CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-496/S005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-496/S-005

Aventis Pharmaceuticals, Inc
Attention: Ms. Cora Collins, US Drug Regulatory Affairs
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

SEP 27 2000

Dear Ms. Collins:

Please refer to your supplemental new drug application dated August 25, 1998, received August 26, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl® (glimepiride) Tablets, 1 mg, 2 mg, and 4 mg.

We acknowledge receipt of your submissions dated April 8 and November 11 and 24, 1999. Your submission of November 11, 1999, constituted a complete response to our June 4, 1999, action letter.

This supplemental new drug application provides for the addition of a "Geriatric Use" subsection to the **PRECAUTIONS** section of the package insert for Amaryl in patients with type 2 diabetes mellitus.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 11, 1999).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-496/S-005." Approval of this submission by FDA is not required before the labeling is used.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

/S/

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-496/S005

APPROVABLE LETTER

Dur file

NDA 20-496/S-005

JUN 4 1999

Hoechst Marion Roussel
Attention: Ms. Cora Collins, US Drug Regulatory Affairs
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Ms. Collins:

Please refer to your supplemental new drug application dated August 25, 1998, received August 26, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl® (glimepiride) Tablets.

We acknowledge receipt of your submission dated February 11, 1999.

This supplement proposes the following change: a "Geriatric Use" subsection in the PRECAUTIONS section of the package insert as per 21 CFR 201.57(f)(10).

We have completed the review of this application, as submitted with final printed labeling (package insert submitted August 1998), and it is approvable. Before this application may be approved, however, it will be necessary for you to provide additional information on your Geriatric population using this chart below.

Patient Age	Number	♂	♀	HbA1C Baseline ± SD (initial)	HbA1C (at end)	Hypoglycemic Events	Severe	Other
65 – 69								
70 –75								
75+								

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, please contact Ms. Jena Weber, Project Manager, at (301) 827-6422.

Sincerely yours,

/S/ 6/4/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-496/S005

FINAL PRINTED LABELING

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

APPEARS THIS WAY
ON ORIGINAL

12 PAGE(S) REDACTED

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-496/S005

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

Date: 11/30/99

From: Saul Malozowski
Medical Team Leader

Subject: Amaryl-Geriatric Labeling, NDA 20-496 SE8-005-BL. Team leader recommendations

To: Sōlomon Sobel
Division Director, DMEDP

The sponsor has sent information regarding the use of this SU in geriatric patients. The data was obtained from non-US and US studies supporting clinical trials as well as from spontaneous adverse reaction reports. Data from clinical studies suggests that the safety profile for this age group does not differ from that seen in younger patients. Spontaneous adverse reaction reports are difficult to analyze because we lack a denominator, but this data does not raise concerns of undue ill effects. The language in the current proposal is fair and alerts to the complications that may occur with the use of this drug. These warnings are quite encompassing because the sponsor expands in more detail than the data provided suggests. In this sense, I think that both health professionals and patients are well served with the current proposed wording.

Conclusion:
I recommend approval of this labeling supplement as proposed by the sponsor.

12-1-99

APPEARS THIS WAY
ON ORIGINAL

Submitted NOV. 24. 1999

Geriatric Use

In US clinical studies of AMARYL, 608 — of 1986 — patients were 65 and over (Hypoglycemia Table). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, [redacted] but greater sensitivity of some older individuals cannot be ruled out (Hypoglycemia Tables 1 and 2, Tabs 1 through 14, and 21 CFR 201.57(f)(10)(ii)(B)).

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

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (21 CFR 201.57(f)(10)(ii)(B)).

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

ORIGINAL

Memorandum

151

Date: 1/17/99

From: Saul Malozowski
Acting Medical Team Leader

Subject: Amaryl, Geriatric Labeling (NDA 20-496-Slr-005)

To: Solomon Sobel
Division Director, DMEDP

In reviewing the information submitted by the sponsor regarding the labeling of this product for geriatric populations it appears that the sponsor has followed in excess of 400 subjects using this medication. Data collected from this group could be invaluable to better label this section. The sponsor states in the label in general terms that the efficacy and safety of Amaryl appears to be the same as that observed in the pivotal studies. Because the data is available, I believe that this claim should be better substantiated with the available data and its analysis.

ddition, an implicit warning regarding the unknown safety profile for this age group should also listed unless the data shows otherwise.

Cc: Drs. Misbin/Koller

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-496/S005

ADMINISTRATIVE DOCUMENTS

Hoechst Marion Roussel

May 30, 1997

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Centeral Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject: NDA 20-496: Amendment of Patent Information

Dear Sir:

The undersigned submits the following amendment to the patent information previously submitted for Amaryl™ in NDA 20-496.

PATENT NUMBER: United States Patent No. 4,379,785

NEW EXPIRATION DATE: April 6, 2005

PATENT OWNER: Hoechst Aktiengesellschaft
65926 Frankfurt am Main
Federal Republic of Germany

TYPE OF PATENT: Drug substance, Drug Product Composition and Method of Use.

The undersigned declares that United States Patent No. 4,379,785 covers glimepiride, the drug substance contained in the drug product Amaryl™ which is the subject of NDA 20-496. Amaryl™ is currently approved under Section 505(b)(1) of the Federal Food, Drug and Cosmetics Act.

Two copies of this declaration are submitted. Please list the above patent in the Orange Book Publication.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 20-496 SUPPL # 025

Trade Name Amaryl Generic Name Glimepiride

Applicant Name HMR Aventis Pharm. HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE8

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

YES /✓/ NO /___/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

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

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /✓/ NO /___/

If yes, NDA # 20-496. Drug Name Ambyl.

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

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

YES /___/ NO /✓/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

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

NDA# 20-496 Amaryl

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /✓/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

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

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

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

YES /✓/ NO /__/

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

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

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

YES /✓/ NO /__/

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

_____

_____

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

YES /__/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

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

YES /___/ NO /✓/

If yes, explain: _____

_____

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

_____

_____

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

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

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

IN ORIGINAL NDA

Investigation #1 YES /✓/ NO /__/

Investigation #2 YES /✓/ NO /__/

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

_____ _____

_____ _____

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

IN ORIGINAL NDA

Investigation #1 YES /✓/ NO /__/

Investigation #2 YES /✓/ NO /__/

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

This NDA, 20-496

_____ _____

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

No new clin. investigations

_____ _____

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

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor? None.

APPEARS THIS WAY ON ORIGINAL

Investigation #1	NOT APPLICABLE
IND # _____, YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

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

Investigation #1	
YES /___/ Explain _____	NO /___, Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /_ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /__

If yes, explain: _____

_____

/S/

Signature
Title: RHPM

4/27/99

Date

/S/

Signature of Office/
Division Director

6/3/99

Date

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

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-496 Supplement # 005 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE8

HFD 510 Trade and generic names/dosage form: Amaryl 5 Glimepiride Action: AP AE NA AP 9/27/00

Applicant HMR Therapeutic Class ORAL hypoglycemic

Indication(s) previously approved SN 11/30/95 ADJUNCT TO DIET & EXERCISE TO ↓ — IN patients with TYPE 2 DIABETES.

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate N/A

Proposed indication in this application GERIATRIC USE SUBSECTION added TO PRECAUTIONS SECTION

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecants(12-16yrs)

___1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

✓ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from MEDICAL REVIEW (e.g., medical review, medical officer, team leader)

RHAM 4/6/99

Signature of Preparer and Title Date

Orig NDA/BLA # 20-496/S-005

HFD 510 Div File

Hoechst Marion Roussel

April 8, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
Debarment Certification for Supplement 005

Dear Dr. Sobel:

Reference is made to our Amaryl supplement 005 containing the Geriatric Use subsection submitted on August 25, 1998. Enclosed is the debarment certification for supplement 005.

Please contact me at 816-966-5381 (FAX. 816-966-6794) if you have any questions regarding this debarment certification.

Sincerely,

Carol Childers

Carol Childers, PharmD
Associate Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.

APPEARS THIS WAY
ON ORIGINAL

Enclosure

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with Supplement 005 for Amaryl® (glimepiride tablets).

J. Michael Nicholas, PhD
Director, Marketed Products
US Regulatory Affairs

9/8/98
Date

APPEARS THIS WAY
ON ORIGINAL

APR - 6 1999

NDA 20-496/S-005
Amaryl (glimepiride) Tablets
HMR

Date of original submission: August 25, 1998, one amendment dated February 11, 1999

Supplement provides for a Geriatric Use subsection in the PRECAUTIONS section of the package insert as per 21 CFR 210.57(f)(10).

1. NO DSI audit was needed or requested.

2. No safety update was required as all of the studies referenced in this submission were part of the original NDA, and were previously reviewed.

3. No integrated summaries of safety and efficacy were part of the medical officer's review, as none were required.

4. No statistical, chemistry, biopharmacology or pharmacology reviews are included in this action package, as they were not required.

5. For this submission, the group leader's review is the same as the medical officer's.

/S/ 4/6/99
Saul Malozowski, M.D.

/S/ 4/6/99
Jena Weber, RHPM

APPEARS THIS WAY
ON ORIGINAL

NDA 20-496/S-005
Amaryl (glimepiride) Tablets
HMR

NO EER WAS NEEDED FOR THIS SUBMISSION.

NDA 20-496/S-005
Amaryl (glimepiride) Tablets
HMR

FONSI REVIEW/ACTION WAS NOT NEEDED FOR THIS SUBMISSION.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-496/S-005

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, Missouri 64134-0627

SEP 4 1998

Attention: Cora Collins
US Drug Regulatory Affairs, Marketed Products

Dear Ms. Collins:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Amaryl® (glimepiride tablets)
NDA Number:	20-496
Supplement Number:	S-005
Date of Supplement:	August 25, 1998
Date of Receipt:	August 26, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 25, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-496/S005

CORRESPONDENCE

TELEFAX

TO: Carol Childers

"Revised" chant for Geriatric Population

FAX: 816-966-6794

PHONE:

FROM: Jean Weber

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

Please provide additional information on your Geriatric population using this chart below.

Patient Age	Number	♂	♀	HbA1C Baseline ± SD (initial)	HbA1C (at end)	Hypoglycemic Events	Severe	Other
65 – 69								
70 –75								
75+								

Please include (info) in the above chart for AE.

APPEARS THIS WAY
ON ORIGINAL

REVISED 3/1/93

ORIGINAL

NDA SUPP AMEND
SE8-005 BL

Hoechst Marion Roussel

vember 24, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
Amendment (Number 2) for Prior Approval
Geriatric Labeling Supplement (S-005)

Dear Dr. Sobel:

Reference is made to our supplemental new drug application dated August 25, 1998, to the approvable letter dated June 4, 1999, and the first amendment sent to the FDA on November 11, 1999.

The November 11, 1999 amendment, the annotated draft labeling tab contained draft labeling that was not annotated. The enclosed annotated draft November 1999 prescribing information should replace what was submitted behind the annotated draft labeling tab in the November 11, 1999 amendment.

Please contact me at 816-966-5381 (FAX: 816-966-6794) if you have any questions regarding this submission.

Sincerely,

Carol J. Childers

Carol Childers, PharmD
Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.

cc: Jena Weber, Project Manager
Enclosure

REVIEWS COMPLETED

OSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

OSE INITIALS DATE

Kim Davis
973-394-6493
To replace C. Childers

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

Hoechst Marion Roussel

...LICATE

June 15, 1999 NDA SUPP AMEND

Hoechst Marion Roussel, Inc.

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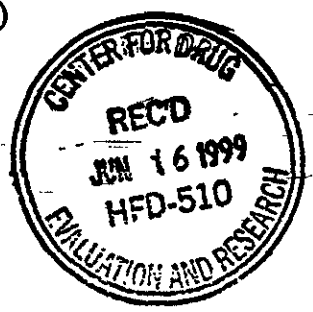
Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857



Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
Intent to File An Amendment for Supplement 005

Dear Dr. Sobel:

Reference is made to our supplemental new drug application dated August 25, 1998 and to your response dated June 4, 1999 which I received on June 15, 1999.

This correspondence is to notify you of our intent to file an amendment under 21 CFR 314.110.

This letter is being faxed and a hard copy is being sent via UPS today, June 15, 1999.

Please contact me at 816-966-5381 (FAX: 816-966-6794) if you have any questions regarding this correspondence.

Sincerely,

Carol J. Childers

Carol Childers, PharmD
Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.

APPEARS THIS WAY
ON ORIGINAL

cc: Jena Weber, Project Manager

Hoechst Marion Roussel

April 8, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
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Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
Debarment Certification for Supplement 005

Dear Dr. Sobel:

Reference is made to our Amaryl supplement 005 containing the Geriatric Use subsection submitted on August 25, 1998. Enclosed is the debarment certification for supplement 005.

Please contact me at 816-966-5381 (FAX 816-966-6794) if you have any questions regarding this debarment certification.

Sincerely,

Carol Childers

Carol Childers, PharmD
Associate Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Hoechst Marion Roussel

February 11, 1999

ORIGINAL

NDA SUPP AMEND
SUR-005 AE

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
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Telephone (816) 966-5000
U.S. Web site: www.hmri.com

Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

FEB 12 1999

Subject: ~~Amaryl® (glimepiride Tablets)~~
NDA 20-496
FINAL PRINTED LABELING
FOR GERIATRIC LABELING SUPPLEMENT (S-005)

Dear Dr. Sobel:

eference is made to our Changes Being Effected Geriatric Labeling Supplement sent to the Division of Metabolic and Endocrine Drug Products on August 25, 1998 and the Agency's Acknowledgement letter dated September 4th, 1998. Enclosed are 16 copies of the FPL for Amaryl®, edition date August 1998, which are identical to the draft labeling submitted on August 25th, 1998. Ten of these 16 copies are individually mounted on heavy-weight paper.

Please contact me at 816-966-5381 (FAX: 816-966-6794) if you have any questions regarding this submission.

Sincerely,

Carol J. Childers

Carol Childers, PharmD
Asscciate Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.

Enclosures

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Hoechst

[redacted]

Hoechst Marion Roussel

NDA NO. 20496 REF. NO. 005

NDA SUPPLEMENT

NDA SUPPL FOR SLR

August 25, 1998

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 26 1998
HFD-510

Solomon Sobel, MD
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research (HFD-510)
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-496
AMARYL®
(glimepiride tablets)

GERIATRIC LABELING SUPPLEMENT
CHANGES BEING EFFECTED

Dear Dr. Sobel:

Enclosed is draft prescribing information for Amaryl Tablets which has been revised to include a "Geriatric Use" subsection in the PRECAUTIONS section per 21 CFR §201.57(f)(10) as follows:

9/28/98

For your reference, the following are enclosed:

Revised prescribing information with changes highlighted.
Annotated prescribing information.
Current prescribing information, edition date 11/96.

9/25/98

Hoechst

August 25, 1998
NDA 20-496
Amaryl
Geriatric Labeling Supplement (continued)
Page 2

If you have any questions or need additional information, please contact me at 816/966-4349 (Fax 816/966-6794.).

Sincerely,

Cora Collins

Cora Collins
US Drug Regulatory Affairs, Marketed Products

ljg
Enclosure

Name ref doc
part of orig NDA
✓ new/orig. lbl
moving of data/info
Age sub group anal at
NDA time —
OK > appvl
Reanalysis NO

November 11, 1999

ORIGINAL

NDA SUPP AMEND
SE8-005 BL

Hoechst Marion Roussel

Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
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US Web site: www.hmri.com

Yearly sales Vol. from Europe (France)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 12 1999
HFD-510

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
Amendment for Prior Approval
Geriatric Labeling Supplement (S-005)

Dear Dr. Sobel:

Reference is made to our supplemental new drug application dated August 25, 1998 and to the approvable letter dated June 4, 1999. Hoechst Marion Roussel, Inc. is providing additional information on the geriatric population as requested in the approvable letter. A revised Geriatric Use subsection within PRECAUTIONS is included in the draft November 1999 Amaryl PI and is in accordance with 21 CFR 201.57(f)(10)(ii)(B). This amendment responds to all deficiencies listed in the June 4, 1999 letter.

For the Geriatric Use subsection in the draft November 1999 Amaryl PI within this submission, the numerator and denominator patient numbers are different than the numbers submitted in the August 25, 1998 Geriatric Use supplement. This is due to interim analysis being used for US Protocol 301, since this protocol had not been completed at the time of the original NDA submission. For the data listings in this submission under Tabs 7 and 8, the final analysis for US Protocol 301 was available in the US Clinical Database. These differences between the November 1999 PI and what was submitted on August 24, 1998 are noted for deletions as red strikeouts and additions as blue double-underlines.

The following information is listed in the Table of Contents and provides support for these changes:

1. Draft labeling (November 1999 edition)
2. Annotated draft labeling (all changes are highlighted)
3. Tables 1 – 4 provide additional geriatric information as requested in the June 4, 1999 approvable letter.
4. Geriatric Use Regulation
5. Diaβeta approvable letter
6. Tabs 1 – 22 contain listings that support Tables 1- 4

Please contact me at 816-966-5381 (FAX: 816-966-6794) if you have any questions regarding this submission.

Sincerely,

Carol J. Childers

Carol Childers, PharmD
Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.

PREVIEWS COMPLETED
ACTION:
LETTER N.A.I. MEMO
DATE
CDD INITIALS

cc: Jena Weber, Project Manager
Enclosures

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst