CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020496/S002

Trade Name: AMARYL

Generic Name: GLIMEPIRIDE TABLETS

Sponsor: HOESCHT MARION ROUSSEL, INC

Approval Date: 02/24/99

Indication(s): ADJUNCT TO DIET IN NIDDM PATIENTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:

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	Included	Pending Completion	Not Prepared	Not Required
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020496/S002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-496/S-002

FEB 24 1999

Hoechst Marion Roussel, Inc.
Attention: J. Michael Nicholas, Ph.D.
Director, U.S. Regulatory Affairs
10236 Marion Park Drive
Kansas City, MO 64134-0627

Dear Dr. Nicholas:

Please refer to your supplemental new drug application dated November 3, 1997, received February 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride tablets) 1, 2 and 4 mg.

We acknowledge receipt of your submission dated August 25, 1998, received August 27, 1998, submitted in response to our August 10, 1998, approvable letter. We also acknowledge receipt of your November 12, 1998, submission.

This supplemental new drug application provides for the use of Amaryl tablets concomitantly with metformin when diet, exercise, and Amaryl or metformin alone do not result in adequate glycemic control.

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 dated August 1997, submitted on November 3, 1997. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 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. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-496/S-002." 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-40
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 contact Ms. Jena Weber, Project Manager, at (301) 827-6422.

Sincerely,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020496/S002

MEDICAL REVIEW(S)

NDA 20496
Sponsor: Hoechst Marion Roussl
Drug: Glimepiride tablets

Received:3/3/98
Reviewed: 7/28/98
Doct: N20496S

MEDICAL OFFICER'S REVIEW OF LABELING AMENDMENT TO NDA

NATURE OF THE AMENDMENT

The Company is proposing to add the following sentences to its present labeling:

1. [redacted]

2. [redacted]

3. [redacted]

GENERAL INFORMATION

Name of Drug

Generic: Glimepiride
Trade: Amaryl
Chemical: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-beta-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexy)urea.

Proposed amendment

The manufacturer would like to recommend the combined use of glimepiride with metformin in precisely defined circumstances; essentially, failing monotherapy.

Pharmacologic Category

Glimepiride is an oral blood-glucose-lowering drug of the sulfonylurea class. Metformin is a biguanide. As is well known, a number of sulfonylureas have been introduced in the marketplace during the last two decades or so. In fact, for endless years, only hypoglycemic sulfonylureas were available for sale in the United States until the FDA finally approved Metformin, an hypoglycemic agent with an entirely different mechanism of action than sulfonylureas, and the product was just launched in the marketplace.

Over the years, different sulfonylureas have been introduced to improve on one or another feature of older drugs, particularly the tendency of some of them to sometimes produce rather severe hypoglycemic episodes. Regardless of such improvements, the sulfonylureas have a common failing: primary or secondary inefficacy.

Historical information

The amendment proposes the combined use of Amaryl (glimepiride) with Metformin. As a class, sulfonylureas increase endogenous insulin secretion resulting in an hypoglycemic effect but also in hyperinsulinemia and weight gain -- unwelcome side-effect due to the fact that increased insulin secretion down-regulates insulin receptor sensitivity. On the other hand, metformin acts through an entirely different set of mechanisms to also, ultimately, correct hyperglycemia. It decreases hepatic glucose production, increases peripheral insulin sensitivity, possesses a mild corrective effect on certain circulating lipids and, finally, often reduces weight and, at the very least, doesn't promote weight gain as sulfonylureas do.

Keeping all this in mind, this Reviewer was instrumental in convincing (some long years ago) Lipha, the developper of metformin, to perform a controlled clinical trial with three arms: (1) metformin alone; (2) glyburide alone; and, (3) metformin with glyburide.

The hypothesis was that there would be synergism between the two drugs whilst the frequency of hypoglycemic episodes (mild or severe), produced by sulfonylureas, would be reduced, but the glycemic control would further improve.

That synergism could be expected was predicated on the well known observation that any mechanism through which glycemia is improved would result in an increase in peripheral insulin sensitivity. Also, in broad pharmacological terms, when two drugs achieve the same end-effect albeit through different and independent routes, synergism can be expected.

In any event, the results confirmed the initial hypothesis, in that they showed conclusively that there indeed was synergism between the two drugs as far as glycemic control was concerned, i.e., the combined effect was greater than the sum of individual effects.

After the approval and marketing of metformin, Industry was fast to try to capitalize on this observation. Requests began coming in from sulfonylurea manufacturers. This Reviewer has consistently stated that all sulfonylurea manufacturers should be permitted to recommend combinatorial use, since this would greatly improve the control of hyperglycemia in diabetes. Since many of the complications of diabetes are linked to sustained and long-term hyperglycemia, its correction would result in a significant improvement in public health.

The technical difficulty, from a regulatory viewpoint, seemed to be that the metformin-glyburide study by Lipha was confidential and proprietary since it had been submitted to its NDA but wasn't published. In September of 1995, this Reviewer send a report listing all the published studies proving that the sulfonylurea-biguanide combination had synergistic effects. I have since maintained, and am glad to have received the concurrence of my Division, that provision for combination therapy can be added to the drug product labels of sulfonylureas without formal evaluation of individual studies specifically designed to show efficacy and safety of each combination. The promotional strength of Industry can now be put to good and honest use in order to significantly improve the lot of diabetics, particularly since drugs that were tested to see if they directly improved the diabetic complications have failed so far.

REVIEW OF THE AMENDMENT

Hermann LS et al. [Diabetes Care17:1100-9 (1994)] have shown that under sulfonylurea monotherapy some 36% of the treated subjects will show insufficient and worsening glycemic control within a relatively short period of time, i.e., they would elicit what is called a secondary

therapeutic failure. Some diabetics may even be practically insensitive to sulfonylureas from day one, thus showing so-called primary failure.

It is now proven that the adjunction of metformin will result in near normal glycemic control, even in cases of advanced type 2 diabetes (NIDDM). Indeed, the following recent reports present and discuss clinical trials (comprising, each, from 12 to 1853 subjects treated for an average of about 12 weeks of treatment), supporting the significant benefits of the sulfonylurea-metformin combination therapy. These trials used mostly glyburide though some used, albeit rarely, other sulfonylureas; e.g., glibenclamide.

1. D'Argenzio R et al., Minerva Endocrinol 21: 101-10 (1996).
2. Raptis AE et al., Horm Metab Res 28: 89-94 (1996).
3. Jeppesen J et al., Diabetes Care 17: 1093-9 (1994)
4. Aguilar CA et al., Rev Invest Clin 44: 71-6 (1992)
5. Trischitta V et al., Diabetes Care 15: 539-42 (1992)
6. Reaven GM et al., JCEM 74: 1020-6 (1992)
7. Laurenti O et al., Clin Ter 140: 259-63 (1992)
8. Haupt V et al., Diabete Metab 17(pt2): 224-31 (1991)
9. Groop L et al., Diabete Metab 17(pt2): 218-23 (1991)
10. Viguerie R et al., Diabete Metab 17(pt2): 232-4 (1991)
11. Klein W, Diabete Metab 17(pt2): 235-401)
12. Jennings AM et al., Diabetes Care 12: 203-8 (1989)

As I see it, the following are the additional benefits when metformin is added to a sulfonylurea, either initially or during secondary failure of sulfonylurea treatment:

1. As stated earlier, metformin improves glycemia using a different pharmacological pathway than sulfonylureas. By improving glycemia, sensitivity to sulfonylurea may be restored.

2. As the UKPDS report has shown [BMJ 310: 83-8 (1995)], bodily weight increases significantly during sulfonylurea therapy while it tends to either remain constant or slightly decrease during metformin therapy. Such an effect also results in an improved sensitivity of insulin. Indeed, as shown by Groop L & Widen E (cited above, ref. 9) and by Klein W (also cited above, ref. 11), the adjunction of metformin to a sulfonylurea does improve insulin sensitivity. By and large, many authors now prefer to use this particular combination instead of adding insulin

to sulfonylureas when glycemic control is not quite effective with sulfonylureas alone.

3. Sulfonylurea monotherapy (as well as combined sulfonylurea plus insulin therapy) result in hyperinsulinemic and hypoinsulinemic untoward events. In fact, hypoinsulimic episodes (mild or severe) are the most common side effect of sulfonylurea. The adjunction of metformin to a sulfonylurea allows better glycemic control with reduced sulfonylurea dosage and reduced frequency of hypoinsulinemic episodes.

4. As shown by Haupt V et al (cited above, ref. 8) and others, the addition of metformin to sulfonylurea also slightly improves the lipemic picture. In the diabetic population, where macrovascular disease is a common and significant occurrence, even a slight eulipemic effect is welcome.

For all the above reasons, it is highly desirable to encourage, whenever appropriate, the combination use of sulfonylureas and metformin, provided that the dosing is carefully titrated in each patient in order to obtain the maximal effect with the minimal dose of each drug. Titration should be followed by FPG measurements (to assert short term effects on glycemia) and by an HbA1c measurement every 6 mos. (to appreciate long-term effects on glycemia). The object of treatment should be to maintain glycemia in the upper normal or lower abnormal range, in order to improve the course of the disease, without subjecting the patient to the probaility of all too frequent hypoglycemic episodes or to drug overexposure.

One last word should address the lactic acidosis situation, exceptionally seen in patients treated with metformin. It is now becoming clear that if all the contraindications to metformin therapy are rigorously respected, lactic acidosis is highly infrequent and does not result in the death of the patient. In any event, a phase IV study is now further assessing the overall morbidity and mortality resulting from any adverse effect that metformin may possess.

RECOMMENDED REGULATORY ACTION

The amendment proposed by the Company is recommended for approval, as per the rationale provided above, particularly since it agrees (at least in implied form) with

the following set of practical guildelines recommended by this Reviewer long-time ago.

1. HbA1c measurements should be used, as appropriate, to insure that the patient is not subjected to drug overexposure.

2. Retitration may be mandatory when, in the course of therapy, glycemic control begins to deteriorate, indicating the possibility of a secondary failure to sulfonylurea therapy.

The company should be advised that the label should refer physicians to the metformin labeling and state that all contradictions to metformin therapy should be rigorously adhered to. Such an admonition should be in **bold type** in order to be immediately visible and legible.

APPEARS THIS WAY
ON ORIGINAL

/S/

John L. Gueriguian
Medical Officer
7/28/98

cc.
The File
Dr. Troendle
Dr. Fleming
Dr. Gueriguian

/S/ 7/28/98

APPEARS THIS WAY
ON ORIGINAL

FEB 23 1999

Division Director's Memo: **February 22, 1999**

I discussed the last paragraph (Given the short duration of the studies and the data in the UKPDS study suggesting that combination therapy may be deleterious in the long term, we should be cautious and state that **"the long term efficacy and safety of this combination remains unknown,"** in the label.), with Dr. Malozowski and he agreed that at this time we should not make any inferences from UKPDS. The data base in that study in reference to the combination of sulfonylureas and metformin is very small and it is the consensus of the diabetologists in our group as well as the diabetes experts outside of the Agency that the question of increased problems with metformin and SU remains to be defined. Therefore, we will not include the bolded statement in the labeling for this product.

/S/ 2/22/99

Solomon Sobel, M.D.
Division Director, HFD-510

APPEARS THIS WAY
ON ORIGINAL

NDA 20-496
S-002

FEB 11 1999

Safety Update Review

We issued Hoechst Marion Roussel an **approvable** letter on August 10, 1998. In that letter, we asked that they provide material (literature) that reflects any safety data on the usage of metformin and glimepiride as used in combination.

On November 12, 1998, HMR responded with additional information from a French abstract. The contents from this publication, and the synopsis were found to be satisfactory. No further safety data are available for review. Thus, the decision was made to approve this supplement based upon the information submitted.

/S/ 2/11/99

Saul Malozowski, M.D.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES — Food and Drug Administration

Memorandum

Date: 11/17/98 /S/

From: Saul Malozowski
Acting Medical Team Leader

FEB 22 1999

Subject: Amaryl, safety review (NDA 20496-SEI-002)

To: Solomon Sobel
Division Director, DMEDP

In reviewing the information submitted by the sponsor regarding the safety of the metformin-Amaryl combination therapy, it appears that the only substantial concern is the increment in hypoglycemia events. Although bothersome per se, this side effect underlines the potential benefit of this combination in reducing glycemia, and therefore improving glycemic control. Therefore the information provided, provides some reassurance on the safety of this combination therapy and supports its approval.

Finally, I do not agree with the previous reviewers, Dr. Fleming and Dr. Gueriguian, that were willing to accept changes in the label without any assurances of safety. It is required that we make sure that each chemical entity or their combinations are safe when administered together. I could accept that class actions be extrapolated by I can not accept the same approach to safety claims. There is room for speculation in biology and medicine, but only experimentation can provide the answers we need.

Concur /S/ 2/18/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020496/S002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 20-496** **Approved:** 30-NOV-1995
NAME AND ADDRESS OF APPLICANT Hoechst-Roussel Pharmaceuticals Inc. Route 202-449 P.O. Box 2500 Somerville, NJ 08876-1258 (908) 231-2107	**SUPPLEMENT** S-002 Doc 03-NOV-1998 Rec 04-NOV-1998 **NAME OF THE DRUG** Amaryl Tablets **NONPROPRIETARY NAME** Glimepiride Tablets
SUPPLEMENT PROVIDES for the use of Amaryl (glimepiride) tablets concomitantly with metformin when diet, exercise, and Amaryl or metformin alone do not result in adequate glycemic control.	**NEW CORRESPONDENCE** SEI-002 Doc 12-APR-1998 Rec 16-APR-1998

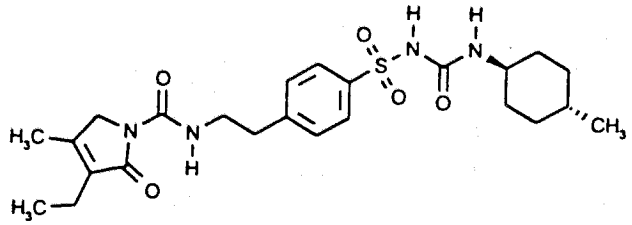
PHARMACOLOGICAL CATEGORY Antihyperglycemic Agent	**HOW DISPENSED** Oral Rx	**RELATED** –
DOSAGE FORM Tablets	**POTENCY** 1, 2, and 4 mg	

CHEMICAL NAME AND STRUCTURE

Glimepiride

$C_{24}H_{34}N_4O_5S$

MW = 490.62
CAS 93479-97-1



1*H*-Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-*N*-[2-[4-[[[[(4-methylcyclohexyl)amino] carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo, *trans*-

COMMENTS This **efficacy supplement** provides for the use of Amaryl (glimepiride) tablets concomitantly with metformin when diet, exercise, and Amaryl or metformin alone do not result in adequate glycemic control. There are no changes regarding Chemistry and Manufacture Controls. The applicant meet the criteria for categorical exclusion of Environmental Assessment requests, 21 CFR §25.31(b). Although the use of the drug substance will increase, the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below _____ (exclusion criteria).

CONCLUSIONS AND RECOMMENDATIONS There are no changes pertaining Chemistry and Manufacture Controls. The applicant meets the requirement for categorical exclusion of Environmental Impact Assessment requirements. **From the Chemistry viewpoint this application can be approved**.

REVIEWER NAME (AND SIGNATURE) /S/

Xavier Ysern, PhD

DATE COMPLETED: 21-APR-1998

R/D INITIATED

filename: /nda/20496s02.doc

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/S/
4/21/98