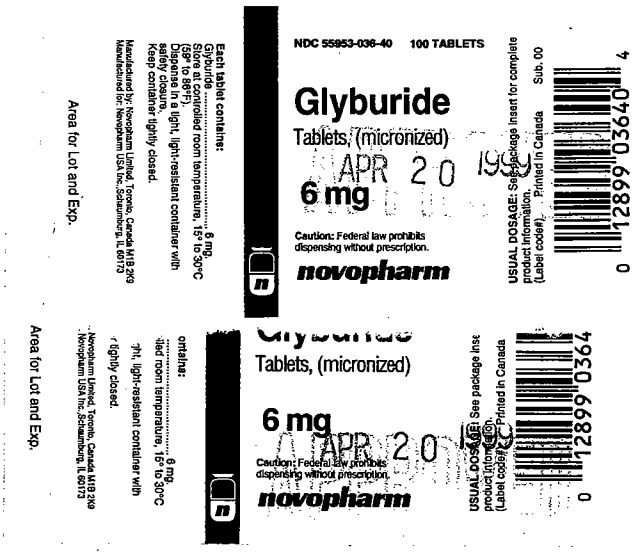
Each tablet contains:
Glyburide ..... 6 mg
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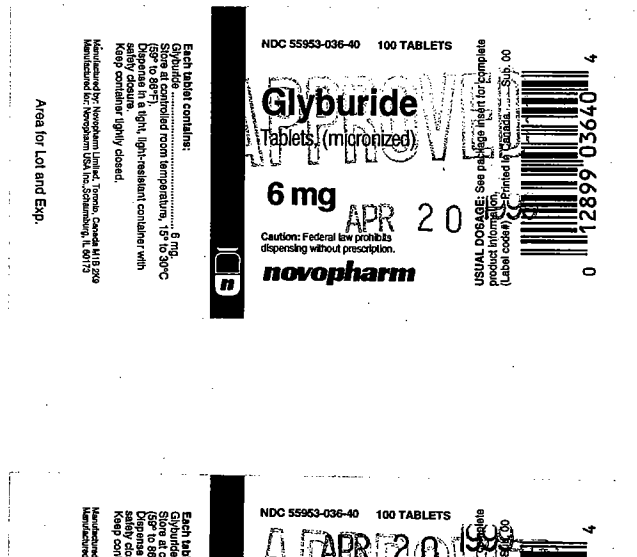
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.
NDC 55953-036-40 100 TABLETS
Glyburide
Tablets, (micronized)
APR 20 1999
6 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#) Printed in Canada Sub. 00
0 12899 03640 4
Tablets, (micronized)
6 mg
APR 20
Caution: Federal law prohibits dispensing without prescription.
novopharm
0 12899 03640 4


Each tablet contains:
Glyburide ..... 6 mg
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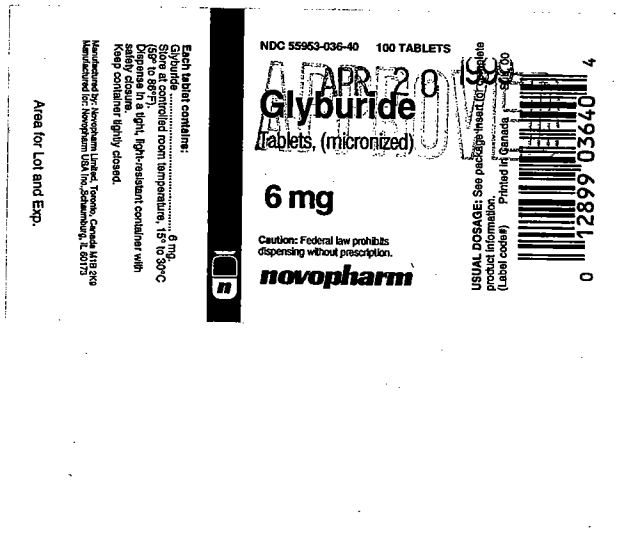
Dispense in a tight, light-resistant container with safety closure.
Keep container tightly closed.
Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173
Area for Lot and Exp.
NDC 55953-036-40 100 TABLETS
APPROVED
Glyburide
Tablets, (micronized)
6 mg
APR 20
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#) Printed in Canada Sub. 00
0 12899 03640 4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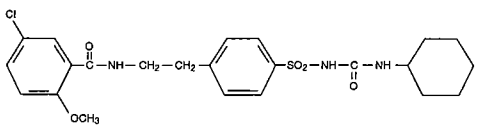
Area for Lot and Exp.
NDC 55953-036-40 100 TABLETS
APPROVED
APR 20
Glyburide
Tablets, (micronized)
6 mg
Caution: Federal law prohibits dispensing without prescription.
novopharm
USUAL DOSAGE: See package insert for complete product information.
(Label code#) Printed in Canada Sub. 00
0 12899 03640 4

GLYBURIDE TABLETS (MICRONIZED)

DESCRIPTION

Glyburide tablets (micronized) contain smaller particle size. Glyburide is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound. Each tablet, for oral administration, contains 1.5 mg, 3 mg, 4.5 mg or 6 mg of glyburide. Inactive ingredients: microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate. In addition, the 3 mg, 4.5 mg and 6 mg strengths contain FD&C Blue No. 1 and FD&C Blue No. 2. The chemical name for glyburide is 1-[[*p*-[2-(5-Chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea. The molecular formula is $C_{23}H_{28}ClN_3O_5S$, and the molecular weight is 494.01. The structural formula is represented below:



CLINICAL PHARMACOLOGY

Actions

Glyburide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs. The combination of glyburide and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

Some patients who are initially responsive to oral hypoglycemic drugs, including glyburide, may become unresponsive or poorly responsive over time. Alternatively, glyburide may be effective in some patients who have become unresponsive to one or more other sulfonylurea drugs.

In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance. Disulfiram-like reactions have very rarely been reported in patients treated with glyburide.

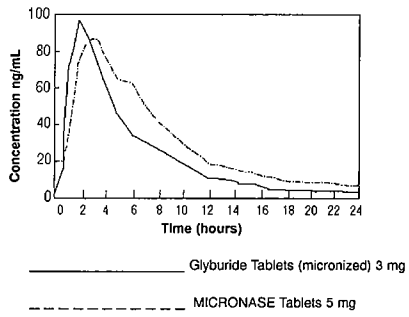
Pharmacokinetics

Single dose studies with glyburide tablets (micronized) in normal subjects demonstrate significant absorption of glyburide within one hour, peak drug levels at about two to three hours, and low but detectable levels at twenty-four hours.

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent those from nonmicronized glyburide tablets 5 mg. Therefore, the patient should be retitrated.

It has been reported that in a single-dose bioavailability study (see Figure A) in which subjects received Glyburide Tablets (micronized) 3 mg and MICRONASE Tablets 5 mg with breakfast, the peak of the mean serum glyburide concentration-time curve was 97.2 ng/mL for Glyburide Tablets (micronized) 3 mg and 87.5 ng/mL for MICRONASE Tablets 5 mg. The mean of the individual maximum serum concentration values of glyburide (C_{max}) from Glyburide Tablets (micronized) 3 mg was 106 ng/mL and that from MICRONASE tablets 5 mg was 104 ng/mL. The mean glyburide area under the serum concentration-time curve (AUC) for this study was 568 ng x hr/mL for Glyburide Tablets (micronized) 3 mg and 746 ng x hr/mL for MICRONASE tablets 5 mg.

Figure A



Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no buildup of drug in tissue depots.

In a steady-state study in diabetic patients receiving micronized glyburide tablets 6 mg once daily or micronized glyburide tablets 3 mg twice daily, no difference was seen between the two dosage regimens in average 24 hour glyburide concentrations following two weeks of dosing. The once-daily and twice-daily regimens provided equivalent glucose control as measured by fasting plasma glucose levels, 4 hour postprandial glucose AUC values, and 24 hour glucose AUC values. Insulin AUC response over the 24 hour period was not different for the two regimens. There were differences in insulin response between the regimens for the breakfast and supper 4 hour postprandial periods, but these did not translate into differences in glucose control.

The serum concentration of glyburide in normal subjects decreased with a half-life of about four hours.

In single dose studies in fasting normal subjects who were administered nonmicronized tablets in doses ranging from 1.25 mg to 5 mg, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning doses in nonfasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A one year study of diabetic patients treated with glyburide showed no reliable correlation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-transhydroxy derivative. A second metabolite, the 3-cishydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominately non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide in clinical use.

INDICATIONS AND USAGE

Glyburide tablets (micronized) are indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone.

Glyburide may be used concomitantly with metformin when diet and glyburide or diet and metformin alone do not result in adequate glycemic control (see metformin insert).

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of glyburide must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitution or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of glyburide.

During maintenance programs, glyburide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgment should be based on regular clinical and laboratory evaluations.

In considering the use of glyburide in asymptomatic patients, it should be recognized that controlling blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

Glyburide is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. Type I diabetes mellitus, as sole therapy.

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 (Suppl. 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 2½ 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 glyburide 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

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from nonmicronized glyburide tablets 5 mg. Therefore, patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents.

General

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated drug levels of glyburide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary 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. 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. The risk of hypoglycemia may be increased with combination therapy.

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 discontinue glyburide and administer insulin.

The effectiveness of any hypoglycemic drug, including glyburide, 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 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 glyburide is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients: Patients should be informed of the potential risks and advantages of glyburide and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or 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. Primary and secondary failure also should be explained.

Laboratory Tests

Therapeutic response to glyburide tablets (micronized) should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

Drug Interactions

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

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism of action for this interaction is not known.

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.

Metformin: In a single-dose interaction study in NIDDM subjects, decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Coadministration of glyburide and metformin did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay.

No drug-related effects were noted in any of the criteria evaluated in the two-year oncogenicity study of glyburide in mice.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 500 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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 blood glucose as close to normal as possible.

Nonteratogenic Effects: 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. If glyburide is used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS** and **OVERDOSAGE** Sections.

Gastrointestinal Reactions: Cholestatic jaundice and hepatitis may occur rarely; glyburide should be discontinued if this occurs.

Liver function abnormalities, including isolated transaminase elevations, have been reported.

Gastrointestinal disturbances, *eg*, nausea, epigastric fullness, and heartburn are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, *eg*, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.5% of treated patients during clinical trials. These may be transient and may disappear despite continued use of glyburide. If skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions 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 and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with glyburide and disulfiram-like reactions have been reported very rarely.

Cases of hyponatremia have been reported with glyburide 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 have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia and vasculitis have been reported

OVERDOSAGE

Overdosage of sulfonylureas, including glyburide, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological 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 which 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, since hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

Patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents.

There is no fixed dosage regimen for the management of diabetes mellitus with glyburide tablets (micronized) or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *ie*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *ie*, loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

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

Usual Starting Dose

The suggested starting dose of glyburide tablets (micronized) is 1.5 to 3 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 0.75 mg daily. (See **PRECAUTIONS** Section for patients at increased risk.) 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.

Transfer From Other Hypoglycemic Therapy; Patients Receiving Other Oral Antidiabetic Therapy: Patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents. The initial daily dose should be 1.5 to 3 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to micronized glyburide tablets, no transition period and no initial or priming dose are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first two weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Patients Receiving Insulin: Some Type II diabetic patients being treated with insulin may respond satisfactorily to micronized glyburide. If the insulin dose is less than 20 units daily, substitution of glyburide tablets (micronized) 1.5 to 3 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on glyburide tablets (micronized) 3 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to micronized glyburide. In these patients, insulin dosage is decreased by 50% and glyburide tablets (micronized) 3 mg daily is started. Please refer to **Titration to Maintenance Dose** for further explanation.

Titration to Maintenance Dose

The usual maintenance dose is in the range of 0.75 to 12 mg daily, which may be given as a single dose or in divided doses (see **Dosage Interval** Section). Dosage increases should be made in increments of no more than 1.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between micronized glyburide and the other oral hypoglycemic agents, including nonmicronized glyburide tablets. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 3 mg of glyburide tablets (micronized) should be observed. A maintenance dose of 3 mg of glyburide tablets (micronized) provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 5 mg of nonmicronized glyburide, 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of glyburide tablets (micronized) 3 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of glyburide tablets (micronized) in increments of 0.75 to 1.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and glyburide tablets (micronized) are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

Concomitant Glyburide and Metformin Therapy: Glyburide tablets (micronized) should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks (see **Usual Starting Dose** and **Titration to Maintenance Dose**). Refer to metformin package insert.

With concomitant glyburide 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 optimal dose of each drug needed to achieve this goal. With concomitant glyburide and metformin therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see **PRECAUTIONS** section).

Maximum Dose

Daily doses of more than 12 mg are not recommended.

Dosage Interval

Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 6 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations

Glyburide is not recommended for use in pregnancy or for use in pediatic patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See **PRECAUTIONS** Section.)

HOW SUPPLIED

Glyburide tablets (micronized) are supplied as follows:

Glyburide Tablets (micronized) 1.5 mg White, oval shaped, flat face, beveled-edge, compressed tablets, engraved with **1.5 I 034** on one side and stylized **N** on the reverse. They are supplied as follows:

Plastic bottles of 100	NDC 55953-034-40
Unit dose package of 100	NDC 55953-034-41

Glyburide Tablets (micronized) 3 mg Pale blue colored, oval shaped, flat face, beveled-edge, compressed tablets, engraved with **3 I 035** on one side and stylized **N** on the reverse. They are supplied as follows:

Plastic bottles of 100	NDC 55953-035-40
Plastic bottles of 500	NDC 55953-035-70
Plastic bottles of 1000	NDC 55953-035-80
Unit dose package of 100	NDC 55953-035-41

Glyburide Tablets (micronized) 4.5 mg Medium blue colored, oval shaped, flat face, beveled-edge, compressed tablets, engraved with **4.5 I 044** on one side and stylized **N** on the reverse. They are supplied as follows:

Plastic bottles of 100	NDC 55953-044-40
Plastic bottles of 500	NDC 55953-044-70
Unit dose package of 100	NDC 55953-044-41

Glyburide Tablets (micronized) 6 mg Dark blue colored, oval shaped, flat face, beveled-edge, compressed tablets, engraved with **6 I 036** on one side and stylized **N** on the reverse. They are supplied as follows:

Plastic bottles of 100	NDC 55953-036-40

The Glyburide tablet (micronized) can be easily divided in half for a more flexible dosing regimen. Press gently on the score and the tablet will split in even halves.

Caution: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container with safety closure. Keep container tightly closed.

Manufactured by: Novopharm Limited
Toronto, Canada
M1B 2K9

Manufactured for: Novopharm USA Inc.
Schaumburg, IL 60173

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73452 Sub. 03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING #1

ANDA

DRAFT

DATE OF REVIEW: January 3, 1995

ANDA #: 74-686

NAME OF FIRM: Novopharm Limited

NAME OF DRUG: Glyburide Tablets (micronized), 1.5 mg, 3 mg, and 6 mg

DATE OF SUBMISSION: June 5, 1995 and July 31, 1995

COMMENTS:

GENERAL COMMENT:

We acknowledge your comments regarding the withdrawal of the 4.5 mg strength from the application.

CONTAINER: 100s (1.5 mg, 3 mg, 6 mg), 500s (3 mg), and 1000s (3 mg)

1. Revise the established name to read as follows:

   Glyburide Tablets (micronized)

2. Revise the dispensing statement to read:

   Dispense in a tight, light-resistant container...

UNIT DOSE BLISTER: 100s (1.5 mg, 3 mg)

When the draft unit-dose blisters are compared side by side, they appear very similar. We would encourage you to differentiate between the different strengths as seen on your carton labeling.

UNIT DOSE CARTON: 100s (1.5 mg, 3 mg)

See comment 1 and 2 under CONTAINER.

INSERT:

1. TITLE

See comment 1 under CONTAINER.

2. DESCRIPTION

a. Revise to read:

Glyburide tablets (micronized) contain smaller particle size. Glyburide is an oral blood...crystalline compound. Each tablet, for oral administration, contains 1.5 mg, 3 mg, or 6 mg of glyburide. Inactive ingredients:...In addition, the 3 mg and 6 mg strengths...

b. Include the molecular formula.

c. Revise the molecular weight to read "494.01" rather than "———".

d. Italicize "-*o*-" in the chemical name.

3. CLINICAL PHARMACOLOGY

a. Pharmacokinetics

i. Paragraph 1, line 1 - ...with glyburide tablets (micronized) in normal...

ii. Revise to read paragraph 2 as follows:

...that micronized glyburide tablets 3 mg provide serum...those from nonmicronized glyburide tablets 5 mg.

iii. Delete paragraph 3 and figure A.

4. INDICATIONS AND USAGE

a. Revise paragraph 1 to read:

Glyburide tablets (micronized) are indicated...

b. Replace "[redacted]" with "glyburide" in paragraphs 2, 3, and 4. [3 places]

5. CONTRAINDICATIONS

a. Glyburide is contraindicated...

b. SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY - Revise paragraph 2 to read:

...of glyburide and of alternative modes of therapy.

6. PRECAUTIONS

a. Revise paragraph 1 to read as follows:

...that micronized glyburide tablets 3 mg...from nonmicronized glyburide tablets. Therefore, patients...from nonmicronized glyburide tablets or other...

b. Loss of Control of Blood Glucose - Replace "[redacted]" with "glyburide". [3 places]

c. Information for Patients - ...advantages of glyburide and of alternative...

d. Laboratory Tests - ...to glyburide tablets (micronized) should...

e. Carcinogenesis, Mutagenesis, and Impairment of Fertility - Delete "and" from the subsection heading.

f. Pregnancy, Nonteratogenic Effects - ...If glyburide is used during pregnancy...

g. Pediatric Use - ...in pediatric patients have...

7. ADVERSE REACTIONS

Gastrointestinal Reactions - ...rarely; glyburide should be...

8. DOSAGE AND ADMINISTRATION

a. Revise paragraph 1 to read as follows:

...from nonmicronized glyburide tablets or other...

b. Paragraph 2 - ...with glyburide tablets (micronized) or any other...

c. Paragraph 3 - ...of glyburide may be sufficient...

d. Usual Starting Dose - ...of glyburide tablets (micronized) is...

e. Transfer From Other Hypoglycemic Therapy - Revise to read:

...from nonmicronized glyburide tablets or other oral...than chlorpropamide to micronized glyburide tablets, no transition...

f. Patients Receiving Insulin - Revise to read:

...to micronized glyburide. If the...of glyburide tablets (micronized) 1.5 to 3 mg...may be placed directly on glyburide tablets (micronized) 3 mg daily...conversion to micronized glyburide. In these patients,...5% and glyburide tablets (micronized) 3 mg daily...

g. Titration to Maintenance Dose

i. Revise paragraph 2 to read:

...between micronized glyburide and the other hypoglycemic agents, including nonmicronized glyburide tablets. Although...of 3 mg of glyburide tablets (micronized) should be

observed. A maintenance dose of 3 mg of glyburide tablets (micronized) provide approximately...tolazamide, 5 mg of nonmicronized glyburide, 500 to...

ii. Replace "[redacted]" with "glyburide tablets (micronized)". [3 places]

h. Specific Patient Populations - Glyburide is not recommended...

9. HOW SUPPLIED

a. Replace "[redacted]" with "Glyburide Tablets (micronized)".

b. Delete the reference to the 4.5 mg strength tablets.

c. Place the "Caution: Federal Law..." statement on a separate line.

d. See comment 2. under CONTAINER.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels unit dose carton labeling and package insert labeling, then prepare and submit final printed container labels, unit dose blister labels, unit dose carton and insert labeling. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Glynase Prestab Tablets; Approved September 24, 1993; Revised September 1993)) with modifications to the Pharmacokinetic subsection. See FTR dated 5/3/95.

2. Patent/ Exclusivities:

Patent expires April 10, 2007. Exclusivity for new product expired March 04, 1995 and new chemical entity expired May 1, 1994.

3. Storage/Dispensing Conditions:

NDA: CRT; Dispense in a tight, light-resistant container. Keep container tightly closed.

ANDA: CRT; Dispense in ———— container with safety closure. Keep container tightly closed. See comment 2 under CONTAINER.

USP: Not the subject of a USP monograph. Glyburide - Preserve in tight containers.

4. Scoring:

NDA: All strengths are SCORED.

ANDA: All strengths are SCORED.

5. Product Line:

The innovator markets their product in 1.5 mg (100s, 1000s and unit-dose 100s); 3 mg (100s, 500s, 1000s and unit-dose 100s); 6 mg (100s and 500s).

The applicant proposes to market their product in 1.5 mg (100s and unit-dose 100s); 3 mg (100s, 500s, 1000s, and unit-dose 100s); 6 mg (100s). The generic firm has withdrawn the 4.5 mg strength from this application according to the amendment dated July 31, 1995. The firm was sent a "refuse to file" letter stating the innovator voluntarily withdrew the 4.5 mg strength from sale within the United States and had the option of submitting a citizens petition to determine if it was withdrawn for safety or effectiveness reasons. They declined and withdrew the strength.

6. The tablet embossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for

Human Use; Final Rule, effective 9/13/95). See pages 2606, 2632 and 2537.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 2726-2729 (Volume 1.2).

8. Container/Closure:

This product will be packaged in HDPE bottles with the 100s having a CRC cap and the 500s and 1000s a regular cap.

9. All manufacturing is to be completed by Novopharm in Ontario, Canada, yet Toronto, Canada is listed on the labels and labeling. All outside firms are utilized for the bioequivalence study. See pages 2829 and 2838 (vol. 1.2).

Carol Zimmermann

cc: ANDA 74-686
Dup/Division File
HFD-613/CZimmermann/CHoppes/JPhillips (no cc:)
HFD-600/RF
njg/1/19/96/firmsnz\novopharm\ltrs&rev\74686NA1.L
Review
Final

CZimmermann 1/19/96
CHoppes 1/19/96
JPhillips 1/23/96

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

Date of Review: November 18, 1996

Date of Submission: October 9, 1996

Primary Reviewer: Carol Holquist

ANDA Number: 74-686 **Review Cycle: 2 - (Major Amendment) FPL container labels and insert labeling. Draft labels and labeling for the 4.5 mg strength.**

Applicant's Name [as seen on 356(h)]: Novopharm Limited

Manufacturer's Name (If different than applicant): Same

Established Name: Glyburide Tablets (micronized) 1.5 mg, 3 mg, 4.5 mg and 6 mg

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

B. LABELING DEFICIENCIES

1. CONTAINER

a. 100s (1.5 mg, 3 mg, and 6 mg), 500s (3 mg), and 1000s (3 mg)

Satisfactory in final print.

b. 100s and 500s (4.5 mg)

It is difficult to determine from the draft label submitted, if this strength has been differentiated from your previously submitted strengths. We encourage you to differentiate this product strength as seen on your container labels for the 1.5 mg, 3 mg and 6 mg.

2. UNIT DOSE BLISTER

a. (1.5 mg, and 3 mg)

Satisfactory in final print.

b. (4.5 mg)

Satisfactory in draft.

3. UNIT DOSE CARTON:

a. 100s (1.5 mg, and 3 mg)

Satisfactory in final print.

b. 100s (4.5 mg)

See comment b under CONTAINER.

4. INSERT

Due to changes in the labeling of the listed drug (Glynase® PresTab® Tablets; Upjohn; Approved September 16, 1996; Revised March 1996), we request you revise your insert as follows:

a. CLINICAL PHARMACOLOGY

Pharmacokinetics

i. Paragraph two - Insert the following text as the last sentence:

Therefore, the patient should be retitrated.

ii. After further review, we request that you insert paragraph three and figure A from the reference listed drug's insert labeling. In addition, revise the first sentence to read as follows:

It has been reported that in a single-dose bioavailability...

iii. Paragraph five - Revise the first sentence to read as follows:

In single dose studies in fasting normal subjects who were administered nonmicronized tablets in doses ranging from 1.25 mg to 5 mg, the degree and duration...

b. CONTRAINDICATIONS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY - Italicize "*Diabetes*" in the last sentence of paragraph one.

c. PRECAUTIONS

i. Paragraph one - Revise the first sentence to read as follows:

...from nonmicronized glyburide tablets 5 mg.

ii. General, Hypoglycemia - Insert the following text as the last sentence:

The risk of hypoglycemia may be increased with combination therapy.

iii. Drug Interactions - Insert the following text to appear as the last paragraph:

Metformin: In a single-dose interaction study in NIDDM subjects, decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Coadministration of glyburide and metformin did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

Please revise labeling, as instructed above, and submit final printed insert labeling. 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. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: Satisfactorily submitted on October 9, 1996 for 100s (1.5 mg, 3 mg, and 6 mg), 500s (3 mg), and 1000s (3 mg).

Unit Dose Blister Label: Satisfactorily submitted on October 9, 1996 for (1.5 mg, and 3 mg).

Unit Dose Carton Label: Satisfactorily submitted on October 9, 1996 for 100s (1.5 mg, and 3 mg).

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes, see page 148 in Vol. 3.2 regarding the 4.5 mg strength.

What is the RLD on the 356(h) form: Glynase® PresTab®

NDA Number: 20-051

NDA Drug Name: Glynase® PresTab® Tablets

NDA Firm: The Upjohn Company

Date of Approval of NDA Insert and supplement #: September 16, 1996/S-004

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Approved Glynase® PresTab® labels in the file folder.

Basis of Approval for the Carton Labeling: Approved Glynase® PresTab® labeling in the file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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 23, supplement 5. Glyburide is in the USP but not the tablets.		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			
PROPRIETARY NAME			
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?			

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?			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		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	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
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 (page #) 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 page # 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?		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.			

NOTES/QUESTIONS TO THE CHEMIST:

Please note the addition of the 4.5 mg strength.

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Glynase® Prestab® Tablets; Approved September 16, 1996; Revised March 1996) with modifications to the Pharmacokinetics subsection. See FTR dated 5/3/95.

2. Patent/ Exclusivities:

   Patent expires April 10, 2007. Exclusivity for new product expired March 04, 1995 and new chemical entity expired May 1, 1994.

3. Storage/Dispensing Conditions:

   NDA: CRT; Dispense in a tight, light-resistant container. Keep container tightly closed.

   ANDA: CRT; Dispense in a tight, light-resistant container with safety closure. Keep

container tightly closed.

USP: Not the subject of a USP monograph. Glyburide - Preserve in tight containers.

4. Scoring:

NDA: All strengths are SCORED.

ANDA: All strengths are SCORED.

5. Product Line:

The innovator markets their product in 1.5 mg (100s, 1000s and unit-dose 100s); 3 mg (100s, 500s, 1000s and unit-dose 100s); 6 mg (100s and 500s).

The applicant proposes to market their product in 1.5 mg (100s and unit-dose 100s); 3 mg (100s, 500s, 1000s, and unit-dose 100s); 4.5 mg (100s, 500s and unit-dose 100s) 6 mg (100s). The generic firm originally withdrew the 4.5 mg strength from this application according to the amendment dated July 31, 1995. The firm was sent a "refuse to file" letter stating the innovator voluntarily withdrew the 4.5 mg strength from sale within the United States and had the option of submitting a citizens petition to determine if it was withdrawn for safety or effectiveness reasons. They did and it was found not to have been withdrawn for reasons of safety or effectiveness on May 30, 1996. The firm has submitted the labels and labeling for this strength.

6. The tablet embossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 2606, 2632 and 2537. Also see pg 435 in Vol. 3.2 for 4.5 mg strength.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 2726-2729 (Volume 1.2). Also see page 191 in Vol. 3.2 for the 4.5 mg strength.

8. Container/Closure:

This product will be packaged in HDPE bottles with the 100s having a CRC cap and the 500s and 1000s a regular cap.

9. All manufacturing is to be completed by Novopharm in Ontario, Canada. However, Toronto, Canada is listed on the labels and labeling. All outside firms are utilized for the bioequivalence study. See pages 2829 and 2838 (vol. 1.2).

C Holquist
Primary Reviewer

11/21/96
Date

A. Vezza
Secondary Reviewer

11/21/96
Date

John Grace
Team Leader
Labeling Review Branch

11/25/96
Date

cc:

ANDA 74-686
Dup/Division File
HFD-613/CHolquist/AVezza/JGrace (no cc)
njg/11/21/96/firmsnz/novophar/ltrs&rev/74686na2.1
Review

APPEARS THIS WAY
ON ORIGINAL

3.1
Shaik

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

ANDA Number: **74-686** Date of Submission: **July 10, 1997**

Applicant's Name: **Novopharm Limited**

Established Name: **Glyburide tablets (micronized) 1.5 mg, 3 mg, 4.5 mg and 6 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s (1.5 mg, 3 mg, and 6 mg), 500s (3 mg), and 1000s (3 mg) - Satisfactory as of October 9, 1996 submission.
100s and 500s (4.5 mg) - Satisfactory as of July 10, 1997 submission.

Unit Dose Blister Label: (1.5 mg and 3 mg) - Satisfactory as of October 9, 1996 submission
(4.5 mg) - Satisfactory as of July 10, 1997 submission.

Unit Dose Carton Label: 100s (1.5 mg and 3 mg) - Satisfactory as of October 9, 1996 submission.
(4.5 mg) - Satisfactory as of July 10, 1997 submission.

Professional Package Insert Labeling:
Satisfactory as of July 10, 1997 submission.

Revisions needed post-approval: None

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes
Yes, see page 148 in Vol. 3.2 regarding the 4.5 mg strength.

What is the RLD on the 356(h) form: Glynase® PresTab®

NDA Number: 20-051

NDA Drug Name: Glynase® PresTab® Tablets

NDA Firm: The Upjohn Company

Date of Approval of NDA Insert and supplement #: 9/16/96 (S-004)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Approved Glynase® PresTab® labels in the file folder.

Basis of Approval for the Carton Labeling: Approved Glynase® PresTab® labeling in the file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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 23, supplement 5. Glyburide is in the USP but not the tablets.		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			
PROPRIETARY NAME			
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?			
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?			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		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	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
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 (page #) 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 page # 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?		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.			

FOR THE RECORD: (carried forward from previous review) 4/18/97 in dfgt. 20051

1. Review based on the labeling of the listed drug (Glynase® Prestab® Tablets; Approved ~~September 16, 1996; Revised March 1996)~~ with modifications to the Pharmacokinetics subsection. ~~See FTR dated 5/3/95~~. Sh. 11 current 4/6/99

2. Patent/ Exclusivities:

   Patent expires April 10, 2007. Exclusivity for new product expired March 04, 1995 and new chemical entity expired May 1, 1994.

3. Storage/Dispensing Conditions:

   NDA: CRT; Dispense in a tight, light-resistant container. Keep container tightly closed.

   ANDA: CRT; Dispense in a tight, light-resistant container with safety closure. Keep container tightly closed.

   USP: Not the subject of a USP monograph. Glyburide - Preserve in tight containers.

4. Scoring:

   NDA: All strengths are SCORED.

   ANDA: All strengths are SCORED.

5. Product Line:

   The innovator markets their product in 1.5 mg (100s, 1000s and unit-dose 100s); 3 mg (100s, 500s, 1000s and unit-dose 100s); 6 mg (100s and 500s).

   The applicant proposes to market their product in 1.5 mg (100s and unit-dose 100s); 3 mg (100s, 500s, 1000s, and unit-dose 100s); 4.5 mg (100s, 500s and unit-dose 100s)

6 mg (100s). The generic firm originally withdrew the 4.5 mg strength from this application according to the amendment dated July 31, 1995. The firm was sent a "refuse to file" letter stating the innovator voluntarily withdrew the 4.5 mg strength from sale within the United States and had the option of submitting a citizens petition to determine if it was withdrawn for safety or effectiveness reasons. They did and it was found not to have been withdrawn for reasons of safety or effectiveness on May 30, 1996. The firm has submitted the labels and labeling for this strength.

6. The tablet embossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 2606, 2632 and 2537. Also see pg 435 in Vol. 3.2 for 4.5 mg strength.

7. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 2726-2729 (Volume 1.2). Also see page 191 in Vol. 3.2 for the 4.5 mg strength.

8. Container/Closure:

   This product will be packaged in HDPE bottles with the 100s having a CRC cap and the 500s and 1000s a regular cap.

9. **All manufacturing is to be completed by Novopharm in Ontario, Canada. However, Toronto, Canada is listed on the labels and labeling. All outside firms are utilized for the bioequivalence study. See pages 2829 and 2838 (vol. 1.2).**

Date of Review: July 29, 1997 **Date of Submission: 7/10/97**

Primary Reviewer: Adolph Vezza **Date** 7/30/97

AVezza

Team Leader: John Grace **Date** 7/30/97

John Grace

cc:

ANDA 74-686
Dup/Division File
HFD-613/AVezza/JGrace (no cc)
njg/7/30/97/X:\NEW\FIRMSNZ\NOVOPHAR\LTRS&REV\74686AP.L
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 74-686

3. NAME AND ADDRESS OF APPLICANT
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

U.S. Responsible Agent:
Theresa M. Ast, Ph.D., Esq.
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896

4. BASIS OF SUBMISSION
The listed drug product is Glynase[R] Prestab[R] 1.5, 3.0, and 6.0 mg by The Upjohn Company. Patent certification is submitted on page 25. Firm certified that the U.S. Patents # 4,735,805 will expire on 4-5-2005 and 4,916,163 will expire on 4-10-2007. Novopharm certified that their product will not be made available for marketing until the expiration of U.S. Patent # 4,916163 on 4-10-2007. The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strengths, and labeling is same as the listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glyburide Micro Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
*Original submission: 6-5-95
*Amendment: 7-31-95 (To withdraw 4.5 mg strength Tablets)

FDA:
Refuse to file Ltr: 7-14-95
Accepted for filing: 8-1-95 (Ltr. Date: 9-20-95)

10. PHARMACOLOGICAL CATEGORY
To control blood glucose in patients with non-insulin dependant diabetes mellitus (Type II) whose hypoglycemia cannot be satisfactorily controlled by diet alone.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 20-051 (Glynase by Upjohn; Approved 3-4-92, 9-24-93)
ANDA 74-388 Novopharm (approved for 1.25 mg, 2.5 and 5 mg Tablets)
DMF 5490...Novopharm.....Type I (Facility)
DMF [redacted]
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Tablet

14. POTENCY
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg (original submission)
[Note: 4.5 mg is withdrawn per amendment dated 7-31-95]

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: 5-Chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]amino]sulfonyl]ethyl]-2-methoxy- benzamide

Structure: USP 23, page 713

17. COMMENTS
A. GENERAL COMMENTS:
1. Legal basis of ANDA submission based on expiration of referenced US patents is okay. Novopharm certified that this drug product will not be marketed before April 7, 2007.
2. CGMP statement for the manufacturing sites are submitted.
3. Adequate information is submitted regarding container/closure systems. 1.5 mg tablets will be supplied in bottle of 100's and unit dose package of 100's, 3 mg tablets in bottle of 100's, 500's, 1000's and unit package of 100's and 6 mg tablet in bottle of 100's..
4. Composition and components - acceptable. It is identical to that approved for ANDA 74-388.
5. Control number information - adequate.
6. Adequate information is submitted regarding inactive ingredients.
7. Size for post-approval intended production size batches for all three strength is [redacted] tablets. Executed batch size meet OGD PPG's 22-90.

8. All bio/exhibit executed batches are fully packaged.
9. Samples for MV will not be requested as MV was completed without any problem by FDA for ANDA 74-388 which belong to Novopharm and have identical formulation.
10. Environmental issues - satisfactorily addressed.
11. EER is being submitted by M. Shaikh/S. O'Keefe (CSO) for all the facilities.
12. BIO review is pending.

B. COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments listed in sections # 22, 23, 28, 29, 32, 33 and 34.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approved. A NA letter with a major amendment is being issued to the applicant containing all the deficiencies in the section # 17(B).

19. REVIEWER: Mujahid L. Shaikh — DATE COMPLETED 12-14-95

cc: ANDA 74-686
DUP File
Division File
Field Copy

Endorsements:

HFD-625/MShaikh/12/14/95 Mujahid Shaikh 1/30/96
HFD-625/SSherken for MSmela/12/29/95 Stephen Sherken 2/1/96
x:\new\firmsnz\Novopharm\74686rv.1
F/T by: gp/1/24/96

APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #1

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-686

3. NAME AND ADDRESS OF APPLICANT
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

U.S. Responsible Agent:
Theresa M. Ast, Ph.D., Esq.
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896

4. BASIS OF SUBMISSION
Acceptable per CR # 1

Novopharm has included 4.5 mg strength tablet into this ANDA based on notice issued in Federal Register dated 5-21-96 and under FDA's authorization (Docket # 95P-0285/CPI).

Listed drug product: Glynase^{R} Prestab^{R} 1.5, 3.0, 4.5 mg and 6.0 mg by The Upjohn Company.

The U.S. Patents # 4,735,805 covering this drug product will expire on 4-5-2005 and 4,916,163 will expire on 4-10-2007. Novopharm certified that their product will not be made available for marketing until the expiration of U.S. Patent # 4,916163 on 4-10-2007.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glyburide Tablets (micronized)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 6-5-95
Amendment: 7-31-95 (To withdraw 4.5 mg strength Tablets)
* NC (BIO): 4-22-96
* Bio amendment: 9-24-96 (Response to bio letter dated 4-3-96)
* NC: 9-23-96
* Major amendment: 10-9-96 (Response to 4-3-96 NA letter) and 4.5 mg strength tablets is added back to the ANDA)
* NC: 1-8-97
* Telephone amendment (BIO): 1-17-97

FDA:
Refuse to file Ltr: 7-14-95
Accepted for filing: 8-1-95 (Ltr. Date: 9-20-95)
NA letter(Chemistry + Labeling): 2-5-96
Bio deficiency letter: 4-3-96

10. PHARMACOLOGICAL CATEGORY
To control blood glucose in patients with non-insulin dependant diabetes mellitus (Type II) whose hypoglycemia cannot be satisfactorily controlled by diet alone.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 20-051 (Glynase by Upjohn; Approved 3-4-92, 9-24-93)
AND 74-388 Novopharm (approved for 1.25 mg, 2.5 and 5 mg Tablets)
DMF 5490...Novopharm.....Type I (Facility)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Tablet

14. POTENCY
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg (original submission)
[Note # 1: 4.5 mg strength tablet was withdrawn per amendment dated 7-31-95]

[Note # 2: 4.5 mg strength tablet is included in this ANDA per this major amendment]

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: 5-Chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]amino]sulfonyl]ethyl]-2-methoxy- benzamide

Structure: USP 23, page 713

17. COMMENTS
A. GENERAL COMMENTS:
1. The drug product will not be marketed before April 7, 2007.

2. DMF ——— for ——————————— remains inadequate per M. Shaikhs review dated 1-27-97.
3. Samples for MV will not be requested as satisfactory MV was completed by FDA for ANDA 74-388 (Novopharm). The drug product proposed in this ANDA have identical formulation.
4. Raw material controls - satisfactory per this review.
5. Adequate information is submitted for stability section. Expiration dating periods of 18 months for 1.5 mg tablets and 24 months for 3 mg and 6 mg tablets are acceptable based on the stability submitted.
6. FPL is being requested per labeling review dated 11-18-96 completed by C. Holquist.
7. EER is being submitted by M. Shaikh/S. O'Keefe (CSO) for all the facilities concurrent to this review.
8. BIO review of amendments dated 9-24-96 and 1-17-97 are being done.
9. Adequate information is submitted for 4.5 mg strength tablets regarding composition, manufacturing, testing and stability testing.

B. COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments listed in sections # 22, 28, 32, 33 and 34.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approved. A NA letter with a minor amendment is being faxed to the applicant containing all the deficiencies in the section # 17(B).

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED 1-28-97
Revised on 2-6-97.

APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #2

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-686 APPLICANT: Novopharm Ltd., Canada

DRUG PRODUCT: Glyburide Tablets (micronized)

The deficiencies presented below represent MINOR deficiencies.

1. DMF ——— of ——————————————————— is deficient. Please confirm a response to all outstanding deficiencies cited by the recent FDA letter.

2. [redacted]

3. The stability specifications for the ——————————— and ——————————should be tightened slightly for the 1.5 mg tablet.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application. You may wish to contact your supplierof ———— regarding their current status.

2. The review of your bioequivalence data is pending. Deficiencies, if any, will be communicated separately.

Sincerely yours,

2/23/97

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-686
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/M.Shaikh/2-6-97 Mujahid Shaikh 2/14/97
HFD-625/M.Smela/2-7-97
HFD-617/S.O'Keefe/M.Anderson for/2-7-97 S O'Keefe 2/13/97
X:\new\firmsnz\novophar\ltrs&rev\74686.rv2
F/T by: bc/2-10-97

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR M Smela 2/14/97

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-686

3. NAME AND ADDRESS OF APPLICANT
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

U.S. Responsible Agent:
Theresa M. Ast, Ph.D., Esq.
4700 Novopharm Drive N.W.
Wilson, N.C. 27893

4. BASIS OF SUBMISSION
Acceptable per CR # 1

Listed drug product: Glynase^{R} Prestab^{R} 1.5, 3.0, 4.5 mg and 6.0 mg by The Upjohn Company.

The U.S. Patents # 4,735,805 covering this drug product will expire on 4-5-2005 and 4,916,163 will expire on 4-10-2007. According to the information submitted in the original submission, Novopharm certified that their product will not be made available for marketing until the expiration of U.S. Patent # 4,916163 on 4-10-2007. In NC dated 3-21-97, Novopharm submitted Patent Certification to certify that the patents cited above will not be infringed by manufacture, use or sale of glyburide (micronized) for which this application is submitted.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glyburide Tablets (micronized)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 6-5-95
Amendment: 7-31-95 (To withdraw 4.5 mg strength Tablets)
NC (BIO): 4-22-96
Bio amendment: 9-24-96 (Response to bio letter dated 4-3-96)
NC: 9-23-96
Major amendment: 10-9-96 (Response to 2-5-96 NA letter) and 4.5 mg strength tablets is added back to the ANDA)
NC: 1-8-97
Telephone amendment (BIO): 1-17-97
* NC: 2-27-97
* NC: 3-21-97 (Patents)

* NC: 6-11-97 (Labeling)
* Minor Amendment: 7-10-97 (Response to letters dated 2-24-97, and 6-2-97.

FDA:
Refuse to file Ltr: 7-14-95
Accepted for filing: 8-1-95 (Ltr. Date: 9-20-95)
NA letter(Chemistry + Labeling): 2-5-96
Bio deficiency letter: 4-3-96
Bio acceptance letter: 2-4-97
NA letter (Chemistry): 2-24-97
Letter (Labeling): 6-2-97

10. PHARMACOLOGICAL CATEGORY
To control blood glucose in patients with non-insulin dependant diabetes mellitus (Type II) whose hypoglycemia cannot be satisfactorily controlled by diet alone.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 20-051 (Glynase by Upjohn; Approved 3-4-92, 9-24-93) AND 74-388 Novopharm (approved for 1.25 mg, 2.5 and 5 mg Tablets)
DMF 5490...Novopharm.....Type I (Facility)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Tablet

14. POTENCY
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg (original submission)
[Note # 1: 4.5 mg strength tablet was withdrawn per amendment dated 7-31-95 and 4.5 mg strength tablet is included back in this ANDA per major amendment dated 10-9-96]

15. CHEMICAL NAME AND STRUCTURE

CHEMICAL NAME: 5-Chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]amino]sulfonyl]ethyl]-2-methoxy- benzamide

Structure: USP 23, page 713

17. COMMENTS

A. GENERAL COMMENTS:

1. In NC dated 3-21-97, Novopharm submitted Patent Certification to certify that the patents cited above will not be infringed by manufacture, use or sale of glyburide (micronized) for which this application is submitted.
2. DMF ——— for ——————————— became adequate per M. Shaikh's review dated 7-17-97.
3. FPL submitted in this amendment is acceptable per review completed on 7-30-97.
4. BIO Status became acceptable per letter to the firm dated 2-4-97 for 1.5 mg, 3.0 mg and 6 mg tablets. Request for bio waiver for 4.5 mg tablets is pending for an action.
5. EER Status submitted by M. Shaikh/S. O'Keefe for all the facilities is "withhold" as of 2-13-97. EER updated is being requested concurrent to this review.

B. COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments listed in sections # 29 and 33.

18. CONCLUSIONS AND RECOMMENDATIONS

Not-approved. A NA letter with minor amendment is being issued to the firm citing comments listed in Section 17(B) as the firm has failed to respond to a request for a telephone amendment.

19. REVIEWER: Mujahid L. Shaikh — DATE COMPLETED: 8-25-97

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confidential commercial

information from

CHEMISTRY REVIEW #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-686 APPLICANT: Novopharm Ltd., Canada

DRUG PRODUCT: Glyburide Tablets (micronized)

The deficiencies presented below represent Minor deficiencies.

1. We request again to slightly tighten the stability specifications for the [redacted] and [redacted] for the 1.5 mg tablet. Alternatively, you may provide data from several lots of the reference product to justify your current specifications.

2. [redacted]

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Your bioequivalence data for the 4.5 mg tablet are pending review.

3. Please provide any additional stability data that may be available.

Sincerely yours,

9/19/97

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

The firm has not responded to a request for a telephone amendment dtf.

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-686
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/M.Shaikh/8-25-97 Mujahid Shaikh 9/17/97
HFD-625/M.Smela/9-8-97 M Smela 9/18/97
HFD-617/S.O'Keefe, PM/9-8-97 S O'Keefe 9/10/97
X:\new\firmsnz\novophar\ltrs&rev\74686rev.3
F/T by: bc/9-16-97

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

Chemistry Closed

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-686

3. NAME AND ADDRESS OF APPLICANT
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

U.S. Responsible Agent:
Theresa M. Ast, Ph.D., Esq.
4700 Novopharm Drive N.W.
Wilson, N.C. 27893

4. BASIS OF SUBMISSION
Acceptable per CR # 1

Listed drug product: Glynase® Prestab® 1.5, 3.0, 4.5 mg and 6.0 mg by The Upjohn Company.

The U.S. Patents # 4,735,805 covering this drug product will expire on 4-5-2005 and 4,916,163 will expire on 4-10-2007. According to the information submitted in the original submission, Novopharm certified that their product will not be made available for marketing until the expiration of U.S. Patent # 4,916163 on 4-10-2007. In NC dated 3-21-97, Novopharm submitted Patent Certification to certify that the patents cited above will not be infringed by manufacture, use or sale of glyburide (micronized) for which this application is submitted.

In telephone amendment dated 4-3-98, Novopharm has included a copy of the return receipt for the notice provided to the sponsor and patent holder, Pharmacia & Upjohn, concerning Novopharm's Paragraph IV Certification filed on March 21, 1997 for US Patent # 4,916,163 and US Patent # 4,735,805 in Exhibit II. Based on this, Pharmacia & Upjohn has initiated a civil suit against Novopharm and the matter is still pending.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glyburide Tablets (micronized)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Original submission: 6-5-95
Amendment: 7-31-95 (To withdraw 4.5 mg strength Tablets)
NC (BIO): 4-22-96
Bio amendment: 9-24-96 (Response to bio letter dated 4-3-96)
NC: 9-23-96
Major amendment: 10-9-96 (Response to 2-5-96 NA letter) and 4.5 mg strength tablets is added back to the ANDA)
NC: 1-8-97
Telephone amendment (BIO): 1-17-97
NC: 2-27-97
NC: 3-21-97 (Patents)
NC: 6-11-97 (Labeling)
Minor Amendment: 7-10-97 (Response to letters dated 2-24-97, and 6-2-97.
* Minor Amendment: 3-2-98 (Response to NA letter dated 9-23-97).
* Telephone Amendment: 4-3-98

FDA:

Refuse to file Ltr: 7-14-95
Accepted for filing: 8-1-95 (Ltr. Date: 9-20-95)
NA letter(Chemistry + Labeling): 2-5-96
Bio deficiency letter: 4-3-96
Bio acceptance letter: 2-4-97
NA letter (Chemistry): 2-24-97
Letter (Labeling): 6-2-97
NA letter (Chemistry): 9-23-97

10. PHARMACOLOGICAL CATEGORY

To control blood glucose in patients with non-insulin dependant diabetes mellitus (Type II) whose hypoglycemia cannot be satisfactorily controlled by diet alone.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-051 (Glynase by Upjohn; Approved 3-4-92, 9-24-93)
AND 74-388 Novopharm (approved for 1.25 mg, 2.5 and 5 mg Gluburide Tablets)
DMF 5490...Novopharm.....Type I (Facility)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

DMF ———————————————————————————

13. DOSAGE FORM
Tablet

14. POTENCY
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg (original submission)
[Note # 1: 4.5 mg strength tablet was withdrawn per amendment dated 7-31-95 and 4.5 mg strength tablet is included back in this ANDA per major amendment dated 10-9-96]

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: 5-Chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]amino]sulfonyl]ethyl]-2-methoxy- benzamide

Structure: USP 23, page 713

17. COMMENTS
1. DMF ——— for ———————————— became adequate per M. Shaikh's review dated 7-17-97 and remains adequate per 1-13-98 review completed by R. Trimmer. Remains adequate per review conducted by this reviewer on 3-9-98 after review of amendment dated 2-9-98.
2. FPL is acceptable per review completed on 7-30-97.
3. BIO Status became acceptable per letter to the firm dated 2-4-97 for 1.5 mg, 3.0 mg and 6 mg tablets. Request for bio waiver for 4.5 mg tablets is pending for an action.
5. EER Status for all the facilities listed in this ANDA became acceptable on 6-12-97 by M. Egas.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable bio waiver for 4.5 mg strength tablet.

19. REVIEWER: Mujahid L. Shaikh — DATE COMPLETED 4-8-98

cc: ANDA 74-686
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/4/8/98 Mujahid Shaikh 4/9/98
HFD-625/M.Smela/4/8/98
X:\new\firmsnz\novophar\ltrs&rev\74686rev.4
F/T by: gp/4/8/98

M Smela 4/9/98

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CHEMISTRY REVIEW #4

Addendum # 1 to Chemist's Review # 4:

ANDA 74-686 Glyburide Tablets (micronized)

Chemistry Issues were previously closed per Review # 4 completed on 4-8-98. This addendum is being written to discuss following issues:

1. Bio issue: A bio acceptance letter was sent to the firm on 2-24-97 for 1.5 mg, 3.0 mg and 6 mg strength tablets. 4.5 mg strength tablet was not included in this letter because amendment dated October 9, 1996 submitted for bio waiver for 4.5 mg tablet was not included in the review signed off on 2-3-97. This amendment is reviewed and a bio deficiency on 5-1-98 is issued for 1.5 mg, 3 mg, 4.5 mg and 6 mg strength tablets citing following deficiencies:

1. The in-vitro dissolution testing conducted by Novopharm on its Glyburide Micronized Tablets, 4.5 mg and 6 mg, has been found **unacceptable** for the reason that the dissolution method and specification used were incorrect. The dissolution method and specifications as stated in the 2-24-97 DBE letter were incorrect.

The dissolution testing should be conducted in 900 ml of pH 7.5 0.05M phosphate buffer at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The sampling times should be 15, 30, 45, and 60 minutes.

2. The waiver request for *in vivo* bioequivalence study requirements for the 4.5 mg strength of Novopharm's Glyburide Micronized Tablets can not be reviewed at this time pending acceptable dissolution testing of the test product of **all strengths.**

2. EER Status: EER for all the facilities listed in Section # 33 of CR # 4 are acceptable as of June 12, 1997 by M. Egas. This reviewer generated EER report on 6-16-98. Based on this, updated status need to be established.

Comment: Not approved based on unacceptable status of the bio. A NA letter is being issued citing deficiencies from chemistry point-of-view which need to be addressed based on the bio deficiency letter dated May 1, 1998.

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-686 APPLICANT: Novopharm Ltd., Canada

DRUG PRODUCT: Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

The deficiencies presented below represent facsimile deficiencies.

1. Dissolution testing for these drug products has not been established. Please reference and respond to the communication dated May 1, 1998 from the Division of Bioequivalence.

2. The corrected dissolution test should be included in your release and stability programs. Additionally, please demonstrate that your analytical method remains suitable with the new dissolution medium.

3. Please provide dissolution data using the new method at the next test station for the stability samples of all four strengths.

Sincerely yours,

Hilayat Sayed for 6/25/98

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-686
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/M.Shaikh/6-16-98 Mujahid Shaikh 6/25/98
HFD-625/M.Smela/6-16-98 M Smela
HFD-617/D.Huie,PM/6-18-98 6/24/98 6/25/98
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F/T by: bc/6-22-98

CHEMISTRY REVIEW - NOT APPROVABLE - facsimile

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 74-686

3. NAME AND ADDRESS OF APPLICANT
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

U.S. Responsible Agent:
Dietrich Bartel, B.Sc.
4700 Novopharm Drive N.W.
Wilson, N.C. 27893
[Note: Change of U.S. Agent cited in amendment 8-27-98]

4. BASIS OF SUBMISSION
Acceptable per CR # 1

Listed drug product: Glynase^{R} Prestab^{R} 1.5, 3.0, 4.5 mg and 6.0 mg by The Upjohn Company.

The U.S. Patents # 4,735,805 covering this drug product will expire on 4-5-2005 and 4,916,163 will expire on 4-10-2007. According to the information submitted in the original submission, Novopharm certified that their product will not be made available for marketing until the expiration of U.S. Patent # 4,916163 on 4-10-2007. In NC dated 3-21-97, Novopharm submitted Patent Certification to certify that the patents cited above will not be infringed by manufacture, use or sale of glyburide (micronized) for which this application is submitted.

In telephone amendment dated 4-3-98, Novopharm has included a copy of the return receipt for the notice provided to the sponsor and patent holder, Pharmacia & Upjohn, concerning Novopharm's Paragraph IV Certification filed on March 21, 1997 for US Patent # 4,916,163 and US Patent # 4,735,805 in Exhibit II. Based on this, Pharmacia & Upjohn has initiated a civil suit against Novopharm and the matter is still pending.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glyburide Tablets (micronized)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Original submission: 6-5-95
Amendment: 7-31-95 (To withdraw 4.5 mg strength Tablets)
NC (BIO): 4-22-96
Bio amendment: 9-24-96 (Response to bio letter dated 4-3-96)
NC: 9-23-96
Major amendment: 10-9-96 (Response to 2-5-96 NA letter) and 4.5 mg strength tablets is added back to the ANDA)
NC: 1-8-97
Telephone amendment (BIO): 1-17-97
NC: 2-27-97
NC: 3-21-97 (Patents)
NC: 6-11-97 (Labeling)
Minor Amendment: 7-10-97 (Response to letters dated 2-24-97, and 6-2-97.
Minor Amendment: 3-2-98 (Response to NA letter dated 9-23-97).
Telephone Amendment: 4-3-98
* NC: 5-5-98
* NC: 6-30-98
* Bio amendment: 6-30-98 (Response to 5-1-98 bio letter)
* Minor Amendment: 8-27-98 (Response to letter dated 7-1-98 from Dr. Patel and letter dated 8-6-98 from bio)

FDA:

Refuse to file Ltr: 7-14-95
Accepted for filing: 8-1-95 (Ltr. Date: 9-20-95)
NA letter(Chemistry + Labeling): 2-5-96
Bio deficiency letter: 4-3-96
Bio acceptance letter: 2-24-97
NA letter (Chemistry): 2-24-97
Letter (Labeling): 6-2-97
NA letter (Chemistry): 9-23-97
Bio deficiency letter: 5-1-98
NA (Facsimile Amendment) ltr: 7-1-98
Bio acceptance letter: 8-6-98

10. PHARMACOLOGICAL CATEGORY

To control blood glucose in patients with non-insulin dependant diabetes mellitus (Type II) whose hypoglycemia cannot be satisfactorily controlled by diet alone.

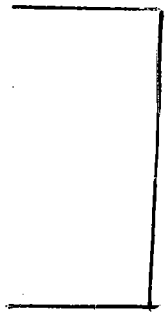
11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-051 (Glynase by Upjohn; Approved 3-4-92, 9-24-93) AND 74-388 Novopharm (approved for 1.25 mg, 2.5 and 5 mg Gluburide Tablets)
DMF 5490...Novopharm.....Type I (Facility)
DMF
DMF

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF



13. DOSAGE FORM
Tablet

14. POTENCY
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg (original submission)
[Note # 1: 4.5 mg strength tablet was withdrawn per amendment dated 7-31-95 and 4.5 mg strength tablet is included back in this ANDA per major amendment dated 10-9-96]

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: 5-Chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]amino]sulfonyl]ethyl]-2-methoxy- benzamide

Structure: USP 23, page 713

17. COMMENTS
1. DMF ——— for ——————————— is adequate per last review conducted by this reviewer on 3-9-98. There is no new information is submitted after this review.
2. BIO Status became acceptable per letter to the firm dated 8-6-98 for 1.5 mg, 3.0 mg, 4.5 mg and 6 mg tablets.
3. EER Status for all the facilities listed in this ANDA became acceptable on 6-25-98 by M. Egas.
4. Firm has responded adequately in their amendment dated 8-27-98 for all the issues which were cited in 7-1-98 NA letter.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED 10-2-98

cc: ANDA 74-686
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/10-2-98 Mirpad Shaikh 10/8/98
HFD-625/M.Smela/10-5-98
X:\new\firmsnz\novophar\ltrs&rev\74686rev.5
F/T by: bc/10-5-98

M Smela
10/8/98

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confidential commercial

information from

CHEMISTRY REVIEW #5

Addendum to Chemist's Review # 5:

ANDA 74-686 [Glyburide Tablets (micronized), 1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg]

* Telephone Amendment: 10-27-98

Chemistry Issues were previously closed per Review # 5 and the approval package was prepared by this reviewer. This approval package for the ANDA was reviewed by Allen Rudman and find it deficient with respect to issues regarding ——————— and ——— Mike Smela clarified to Allen Rudman that the issue of ——————— has been addressed in the referenced DMF ——— and has been found adequate. Other two issues mentioned above need action from the firm.

Based on above background, Mike Smela and this reviewer called the U.S. Agent for Novopharm - Dietrich Bartel on 10-15-98 and both issues were discussed in telecon.

On 10-27-98, Novopharm submitted a telephone amendment and responded to both issues discussed in the telecon.

[redacted]

Comment: Remains approved based on acceptable response.

c.c: ANDA 74-686
Division File
FIELD COPY

Endorsements:

HFD-625/M. Shaikh/ Mujahid Shaikh 10/28/98
HFD-625/M. Smela/
x:\new\firmsnz\novophar\ltrs&rev\74686rv5.add
F/T by: M Smela 10/28/98

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 74-686

3. NAME AND ADDRESS OF APPLICANT
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

U.S. Responsible Agent:
Jonathan Ng, B.Sc.
4700 Novopharm Drive N.W.
Wilson, N.C. 27893

4. BASIS OF SUBMISSION
Listed drug product: Glynase[R] Prestab[R] 1.5, 3.0, 4.5 mg and 6.0 mg by The Upjohn Company.

Novopharm was issued a tentative approval on 11-10-98. Now Novopharm submitted this minor amendment requesting the final approval for the drug product based on the court judgement rendered on 2-2-98.

U.S. Patents # 4,735,805 covering this drug product will expire on 4-5-2005 and 4,916,163 will expire on 4-10-2007.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glyburide Tablets (micronized)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original submission: 6-5-95
Amendment: 7-31-95 (To withdraw 4.5 mg strength Tablets)
NC (BIO): 4-22-96
Bio amendment: 9-24-96 (Response to bio letter dated 4-3-96)
NC: 9-23-96
Major amendment: 10-9-96 (Response to 2-5-96 NA letter) and 4.5 mg strength tablets is added back to the ANDA)
NC: 1-8-97
Telephone amendment (BIO): 1-17-97
NC: 2-27-97
NC: 3-21-97 (Patents)
NC: 6-11-97 (Labeling)
Minor Amendment: 7-10-97 (Response to letters dated 2-24-97, and 6-2-97.
Minor Amendment: 3-2-98 (Response to NA letter dated 9-23-97).
Telephone Amendment: 4-3-98

NC: 5-5-98
NC: 6-30-98
Bio amendment: 6-30-98 (Response to 5-1-98 bio letter)
Minor Amendment: 8-27-98 (Response to letter dated 7-1-98 from Dr. Patel and letter dated 8-6-98 from bio)
Telephone: Amendment: 10-27-98
Amendment: 11-9-98

- Bio amendment: 1-13-99
- Minor Amendment:3-15-99
- Telephone Amendment: 3-24-99

FDA:

Refuse to file Ltr: 7-14-95
Accepted for filing: 8-1-95 (Ltr. Date: 9-20-95)
NA letter(Chemistry + Labeling): 2-5-96
Bio deficiency letter: 4-3-96
Bio acceptance letter: 2-24-97
NA letter (Chemistry): 2-24-97
Letter (Labeling): 6-2-97
NA letter (Chemistry): 9-23-97
Bio deficiency letter: 5-1-98
NA (Facsimile Amendment) ltr: 7-1-98
Bio acceptance letter: 8-6-98
Tentative Approval: 11-10-98

10. PHARMACOLOGICAL CATEGORY
To control blood glucose in patients with non-insulin dependant diabetes mellitus (Type II) whose hypoglycemia cannot be satisfactorily controlled by diet alone.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 20-051 (Glynase by Upjohn; Approved 3-4-92, 9-24-93)
AND 74-388 Novopharm (approved for 1.25 mg, 2.5 and 5 mg Gluburide Tablets)
DMF 5490...Novopharm.....Type I (Facility)
DMF
DMF
DMF
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DMF
DMF
DMF
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DMF

13. DOSAGE FORM
Tablet

14. POTENCY
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: 5-Chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]amino]sulfonyl]ethyl]-2-methoxy- benzamide

Structure: USP 23, page 713

17. COMMENTS
1. DMF ——— for ——————————. is adequate per last review conducted by this reviewer on 3-9-98. There is no new information is submitted after this review.
2. BIO Status became acceptable again with final dissolution specifications for 1.5 mg, 3.0 mg, 4.5 mg and 6 mg tablets.
3. EER Status for all the facilities listed in this ANDA is acceptable since 6-25-98 by M. Egas. However, in amendment dated 1-13-99, Novopharm has included alternate testing facility of ———————— for which EER status is required.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER status for ———————— as an alternate testing facility.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED 3-29-99

cc: ANDA 74-686
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/3-29-99 Mujahid Shaikh 4/7/99
HFD-625/M.Smela/3-29-99
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F/T by: bc/3-31-99

M. Smela 4/7/99

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CHEMISTRY REVIEW #6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

BIOEQUIVALENCE REVIEW(S)

MAR 26 1996

Glyburide ——— Tablets
1.5 mg, 3.0 mg & 6.0 mg
ANDA # 74-686
Reviewer: Hoainhon Nguyen
WP# 74686sdw.695

Novopharm Ltd.
Stouffville, Ontario, Canada
Submission Date:
June 5, 1995

Review of Two Bioequivalence Studies, Dissolution Data and Waiver Requests

I. Background:

Glyburide is a sulfonylurea antidiabetic agent, indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone. The drug appears to lower blood glucose concentration principally by stimulating secretion of endogenous insulin from the beta cells of the pancreas. The solubility of glyburide in water increases with increasing pH, from approximately 4 mcg/ml at pH 4 to 600 mcg/ml at pH 9.

Glyburide appears to be almost completely absorbed following oral administration and food apparently does not affect the rate or extent of absorption of the drug. Following oral administration of a single 5-mg dose of glyburide, the drug appears in plasma or serum within 15-60 minutes and an average peak plasma or serum concentrations of approximately 140-350 ng/ml usually are attained within 2-4 hours (range 2-8 hours). The area under the serum concentration-time curve (AUC) for glyburide increases in proportion to increasing doses.

Following single oral doses of glyburide in nonfasting diabetic or healthy individuals, plasma insulin concentration generally begins to increase within 15-60 minutes and is maximal within 1-2 hours; in diabetic patients, increases in plasma insulin concentration may persist for up to 24 hours. Following single oral doses of the drug in fasting healthy individuals, the degree and duration of lowering of blood glucose

concentration are proportional to the dose administered and the AUC; the hypoglycemic action generally begins within 45-60 minutes and is maximal within 1.5-3 hours. In nonfasting diabetic patients, the hypoglycemic action of a single morning dose of glyburide may persist for up to 24 hours.

Serum concentrations of glyburide appear to decline in a biphasic manner. The terminal half-life has reportedly averaged 1.4-1.8 hours (range: 0.7-3 hours). Glyburide appears to be completely metabolized, probably in the liver. The drug is metabolized at the cyclohexyl ring principally to 4-trans-hydroxyglyburide. It also is metabolized to 3-cis-hydroxy derivative and another unidentified metabolite. The activity of the metabolites is generally considered clinically unimportant.

Glyburide is excreted as metabolites in urine and feces in approximately equal proportions. Most urinary excretion occurs within the first 6-24 hours after oral administration of the drug. Following oral administration of a single 5-mg dose of glyburide in healthy individuals, approximately 30-50% of the dose is excreted in urine as metabolites within 24 hours; about 80% of the urinary excretion occurs as the 4-trans-hydroxy metabolite, 15% as the 3-cis-hydroxy metabolite, and 5% as an unidentified metabolite. Fecal excretion occurs more slowly, but a single oral dose of the drug is completely excreted in urine and feces within 3-5 days in healthy individuals.

Adverse reactions associated with glyburide include severe hypoglycemia, nausea, epigastric fullness and heartburn and allergic skin reactions.

Reference product for micronized glyburide tablets is Glynase^{R} Pretab^{R} tablets, 1.5 mg, 3 mg and 6 mg, manufactured by the Upjohn Company.

The firm has submitted the results of two bioequivalence studies comparing the test and reference product of the 6 mg strength under fasting and non-fasting conditions. Comparative dissolution data for the 6 mg, 3 mg and 1.5 mg strengths are also submitted in support of a request for waiver of in vivo bioequivalence requirements for the two lower strengths.

Note: The firm has withdrawn 4.5 mg strength per 7/31/1995 amendment.

II. Bioequivalence Studies:

A. Protocol No. EP015: Two-Way Crossover Bioequivalence Study of Novopharm Limited and Upjohn U.S. (Glynase Prestabs^{R}) 6 mg Micronized Glyburide Tablets in Fasting Volunteers.

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Novopharm's glyburide micronized tablets, 6 mg, and Upjohn's Glynase Prestabs^{R} Tablets, 6 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at [redacted] between March 25, 1995 and April 1, 1995. The principal investigator was [redacted] M.D., Ph.D.. Plasma samples were assayed by [redacted] under the supervision of [redacted] Ph.D., between April 13, 1995 and May 12, 1995.

Demographics:

Thirty-eight normal, healthy, non-smoking male volunteers between 19-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 60.2 - 93 kgs and 162 - 185 cm., respectively.

Inclusion criteria:

Subjects especially did not have any history or presence of: significant cardiovascular, hepatic, renal, CNS, hematological or gastrointestinal diseases; adrenal or pituitary insufficiency; hypoglycemia; diabetes; alcoholism or drug abuse within the last year;

hypersensitivity or idiosyncratic reaction to glyburide or any other sulfonylureas or sulfonamide.

Restrictions:

They were free of all medications at least 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed 48 hours prior to each drug administration until after the 24-hour postdose blood sample. The subjects fasted for 10 hours prior to and 4 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was 10 hours pre-dose to approximately 24 hours post-dose in each period.

Treatments and Sampling:

The two treatments each consisted of a single 6 mg dose of either the test product or reference product taken orally with 240 ml of 20% glucose solution. In order to minimize any possible hypoglycemic effects, each subject was administered 60 ml of this glucose solution approximately every 15 minutes starting 15 minutes postdose until the 4-hour postdose meal.

Test Product: Novopharm's Glyburide micronized tablets, 6 mg, lot # PD2817 (Batch size of ——— units, potency of 104.7%).

Reference product: Upjohn's Glynase Prestabs^{R} Tablets, 6 mg, lot # 418XF (Potency of 103.7%).

Blood samples were collected at predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours following drug administration. Blood samples were centrifuged under refrigeration and the plasma was separated and immediately stored at -10^{0}C or lower pending assay for glyburide.

Assay Methodology:

The analytical method was developed by———————————————.

Glyburide and the internal standard were assayed using a HPLC method, ———

Assay Specificity:

The method is specific for glyburide with no significant interference seen at the retention time of the drug or internal standard in chromatograms of blank plasma standards and predose subject samples.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of ———

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 14.8% at 12.50 ng/ml, 6.3% at 90.00 ng/ml and 6.2% at 210 ng/ml.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 5.00 ng/ml (CV% = 7.7). Any level below this limit was reported as zero.

Prestudy validation data showed CV% for LOQ of 5.0 ng/ml (n=6) was 11.3.

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: _____

Stability:

Stability of frozen samples was demonstrated in **a pre-study validation study** using frozen control samples which were prepared, stored at -15°C, and analyzed within 118-day period. The controls, 20.0 ng/ml, 150.0 ng/ml and 225.0 ng/ml, analyzed at Times 0 and 118 days had a mean accuracy of 95%, 99.5% and 103%, respectively. No trends were detected. The actual plasma samples were first collected and stored frozen (below -10°C) on 03/25/95 and last analyzed on 05/12/95 (maximum of 38 days). The stability study is therefore acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Thirty-seven of thirty-eight enrolled volunteers completed the clinical portion of the study. Subject # 30 withdrew from the study for personal reasons. Samples from

Subject #37 were analyzed in place of Subject #30 and samples of alternate Subject #38 were not analyzed. The statistical analysis was performed using 36 data sets.

There were significant differences (alpha=0.05) between treatments for AUC (0-T)(p=0.0417), CMAX (p=0.0217), KEL (p=0.0381), lnAUC(0-T) (p=0.0044), lnAUC(0-Infinity) (p=0.0135) and lnCMAX (p=0.0238). There was no significant difference between treatments for AUC(0-Inf) and TMAX. The results are summarized in the tables below:

Table I

Glyburide Comparative Pharmacokinetic Parameters
Fasting Study; Dose = 6 mg; n = 36

Parameters	Novopharm's Mean (CV)	Glynase[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	913.3*	1016*	[0.85;0.95]	0.90
AUC (0-Inf) ng.hr/ml	1010*	1102*	[0.88;0.97]	0.92
CMAX(ng/ml)	133.5*	153.4*	[0.79;0.96]	0.87
TMAX (hrs)	6.78(38)	6.65(36)		
KEL (1/hrs)	0.18(48)	0.21(47)		
T1/2 (hrs)	4.68(42)	4.01(43)		

*Geometric means

Table II

Comparative Mean Plasma Levels of Glyburide, ng/ml(CV)

Fasting Study; Dose = 6 mg; n = 36

Hour	Novopharm's	Glynase[R]
0	0	0
0.50	11.14(199)	8.32(250)
1.00	29.54(185)	22.18(153)
1.50	35.42(170)	30.47(157)
2.00	31.79(143)	31.00(121)
2.50	32.57(134)	33.98(110)
3.00	37.46(152)	35.45(92)
3.50	34.48(136)	36.05(94)
4.00	32.86(125)	37.22(81)
5.00	58.34(64)	69.26(72)
6.00	87.69(49)	103.41(48)
8.00	98.30(48)	119.32(53)
10.00	85.15(61)	99.08(54)
12.00	48.29(69)	52.37(64)
16.00	22.57(101)	20.83(81)
24.00	8.07(80)	8.02(90)
AUC(0-T)ng.hr/ml	990.0(46)	1082 (38)
AUC(0-Inf)ng.hr/ml	1086 (44)	1166 (37)
CMAX	140.8(33)	161.0(31)

Adverse Effects:

All complaints were judged mild to moderate in intensity. The complaints that were considered possibly related to the drug by the investigator were: nausea, drowsy, palpitations, perspiring, shaky, felt faint, burning sensation in stomach, headache, felt warm, dizzy, lethargic and acid taste in throat.

B. Protocol No. EP027: Three-Way Crossover Bioavailability Study of Novopharm

Limited and Upjohn U.S. (Glynase Prestabs^{R}) 6 mg Micronized Glyburide Tablets in Fed and Fasting Volunteers.

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Novopharm's glyburide micronized tablets, 6 mg, and Upjohn's Glynase Prestabs^{R} Tablets, 6 mg, under non-fasting conditions.

Study Investigators and Facilities:

The study was conducted at ——————————————————————— between March 23, 1995 and April 6, 1995. The principal investigator was ——————— M.D., Ph.D.. Plasma samples were assayed by ——————————————————————— under the supervision of ——————— Ph.D., between April 27, 1995 and May 16, 1995.

Demographics:

Twenty-one normal, healthy, non-smoking male volunteers between 19-41 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 62.2 - 85.2 kgs and 160 - 186 cm., respectively.

Inclusion criteria and Restrictions:

See Protocol EP015 above (except for fasting conditions which are described below).

Treatments and Sampling:

The three treatments each consisted of a single 6 mg dose of either the test product or reference product taken orally with 240 ml of 20% glucose solution. In order to

minimize any possible hypoglycemic effects, each subject was administered 60 ml of this glucose solution approximately every 15 minutes starting 15 minutes postdose until the 4-hour postdose meal.

Treatment A: Novopharm's Glyburide micronized tablets, 6 mg, lot # PD2817 (Batch size of ——— units, potency of 104.7%), given after 10 hours fast.

Treatment B: Novopharm's Glyburide micronized tablets, 6 mg, lot # PD2817 (Batch size of ——— units, potency of 104.7%), given after a standard breakfast.

Treatment C: Upjohn's Glynase Prestabs^{R} Tablets, 6 mg, lot # 418XF (Potency of 103.7%), given after a standard breakfast.

A standard breakfast consisted of 240 ml of whole milk, one fried egg, one slice of Canadian bacon, one slice of American cheese, one serving of hash brown potatoes, one buttered English muffin, and 180 ml of orange juice. The breakfast was served after a 9.5 hour overnight fast and 30 minutes prior to drug administration.

Blood samples were collected at predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours following drug administration. Blood samples were centrifuged under refrigeration and the plasma was separated and immediately stored at -10^{0}C or lower pending assay for glyburide.

Assay Methodology:

The analytical method was developed by ———————————
Glyburide and the internal standard were assayed using a HPLC method, ———————
———————————

Assay Specificity:

The method is specific for glyburide with no significant interference seen at the retention time of the drug or internal standard in chromatograms of blank plasma standards and predose subject samples.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of ————————

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 18.1% at 12.50 ng/ml, 8.3% at 90.00 ng/ml and 3.9% at 210 ng/ml.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 5.00 ng/ml (CV% = 6.3). Any level below this limit was reported as zero.

Prestudy validation data showed CV% for LOQ of 5.0 ng/ml (n=6) was 11.3.

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: ————————

Stability:

See under Assay Methodology of Protocol EP015 above. Actual storage duration for study samples of Protocol EP027 was 54 days.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Twenty of twenty-one enrolled volunteers completed the clinical portion of the study. Subject # 21 withdrew from the study due to the difficulty in getting a pre-dose blood sample (by catheter or venipuncture). Samples from the first 18 subjects were analyzed per protocol.

There were significant differences (alpha=0.05) between treatments for AUC (0-T)(p=0.0017) and lnAUC(0-T) (p=0.0023). There was no significant difference between treatments for other parameters. The results are summarized in the tables below:

Table III

Glyburide Comparative Pharmacokinetic Parameters
Non-Fasting Study; Dose = 6 mg; n = 18

Parameters	Novopharm's Fasted Mean(CV)	Novopharm's Fed Mean(CV)	Glynase^{R} Fed Mean(CV)	90% C.I. T_{fed} vs R_{fed}	Ratio T_{fed}/R_{fed}
AUC (0-T) ng.hr/ml	836.8*	981.4*	960.8*	[0.95;1.10]	1.02
AUC (0-Inf) ng.hr/ml	981.8*	1056*	997.1*	[0.97;1.10]	1.06
CMAX (ng/ml)	144.1*	149.1*	165.9*	[0.77;1.06]	0.90
TMAX (hrs)	6.42(24)	6.78(30)	5.61(30)		
KEL (1/hrs)	0.22(47)	0.24(31)	0.28(27)		
T1/2 (hrs)	4.76(110)	3.15(33)	2.68(38)		

*Geometric means

Table IV

Comparative Mean Plasma Levels of Glyburide, ng/ml(CV)

Non-Fasting Study; Dose = 6 mg; n = 18

Hour	Novopharm's Fasted	Novopharm's Fed	Glynase[R] Fed
0	0	0	0
0.50	2.77(198)	2.61(184)	4.58(160)
1.00	11.92(151)	14.72(100)	22.49(132)
1.50	18.64(121)	26.65(80)	42.50(132)
2.00	26.19(123)	37.71(80)	59.72(105)
2.50	30.10(123)	46.68(91)	70.78(87)
3.00	28.55(119)	51.83(95)	75.93(88)
3.50	29.22(113)	50.22(87)	76.92(70)
4.00	28.10(100)	52.94(84)	71.88(61)
5.00	61.25(63)	91.20(59)	124.90(53)
6.00	101.01(59)	134.38(34)	150.47(43)
8.00	106.83(53)	113.84(30)	94.02(30)
10.00	69.94(46)	78.72(63)	52.64(39)
12.00	35.30(48)	37.50(63)	27.34(48)
16.00	13.88(40)	11.82(50)	9.16(48)
24.00	6.34(104)	3.64(95)	1.09(230)
AUC(0-T) ng.hr/ml	854.8(20)	1015(28)	982.8(22)
AUC(0-Inf) ng.hr/ml	1008(26)	1086(25)	1020(22)
CMAX	149.3(27)	156.3(29)	177.4(35)

Adverse Effects:

All complaints were judged mild to moderate in intensity. The complaints that were considered possibly or probably related to the drug by the investigator were: drowsy, palpitations, perspiring, shaky, felt faint, felt clammy, nausea, oesophageal burning,

heartburn, headache, felt warm, dizzy, lethargic and acid taste in throat.

III. Dissolution Testing:

Drug (Generic Name): Glyburide ——— Tablets Firm: Novopharm Ltd.
Dose Strength: 1.5 mg, 3 mg & 6 mg ANDA # 74-686
Submission Date: 06-05-95

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle X RPM 75 No. Units Tested: 12

Medium: pH 9.5 0.05M borate buffer Volume: 500 ml

Reference Drug: (Manuf.) Glynase[R] Tablets; Upjohn

Assay Methodology: HPLC ———

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # PD2814 Strength (mg) 1.5 Mean % Dissolved	Range	(CV)	Reference Product Lot # 850JC Strength (mg) 1.5 Mean % Dissolved	Range	(CV)
10	103.1		(0.8%)	97.4		(4.2%)
20	103.4		(1.1%)	99.5		(2.5%)
30	103.5		(0.9%)	99.0		(3.0%)
40	103.8		(0.9%)	98.7		(3.5%)
50	103.6		(1.2%)	98.2		(4.0%)
60	103.9		(1.1%)	97.9		(4.2%)
	Lot # PD2815 Strength (mg) 3			Lot # 203JP Strength (mg) 3		
10	102.2		(1.1%)	95.6		(4.0%)
20	102.6		(1.1%)	100.5		(2.6%)
30	102.7		(0.9%)	100.1		(2.6%)
40	102.4		(1.2%)	99.8		(3.4%)
50	102.9		(0.9%)	99.8		(4.5%)
60	103.0		(0.9%)	99.1		(4.4%)

	Lot # PD2817		Lot # 418XF	
	Strength (mg) 6		Strength (mg) 6	
10	108.2	(2.8%)	105.5	(2.7%)
.0	108.2	(2.6%)	105.5	(2.2%)
30	108.0	(2.1%)	105.2	(2.1%)
40	108.7	(2.0%)	105.6	(2.2%)
50	108.6	(2.0%)	106.3	(1.0%)
60	109.3	(1.2%)	106.6	(1.1%)

Specifications: NLT —% in 45 min

APPEARS THIS WAY
ON ORIGINAL

IV. Deficiency:

1. Under fasting conditions, the test and reference products are not considered equivalent in the rate of absorption as measured by CMAX since the 90% confidence interval for log-transformed CMAX is [0.79;0.96] and outside the acceptable limit of [0.80;1.25].

It is recognized that under non-fasting conditions, the ratios of test to reference (geometric) means of AUC(0-T), AUC(0-Infinity) and CMAX are within 0.80;1.25.

V. Comments:

1. Under non-fasting conditions, the ratios of test to reference (geometric) means of AUC(0-T), AUC(0-Infinity) and CMAX are within 0.80;1.25. The test and reference products are, therefore, considered equivalent under non-fasting conditions. It should be noted that glyburide micro tablets are recommended to be taken with meals.

2. The in vitro dissolution data for the 1.5 mg, 3 mg and 6 mg strengths of the test product are acceptable.

3. Comparative formulations given for the 1.5 mg, 3 mg and 6 mg strengths of the test product show that the 1.5 mg and 3 mg strengths are proportionally similar to the 6 mg strength. (See attachment)

VI. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Glyburide —— Tablets, 6 mg, lot # PD2817, comparing it with the reference product, Glynase^{K} Tablets, 6 mg, lot # 418XF, has been found unacceptable due to the reason cited in Deficiency #1 above.

2. The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Glyburide —— Tablets, 6 mg, lot # PD2817, comparing it with the reference product, Glynase^{K} Tablets, 6 mg, lot # 418XF, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under non-fasting conditions.

3. The in-vitro dissolution testing conducted by Novopharm Ltd. on its Glyburide —— Tablets, 1.5 mg, 3 mg and 6 mg has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of pH 9.5, 0.05M borate buffer at 37C using USP XXIII apparatus II(paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. The firm has demonstrated that the formulation of its Glyburide —— Tablets, 1.5 mg and 3 mg, are proportionally similar to the 6 mg strength that underwent in vivo bioequivalence testing. However, the waiver of in vivo bioequivalence study requirements for the 1.5 mg and 3 mg strengths can not be granted since the test and reference products are not considered bioequivalent under fasting conditions.

3-21-96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 3/25/96

Concur: _____ Date: 3/26/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-686 (original, duplicate), HFD-630(OGD), HFD-600(Hare), HFD-652(Huang, Nguyen), HFD-344(CViswanathan), Drug File, Division File

HNguyen/03-11-96/WP #74-686sdw.695

Attachments: 3 pages

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

3/26/96 BIOEQUIVALENCY REVIEW [ATTACHMENT 1]

WP#74686 sdw. 695 Attachment (2 of 3)

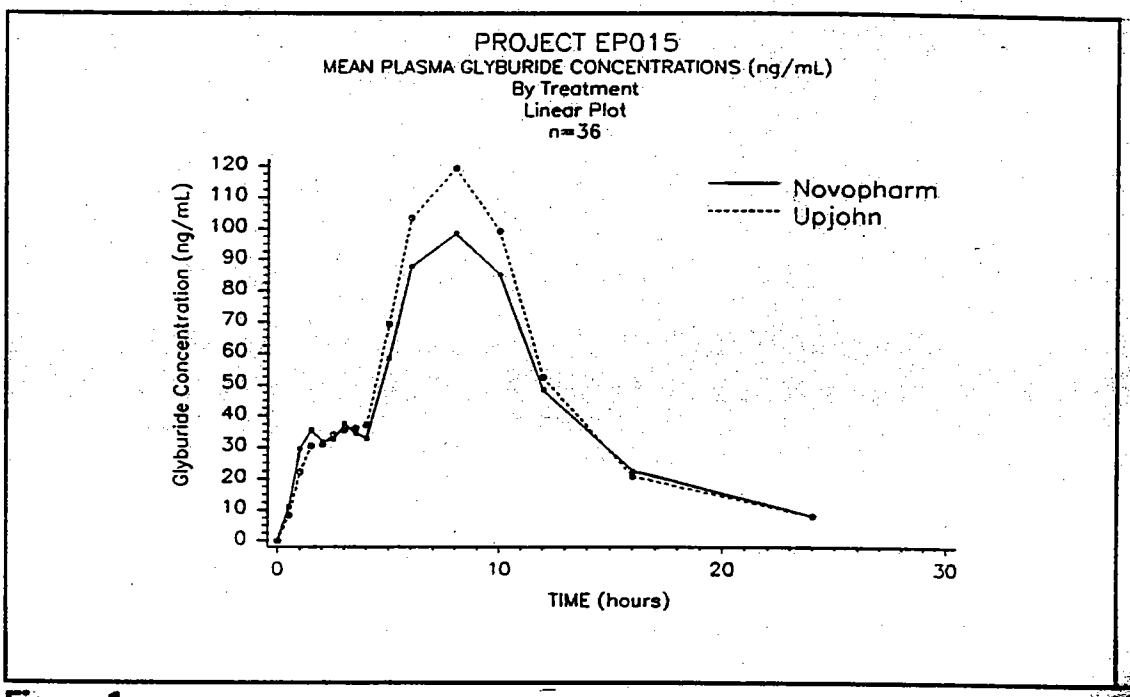

Figure 1

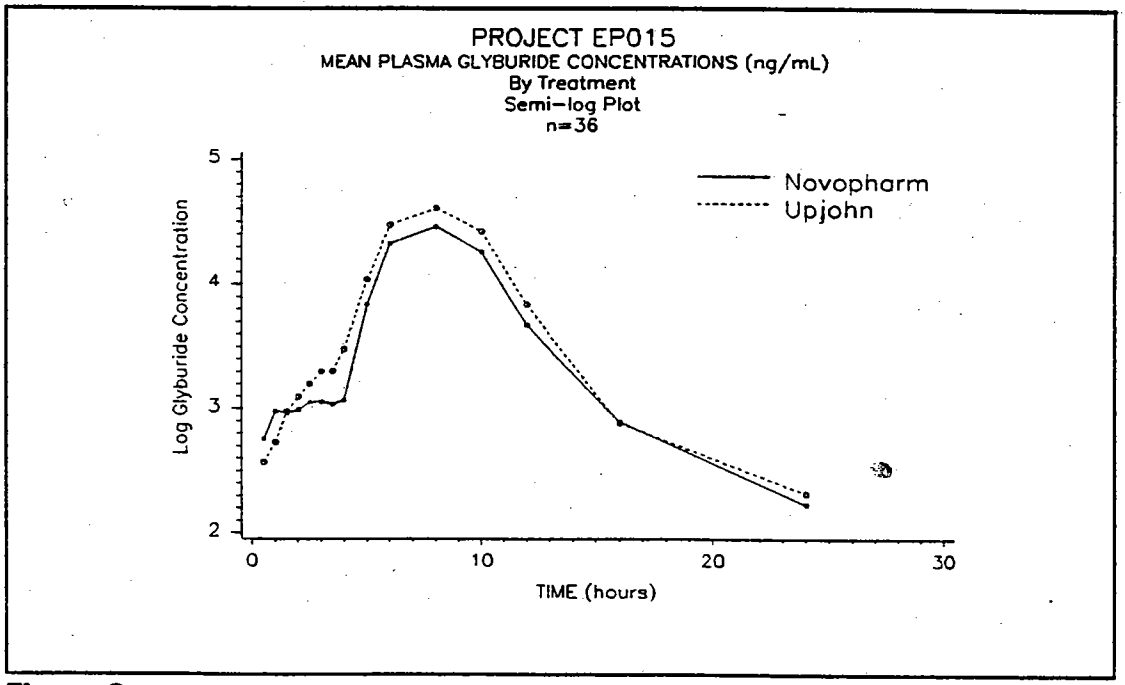

Figure 2

[..\graep015.doc]

WP # 74686 sdw. 695 Attachment (3 of 3)

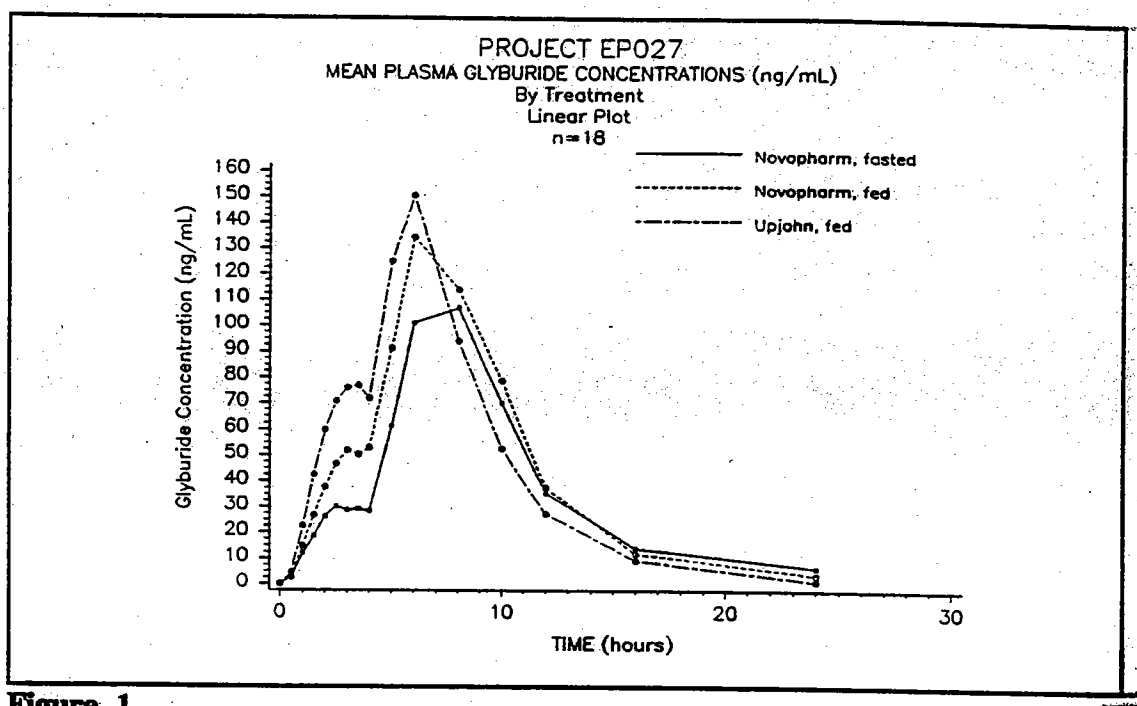

Figure 1

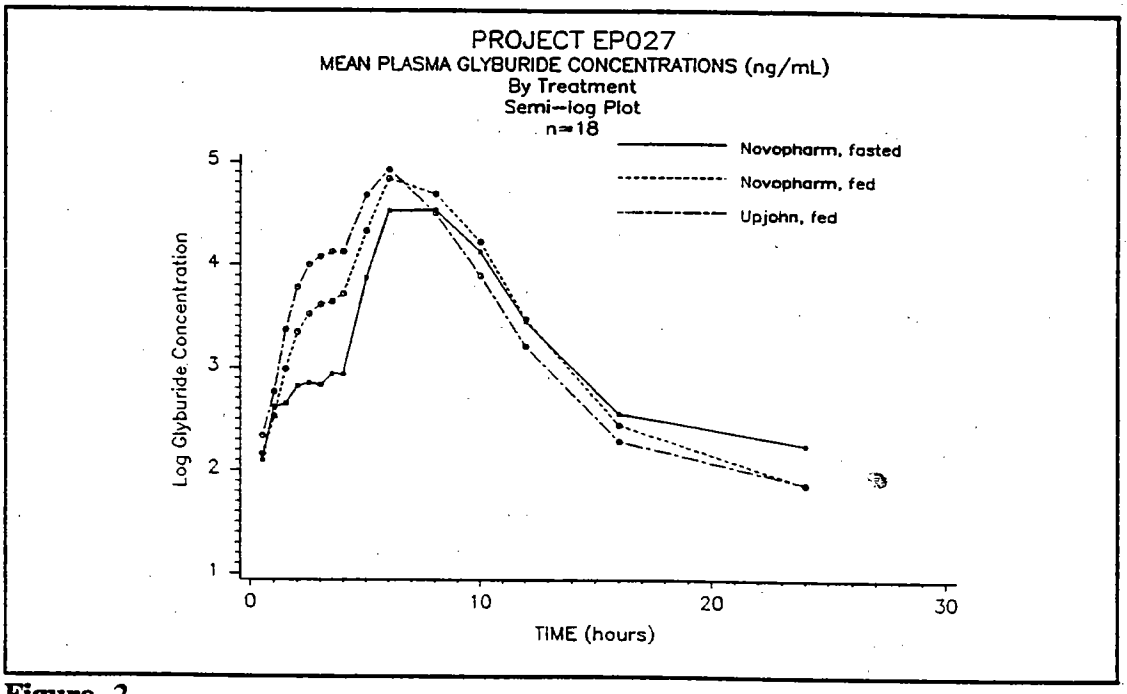

Figure 2

FEB 3 1997

Glyburide Micronized Tablets
1.5 mg, 3.0 mg & 6.0 mg
ANDA # 74-686
Reviewer: Hoainhon Nguyen
WP # 74686a.996

Novopharm Ltd.
Stouffville, Ontario, Canada
Submission Date:
September 24, 1996
January 17, 1997

Review of a Fasting Bioequivalence Study

The firm has submitted the results of the **second fasting**, single-dose bioequivalence study comparing Novopharm's Glyburide Micronized Tablets, 6 mg, with the RLD product, Upjohn's Glynase Tablets, 6 mg. The first fasting bioequivalence study comparing the two products, submitted June 5, 1995, was found **unacceptable** due to the fact that the 90% confidence interval for log-transformed CMAX was [0.79;0.96] and outside the acceptable limit of [0.80;1.25]. The non-fasting bioequivalence study comparing the same two products, also submitted on June 5, 1995, was found **acceptable**, however.

In this second biostudy, the biolot was the same for the test product (Lot No. PD2817) but different for the reference lot (Lot No. 258JT). **The number of subjects was increased** from 36 used in the first study to **48** for the second study.

I. Bioequivalence Study: (Protocol No. EP303) Two-Way Crossover Bioequivalence Study of Novopharm Limited and Upjohn U.S. (Glynase Prestabs®) 6 mg Micronized Glyburide Tablets in Fasting Volunteers.

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Novopharm's glyburide micronized tablets, 6 mg, and Upjohn's Glynase Prestabs® Tablets, 6 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at ——————————
—————————— between June 12, 1996 and June 19, 1996. The principal investigator was ———— M.D., Ph.D.. Plasma samples were assayed by ——————————

_____ under the supervision of _____, Ph.D., between August 2, 1996 and August 19, 1996.

Demographics:

Forty-eight normal, healthy, non-smoking Caucasian male volunteers between 18-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 61.0 - 92.4 kgs and 156 - 185 cm., respectively.

Inclusion criteria:

Subjects especially did not have any history or presence of: significant cardiovascular, hepatic, renal, CNS, hematological or gastrointestinal diseases; adrenal or pituitary insufficiency; hypoglycemia; diabetes; alcoholism or drug abuse within the last year; hypersensitivity or idiosyncratic reaction to glyburide or any other sulfonylureas or sulfonamide.

Restrictions:

They were free of all medications at least 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed 48 hours prior to each drug administration until after the 24-hour postdose blood sample. The subjects fasted for 10 hours prior to and 4 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was 10 hours pre-dose to approximately 24 hours post-dose in each period.

Treatments and Sampling:

The two treatments each consisted of a single 6 mg dose of either the test product or reference product taken orally with 240 ml of 20% glucose solution. In order to minimize any possible hypoglycemic effects, each subject was administered 60 ml of this glucose solution approximately every 15 minutes starting 15 minutes postdose until the 4-hour postdose meal.

Test Product: Novopharm's Glyburide micronized tablets, 6 mg, lot # PD2817 (Batch size of ——— units, potency of 102.3%).

Reference product: Upjohn's Glynase Prestabs^{R} Tablets, 6 mg, lot # 258JT (Potency of 100.8%).

Blood samples were collected at predose, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0 and 24.0 hours following drug administration. Blood samples were centrifuged under refrigeration and the plasma was separated and immediately stored at -10°C or lower pending assay for glyburide. Samples were also collected for glucose testing, before dosing and at 2, 4, and 8 hours after dosing.

NOTE: The protocol of the second fasting bioequivalence study was similar to that of the first except that **48 instead of 38 subjects** were enrolled in the second study, and **blood sampling schedule was modified** to eliminate some earlier sampling time points (0.5, 1.50, 2.50 and 3.50 hours were omitted) and to add some later time points (7.0, 9.0, 11.0, 14.0 were added).

Assay Methodology:

The analytical method was developed by ———————————— ———. Glyburide and the internal standard were assayed using a HPLC method, ————————————————————

Assay Specificity:

The method is specific for glyburide with no significant interference seen at the retention time of the drug or internal standard in chromatograms of blank plasma standards and predose subject samples.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of ————————

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 7.7% at 12.50 ng/ml, 3.5% at 120.0 ng/ml and 4.7% at 210.0 ng/ml.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 5.00 ng/ml (CV% = 10.0). Any level below this limit was reported as zero.

Prestudy validation data showed CV% for LOQ of 5.0 ng/ml (n=6) was 11.3.

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were:

Stability:

Stability of frozen samples was demonstrated in **a pre-study validation study** using frozen control samples which were prepared, stored at -15°C, and analyzed within 118-day period. The controls, 20.0 ng/ml, 150.0 ng/ml and 225.0 ng/ml, analyzed at Times 0 and 118 days had a mean accuracy of 95%, 99.5% and 103%, respectively. No trends were detected. The actual plasma samples were first collected and stored frozen (below -10°C) on 06/12/96 and last analyzed on 08/19/96 (maximum of 67 days). The stability study is therefore acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

All forty-eight enrolled volunteers completed the clinical portion of the study. The statistical analysis was performed using 48 balanced data sets.

There were significant differences (alpha=0.05) between treatments for AUC (0-T)(p=0.0089), AUC(0-Inf)(p=0.0042), KEL (p=0.0001), T1/2(p=0.0125), lnAUC(0-T) (p=0.0037) and lnAUC(0-Inf)(p=0.0041). There was no significant difference between treatments for CMAX, lnCMAX and TMAX. The results are summarized in the tables below:

Table I
Glyburide Comparative Pharmacokinetic Parameters
Fasting Study; Dose = 6 mg; n = 48

Parameters	Novopharm's Mean (CV)	Glynase[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	857.6*	938.8*	[0.87;0.96]	0.91
AUC (0-Inf) ng.hr/ml	929.0*	1028*	[0.88;0.96]	0.90
CMAX(ng/ml)	131.5*	142.8*	[0.85;1.00]	0.92
TMAX (hrs)	7(26)	7(37)		
KEL (1/hrs)	0.17(46)	0.26(48)		
T1/2 (hrs)	4.8(42)	3.6(70)		

*Geometric means

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Table II

Comparative Mean Plasma Levels of Glyburide, ng/ml(CV)

Fasting Study; Dose = 6 mg; n = 48

Hour	Novopharm's	Glynase[R]
0	0	0
1.00	14.13(153)	30.91(112)
2.00	23.72(111)	49.25(92)
3.00	28.18(107)	49.35(86)
4.00	29.12(97)	43.89(75)
5.00	54.73(71)	60.47(67)
6.00	99.82(55)	85.11(61)
7.00	98.71(56)	89.37(67)
8.00	94.39(50)	83.23(64)
9.00	91.63(54)	88.38(63)
10.00	78.81(59)	89.41(61)
11.00	58.12(55)	74.30(61)
12.00	44.25(55)	56.11(62)
14.00	26.09(55)	30.78(58)
16.00	19.72(88)	19.60(66)
24.00	7.26(79)	4.97(144)
AUC(0-T)ng.hr/ml	906.0(33)	980.1(30)
AUC(0-Inf)ng.hr/ml	978.1(32)	1070(29)
CMAX	139.9(37)	150.0(31)

Adverse Effects:

All complaints were judged mild to moderate in intensity. The complaints that were considered probably and possibly related to the drug by the investigator were: feeling faint, fainting, tingling sensation, hot flashes, shaking, cramps, headache, weakness, low blood sugar, nausea, lightheadedness and dizziness (15 and 9 complaints under test and reference treatments, respectively).

II. Comments:

1. Under fasting conditions, with sufficient number of subjects (48), the 90% confidence intervals for log-transformed AUC(0-T), AUC(0-Inf) and CMAX are within the acceptable limit of [0.80;1.25]. The test and reference products are demonstrated to be equivalent in the extent and rate of absorption.

2. As shown in the review of the previous submission dated June 5, 1995, under non-fasting conditions, the ratios of test to reference (geometric) means of AUC(0-T), AUC(0-Infinity) and CMAX are within 0.80;1.25. The test and reference products are, therefore, considered equivalent under non-fasting conditions. It should be noted that glyburide —— tablets are recommended to be taken with meals.

3. Also shown in the previous review, the in vitro dissolution data for the 1.5 mg, 3 mg and 6 mg strengths of the test product are acceptable.

4. Comparative formulations given for the 1.5 mg, 3 mg and 6 mg strengths of the test product show that the 1.5 mg and 3 mg strengths are proportionally similar to the 6 mg strength. (See attachment)

III. Recommendations:

1. The single-dose, fasting bioequivalence study (Protocol No. EP303) conducted by Novopharm Ltd. on its test product, Glyburide —— Tablets, 6 mg, lot # PD2817, comparing it with the reference product, Glynase® Tablets, 6 mg, lot # 258JT, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Novopharm's Glyburide Micronized Tablets, 6 mg, is bioequivalent to the reference product, Glynase Tablets, 6 mg, manufactured by Upjohn, under fasting conditions.

2. The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Glyburide —— Tablets, 6 mg, lot # PD2817, comparing it with the reference product, Glynase® Tablets, 6 mg, lot # 418XF, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under non-fasting conditions.

3. The in-vitro dissolution testing conducted by Novopharm Ltd. on its Glyburide —— Tablets, 1.5 mg, 3 mg and 6 mg has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of pH 9.5, 0.05M borate buffer at 37C using USP XXIII apparatus II(paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. The firm has demonstrated that the formulation of its Glyburide —— Tablets, 1.5 mg and 3 mg, are proportionally similar to the 6 mg strength that underwent in vivo bioequivalence testing. The request for waiver of in vivo bioequivalence study requirements for the 1.5 mg and 3 mg strengths therefore can be granted. Novopharm's Glyburide Micronized Tablets, 1.5 mg and 3 mg, are deemed to be bioequivalent to the reference product, Glynase Tablets, 1.5 mg and 3 mg, respectively, manufactured by Upjohn.

1/21/97
Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 1/21/97

Concur: _____ Date: 2/3/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA # 74-686 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
Nguyen/01-10-97/WP #74686a.996

Attachments: 3 pages

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confidential commercial

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2/3/97 BIOEQUIVALENCE REVIEW - ATTACHMENT 1

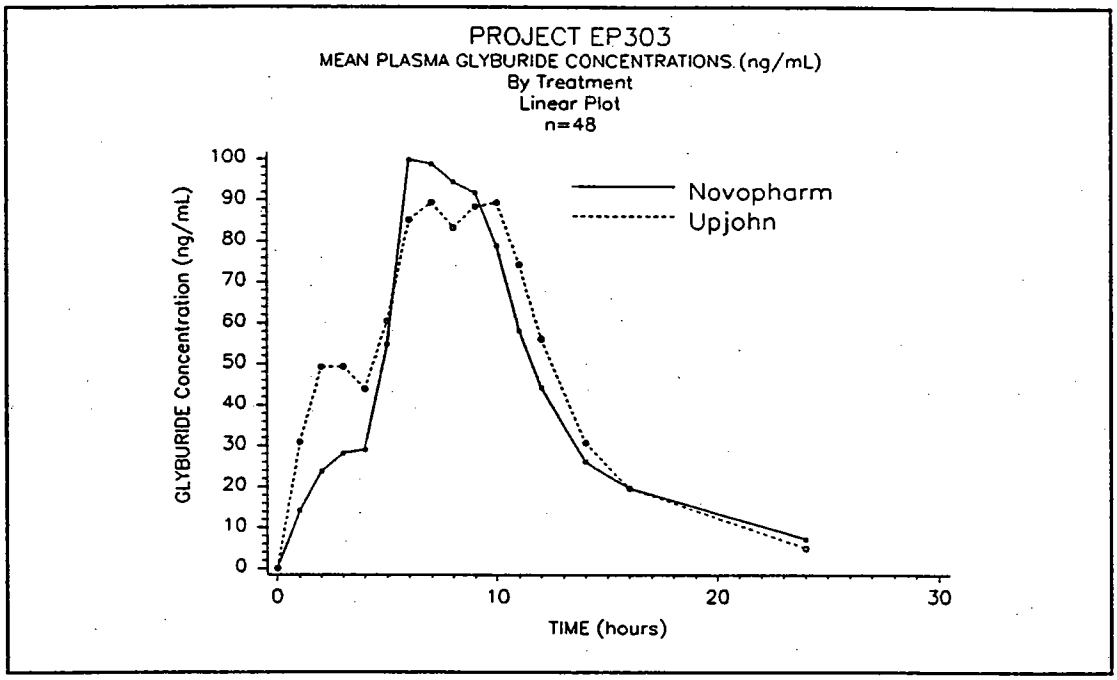

Figure 1

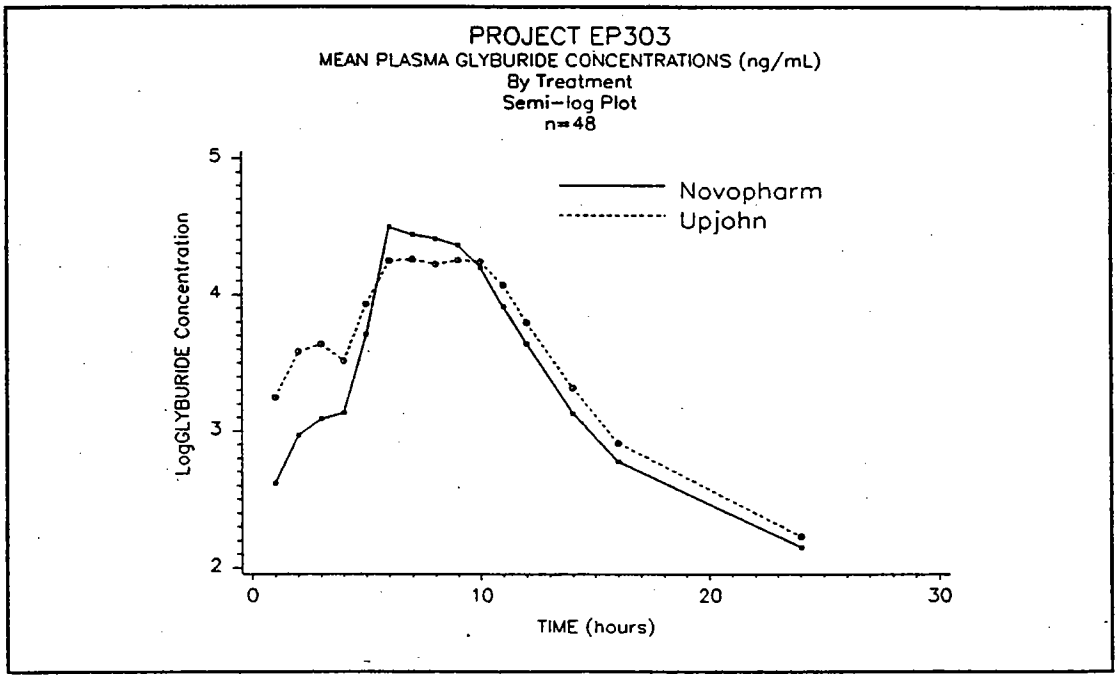

Figure 2

WP # 74686a.996 Attachment (3 of 3)

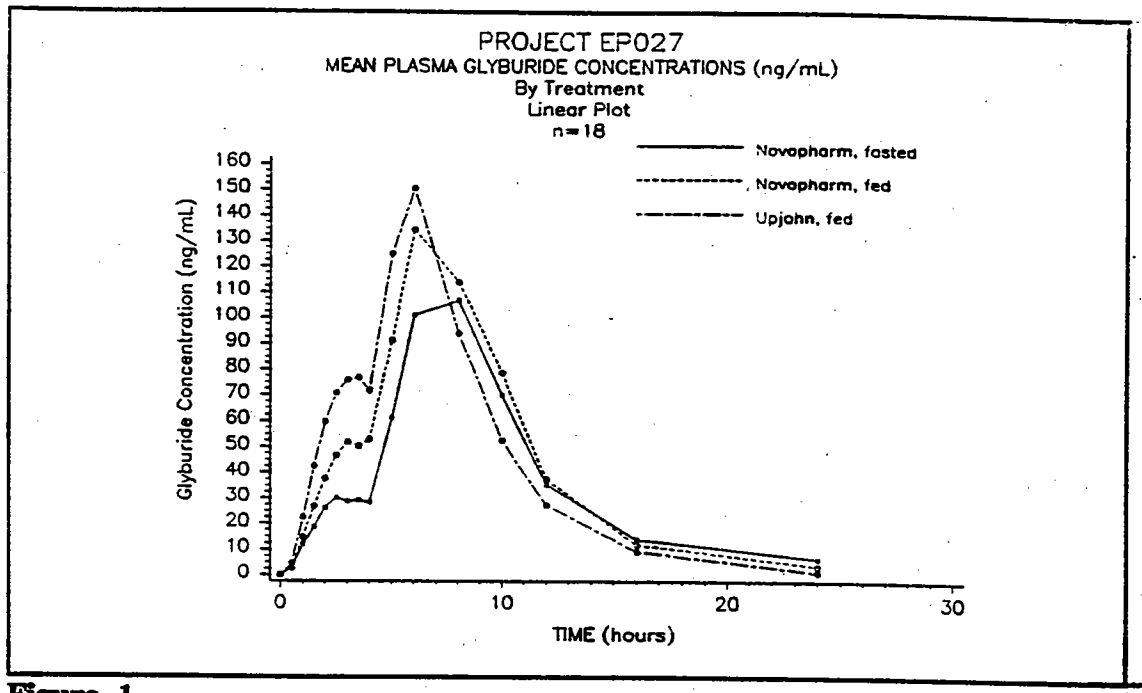

Figure 1

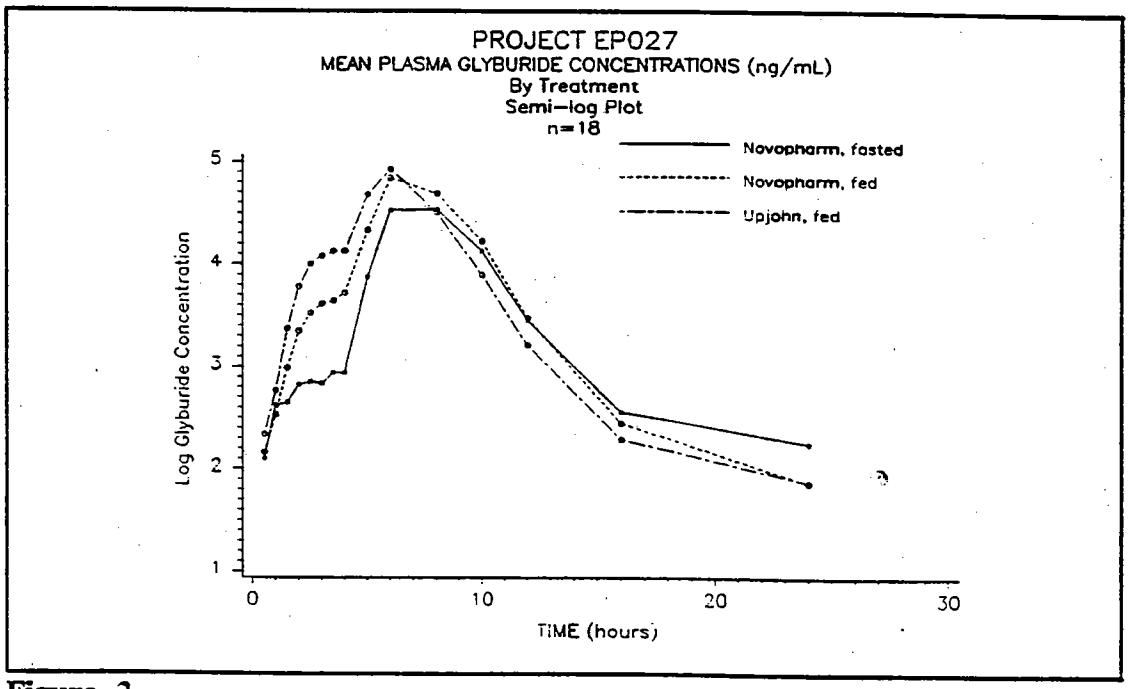

Figure 2

Glyburide Micronized Tablets
1.5 mg, 3.0 mg, 6.0 mg & 4.5 mg
ANDA# 74-686
Reviewer: Hoainhon Nguyen
WP#74686dw.o96

Novopharm, Ltd.
Stouffville, Ontario, Canada
Submission Date:
October 9, 1996

Review of Dissolution Data and Waiver Request

The firm has submitted comparative dissolution data in support of its request for waiver of *in vitro* bioequivalence requirements for its Glyburide Micronized Tablets, 4.5 mg.

In accordance with 21 CFR 320.22(d)(2), the waiver request is also based on the acceptability of the bioquivalence studies of the 6.0 mg strength of the test product (See the review of the ANDA amendment dated September 24, 1996), the similar proportionality of the 4.5 mg formulation to that of the 6.0 mg strength.

Since there is no innovator reference product for the 4.5 mg strength on which bioequivalence demonstration could be based, Novopharm has received FDA's authorization Docket No. 95P-0285/CP1 for submitting an ANDA for a change in strength from that of the listed drug product; i.e., the submission of a 4.5 mg strength in addition to a 6 mg strength.

Dissolution Testing:

Drug (Generic Name): Glyburide ——— Tablets Firm: Novopharm Ltd.
Dose Strength: 1.5 mg, 3 mg & 6 mg ANDA # 74-686
Submission Date: Oct 9, 1996

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle X RPM 75 No. Units Tested: 12
Medium: pH 9.5 0.05M borate buffer Volume: 500 ml
Reference Drug: (Manuf.) Glynase® Tablets; Upjohn
Assay Methodology: HPLC;

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # PD2816 Strength (mg) 4.5 Mean %	Range	(CV)
10	102.2		(1.1%)
30	102.7		(0.9%)
30	102.7		(0.9%)
40	102.4		(1.2%)
50	102.9		(0.9%)
60	103.0		(0.9%)

	Lot # PD2817 Strength (mg) 6 Mean %	Range	(CV)	Lot # 418XF Strength (mg) 6 Mean %	Range	(CV)
10	108.2		(2.8%)	105.5		(2.7%)
20	108.2		(2.6%)	105.5		(2.2%)
30	108.0		(2.1%)	105.2		(2.1%)
40	108.7		(2.0%)	105.6		(2.2%)
50	108.6		(2.0%)	106.3		(1.0%)
60	109.3		(1.2%)	106.6		(1.1%)

Specifications: NLT —% in 45 min

Comment:

The formulation of the 4.5 mg strength of the test product is proportionally similar to that of the 6.0 mg strength (See comparative formulations attached).

Deficiency:

An incorrect dissolution method and specification were stated in the February 24, 1997 letter. For the dissolution testing of micronized glyburide tablets (Glynase-type products, such as the test product), the following dissolution testing is recommended:

Paddle @ 50 rpm, 900 ml of 0.05 M phosphate buffer, pH 7.5, sampling times of 15, 30, 45 and 60 minutes.

The firm should repeat the dissolution testing using the correct procedure.

Recommendation:

1. The in-vitro dissolution testing conducted by Novopharm on its Glyburide Micronized Tablets, 4.5 mg and 6 mg, has been found **unacceptable** for the reason cited in the Deficiency comments above.

The dissolution testing should be conducted in 900 ml of pH 7.5 0.05M phosphate buffer at 37°C using USP XXIII apparatus II (paddle) at 50 rpm.

2. The waiver request for *in vivo* bioequivalence study requirements for the 4.5 mg strength of Novopharm's Glyburide Micronized Tablets can not be reviewed at this time pending acceptable dissolution testing of the test product of **all strengths**.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 4/28/98

Concur: Dale P. Conner Date: 4/30/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-686 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/04-22-98/WP #74686dw.o96

Attachments: 1 page

BIOEQUIVALENCE DEFICIENCY

ANDA: 74-686 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg & 6.0 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 in-vitro dissolution testing conducted by Novopharm on its Glyburide Micronized Tablets, 4.5 mg and 6 mg, has been found **unacceptable** for the reason that the dissolution method and specifications used were **incorrect**. The dissolution method and specifications as stated in the February 24, 1997 letter were incorrect. For the dissolution testing of **micronized** glyburide tablets (Glynase-type products, such as the test product), the following dissolution testing is recommended by the agency:

The dissolution testing should be conducted in 900 mL of pH 7.5, 0.05M phosphate buffer at 37°C using USP 23 apparatus II(paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

You should repeat the dissolution testing using the correct procedure **for all strengths** of the test and reference products.

Sincerely yours,

Dale P. Conner

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

CC: ANDA 74-686
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
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Printed in final on / /98

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 4/28/98
HFD-650/ D. Conner 4/30/98

BIOEQUIVALENCY - ACCEPTABLE

DISSOLUTION WAIVER (DIW)

Strengths: 4.5 mg
Outcome: UN

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:

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4/30/98 BIOEQUIVALENCE REVIEW ATTACHMENT 1

Glyburide Tablets (Micronized)
ANDA # 74-686: 1.5, 3, 4.5 and 6 mg
Reviewer: Hoainhon Nguyen
WP # 74686a.698

Novopharm Ltd.
Ontario, Canada
Submission Date:
June 30, 1998

Review of a Study Amendment: Dissolution Data and Waiver Requests

The firm has recently amended the ANDA in response to the Division of Bioequivalence's deficiency comments sent to the firm in the letter dated May 1, 1998 concerning the dissolution testing of the test product. The comments were as follows:

'The in-vitro dissolution testing conducted by Novopharm on its Glyburide Micronized Tablets, 4.5 mg and 6 mg, has been found unacceptable for the reason that the dissolution method and specifications used were incorrect. The dissolution method and specifications as stated in the February 24, 1997 letter were incorrect. For the dissolution testing of micronized glyburide tablets (Glynase-type products, such as the test product), the following dissolution testing is recommended by the agency:

The dissolution testing should be conducted in 900 mL of pH 7.5, 0.05M phosphate buffer at 37 °C using USP 23 apparatus II(paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

You should repeat the dissolution testing using the correct procedure for all strengths of the test and reference products.'

Firm's Response:

The firm has repeated the dissolution testing as requested. The results are summarized below.

Dissolution Testing:

Drug (Generic Name): Glyburide —— Tablets
Dose Strength: 1.5 mg, 3 mg & 6 mg
Submission Date: Oct 9, 1996

Firm: Novopharm Ltd.
ANDA # 74-686

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle X RPM 50 No. Units Tested: 12

Medium: pH 7.5 0.05M phosphate buffer Volume: 900 ml

Reference Drug: (Manuf.) Glynase[R] Tablets; Upjohn

Assay Methodology: HPLC/ ____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Mean %	Range	(CV)	Reference Product Mean %	Range	(CV)
	Lot # PD2816			No reference product at this strength (Suitability Petition Docket No. 95P-0285/CP1)		
	Strength (mg) 4.5					
15	46.5		(5.7%)			
30	58.0		(5.6%)			
45	64.9		(5.4%)			
60	69.2		(5.4%)			
	Lot # PD2817			Lot # 258JT		
	Strength (mg) 6			Strength (mg) 6		
15	40.5		(3.2%)	88.7		(1.2%)
30	51.1		(3.5%)	97.2		(2.1%)
45	58.0		(2.7%)	99.5		(1.1%)
60	62.5		(2.9%)	100.1		(1.1%)
	Lot # PD2814			Lot # 850JC		
	Strength (mg) 1.5			Strength (mg) 1.5		
15	55.2		(4.3%)	93.0		(2.0%)
30	66.4		(3.4%)	97.5		(1.9%)
45	72.1		(2.9%)	98.5		(1.8%)
60	75.6		(3.1%)	99.9		(1.9%)
	Lot # PD2815			Lot # 203JP		
	Strength (mg) 3			Strength (mg) 3		
15	48.6		(4.1%)	84.8		(2.8%)
30	59.5		(2.6%)	96.8		(1.6%)
45	65.5		(3.3%)	99.7		(1.2%)
60	69.5		(2.4%)	100.8		(1.2%)

DBE's Comments:

1. The dissolution data as submitted were obtained (June 23, 1998) after the lots of the test product (including the biolot of the 6 mg strength) were expired (See the internal email from Nancy Chamberlin attached). At the time of this review, the firm does not have any fresh lots of the test product in house for any further dissolution testing. In addition, the recently amended dissolution profiles of the test and reference products at all strengths were found different, with the test product's profiles being consistently much slower **and incomplete.** Approximately only —% of the labeled amount of the drug was dissolved in 60 minutes. It is not clear, based on these dissolution data, whether the difference in dissolution profiles between the test and reference listed drug products is due to the degradation of the test product after the expiration date, or due to the formulation difference.

However, the *in vivo* and *in vitro* bioequivalence requirements for all strengths of the test product are considered ***tentatively met*** because of the following reasons:

a/ The *in vivo* bioequivalence studies conducted on the 6 mg strength have demonstrated that the test product is bioequivalent to the RLD product. In addition, the formulations of the lower strengths, 1.5 mg, 3 mg and 4.5 mg, are proportionally similar to that of the 6 mg strength (See the reviews of the submissions dated June 5, 1995, September 24, 1996 and January 17, 1997. See also formulation of the 4.5 mg submitted in this current submission). Although there is difference between the profiles of the test and reference products, the dissolution profiles between all strengths within the test product are similar.

b/ The Division of Bioequivalence currently does not have specifications established for the drug product using the current FDA-recommended dissolution testing procedure (i.e., in 900 mL of pH 7.5 0.05 M phosphate buffer, using USP paddle apparatus at 50 rpm).

c/ All strengths of the test product easily met the specification of 'NLT —% of the labeled amount of the drug being dissolved in 45 minutes' when tested originally using the *in vitro* dissolution testing procedure that requires higher pH (pH 9.5) (The original *in vitro* dissolution testing procedure also requires the tested product to be in 500 mL of pH 9.5 0.05 M borate buffer and the USP paddle apparatus at 75 rpm.). 100% of the labeled amount of the drug in the test product of all strengths

was dissolved in the first 15 minutes. As similarly observed with other micronized glyburide tablet drug products, including the reference listed drug product Glynase®, **the decrease in pH of the dissolution medium as well as the paddle speed contributed significantly to the decrease in the dissolution rate of these drug products, and produced more discriminating dissolution profiles.**

2. In order to adopt a sufficiently **discriminating and complete** *in vitro* dissolution method for a micronized glyburide tablet drug product that has been shown to be bioequivalent to the RLD product, such as the above test product, the Division of Bioequivalence has now requested that all strengths of the test and reference listed drug product be tested for *in vitro* dissolution further in several different pHs (pH 7.5, 8 and 8.5), with all other parameters of the dissolution procedure remaining the same. An acceptable (i.e., discriminating and complete) release specification will be established for the test product based on these data. As the only condition for approval of the test product, the firm is asked to commit to carry out this additional dissolution testing at the above-specified pHs and to submit the data in an application supplement within approximately 30 days of the manufacturing of the first production lot of each strength of the test product.

3. Until new dissolution procedure and specifications are established for the test product, the **interim** specification and the **interim** dissolution method will be respectively as follows:

Specification: NLT —% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes

Dissolution method: 900 mL of pH 7.5 0.05 M phosphate buffer as the dissolution medium, and with the USP paddle apparatus at 50 rpm.

<u>Recommendations:</u>

1. The in-vitro dissolution testing conducted by Novopharm on its Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg and 6 mg, has been found **tentatively acceptable** as discussed in the Comments above.

As a condition for approval of the test product, further dissolution testing is

recommended to be conducted in 900 ml of 0.05M phosphate buffer of **the pHs 7.5, 8.0 and 8.5**, at 37°C using USP XXIII apparatus II (paddle) at 50 rpm.

2. The firm has demonstrated that the formulation of its Glyburide Micronized Tablets, 4.5 mg, is proportionally similar to the 6 mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 4.5 mg tablets is granted.

Other Recommendations for ANDA#74-686 From Previous Reviews (of Submissions dated June 5, 1995, September 24, 1996 and January 17, 1997):

1. The single-dose, fasting bioequivalence study (Protocol No. EP303) conducted by Novopharm Ltd. on its test product, Glyburide —— Tablets, 6 mg, lot # PD2817, comparing it with the reference product, Glynase[R] Tablets, 6 mg, lot # 258JT, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Novopharm's Glyburide Micronized Tablets, 6 mg, is bioequivalent to the reference product, Glynase Tablets, 6 mg, manufactured by Upjohn, under fasting conditions.

2. The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Glyburide —— Tablets, 6 mg, lot # PD2817, comparing it with the reference product, Glynase[R] Tablets, 6 mg, lot # 418XF, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under non-fasting conditions.

3. The firm has demonstrated that the formulation of its Glyburide —— Tablets, 1.5 mg and 3 mg, are proportionally similar to the 6 mg strength that underwent in vivo bioequivalence testing. The request for waiver of in vivo bioequivalence study requirements for the 1.5 mg and 3 mg strengths therefore can be granted. Novopharm's Glyburide Micronized Tablets, 1.5 mg and 3 mg, are deemed to be bioequivalent to the reference product, Glynase Tablets, 1.5 mg and 3 mg, respectively, manufactured by Upjohn.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG Y Huang 7/31/98

Concur: Dale P. Conner Date: 8/4/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-686 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
Hnguyen/07-10-98/WP #74686a.698/Revised 07-30-98

Attachments: 1 page

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BIOEQUIVALENCY COMMENTS

ANDA: 74-686 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg and 6 mg

As discussed with the firm's representatives in the telephone conference on July 30, 1998, at this time the Division of Bioequivalence has completed its review and has no further questions concerning the *in vivo* bioequivalence requirements, but it has the following recommendations concerning the *in vitro* testing requirements for the test product:

1. In order to adopt a sufficiently **discriminating and complete** *in vitro* dissolution method for a micronized glyburide tablet drug product that has been shown to be bioequivalent to the RLD product, such as the above test product, the Division of Bioequivalence has now requested that all strengths of the test and reference listed drug product be tested for *in vitro* dissolution by you **further in several different pHs (pH 7.5, 8 and 8.5)**, with all other parameters of the dissolution procedure remaining the same. An acceptable (i.e., discriminating and complete) release specification will be established for the test product based on these data. The division understands that presently you do not have any fresh lot of any strength of the test product available in house, and will be manufacturing the first production batches in September of 1998. As the only condition for approval of the test product, you are asked to commit, in writing, to carry out this additional dissolution testing at the above-specified pHs and to provide such data in an application supplement within approximately 30 days of the manufacturing of the first production lot of each strength of the test product. The supplement may be requested by you for an expedite review.

2. Until new dissolution procedure and specifications are established for the test product following the review of the above-mentioned supplement, the **interim** specification and the **interim** dissolution method for your test product will be respectively as follows:

> Tolerance Specification: NLT —% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes

Dissolution method: 900 mL of pH 7.5 0.05 M phosphate buffer as the dissolution medium, and with the USP paddle apparatus at 50 rpm.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

CC:ANDA 74-686
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen

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Printed in final on / /98

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 7/31/98
HFD-65 / D. Conner 8/4/98

DISSOLUTION - ACCEPTABLE

STUDY AMENDMENT (STA) Strengths: All

Outcome: AC

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA/AADA #74-686 SPONSOR : Novopharm Ltd.
DRUG & DOSAGE FORM : Glyburide Micronized Tablets
STRENGTHS : 1.5, 3, 4.5 and 6 mg

TYPE OF STUDY: SD		
STUDY:	Xacceptable	☐Not Applicable
TYPE OF STUDY: SDF		
STUDY:	XAcceptable	☐Not Applicable
DISSOLUTION :	Xacceptable*	☐Not Applicable

NOTE: Additional data have been requested. See review.

WAIVER:	XAcceptable	☐Not Applicable

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: HN DATE: 7/31/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : YH DATE: 7/31/98

DIRECTOR: Dale Conner, Pharm.D. DIVISION OF BIOEQUIVALENCE
INITIAL : DC DATE : 8/4/98

WP# 74686a. 698 Attachment

Printed by Lizzie Sanchez

Electronic Mail Message

Date: 23-Jul-1998 05:22pm
From: Nancy Chamberlin
CHAMBERLINN
Dept: HFD-615 MPN2 E107
Tel No: 301-827-5862 FAX 301-594-6593

TO: See Below
Subject: ANDA 74-686 GLYBURIDE MICronized product novopharm

In a telecon on 4/23/98 at 3:00 Pm Rabi, Mike Smela , YC and Nancy and with Deterick Bartel of Novopharm we proposed that the firm conduct dissolution testing using 50 RPM, paddle, 0.05 M phosphate buffer 900 ml at 8.0 and 8.5 ph. Using 12 test and 12 reference.

Rabi suggested that they start with the 6 mg which dissolved slower and that was the one that the biostudy was started on. However, it became apparent from Deterick that there product was old and he stated that there was no production lot. We ended the phone call with him calling the firm in canada to check on the expiration data of all the strengths.

Jonathan Eng, Novopharm Canada (905-642-4550 ext 7030) called at 4:15 on 3/98 and stated that all strengths (1.5, 3, 4.5 and 6 mg) were expired, 3 /years old , and made Jan 95. He said there was no production lot. I told him that we would get back with him as to what they should do.

Please note that :Mike Smela informed that firm that they must respond to the bio change in methodology prior to answering the chemistry. They need to do the acceptable methodology that bio sets for their chemistry stability & QC. Chemistry will need data on all strengths, excute batch records and certificate of analysis for additional dissolution lots.

Conclusion: we need to let them know what to do--we want additional dissolution and there lots are expired.

Distribution:

TO: Michael Smela (SMELA)
TO: Rabindra Patnaik (PATNAIK)
TO: Yih Chain Huang (HUANGY)
TO: Dale Conner (CONNERD)
TO: Hoainhon Nguyen (NGUYENHO)

CC: Lizzie Sanchez (SANCHEZL)
CC: Denise Huie (HUIED)

4.1

Glyburide Micronized Tablets
1.5 mg, 3 mg, 4.5 mg & 6 mg
ANDA # 74-686
Reviewer: Hoainhon Nguyen
W #74686d.199

Novopharm Ltd.
Ontario, Canada
Submission Date:
January 13, 1999

Review of Dissolution Data

The firm has submitted additional *in vitro* dissolution data as requested by the agency in the letter dated November 10, 1998 (A copy of the letter is attached.).

Since the current interim dissolution method is not sufficiently discriminating and complete, the firm has been recommended to conduct further dissolution testing at higher pH's (7.5, 8 and 8.5) as to improve the release rate of the test product. The results of the additional dissolution testing are summarized below.

Dissolution Testing Results:

I. Conditions for Dissolution Testing: **pH 7.5**
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: Phosphate Buffer Volume: 900 ml
Reference Drug: (Manuf.) Glynase Pres Tablets (Upjohn)
Assay Methodology: HPLC
Specifications: Not determined

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 3310PD Strength (mg) 1.5 Mean % Dissolved(CV%)	Range	Reference Product Lot # 338WT Strength (mg) 1.5 Mean % Dissolved(CV%)	Range
15	56(5.0)		98(2.6)	
30	66(4.2)		102(2.0)	
45	71(4.0)		103(2.2)	
60	74(3.7)		106(1.9)	

Sampling Times (Min.)	Test Product Lot # 3348PD Strength (mg) 3		Reference Product Lot # 101XF Strength (mg) 3	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	48(4.1)		96(5.1)	
30	59(3.7)		100(2.2)	
45	64(3.6)		102(1.4)	
60	68(3.2)		102(1.2)	

Sampling Times (Min.)	Test Product Lot # 3349PD Strength (mg) 4.5		Reference Product Lot # Strength (mg)
	Mean % Dissolved(CV%)	Range	
15	49(5.4)		No reference product at this strength (Suitability Petition Docket No. 95P-0285/CP1)
30	59(4.1)		
45	65(3.2)		
60	69(3.4)		

Sampling Times (Min.)	Test Product Lot # 3350PD Strength (mg) 6		Reference Product Lot # 258JT Strength (mg) 6	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	40(7.7)		88(4.2)	
30	52(6.2)		95(1.4)	
45	58(6.0)		98(1.0)	
60	62(5.7)		99(1.1)	

I. Conditions for Dissolution Testing: **pH 8.0**
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: Phosphate Buffer Volume: 900 ml
Reference Drug: (Manuf.) Glynase Pres Tablets (Upjohn)
Assay Methodology: HPLC
Specifications: Not determined

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 3310PD Strength (mg) 1.5 Mean % Dissolved(CV%)	Range	Reference Product Lot # 338WT Strength (mg) 1.5 Mean % Dissolved(CV%)	Range
15	85(3.4)		101(1.6)	
30	89(3.8)		100(1.7)	
45	90(3.5)		100(1.7)	
60	91(3.6)		100(1.7)	

Sampling Times (Min.)	Test Product Lot # 3348PD Strength (mg) 3 Mean % Dissolved(CV%)	Range	Reference Product Lot # 101XF Strength (mg) 3 Mean % Dissolved(CV%)	Range
15	78(5.2)		103(1.8)	
30	89(5.7)		104(1.3)	
45	94(6.0)		103(1.1)	
60	96(5.9)		103(1.5)	

Sampling Times (Min.)	Test Product Lot # 3349PD Strength (mg) 4.5 Mean % Dissolved(CV%)	Range	Reference Product Lot # Strength (mg)
15	67(4.5)		No reference product at this strength (Suitability Petition Docket No. 95P-0285/CP1)
30	82(4.7)		
45	88(5.2)		
60	92(5.7)		

Sampling Times (Min.)	Test Product Lot # 3350PD Strength (mg) 6		Reference Product Lot # 258JT Strength (mg) 6	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	71(3.6)		99(2.1)	
30	84(3.6)		102(1.2)	
45	91(3.9)		102(1.6)	
60	95(4.2)		102(1.2)	

I. Conditions for Dissolution Testing: **pH 8.5**
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: Phosphate Buffer Volume: 900 ml
Reference Drug: (Manuf.) Glynase Pres Tablets (Upjohn)
Assay Methodology: HPLC
Specifications: Not determined

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 3310PD Strength (mg) 1.5		Reference Product Lot # 338WT Strength (mg) 1.5	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	95(6.2)		102(1.7)	
30	97(5.6)		102(1.4)	
45	98(4.8)		102(1.5)	
60	99(3.9)		102(1.4)	

Sampling Times (Min.)	Test Product Lot # 3348PD Strength (mg) 3		Reference Product Lot # 101XF Strength (mg) 3	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	87(6.8)		102(1.3)	
30	93(6.6)		102(1.0)	
45	94(5.5)		102(1.0)	
60	95(5.1)		103(1.1)	

Sampling Times (Min.)	Test Product Lot # 3349PD Strength (mg) 4.5 Mean % Dissolved(CV%)	Range	Reference Product Lot # Strength (mg)
15	89(5.2)		No reference product at this strength (Suitability Petition Docket No. 95P-0285/CP1)
30	97(4.6)		
45	99(4.2)		
60	100(4.2)		

Sampling Times (Min.)	Test Product Lot # 3350PD Strength (mg) 6 Mean % Dissolved(CV%)	Range	Reference Product Lot # 258JT Strength (mg) 6 Mean % Dissolved(CV%)	Range
15	82(6.2)		102(1.1)	
30	91(6.7)		101(1.4)	
45	93(6.7)		102(1.3)	
60	94(6.4)		102(1.3)	

Comments and Recommendation:

The additional dissolution testing in pH 7.5, 8.0 and 8.5 is acceptable. Based on the data submitted, the following dissolution method and specification for the test product are recommended.

Dissolution Method: The dissolution testing should be conducted in 900 ml of pH 8.5, 0.05 M phosphate buffer at 37°C using USP 23 apparatus II(paddle) at 50 rpm.

Tolerance: NLT —% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG Y Huang 3/5/99

Concur: Dale P. Conner Date: 3/5/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-686 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/03-03-99/W #74686d.199
Also as V:\firmsnz\novophar\ltrs&rev\74686d.199
Attachment: 1 page

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 74-686 APPLICANT: Novopharm

DRUG PRODUCT: Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg & 6 m g

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

The following, FDA-recommended dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of pH 8.5 phosphate buffer (0.05M), at 37 C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than ~ %(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

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

CC:ANDA 74-686
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 3/5/99
HFD-617/ E. Hu 3/5/99
HFD-650/ D. Conner 3/5/99

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 01-13-99

1. STUDY AMENDMENT (STA) Strengths: 1.5 mg, 3 mg, 4.5 mg & 6 mg
Outcome: **AC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

All pages are accounted for in this document.
A pagination error occurred.

W#74686d.199 Attachment (Page 1 of 2)

BIOEQUIVALENCY COMMENTS

ANDA: 74-686 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg and 6 mg

As discussed with the firm's representatives in the telephone conference on July 30, 1998, at this time the Division of Bioequivalence has completed its review and has no further questions concerning the *in vivo* bioequivalence requirements, but it has the following recommendations concerning the *in vitro* testing requirements for the test product:

1. In order to adopt a sufficiently **discriminating and complete** *in vitro* dissolution method for a micronized glyburide tablet drug product that has been shown to be bioequivalent to the RLD product, such as the above test product, the Division of Bioequivalence has now requested that all strengths of the test and reference listed drug product be tested for *in vitro* dissolution by you **further in several different pHs (pH 7.5, 8 and 8.5)**, with all other parameters of the dissolution procedure remaining the same. An acceptable (i.e., discriminating and complete) release specification will be established for the test product based on these data. The division understands that presently you do not have any fresh lot of any strength of the test product available in house, and will be manufacturing the first production batches in September of 1998. As the only condition for approval of the test product, you are asked to commit, in writing, to carry out this additional dissolution testing at the above-specified pHs and to provide such data in an application supplement within approximately 30 days of the manufacturing of the first production lot of each strength of the test product. The supplement may be requested by you for an expedite review.

2. Until new dissolution procedure and specifications are established for the test product following the review of the above-mentioned supplement, the **interim** specification and the **interim** dissolution method for your test product will be respectively as follows:

> Tolerance Specification: NLT ~ % of the labeled amount of the drug in the dosage form is dissolved in 60 minutes

Dissolution method: 900 mL of pH 7.5 0.05 M phosphate buffer as the dissolution medium, and with the USP paddle apparatus at 50 rpm.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

(2)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA: 74-686 SPONSOR : Novopharm
DRUG & DOSAGE FORM : Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg & 6 mg

TYPE OF STUDY:	SD	SDF
STUDIES:	XAcceptable	
DISSOLUTION :	XAcceptable	
WAIVER:	XAcceptable	

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: HN DATE : 3/4/99

TEAMLEADER: Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : YH DATE : 3/5/99

DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL : DPC DATE : 3/5/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

DATE: 7-22-97

PRODUCT NAME: Glyburide Tablets (micronized)

ANDA NUMBER: 74-686

FIRM NAME: Novopharm Ltd.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Therese Ast, Ph.D., U.S. Agent

PARTICIPANT(S) TELEPHONE: 919 - 234-2222

MINUTES OF CONVERSATION:

Background:

According to deficiency letter dated 2-24-97, Novopharm was asked to tightened slightly their limit for ——— and ——— for 1.5 mg tablets. Novopharm has proposed NMT —% and NMT -% for ——— and ———, respectively. Novopharm responded that the current limits for these ——— are reasonable. The amount of ——— and ——— ——— for the exhibit batch (lot # PD2814) during shelf-life testing at 18 months are ——— and ———, respectively. ANDA 74-792 for Glyburide Tablets (micronized) has already been approved with ——— limits.

Telecon:

Based on above background, Mike Smela and I call the U.S. Agent for Novopharm - Therese Ast, Ph.D. Mike told her that the limit for ——— and ——— should be tightened according to the prevailing information available to us for the subject drug product. Similar request was made in the deficiency letter to Novopharm dated 2-24-97. Mike asked Therese Ast to submit telephone amendment for their response. Therese Ast told us that he will talk to Novopharm and ask them to submit their response or somebody from Novopharm will call us in this regard. Shaikh told her that Novopharm has -% in the middle to play between their proposed limits and the 18 months stability data on 1.5 mg tablets for these———. Therefore, Novopharm can easily set limits for these ———. We gave her the fax number.

End of Conversation.

Mujahid Shaikh 7/22/97

NAME OF OGD REPRESENTATIVE: M. Shaikh/Mike Smela

SIGNATURE OF OGD REPRESENTATIVE: M Smela 7/22/97

DIVISION/BRANCH: I/II

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RECORD OF TELEPHONE CONVERSATION

DATE: 8/29/97

FROM: Sheila O'Keefe, CSO, Branch 2, Division of Chemistry I, Office of Generic Drugs.

NAME/TITLE OF INDIVIDUAL: Dietrich Bartel
FIRM: Novopharm
PRODUCT NAME: Glyburide Tablets (micronized)
TEL #:
ADDITIONAL PARTICIPANT: Steve Sherken, Acting Team Leader

SUBJECT: Follow up on our request for telephone amendment issued 7/22/97.

MINUTES OF CONVERSATION:

I had called Mr. Bartel on approximately August 20 and told him that we would have to have his telephone amendment by August 24th or we would have to issue a Not Approvable letter. He called back approximately August 25 and said he had to speak to us about the issue. Steve Sherken and I called him on August 29 and asked him again to tighten his specifications for ————. We told him as Mike Smela had in the previous telecon that his stability data suppported this change. We also told him that the innovator has tighter specs and all the applications that are approved for this drug have tighter specs. He said he does not want to tighten the specs. He said we have already approved their application for glyburide, 74-388 with higher specs and he does not want to make the change. We said we would check further and get back to him the first week of September.

They thanked us for our help.

We then terminated the conversation.

SIGNATURE OF OGD REPRESENTATIVES:

Sheila O'Keefe S. O'Keefe 9/2/97

Steve Sherken S. Sherken 9/2/97

DIVISION/BRANCH: Div. of Chemistry I, Branch #2

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RECORD OF TELEPHONE CONVERSATION

DATE: 3-17-98

PRODUCT NAME: Glyburide Tablets (micronized)

ANDA NUMBER: 74-686

FIRM NAME: Novopharm Ltd.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Therese Ast, Ph.D., U.S. Agent

PARTICIPANT(S) TELEPHONE: 919 - 234-2222

MINUTES OF CONVERSATION:

Background:

According to deficiency letter dated 9-23-97, Novopharm was asked to tightened slightly their limit for [redacted] and [redacted] for 1.5 mg tablets. Novopharm has proposed NMT [redacted]% and NMT [redacted]% for [redacted] and [redacted], respectively. In order to consistent with already approved ANDA and listed drug product, proposed limit for [redacted] need to be tightened and based on 18 months of CRT stability data for exhibit batch, Novopharm can [redacted] the limit.

The amount of [redacted] and [redacted] for the exhibit batch (lot # PD2814) during shelf-life testing at 18 months are [redacted]% and [redacted]%, respectively. ANDA 74-792 for Glyburide Tablets (micronized) has already been approved with [redacted] limits.

Telecon:

Based on above background, Steve Sherken and M. Shaikh called the U.S. Agent for Novopharm - Therese Ast, Ph.D. M. Shaikh told her that the limit for [redacted] should be [redacted] further according to the prevailing information available to us for the subject drug product. M. Shaikh asked Therese Ast to submit telephone amendment for their response. Therese Ast told us that she will talk to Novopharm and ask them to submit their response. Therese Ast asked M. Shaikh what is the appropriate limit for [redacted]. M. Shaikh told her that Novopharm can propose limits based on the available 18 months stability data on 1.5 mg tablet for exhibit batch for [redacted]. M. Shaikh gave her the fax number.

End of Conversation.

Mujaid Shaikh 3/17/98

NAME OF OGD REPRESENTATIVE: Steve Sherken/M. Shaikh

SIGNATURE OF OGD REPRESENTATIVE: Stephen Sherken 3/17/98

DIVISION/BRANCH: I/II

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RECORD OF TELEPHONE CONVERSATION

DATE: 3-30-98

PRODUCT NAME: Glyburide Tablets (micronized)

ANDA NUMBER: 74-686

FIRM NAME: Novopharm Ltd.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Jonathan Ng

PARTICIPANT(S) TELEPHONE: 919 - 234-2222

MINUTES OF CONVERSATION:

Background:

According to deficiency letter dated 9-23-97, Novopharm was asked to tightened slightly their limit for ——— and ——— for 1.5 mg tablets. Novopharm has proposed NMT —% and NMT —% for ——— and ———, respectively. In order to be consistent with already approved ANDA and listed drug product, proposed limit for ——— need to be tightened more and based on 18 months of CRT stability data for exhibit batch, Novopharm can ——— the limit.

Telecon:

Based on above background, Steve Sherken and M. Shaikh called the U.S. Agent for Novopharm - Therese Ast, Ph.D. on 3-17-98. M. Shaikh told her that the limit for ——— should be tightened further according to the prevailing information available to us for the subject drug product. Therese Ast told us that she will talk to Novopharm and ask them to submit their response. Novopharm failed to submit response. Therefore, M. Shaikh called the firm to submit their response on March 25 and again on March 30, 1998. On March 30, 1998, Mike and Shaikh talked to Jonathan Ng regarding this issue. Mike told Ng that tighter limit for ——— is being asked in order to be consistent with already approved reference drug product and ANDA for Glyburide micronized tablets. M. Shaikh also emphasized the same. Mr. Ng mentioned that their Glyburide micronized Tablet is same as the already approved Gylburide Tablets. M. Shaikh told him that we are aware the exact situation but we are asking you in order to be consistent with already approved reference drug products. At this point of conversation, Mr. Ng understood and he told us that Novopharm will submit telephone amendment at the end of this week or early part of the next week. M. Shaikh gave Mr. Ng the fax number so that he can fax the amendment.

End of Conversation.

Mujabil Shaikh 3/30/98

NAME OF OGD REPRESENTATIVE: Mike Smela/M. Shaikh

SIGNATURE OF OGD REPRESENTATIVE: M Smela 3/30/98

DIVISION/BRANCH: I/II

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APPEARS THIS WAY
ON ORIGINAL

TELEPHONE MEMO

To: Therese Ast
Novopharm (Granutec)
(919) 234-2231

REF # ANDA 74-686

From: Lizzie Sanchez

Date: 4/28/98

Subject: **Glyburide Micronized Tabs**

Requested by: Yi Chain Huang

Dissolution testing should be conducted on the following method: for all strengths.

0.05M Phosphate buffer, pH 7.5
Paddle at 50 rpm
at 15, 30, 45 and 60 min

Please submit within 10 days to avoid a deficiency letter. You may fax this information and follow with a hard copy. Label Bioequivalence Telephone amendment.

RECORD OF TELEPHONE CONVERSATION

DATE: 10-15-98

PRODUCT NAME: Glyburide Tablets (micronized)

ANDA NUMBER: 74-686

FIRM NAME: Novopharm Ltd.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dietrich Bartel

PARTICIPANT(S) TELEPHONE: 919 - 234-2222

MINUTES OF CONVERSATION:

Background:

The approval package for the ANDA is reviewed by Allen Rudman and found it deficient with respect to issues regarding [redacted] and [redacted] of the [redacted]. The issue of [redacted] has been addressed in the referenced DMF [redacted] and is found adequate. Other two issues need action from the firm.

Telecon:

Based on above background, Mike Smela and M. Shaikh called the U.S. Agent for Novopharm - Dietrich Bartel on 10-15-98. Mike told him that based on the data the [redacted] for the batch of the [redacted]

Mike discussed the second issue of [redacted] Based on the master manufacturing batch record for all four strength tablets submitted on July 10, 1997, your firm will conduct [redacted]

way, there is no need submit complete master batch. Mike gave him the fax number so that he can fax to OGD an amendment followed by hard copy if there is no need to discuss these issues again by him.

End of Conversation.

NAME OF OGD REPRESENTATIVE: Mike Smela/M. Shaikh 10/16/98

SIGNATURE OF OGD REPRESENTATIVE: M Smela 10/16/98

DIVISION/BRANCH: I/II

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APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE:10/15/98

NAME/TITLE OF INDIVIDUAL(S): Jonathan Ng
FIRM:Novopharm
PRODUCT NAME: Glyburide
TEL #: He called
Reference:ANDA 74686

Notes of Conversation: He called in follow-up to conversation Mujahid Shaikh and I had with Dietrich Bartel earlier in the day. He wished to discuss the 2 issues further.

_____ He stated that the SOP referenced in the MBRs did, in fact, call for _____ in duplicate. He also said that they prefer to set an RSD criteria after validation. I said he could either submit the SOP or state what was in it, and that a RSD criteria needs to be established prior to approval.

Jonathan advised that the Novopharm organization takes at least a week to clear spec changes. I asked that if a Telephone Amendment is not submitted in a week, he call me back.

SIGNATURE OF OGD REPRESENTATIVES:

M Smela 10/16/98

Location of Electronic Copy:
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RECORD OF TELEPHONE CONVERSATION

DATE: 3-24-99

PRODUCT NAME: Glyburide (micronized) Tablets

ANDA NUMBER: 74-686

FIRM NAME: Novopharm Limited

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Johnathan Ng

PARTICIPANT(S) TELEPHONE: 1-800-361-3313

MINUTES OF CONVERSATION:

Telecon:
Mike Smela and M. Shaikh called Johnathan Ng in order to inform the approved dissolution specification for all strength tablets in 3-15-99 bio review. Based on this dissolution specification, Mike Smela requested him to a telephone amendment with revised release and stability specifications and validation of their method based on dissolution method approved by DBE of OGD. He told us that they are already working on it and will submit ASAP.

Shaikh gave have him the fax number.

End of Conversation.

NAME OF OGD REPRESENTATIVE: Mike Smela/M. Shaikh

SIGNATURE OF OGD REPRESENTATIVE:

DIVISION/BRANCH: I/II

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Glynase Prestab
NDA = 20051

OGD APPROVAL ROUTING SUMMARY

NDA # 74-686, Applicant Novopharm Limited

g Glyburide Tablets USP

Strength 1.5mg, 3mg, 4.5, 6mg

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

4.5mg D/C List of Orange Book

REVIEWER:

1. Project Manager Dhue
   Review Support Br 2

DRAFT RECEIPT
Date 4/6/99
Initials DH

FINAL ACTION
Date _____
Initials _____

Application Summary:

Original Rec'd date 6/6/95
Date Acceptable for Filing 8/1/95 ✓
Patent Certification (type) IV — 4916,163 Exp 4/10/2007
4735805 Exp 4/5/2005
Date of Office Bio Review 3/5/99
Methods Val. Samples Pending Yes ☐ No ☒
30 Day Clock Start USP End _____
Commitment rcd. from Firm Yes ☐ No ☐
First Generic Yes ☐ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3/30/99
Date Patent in effect _____
Citizens Petition/Legal Case Yes ☒ No ☐
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked 4/6/99
Nothing Submitted ☐ 4/6
Written request issued ☐
Study Submitted ☐

Comments:

2. Div. Dir./~~Deputy Dir.~~
   Chemistry Div. I ~~or II~~
   Date 4/9/99 Initials RC
   Date 4/9/99 Initials RS
   Comments: The CMC section is satisfactory (4.5mg & P-4 discontinued).

3. Office Level Chem Review **(1st Generic Only)**
   Chemistry Div. (I) or II
   Date _____ Initials _____
   Date _____ Initials _____ 4/20/99
   Comments: N/A Multiple generic ANDAs currently approved for this drug product (RLD = Glynase)

4. Pat Beers Block RLD=20051
   Supv., Review Support Branch
   Date 4/13/99 Initials PMBB
   Date 4/15/99 Initials PMBB
   Comments:

- EER acceptable for all facilities as of 3/30/99 (printed 4/15/99; more OAI)
- Bioequivalence clinical + analytical site:
- Bioequivalence review completed 3/5/99 - included review of dissolution data received 1/13/99. Bioequivalence found acceptable for approval 3/5/99
- Final product labeling - approved summary prepared 7/30/97 found still acceptable as labeling for the RLD still current labeling (as of 4/16/99)
- Patent: firm submitted evidence that court case upheld patent # 4916163 in their amendment dated 3/16/99 (Judgment Date 2/2/99)
- Submitted Pat # 95P-0285/CP1

x:\wpfile\beersbl\aprovrou

	DRAFT RECEIPT	FINAL ACTION
REVIEWER:		
Peter Rickman D Greenberg 4/16/99	Date 4/16/99	Date 4/16/99
Supv., Reg. Support Branch	Initials HG	Initials HG
Contains certification Yes ☒ No ☐	Determ. of involvement? Yes ☐ No ☒ N/A	
(required by the GDEA if sub after 6/1/92)	Pediatric Exclusivity Tracking System	
Paragraph 4 Certification Yes ☒ No ☐	Date Checked 4/16/99 Checked N/A RW	
TA'd = Nov 10, 1998 (patent "163" 4/10/07 "805" 7/15/05)	Nothing Submitted ☐	
no unexpired exclusivity →	Written request issued ☐	
	Study Submitted ☐	
SER acceptable 3/30/99, BE inspectional sites acceptable - see 4/15/99 E-mail		

Comments:
Firm notified dated March 16, 1999 final judgment from the District Court of the Northern District of Illinois and in which NO appeal has been taken — Ok for Approval

6. ~~Jerry Phillips~~	Date 4/20/99	Date 4/20/99
Dir. Div. Labeling & Prog. Support	Initials RW	Initials for Sid

Comments: This ANDA was tentatively approved on 11/10/98. Acceptable CS dated 3/3/99 (Verified 4/20/99). No OAI objects noted. Office Lab/Bio endorsed 3/4/99. Additional dissolution studies submitted, reviewed, and found acceptable. Office Bio endorsed 3/29/99 (D Owen). CMC Acceptable 4/7/99. Methods validation waived. FOI endorsed 4/6/99. BE test sites O.K. to DSI. Recommend Approval

7. Gordon Johnston	Date 4/20/99	Date 4/20/99
Deputy Director, OGD	Initials RW	Initials RW for Sid
Patent Cert - P, Yes ☒ No ☐	Petition Status None	
Pend. Legal Action Yes ☒ No ☐		

Comments: Applicant submitted a Citizens Petition for determination of safety issues related to 45 mg strength tablets in discontinued section of Orange Book. Agency concluded no safety issues. Novopharm was notified by Pharmaceutical Up-front on '163 patent. Novopharm prevailed + Pharmaceutical Up-front did not appeal. OK to Approve tentative approval - Law suit (97 cv 8) listed. No pediatric study submitted under FDAMA.

8. Doug Sporn	Date 4-20-99	Date 4-20-99
Dir., OGD	Initials DS	Initials DS
Comments:		

Roger Williams, M.D.	Date	Date
Dep. Dir., CDER	Initials	Initials
First Generic Approval ☐		
PD or Clinical for BE ☐		
Special Scientific or Reg. Issue ☐		

9. Project Manager Denise Hure	Date	Date
Review Support Branch	Initials	Initials

RW N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:

8:40 AM Time notified of approval by phone _____ Time approval letter faxed

4/21/99

FDA Notification:

4-21-99 Date e-mail message sent to "OGD approvals" account

4-21-99 Date Approval letter copied to "//cder/drugapp" directory

JB

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-686

CORRESPONDENCE

Harvey Healey RPh 6/26/95

novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Labeling revised completed 1/5/96 JMcNamara

RE: **Abbreviated New Drug Application**
GLYBURIDE ——— TABLETS,
1.5 MG, 3.0 MG, 4.5 MG AND 6.0 MG

We are pleased at this time to submit an original Abbreviated New Drug Application for our product - Glyburide —— Tablets, 1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg.

The purpose of this application is to gain FDA approval to market Glyburide —— Tablets, 1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg in the U.S.A. The drug product described above is the same as GLYNASE®PRESTAB® Tablets, manufactured by The Upjohn Company. We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form, comparing active ingredient, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Novopharm Limited and by The Upjohn Company.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA. The number of volumes in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy	- 11 volumes
Orange Review Copy	- 7 volumes
Red Review Copy	- 5 volumes
Burgundy Field Copy	- 5 volumes

We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application.

Cont'd .../2

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

re. Glyburide — Tablets
1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg
Page 2 of 2

In addition, for the Bioequivalence Section, we have also enclosed a computer diskette with the analytical data and bioavailability parameters in the format prescribed by the FDA. This diskette is located at the front of Section VI of the Orange Review Copy of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

A letter of authorization, allowing Dr. Ast to act as our U.S. agent, is included in Section XXI.2.b of this application.

Yours sincerely,

Dietrich Bartel

JUN 05 1995

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896

Via PUROLATOR COURIER (Waybill # 858 062 5658)

ANDA 74-686

Granutec Inc.
Attention: Therese M. Ast, Ph.D.
U.S. agent for: Novopharm Limited JUL 14 1995
4409 Airport Drive NW
Wilson, NC 27896

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated June 5, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Glyburide Tablets (micronized) 1.5 mg, 3 mg, 4.5 mg and 6 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have referenced, glyburide tablets (micronized) 4.5 mg, a strength of the reference listed drug product that has been voluntarily withdrawn from sale in the United States. Please refer to Approved Drug Products With Therapeutic Equivalence Evaluations, 15th Edition. In accord with Section 314.122 you are required to submit a citizens petition under 21 CFR 10.25(a) and 10.30 seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

You list ——————————— as the manufacturer of the ——— ——————— in DMF ——— on page 2736. However, your certificate of analysis is from ——————————— . Please clarify this issue.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Yana Ruth Mille 7/14/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-686
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
Endorsement: HFD-615/PRickman, Acting Chief 6/30/95 date
HFD-615/HGreenberg, CSO date
HFD-610/JPhillips, Chief, LRB date
HFD-625/MSmela, Sup. Chem. date 7/1/95
WP File x:\wpfile\greenberg\74686.rtf
F/T by Fox 6/28/95
ANDA Refuse to File!

BIOAVAILABILITY

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

July 31, 1995

AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

NDA ORIG AMENDMENT
AC

SUBJECT: **ANDA # 74-686**
Glyburide —— Tablets, 1.5 mg, 3 mg, 4.5 mg and 6 mg

This amendment to our abbreviated new drug application is in response to your letter dated July 14, 1995 from Ms. Yana Ruth Mille of the Division of Labeling and Program Support, which we received on July 18, 1995.

We are amending our application to withdraw the 4.5 mg strength from the submission. Therefore, any reference in the ANDA to the 4.5 mg strength should be disregarded during the Agency's review. The file will remain open for the 1.5 mg, 3 mg and 6 mg strengths.

In addition, we note that the drug master file holder for the ———— is ————(DMF # ——). We have listed ———— as the manufacturer of the ———— in DMF #—— since ———— is the manufacturing site for ————.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

JUL 3 1 1995
(date)

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 2971)

RECEIVED
AUG 0 1 1995
GENERIC DRUGS

ANDA 74-686

Granutec Inc.
Attention: Therese M. Ast, Ph.D.
U.S. agent for: Novopharm Limited
4409 Airport Drive NW
Wilson, NC 27896

SEP 20 1995

Dear Madam:

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

Reference is also made to our "Refuse to File" letter dated July 14, 1995, and your amendment dated July 31, 1995.

NAME OF DRUG: Glyburide Tablets (micronized) 1.5 mg, 3 mg and 6 mg

DATE OF APPLICATION: June 5, 1995

DATE OF RECEIPT: June 6, 1995

DATE ACCEPTABLE FOR FILING: August 1, 1995

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:

David Konigstein
Consumer Safety Officer
(301) 594-0370

Sincerely yours,

Jerry Phillips 9/20/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-686
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief 9/7/95 date
HFD-615/HGreenberg, CSO date
HFD-625/MSmela, Supervisory Chemist 9/8/95 date
HFD-610/YRMille, Chief LRB 9/7/95 date
WP File X:/wpfile/greenberg/74686.ack
F/T Fox 8/17/95
ANDA Acknowledgement Letter!

ANDA 74-686

Granutec Inc.
Attention: Theresa M. Ast, Ph.D., Esq.
U.S. Agent for: Novopharm Ltd., Ontario, Canada FEB 5 1996
4409 Airport Drive N.W.
Wilson, N.C. 27896

Dear Madam:

This is in reference to your abbreviated new drug application dated June 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Glyburide Tablets (micronized), 1.5 mg, 3 mg and 6 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. DMF [redacted] is deficient. Please request them to respond to all outstanding deficiencies cited by the recent FDA letter.

2. [redacted]

3.

4.

5. 

B. Labeling Deficiencies:

GENERAL COMMENT:

We acknowledge your comments regarding the withdrawal of the 4.5 mg strength from the application.

CONTAINER: 100s (1.5 mg, 3 mg, 6 mg), 500s (3 mg), and 1000s (3 mg)

1. Revise the established name to read as follows:

Glyburide Tablets (micronized)

2. Revise the dispensing statement to read:

Dispense in a tight, light-resistant container...

UNIT DOSE BLISTER: 100s (1.5 mg, 3 mg)

When the draft unit-dose blisters are compared side by side, they appear very similar. We would encourage you to differentiate between the different strengths as seen on your carton labeling.

UNIT DOSE CARTON: 100s (1.5 mg, 3 mg)

See comment 1 and 2 under CONTAINER.

INSERT:

1. TITLE

See comment 1 under CONTAINER.

2. DESCRIPTION

a. Revise to read:

Glyburide tablets (micronized) contain smaller particle size. Glyburide is an oral blood...crystalline compound. Each tablet, for oral administration, contains 1.5 mg, 3 mg, or 6 mg of glyburide. Inactive ingredients:...In addition, the 3 mg and 6 mg strengths...

b. Include the molecular formula.

c. Revise the molecular weight to read "494.01" rather than [redacted].

d. Italicize "-*o*-" in the chemical name.

3. CLINICAL PHARMACOLOGY

Pharmacokinetics

a. Paragraph 1, line 1 - ...with glyburide tablets (micronized) in normal...

b. Revise to read paragraph 2 as follows:

...that micronized glyburide tablets 3 mg provide serum...those from nonmicronized glyburide tablets 5 mg.

c. Delete paragraph 3 and figure A.

4. INDICATIONS AND USAGE

a. Revise paragraph 1 to read:

Glyburide tablets (micronized) are indicated...

b. Replace [redacted] with "glyburide" in paragraphs 2, 3, and 4. [3 places]

5. CONTRAINDICATIONS

a. Glyburide is contraindicated...

b. SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY - Revise paragraph 2 to read:

...of glyburide and of alternative modes of therapy.

6. PRECAUTIONS

a. Revise paragraph 1 to read as follows:

...that micronized glyburide tablets 3 mg...from nonmicronized glyburide tablets. Therefore, patients...from nonmicronized glyburide tablets or other...

b. Loss of Control of Blood Glucose - Replace "[redacted]" with "glyburide". [3 places]

c. Information for Patients - ...advantages of glyburide and of alternative...

d. Laboratory Tests - ...to glyburide tablets (micronized) should...

e. Carcinogenesis, Mutagenesis, and Impairment of Fertility - Delete "and" from the subsection heading.

f. Pregnancy, Nonteratogenic Effects - ...If glyburide is used during pregnancy...

g. Pediatric Use - ...in pediatric patients have...

7. ADVERSE REACTIONS

Gastrointestinal Reactions - ...rarely; glyburide should be...

8. DOSAGE AND ADMINISTRATION

a. Revise paragraph 1 to read as follows:

...from nonmicronized glyburide tablets or other...

b. Paragraph 2 - ...with glyburide tablets (micronized) or any other...

c. Paragraph 3 - ...of glyburide may be sufficient...

d. Usual Starting Dose - ...of glyburide tablets (micronized) is...

e. Transfer From Other Hypoglycemic Therapy - Revise to read:

...from nonmicronized glyburide tablets or other oral...than chlorpropamide to micronized glyburide tablets, no transition...

f. Patients Receiving Insulin - Revise to read:

...to micronized glyburide. If the...of glyburide tablets (micronized) 1.5 to 3 mg...may be placed directly on glyburide tablets (micronized) 3 mg daily...conversion to micronized glyburide. In these patients,...5% and glyburide tablets (micronized) 3 mg daily...

g. Titration to Maintenance Dose

i. Revise paragraph 2 to read:

...between micronized glyburide and the other hypoglycemic agents, including nonmicronized glyburide tablets. Although...of 3 mg of glyburide tablets (micronized) should be observed. A maintenance dose of 3 mg of glyburide tablets (micronized) provide approximately...tolazamide, 5 mg of nonmicronized glyburide, 500 to...

ii. Replace '———————————— " with "glyburide tablets (micronized)". [3 places]

h. Specific Patient Populations - Glyburide is not recommended...

9. HOW SUPPLIED

a. Replace '————————————" with "Glyburide Tablets (micronized)".

b. Delete the reference to the 4.5 mg strength tablets.

c. Place the "Caution: Federal Law..." statement on a separate line.

d. See comment 2. under CONTAINER.

Please revise your container labels unit dose carton labeling and package insert labeling, then prepare and submit final printed container labels, unit dose blister labels, unit dose carton and insert labeling. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please submit the currently available room temperature stability data for all executed batches, if have it.

3. We believe that retest dates for drug product components should be no more than 12 months unless justified. The acceptability of your retest program is evaluated by the FDA field investigator.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

2/5/96

Sd/ Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-686
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/M.Shaikh/12/14/96 Mujahid Shaikh 1/30/96
HFD-613/A.Payne/1/26/96 A Payne 1/29/96
HFD-625/SSherken for M.Smela/12/29/95 Stephen Sherken 2/1/96
HFD-610/JPhillips/1/26/96 J Phillips 1/29/96
HFD-617/S.O'Keefe/1/23/96 SOKeefe 1/30/96
X:\new\firmsnz\novopharm\74686ltr.1
F/T by: gp/1/29/96
NOT APPROVABLE - Major

This letter also covers the
7/31/95 amendment
M Smela
2/6/95

1.1

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

February 14, 1996

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville, MD
U.S.A. 20855-2773

ACKNOWLEDGEMENT

SUBJECT: **ANDA 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, and 6 mg

We thank you for your letter dated February 5, 1996 which we received on February 8, 1996 from Dr. Rashmikant M. Patel of the Division of Chemistry I. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313 or our U.S. Agent, Dr. Thérèse Ast at 1-919-291-9100 or 1-919-291-5817.

Yours sincerely,

Dietrich Bartel

Dietrich Bartel
Manager, Pre-Approval
U.S. Regulatory Affairs

cc: Dr. Thérèse Ast (Granutec Inc., 4409 Airport Drive N.W., Wilson, NC 27896)

Via Purolator (Waybill # 317 515 7324)

ANDA 74-686

APR - 3 1996

Novopharm LTD
Attention: Thérèse Ast, Ph.D., Esq.
Authorized U.S. Agent
4409 Airport Drive N.W.
Wilson, NC 27896

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on June 5, 1995 and was acceptable for filing on August 1, 1995, for Glyburide Tablets (micronized) 1.5 mg, 3 mg and 6 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

> Under fasting conditions, the test and reference products are not considered equivalent in the rate of absorption as measured by C_{MAX} since the 90% confidence interval for log-transformed C_{MAX} is [0.79;0.96] which is outside the acceptable limit of [0.80;1.25].

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
ANDA 74-686, Orig File, Dup File
Div File
Field Copy
HFD-615 PRickman
HFD-650 Gross, CST

BIO-FATAL FLAW

Endorsements:

H. Nguyen
Y.C. Huang 4/1/96
J. Gross

DRAFTED	STM	03/27/96	X:\WPFILE\BIO\F74686D1.SDW
FINAL PRINT	STM	03/29/96	X:\WPFILE\BIO\FINAL\F74686.SDW

APPEARS THIS WAY
ON ORIGINAL

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-455(
Fax (905) 642-459

April 22, 1996

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville, MD
U.S.A. 20855-2773

ACKNOWLEDGEMENT
noted NAST 5/1/96

SUBJECT: **ANDA 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, and 6 mg

We thank you for your letter dated April 3, 1996 which we received on April 18, 1996 from Dr. Keith Chan of the Division of Bioequivalence. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313 or our U.S. Agent, Dr. Thérèse Ast at 1-919-291-9100 or 1-919-291-5817.

Yours sincerely,

Dietrich Bartel

Dietrich Bartel
Manager, Pre-Approval
U.S. Regulatory Affairs

cc: Dr. Thérèse Ast (Granutec Inc., 4409 Airport Drive N.W., Wilson, NC 27896)

Via Purolator (Waybill # 317 478 9796)

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

BIOEQUIVALENCE AMENDMENT

voted NAI 8 Oct 10/16/96

NEW CORRESP NC/BIO BIOAVAILABILITY

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg and 6 mg

This amendment to our abbreviated new drug application is in response to your letter dated April 3, 1996 from Dr. Keith K. Chan of the Division of Bioequivalence, which we received on April 4, 1996.

For the reviewers' convenience, Dr. Chan's comment has been restated in **bold** print and is followed by our response. Enclosed are one (1) archival and one (1) review copy of this amendment.

In addition, we hereby grant authorization for _____ to our ANDA file (# 74-686) for Glyburide Tablets (micronized), 1.5 mg, 3 mg and 6 mg. We also waive the right to have access to these data in compliance with _____ request to have these data remain confidential.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel

SEP 24 1996
(date)

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

RECEIVED
SEP 25 1996
GENERIC DRUGS

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 9091)

4-30-96

MEMBER CDMA

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

NDA ORIG AMENDMENT

N/AC

MAJOR AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

RECEIVED
OCT 15 1996
GENERIC DRUGS

Labeling review completed C. Holquist 11/17/96
(Glynase Prestab 9/16/96 Medical)

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg and 6 mg

This major amendment to our abbreviated new drug application is in response to your letter dated February 5, 1996 from Dr. Patel of the Division of Chemistry I, which we received on February 6, 1996.

For the reviewers' convenience, each comment made by Dr. Patel has been restated in **bold** print and is followed by our response.

In addition, pursuant to 21 CFR 314.60, we are amending our application to provide for an additional strength, Glyburide Tablets (micronized), 4.5 mg. A copy of the supporting data is included in Part. C. of this amendment.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

OCT 09 1996
(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 9059)

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Fax (905) 642-4591

Office of Generic Drugs, HFD-630
Center for Drug Evaluation and Research
Food and Drug Administration
DOCUMENT CONTROL ROOM
Metro Park North
7500 Standish Place, Room 150
Rockville, Maryland
20855, USA

ANDA CORRESPONDENCE
74686
NEW CORRESP
NC

Re: All ANDAs/AADAs Approved and Unapproved for Novopharm Limited and ANDA # 74-488 Tentatively Approved for Granutec Inc.

This letter is to inform you that effective January 6, 1997, Dr. Therese Ast's mailing address, telephone number and fax number have changed.

Dr. Ast will continue to act as Agent for Novopharm Limited of Canada, and you may direct written and telephone communications directly to her at the address below:

Dr. Therese Ast, Ph.D., VP Legal and Scientific Affairs
Novopharm N.C. Inc.
4700 Novopharm Blvd.
Wilson, NC, 27893, USA.
Telephone: (919) 234-2231
Fax: (919) 234-2600

There has also been a mailing address change (the street has been renamed from 30 Nably Court to 30 Novopharm Court) at the Corporate Office for Novopharm Limited. The new address is:

Novopharm Limited
30 Novopharm Court
Scarborough, ON, M1B 2K9, Canada

The accompanying pages include a list of all approved and unapproved ANDAs/AADAs currently held by Novopharm Limited. A copy of this letter for each has been included.

Yours sincerely,

Dietrich Bartel

Dietrich Bartel
Manager, Pre-Approval Activities
U.S. Regulatory Affairs

JAN 0 8 1997
(date)

RECEIVED
JAN 1 0 1997
GENERIC DRUGS

MEMBER

BIOAVAILABILITY Supp to BIO

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

NEW CORRESP

Ms. Saundra Middleton
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

TELEPHONE AMENDMENT

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

Dear Ms. Middleton:

This Telephone Amendment to our abbreviated new drug application is in response to your telephone communication on January 15, 1997 to Dr. Ken Michalko, concerning the potency of the GLYNASE®PRESTAB® lot used in the new bioequivalence study (Study # EP303).

The potency of Upjohn's GLYNASE®PRESTAB® 6 mg lot (lot # 258JT), used in the new bioequivalence study (Study # EP303), is 100.8%, and the potency of Novopharm's 6 mg test lot (lot # PD2817) is 102.3%. We have included in Exhibit I of this amendment a copy of the side by side summary data, certificates of analysis and comparative dissolution profile for the drug products used in the new bioequivalence study.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application and that the field copy has been submitted to the Office of Generic Drugs. Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 234-2231 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

JAN 1 7 1997

Dietrich Bartel
(date)
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Novopharm N.C. Inc.
4700 Novopharm Blvd.
Wilson, N.C. 27893
Via PUROLATOR COURIER (Waybill # 327 238 9663)

RECEIVED
JAN 2 1 1997
GENERIC DRUGS

MEMBER CDMA

3.1

ANDA 74-686

Novopharm LTD
Attention: Thérèse Ast, Ph.D., Esq.
Authorized U.S. Agent
4409 Airport Drive N.W.
Wilson, NC 27896

FEB - 4 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Glyburide Micronized Tablets 1.5 mg, 3.0 mg and 6.0 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of pH 9.5, 0.05M borate buffer at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

   > Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-686, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
H. Nguyen

Letter Out, Bio Acceptable

Endorsements:

L. Sanchez 2/4/97

DRAFTED: STM 2/4/97 X:\WPFILE\BIO\FINAL\N74686.APP

APPEARS THIS WAY
ON ORIGINAL

FEB 24 1997

MINOR AMENDMENT

ANDA/~~AADA~~: 74-686

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT Novopharm PHONE (919) 234- 2231
ATTN: Dr. Therese Ast, Agent FAX (919) 234-2600

FROM: Sheila O'Keefe PROJECT MANAGER (301-594- 0370)

Dear ~~Sir~~/Madam:

This facsimile is in reference to your abbreviated new drug/ ~~antibiotic~~ application dated 6/5/95, submitted pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets (micronized) 1.5mg, 3mg, 4.5mg, 6mg.

Reference is also made to your amendment(s) dated 4/22/96, 9/24/96, 9/23/96, 10/9/96, 1/8/97 and 1/17/97.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactiveated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing. For further clarification or assistance please contact the Project Manager listed above.

SPECIAL INSTRUCTIONS:

x:\new\ogdadmin\faxtrak\faxcov.min

FEB 24 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-686 APPLICANT: Novopharm Ltd., Canada

DRUG PRODUCT: Glyburide Tablets (micronized)

The deficiencies presented below represent MINOR deficiencies.

1. DMF —— of ———————————— is deficient. Please confirm a response to all outstanding deficiencies cited by the recent FDA letter.

2. [redacted]

3. The stability specifications for the ———————— and ———————— should be tightened slightly for the 1.5 mg tablet.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application. You may wish to contact your supplierof ———— regarding their current status.

2. The review of your bioequivalence data is pending. Deficiencies, if any, will be communicated separately.

Sincerely yours,

cc Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: 74-686 Date of Submission: October 9, 1996

Applicant's Name: Novopharm Limited

Established Name: Glyburide Tablets (micronized)
1.5 mg, 3 mg, 4.5 mg and 6 mg

Labeling Deficiencies:

1. CONTAINER

   a. 100s (1.5 mg, 3 mg, and 6 mg), 500s (3 mg), and 1000s (3 mg)

      Satisfactory in final print.

   b. 100s and 500s (4.5 mg)

      It is difficult to determine from the draft label submitted, if this strength has been differentiated from your previously submitted strengths. We encourage you to differentiate this product strength as seen on your container labels for the 1.5 mg, 3 mg and 6 mg.

2. UNIT DOSE BLISTER

   a. (1.5 mg, and 3 mg)

      Satisfactory in final print.

   b. (4.5 mg)

      Satisfactory in draft.

3. UNIT DOSE CARTON:

   a. 100s (1.5 mg, and 3 mg)

      Satisfactory in final print.

   b. 100s (4.5 mg)

      See comment b under CONTAINER.

4. INSERT

Due to changes in the labeling of the listed drug (Glynase® PresTab® Tablets; Upjohn; Approved September 16, 1996; Revised March 1996), we request you revise your insert as follows:

a. CLINICAL PHARMACOLOGY

Pharmacokinetics

i. Paragraph two - Insert the following text as the last sentence:

Therefore, the patient should be retitrated.

ii. After further review, we request that you insert paragraph three and figure A from the reference listed drug's insert labeling. In addition, revise the first sentence to read as follows:

It has been reported that in a single-dose bioavailability...

iii. Paragraph five - Revise the first sentence to read as follows:

In single dose studies in fasting normal subjects who were administered nonmicronized tablets in doses ranging from 1.25 mg to 5 mg, the degree and duration...

b. CONTRAINDICATIONS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY - Italicize "*Diabetes*" in the last sentence of paragraph one.

c. PRECAUTIONS

i. Paragraph one - Revise the first sentence to read as follows:

...from nonmicronized glyburide tablets 5 mg.

ii. General, Hypoglycemia - Insert the following text as the last sentence:

The risk of hypoglycemia may be increased with combination therapy.

iii. Drug Interactions - Insert the following text to appear as the last paragraph:

Metformin: In a single-dose interaction study in NIDDM subjects, decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Coadministration of glyburide and metformin did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

Please revise labeling, as instructed above, and submit final printed insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

NEW CORRESP

February 27, 1997

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville, MD
U.S.A. 20855-2773

ACKNOWLEDGEMENT 3/3/97

SUBJECT: **ANDA 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg, 6 mg

We thank you for your facsimile amendment dated February 24, 1997 which we received on February 25, 1997 from Rashmikant M. Patel , Ph.D., of the Division of Chemistry I and Jerry Phillips of the Division of Labeling and Program Support. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313 or our U.S. Agent, Dr. Thérèse Ast at 1-919-234-2231.

Yours sincerely,

DBartel

Dietrich Bartel, B.Sc.
Manager, Pre-Approval
U.S. Regulatory Affairs

cc: Dr. Thérèse Ast (Novopharm NC Inc, 4700 Novopharm Blvd., Wilson, NC 27893)

Via Purolator (Waybill # 4001 179 1502)

RECEIVED
FEB 28 1997
GENERIC DRUGS

MEMBER CDMA

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

AMENDMENT NEW CORRESP NC noted NAF 3/28/97

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

MINOR AMENDMENT

SUBJECT: **ANDA #74–686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

This amendment to our abbreviated new drug application is made pursuant to Section 505 (j) (2) (A) (vii) of the Federal Food, Drug and Cosmetic Act. We are amending our application to replace the Paragraph III Certification previously filed on June 5, 1995 with a Paragraph IV Certification for U.S. Patent 4,916,163 expiring on April 10, 2007 and U.S. Patent 4,735,805 expiring on April 5, 2005. A copy of the required Patent Certification Statement is included in Exhibit I.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application and that the field copy has been submitted to the Office of Generic Drugs.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 234-2231 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel

MAR 21 1997
(date)

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, Ph. D., Esq., U.S. Agent
Novopharm N.C. Inc.
4700 Novopharm Blvd.
Wilson, N.C. 27893
Via PUROLATOR COURIER (Waybill # 327 238 9689)

RECEIVED
MAR 24 1997
GENERIC DRUGS

3/24/97

MEMBER CDMA

ANDA 74-686

Novopharm Limited
Attention: Therese M. Ast, U.S. Agent
4700 Novopharm Blvd.
Wilson, NC 27893

JUN 2 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated June 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg.

Reference is made to our not approvable fax of February 24, 1997.

The following comments pertain to labeling deficiencies only.

In addition to the comments regarding your insert labeling in our fax of February 24, 1997, revise your insert labeling to be in accord with recent changes in the labeling of the listed drug (Glynase® PresTab®; Pharmacia & Upjohn Company; Approved April 18, 1997) as follows:

1. CLINICAL PHARMACOLOGY

   a. Actions - Insert the following text to appear as the last sentence of paragraph one:

      The combination of glyburide and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

   b. Pharmacokinetics - Insert the following text as the second paragraph following "Figure A":

      In a steady-state study in diabetic patients receiving micronized glyburide tablets 6 mg once daily or micronized glyburide tablets 3 mg twice daily, no difference was seen between the two dosage regimens in average 24 hour glyburide concentrations following two weeks of dosing. The once-daily and twice-daily regimens provided equivalent glucose control as measured by fasting plasma glucose levels, 4 hour postprandial glucose AUC values, and 24 hour glucose AUC values.

Insulin AUC response over the 24 hour period was not different for the two regimens. There were differences in insulin response between the regimens for the breakfast and supper 4 hour postprandial periods, but these did not translate into differences in glucose control.

2. INDICATIONS AND USAGE

Insert the following text to appear as the second paragraph:

Glyburide may be used concomitantly with metformin when diet and glyburide or diet and metformin alone do not result in adequate glycemic control (see metformin insert).

3. DOSAGE AND ADMINISTRATION

a. Titration to Maintenance Dose - Insert the following text as the last two paragraphs:

Concomitant Glyburide and Metformin Therapy: Glyburide tablets (micronized) should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks (see Usual Starting Dose and Titration to Maintenance Dose). Refer to metformin package insert.

With concomitant glyburide 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 optimal dose of each drug needed to achieve this goal. With concomitant glyburide and metformin therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see PRECAUTIONS section).

b. Specific Patient Populations - Revise to read "pediatric patients" rather than "children" in the first paragraph.

Please revise your package insert labeling, and submit in final print with your amendment to our February 24, 1997, fax. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 the differences annotated and explained.

This letter addressed unique issues involving only labeling. Again, we refer you to our fax of February 24, 1997, for the requirements to reopen the file on this application.

Sincerely yours,

John Grace for 6-2-97

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-686
Dup/Division File
HFD-600/Reading File
HFD-610/JPhillips
njg/5/30/97/X:\NEW\FIRMSNZ\NOVOPHAR\LTRS&REV\74686.LOL
LETTER OUT

Endorsements:
HFD-613/CHolquist C Holquist 5/30/97
HFD-613/AVezza A Vezza 5/30/97
HFD-613/JGrace

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

noted
A. Vezza
6/20/97

NEW CORRESP
NEW CORRESP
NC

June 11, 1997

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville MD 20855-2773
U.S.A.

ACKNOWLEDGEMENT

SUBJECT: **ANDA 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

We thank you for your deficiency letter dated June 2, 1997 which we received on June 6, 1997 from Jerry Phillips, Acting Director, Division of Labeling and Program Support. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel

Dietrich Bartel
Manager, Pre-Approval
U.S. Regulatory Affairs

cc: Dr. Thérèse Ast (Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893)

Via Purolator (Waybill #4001 179 1551)

RECEIVED
JUN 12 1997
GENERIC DRUGS

Nadine 6.19.97

MEMBER CDMA

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

MINOR AMENDMENT

NDA ORIG AMENDMENT

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

This minor amendment to our abbreviated new drug application is in response to your facsimile dated February 24, 1997 from Dr. Rashmikant M. Patel of the Division of Chemistry I and Jerry Phillips of the Division of Labeling and Program Support, which we received on February 26, 1997. Reference is also made to your letter dated June 2, 1997, addressing unique issues involving only labeling.

For the reviewers' convenience, each comment made by Dr. Patel and Mr. Phillips has been restated in **bold** print and is followed by our response.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application and that it has been submitted to the Office of Generic Drugs.

Should you have any further questions or comments, you may direct written and telephoned communications to us directly at 1-800-361-3313.

Yours sincerely,

JUL 10 1997
(date)

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Vice President Legal and Scientific Affairs
Novopharm NC Inc.
4700 Novopharm Blvd.
Wilson, N.C.
U.S.A. 27893
Via PUROLATOR COURIER (Waybill # 401 064 7479)

RECEIVED
JUL 11 1997
GENERIC DRUGS

Nadine 7-14-97

MEMBER CDMA

MINOR AMENDMENT

SEP 23 1997

ANDA 74-686

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301 [redacted])

TO: APPLICANT: Novopharm Ltd. PHONE: 919/ 234-2222

ATTN: Therese Ast FAX: 919/ 234-2600

FROM: Sheila O'Keefe PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated June 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets (micronized) 1.5 mg, 3 mg, 4.5 mg and 6 mg.

Reference is also made to your amendment(s) dated February 27, March 21, June 11 and July 11, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, norwill the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

These comments are in follow-up to conversations on 7/22 and 8/20/97 in which specifications were discussed with Mrs. Bartel.

X:\new\ogdadmin\macros\faxmin.frm

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-686 APPLICANT: Novopharm Ltd., Canada

DRUG PRODUCT: Glyburide Tablets (micronized)

The deficiencies presented below represent Minor deficiencies.

1. We request again to slightly tighten the stability specifications for the [redacted] and [redacted] for the 1.5 mg tablet. Alternatively, you may provide data from several lots of the reference product to justify your current specifications.

2. [redacted]

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Your bioequivalence data for the 4.5 mg tablet are pending review.

3. Please provide any additional stability data that may be available.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

novopharm

5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (416) 642-4550

Fax #
(416) 642-4591

NEW CORRESP

NC Noted NAT gilleff 9/29/97

September 23, 1997

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville MD 20855-2773
U.S.A.

ACKNOWLEDGEMENT

SUBJECT: **ANDA 74-686**
Glyburide Tablets (micronized) 1.5 mg, 3 mg, 4.5 mg and 6 mg

We thank you for your facsimile dated September 23, 1997 which we received on September 23, 1997 from Rashmikant M. Patel, Ph.D, of the Division of Chemistry I. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313.

RECEIVED
SEP 25 1997
GENERIC DRUGS

Yours sincerely,

J. Manley

for: Dietrich Bartel, B.Sc.
Manager, Pre-Approval
U.S. Regulatory Affairs

cc: Dr. Thérèse Ast (Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893)

Via FedEx (Waybill #400 3876 2183)

Nadine 9:26:97

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
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Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

MINOR AMENDMENT

NDA ORIG AMENDMENT

N/AM

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized) USP,
1.5 mg, 3 mg, 4.5 mg and 6 mg

This minor amendment to our abbreviated new drug application is in response to your facsimile dated September 23, 1997 from Dr. Rashmikant M. Patel of the Division of Chemistry I, which we received on September 23, 1997.

For the reviewers' convenience, each comment made by Dr. Patel has been restated in **bold** print and is followed by our response.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application and that it has been submitted to the Office of Generic Drugs.

Should you have any further questions or comments, you may direct telephoned communications to us at 1-800-361-3313.

Yours sincerely,

Kenneth Michalko, PharmD, MBA
Director, U.S. Regulatory Affairs
NOVOPHARM LIMITED

MAR 0 2 1998
(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Vice President Legal and Scientific Affairs
Novopharm NC Inc.
4700 Novopharm Blvd.
Wilson, N.C.
U.S.A. 27893
Via Federal Express

RECEIVED
MAR 0 3 1998
GENERIC DRUGS

MEMBER CDMA

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Fax (905) 642-4591

NEW CORRESP

May 5,1998

noted NAI 5/18/98

ACKNOWLEDGEMENT

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Room 150
Rockville MD 20855-2773
U.S.A.

SUBJECT: **ANDA # 74 - 686**
Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg & 6.0 mg

We thank you for your letter dated May 1, 1998, which we received on May 5, 1998 from Dale P. Conner, Pharm. D., Director, Division of Bioequivalence. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313.

Yours sincerely,

Kenneth J. Michalko, PharmD, MBA
Director, US Regulatory Affairs

cc: Dr. Thérèse Ast
(Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893)

Via FedEx (Waybill #400 6603-9083)

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MAY 08 1998
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MEMBER CDMA

96-87-2

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

Mr. Michael Smela, Jr.
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855–2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

Dear Mr. Smela:

This Telephone amendment to our abbreviated new drug application is in response to your telephone communications on March 17, 1998 to Mr. Dietrich Bartel and on March 30, 1998 to Mr. Jonathan Ng, concerning the tightening of stability specifications for the ——— and ———, for the 1.5 mg tablet. Reference is also made to our Minor amendment filed on March 2, 1998 regarding this issue.

We have considered your request to slightly tighten the stability specifications for the 1.5 mg tablets, and we have revised our stability specifications to reflect the following proposed limits: NMT —% for the ———, NMT —% for ——— and NMT —% for———. A copy of the proposed shelf-life stability specifications for Glyburide Tablets (micronized) USP, 1.5 mg, is included in Exhibit I.

Please note that the new limits are lower than the approved ——— limits for Novopharm's Glyburide Tablets USP, 1.25 mg (ANDA#74-388) and that the manufacture of Novopharm's Glyburide Tablets USP, 1.5 mg (ANDA#74-686) and Novopharm's Glyburide Tablets USP, 1.25 mg (ANDA#74-388) both share the same inactive ingredients with similar formulation, except for dosage strength and tablet weight. Please also note that Novopharm's Glyburide Tablets USP, 1.25 mg (ANDA#74-388) is an approved product since 1995, and it has been proven to be safe and effective for consumer use.

RECEIVED
APR 0 6 1998
GENERIC DRUGS

MEMBER CDMA

Thanks
3.1

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

In addition, we have included in this amendment a copy of the return receipt for the notice provided to the sponsor and patent holder, Pharmacia & Upjohn, concerning Novopharm's Paragraph IV Certification filed on March 21, 1997 for U.S. Patent No. 4,916,163, and U.S. Patent No. 4,735,805. A copy of the return receipt for the notice provided to the sponsor and patent holder, Pharmacia & Upjohn, is included in Exhibit II for your review. In response to this notification, Pharmacia & Upjohn have initiated a civil suit against Novopharm Limited, and the matter is still pending.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application and that it has been submitted to the Office of Generic Drugs.

Should you have any further questions or comments, you may direct telephoned communications to us at 1-800-361-3313.

Yours sincerely,

Kenneth Michalko, PharmD, MBA
Director, U.S. Regulatory Affairs
NOVOPHARM LIMITED

APR 0 3 1998
(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Vice President Legal and Scientific Affairs
Novopharm NC Inc.
4700 Novopharm Blvd.
Wilson, N.C.
U.S.A. 27893
Via Federal Express

BIOEQUIVALENCY AMENDMENT

ANDA 74-686

MAY 1 1998

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Novopharm Limited PHONE: (919) 234-2231

ATTN: Therese Ast FAX: (919) 234-2600

FROM: Lizzie Sanchez PROJECT MANAGER (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 9, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Micronized Tablets, 1.5, 3, 4.5, and 6 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached _____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Prod 5/1/98

X:\new\ogdadmin\glossary\biofax.frm

MAY 1 1998

BIOEQUIVALENCE DEFICIENCY

ANDA: 74-686 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg & 6.0 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 in-vitro dissolution testing conducted by Novopharm on its Glyburide Micronized Tablets, 4.5 mg and 6 mg, has been found **unacceptable** for the reason that the dissolution method and specifications used were **incorrect**. The dissolution method and specifications as stated in the February 24, 1997 letter were incorrect. For the dissolution testing of **micronized** glyburide tablets (Glynase-type products, such as the test product), the following dissolution testing is recommended by the agency:

The dissolution testing should be conducted in 900 mL of pH 7.5, 0.05M phosphate buffer at 37°C using USP 23 apparatus II(paddle) at 50 rpm. The sampling times should be 15, 30, 45 and 60 minutes.

You should repeat the dissolution testing using the correct procedure **for all strengths** of the test and reference products.

Sincerely yours,

Dale P. Conner

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

FACSIMILE AMENDMENT

JUL 1 1998

ANDA 74-686

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Novopharm Ltd., Canada PHONE: (919) 234-2231

ATTN: Terry Ast FAX: (919) 234-2600

FROM: Denise Huie PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated June 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg.

Reference is also made to your amendment(s) dated March 2 and 3, 1998.

Attached is (1) page of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

PMOB 7/1/98

X:\new\ogdadmin\macros\faxfax.frm

JUL 1 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-686 APPLICANT: Novopharm Ltd., Canada

DRUG PRODUCT: Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

The deficiencies presented below represent facsimile deficiencies.

1. Dissolution testing for these drug products has not been established. Please reference and respond to the communication dated May 1, 1998 from the Division of Bioequivalence.

2. The corrected dissolution test should be included in your release and stability programs. Additionally, please demonstrate that your analytical method remains suitable with the new dissolution medium.

3. Please provide dissolution data using the new method at the next test station for the stability samples of all four strengths.

Sincerely yours,

Vilayat Sayed for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

NEW CORRESP
NC NAI
7/10

July 2, 1998

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville MD 20855-2773
U.S.A.

ACKNOWLEDEGMENT

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg

We thank you for your letter dated July 1, 1998 which we received on July 2, 1998 from Dr. Rashmikant M. Patel of the Division of Chemistry I. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313.

Yours sincerely,

for Kenneth J. Michalko, PharmD, MBA
Director, US Regulatory Affairs

cc: Dr. Thérèse Ast (Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893)

Via FedEx (Waybill #400 6603 9061)

RECEIVED
JUL 0 6 1998
GENERIC DRUGS

30 Years of Caring

MEMBER CDMA

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

NC

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
USA 20855-2773

AMENDMENT

Subject: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

This amendment to our abbreviated new drug application is to provide additional information concerning Novopharm's paragraph IV certification, filed on March 21, 1997 for U.S. Patent No. 4,916,163, and U.S. Patent No. 4,735,805.

Reference is also made to our telephone amendment dated April 3, 1998.

A Paragraph IV patent certification for U.S. Patent No. 4,916,163 was filed on March 21, 1997, and notice to the patent holder and sponsor, Pharmacia & Upjohn, was provided on April 11, 1997. A copy of the documentation of notice provided was submitted in our telephone amendment dated April 3, 1998. In response to the notification, Pharmacia & Upjohn has initiated a civil suit against Novopharm Limited on June 2, 1997 (Civil Action #97C/3992, Northern District of Illinois). The matter is still pending.

In addition, the paragraph IV patent certification for U.S. patent No. 4,735,805 was filed on March 21, 1997, and notice to the patent holder and sponsor, Pharmacia & Upjohn, was provided on April 11, 1997. A copy of the documentation of notice provided was submitted in our telephone amendment dated April 3, 1997. We note that the statuatory period of 45 days had expired at that Pharmacia & Upjohn has not instituted any civil suit against Novopharm Limited for U.S. Patent No. 4,735,805.

Enclosed are one (1) archival copy, one (1) review copy, and one (1) field copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

ANDA # 74-686
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

If there are any questions with respect to this submission, please do not hesitate to contact Novopharm directly by telephone at 1-800-361-3313 or by fax at 1-905-642-4590.

Yours sincerely,

JUN 3 0 1998

(date)

Jonathan Ng, B.Sc.
Manager, ANDA Approval
US Regulatory Affairs
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, US Agent, Esq., Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
USA 20855-2773

BIOEQUIVALENCE AMENDMENT

Subject: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

This amendment to our abbreviated new drug application is in response to your letter dated May 1, 1998 from Dr. Dale P. Conner of the Division of Bioequivalence, which we received on May 4, 1998.

We have revised our dissolution testing protocol to reflect FDAs' recommended method. We have also included in Exhibit I a copy of the dissolution profiles using the FDA dissolution method.

For the reviewers' convenience, the comment made by Dr. Conner has been restated in **bold** print and is followed by our response. Enclosed are one (1) archival copy, and one (1) review copy of this Amendment.

If there are any questions with respect to this submission, please do not hesitate to contact Novopharm directly by telephone at 1-800-361-3313 or by fax at 1-905-642-4590.

Yours sincerely,

JUN 3 0 1998
(date)

Jonathan Ng, B.Sc.
Manager, ANDA Approval
US Regulatory Affairs
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, US Agent, Esq., Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893

BIOEQUIVALENCY COMMENTS

AUG 6 1998

ANDA 74-686

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Novopharm Limited PHONE: (919) 234-2222

ATTN: Therese M. Ast FAX: (919) 234-2600

FROM: Lizzie Sanchez PROJECT MANAGER (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on June 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets (micronized), 1.5, 3, 4.5, and 6 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\glossary\biofax.frm

AUG 6 1998

BIOEQUIVALENCY COMMENTS

ANDA: 74-686 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Glyburide Micronized Tablets, 1.5 mg, 3 mg, 4.5 mg and 6 mg

As discussed with the firm's representatives in the telephone conference on July 30, 1998, at this time the Division of Bioequivalence has completed its review and has no further questions concerning the *in vivo* bioequivalence requirements, but it has the following recommendations concerning the *in vitro* testing requirements for the test product:

1. In order to adopt a sufficiently **discriminating and complete** *in vitro* dissolution method for a micronized glyburide tablet drug product that has been shown to be bioequivalent to the RLD product, such as the above test product, the Division of Bioequivalence has now requested that all strengths of the test and reference listed drug product be tested for *in vitro* dissolution by you **further in several different pHs (pH 7.5, 8 and 8.5)**, with all other parameters of the dissolution procedure remaining the same. An acceptable (i.e., discriminating and complete) release specification will be established for the test product based on these data. The division understands that presently you do not have any fresh lot of any strength of the test product available in house, and will be manufacturing the first production batches in September of 1998. As the only condition for approval of the test product, you are asked to commit, in writing, to carry out this additional dissolution testing at the above-specified pHs and to provide such data in an application supplement within approximately 30 days of the manufacturing of the first production lot of each strength of the test product. The supplement may be requested by you for an expedite review.

2. Until new dissolution procedure and specifications are established for the test product following the review of the above-mentioned supplement, the **interim** specification and the **interim** dissolution method for your test product will be respectively as follows:

> Tolerance Specification: NLT —% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes

Dissolution method: 900 mL of pH 7.5 0.05 M phosphate buffer as the dissolution medium, and with the USP paddle apparatus at 50 rpm.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

August 11, 1998

NAT
8/13/98

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville MD 20855-2773
U.S.A.

ACKNOWLEDGEMENT

NEW CORRESP

SUBJECT: **ANDA # 74-686**
Glyburide Tablets (micronized) 1.5, 3, 4, 5 and 6 mg

We thank you for your letter dated August 6, 1998 which we received on August 7, 1998 from Dale Conner of the Division of Bioequivalence. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313.

Yours sincerely,

Jonathan Ng, B.Sc.
Manager, US Regulatory Affairs

cc: Dietrich Bartel (Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, NC 27893)

Via FedEx (Waybill #400 9009 1595)

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BIOAVAILABILITY
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Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

AUG 27 1998

NDA ORIG AMENDMENT
AM

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
USA 20855-2773

MINOR AMENDMENT
(CMC & BIO AMENDMENT)

Subject: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

This amendment to our abbreviated new drug application is in response to the letter dated July 1, 1998 from Dr. Rashmikant M. Patel of the Division of Chemistry I, which we received on July 2, 1998 and the letter dated August 6, 1998 from Dr. Dale Conner of the Division of Bioequivalence, which we received on August 7, 1998.

For the reviewers' convenience, each comment made by Dr. Patel has been restated in **bold** print and is followed by our response. We have revised our dissolution testing protocol to reflect FDAs' recommended method as stated in the letter dated May 1, 1998 and the recommended dissolution specification of "NLT —% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes" as referenced in the letter dated August 6, 1998.

As recommended by Dr. Dale Conner in the letter dated August 6, 1998, we commit to provide additional dissolution testing for all strengths of the test and reference listed drug product, tested at several different pHs (pH 7.5, 8 and 8.5), using the FDA recommended methodology with all parameters (except for pH) remaining the same. These data will be submitted within approximately 30 days of the manufacturing of the first production lot of each strength of the drug product. Enclosed are one (1) archival copy, one (1) review copy and one (1) field copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

RECEIVED
AUG 28 1998
GENERIC DRUGS

ANDA # 74-686
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

In addition, pursuant to 21 CFR § 314.50 (a) (5), we hereby inform you that effective August 3, 1998, Novopharm Limited has changed its U.S. Agent. Please find below our new authorized responsible official's name, address, and contact numbers.

Dietrich Bartel, B.Sc.
Director, Regulatory Affairs
Novopharm NC Inc.
4700 Novopharm Blvd.
Wilson, NC, 27893, USA
Tel: (919) 234-2222
(919) 234-2212
Fax: (919) 234-2600

You may direct written communications directly to Dietrich Bartel, or you may contact Novopharm Limited directly at 1-800-361-3313 or by fax at 905-642-4591. Enclosed is a letter of authorization allowing Dietrich Bartel to act ac our authrized U.S. responsible official.

Yours sincerely,

Jonathan Ng, B.Sc.
Manager, ANDA Approvals
U.S. Regulatory Affairs
NOVOPHARM LIMITED

AUG 2 7 1998
(date)

cc: Dietrich Bartel B.Sc.,
Director of U.S. Regulatory Affairs,
Novopharm NC Inc.,
4700 Novopharm Blvd.,
Wilson, NC 27893

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

NDA ORIG AMENDMENT

N/Amn

RE: **ANDA # 74-686**
Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg

We are filing this Telephone Amendment in response to the October 15, 1998 telephone call from Mr. Michael Smela with respect to our ANDA for Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg concerning ——— and ———.

We are including one (1) archival, one (1) review and one (1) field copy of this amendment in accordance with 21 CFR §314.94. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this amendment.

RECEIVED
OCT 29 1998
GENERIC DRUGS

.../2

If there are any questions or comments with respect to this application, please direct all inquiries to the office of Jonathan Ng, Manager ANDA Approvals, by telephone at 1-800-361-3313 or 905-642-4550, ext. 7030, or by fax at 905-642-4590.

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,

OCT 27 1998

Jonathan Ng, B.Sc.
Manager, ANDA Approvals
U.S. Regulatory Affairs
NOVOPHARM LIMITED

(date)

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA Correspondence

RE: **ANDA # 74-686**
Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg

We are filing this ANDA Correspondence in response to the November 6, 1998 telephone call from Mr. Rickman requesting a copy of the Civil Action Suit for Glyburide Tablets (Micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg. Please find enclosed a copy of the Civil Action Suit no. 97C 3992.

If there are any questions or comments with respect to this correspondence, please direct all inquiries to the office of Jonathan Ng, Manager ANDA Approvals, by telephone at 1-800-361-3313 or 905-642-4550, ext. 7030, or by fax at 905-642-4590.

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,

NOV 0 9 1998
(date)

Jonathan Ng, B.Sc.
Manager, ANDA Approvals
U.S. Regulatory Affairs
NOVOPHARM LIMITED

MEMBER

This should be NC not minor amend and assigned to both chem + bio
M Smith 1/10/99

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Office of Generic Drugs, CDER
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Rockville, MD
USA 20855-2773

AMENDMENT
N/AA

Subject: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

We are filing this amendment to provide additional Dissolution Profile data in different pH medium as requested in the letter dated November 10, 1998 from the Division of Bioequivalence. In addition, we are also amending the application to include an alternate analytical laboratory site, [redacted]

Enclosed are one (1) archival copy, (1) review copy and one (1) field copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

If there are any questions or comments with respect to this application, please direct all inquiries to the office of Jonathan Ng, Manager ANDA Approvals, by telephone at 1-800-361-3313 or 905-642-4550, ext. 7030, or by fax at 905-642-4590.

For written comments to be sent exclusively by mail or courier, please direct correspondence to Dietrich Bartel, Director, Regulatory Affairs, Novopharm NC Inc., 4700 Novopharm Blvd., Wilson, N.C., 27839.

Yours sincerely,

Jonathan Ng, B.Sc.
Manager, ANDA Approvals
US Regulatory Affairs
NOVOPHARM LIMITED

JAN 13 1999
(date)

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JAN 19 1999
GENERIC DRUGS

MEMBER CDMA

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NDA ORIG AMENDMENT

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
USA 20855-2773

MINOR AMENDMENT

Subject: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

Pursuant to your letter of November 10, 1998 (tentative approval of Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg), we are advising you that circumstances have arisen that will affect the effective date of final approval of our application.

We are submitting in Exhibit I a copy of the court judgement, rendered on February 2, 1998, from the District Court of the Northern District of Illinois, involving Civil Action No. 97C 3992, in which no appeal was taken by Pharmacia & Upjohn within the required 30-day time period.

References is also made to our amendment, dated January 13, 1999, concerning the submission of additional dissolution profiles as requested by the Agency and addition of another laboratory testing site. We request that the January 13, 1999 Amendment be reviewed in conjunction with this minor Amendment.

In addition, we propose to

[redacted]

sizes, previously submitted in our tentatively approved application. Copies of the revised manufacturing documents are included in Exhibit II for you review.

Furthermore, in accordance with the "Guidance for Industry - Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 (Revised July 1998), the "Rx Only" statement will replace the "Caution: Federal law prohibits dispensing without prescription" statement. Please note that no other changes will be made in our labeling and will be submitted in the next annual report, since our original ANDA was received by the Agency prior to February 19, 1998.

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MEMBER CDMA

ANDA # 74-686
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

We note that apart from the above information there are no other changes made to the application since the date of tentative approval.

Enclosed are one (1) archival copy, one (1) review copy, and one (1) field copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

If there are any questions with respect to this submission, please do not hesitate to contact Novopharm directly by telephone at 1-800-361-3313 or by fax at 1-905-642-4590.

Yours sincerely,

MAR 15 1999

(date)

Jonathan Ng, B.Sc.
Manager, ANDA Approvals
US Regulatory Affairs
NOVOPHARM LIMITED

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TELEPHONE AMENDMENT

NDA ORIG AMENDMENT
N/A M

RE: **ANDA # 74-686**
Glyburide Tablets (micronized) USP, 1.5 mg, 3 mg, 4.5 mg and 6 mg

We are filing this **Telephone Amendment** in response to the March 24, 1999 call from Mr. Michael Smela and Mr. Mujahid Shaikh, FDA. In this call, Mr. Smela and Mr. Shaikh requested that we file updated finished product and shelf-life stability specifications to reflect the dissolution testing method as recommended by the Division of Bioequivalence. A copy of the dissolution testing method and its validation report are included in this Amendment.

Enclosed are one (1) archival, one (1) review, and (1) field copy of this Telephone Amendment. We certify that the field copy is a true copy of the technical sections contained in the archival and review copies of this Amendment and that the field copy has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this Amendment to be evaluated. If there are any questions or comments with respect to this application, please direct all inquiries to the office of Jonathan Ng, Manager ANDA Approvals, by telephone at 1-800-361-3313 or 905-642-4550, ext. 7030, or by fax at 905-642-4590.

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,

Jonathan Ng, B.Sc.
Manager, ANDA Approvals
U.S. Regulatory Affairs
NOVOPHARM LIMITED

MAR 2 4 1999
(date)

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MAR 2 6 1999

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