CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020496/S002

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-496/S-002

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

AUG 10 1998

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) 1, 2 and 4 mg Tablets.

We acknowledge receipt of your submissions dated January 27, February 10, 12, and 26, and March 12, 1998. The user fee goal date for this application is August 10, 1998.

This supplement 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 application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

> Please submit information that reflects any safety data that you may have on the usage of metformin and glimepiride in combination. If such material cannot be provided, a small study of about 3 months' duration should be conducted in at least 50 patients that will provide information on the safety of this combination.

In addition, it will be necessary for you to submit revised draft labeling reflecting the additional safety information. 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.

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 314.120. 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 these changes prior to approval of this supplemental application.

If you have any questions, 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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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 # 002

Trade Name Amaryl Generic Name Glimepiride Tablets

Applicant Name Hoechst Marion Roussel Inc. HFD- 510 Approval Date _____

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 questions about the submission.

a) Is it an original NDA? YES /_/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/

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

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

YES / X / NO /___/

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

_____

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

_____

d) Did the applicant request exclusivity? YES /___/ NO /_X_/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6 (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 /X/ NO /___/

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

NDA # 20-496 _____

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 /___/ *Note: Approved based upon published literature + studies not conducted or sponsored by the applicant.*

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 6:**

_____

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

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

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

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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"):

Investigation #1_, Study # _____

Investigation #2_, Study # _____

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

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

Investigation #1

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

Investigation #2

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

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

Investigation #1

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

Investigation #2

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

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/
Michael F. Johnston, R.Ph. 4-28-98
Signature Date
Title: Project Manager / Consumer Safety Officer

/S/
Solomon Sobel M.D. 8/10/98
Signature of Division Director Date

5

Debarment Certification

Hoechst Marion Roussel, Inc. herby 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 this application for NDA 20-496 Amaryl (glimepiride tablets) Supplement Number S-002.

Elaine Waller

Elaine Waller, Pharm D
Vice President
North American Drug Regulatory Affairs

11 Mar 98
Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Administration

Food and Drug

Memorandum

FEB 22 1999

Date: 11/17/98

From: Saul Malozowski
Acting Medical Team Leader

Subject: Amaryl (Glimepiride), safety review (NDA 20496-SEI-002[8-27-98 and 11-17-98])

To: Solomon Sobel
Division Director, DMEDP

As per our request, the sponsor has submitted information regarding the safety of the metformin-Amaryl combination therapy. Attached to the document is an abstract entitled "Addition of Glimepiride significantly improves glycaemic control in Type 2 diabetic patients insufficiently controlled on Metformin," published in Diabetes, 47, suppl 1, A351, abstract 1355.

This abstract describes a double-blind placebo randomized study in 372 subjects treated for 20 weeks. Glimepiride (G) was given alone (n=150) or in combination with Metformin (M) (n=75.) 147 patients were also treated with M monotherapy. Three patients were excluded from the efficacy analysis due to drug exposure less than 3 days.

For the initial four weeks patients received M alone and then randomized to the three groups for 12 weeks. Further, treatment was extended for 8 weeks for each arm. The M dose was kept constant after randomization.

The mean age was 56 ± 8 years and the disease was present for 8 ± 6 years. BMI was 29.4 ± 4.1 kg/m^2 with baseline HB1 AC 6.5 ± 1.1 % and 190 ± 30 mg/dL fasting glucose.

Relevant results are provided in the following table

	Amaryl (Glimepiride)	Metformin	Amaryl (G)+Metformin
Dose	Range 1-6 mg (QD)	850 mg (TID)	Both
HB1 AC (% change)	+0.28 ± 1.1	+0.07 ± 1.2	-0.75 ± 0.96
Fasting glucose (Δ)	+12 ± 56	+15 ± 64	-32 ± 39
Postpran. glucose (Δ)	-0.02 ± 0.91	+0.19 ± 1.06	-0.45 ± 0.71
AE (All)	46.3 %	52 %	48.3 %
Symptomatic Hypogly	13 %	12 %	22.4 %
GI AE	5.4 %	12 %	6.9 %
Increase Appetite	4 %	4 %	6.8 %

As shown, the combination therapy resulted in better HB1 AC control that either G or M ($p<0.001$.)

In addition patients in the combination therapy (1/147) had one episode of atrial flutter, tachycardia or nodal tachycardia, while none in the single drug arms did.

The incidence of sweating and tremor was higher in the combination arm generally in combination with hypoglycemic symptoms.

Respiratory events also occurred at similar rates in all groups.

One subject in the combination group was discontinued due to a hypoglycemic episode. Drug discontinuation resulted in improvement of this symptom.

In summary, based upon the data provided in tabular form and in an abstract, 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. The information provided, however, is modest and it is possible that when this combination will be marketed, will may learn more that we have so far.

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. This should be added to point #1 in the medical review dated 7/28/98.

2/22/99

I discussed the last paragraph with Dr. Malozowski and he agreed that at this time we should not make any inference 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 diabetes experts outside of the agency that the question of increased problems with met + sulfonylyl remains to be defined. Therefore we will not include the bolded statement

/S/

Hoechst Marion Roussel

March 12, 1998

Solomon Sobel, M. D
Director
Division of Metabolism and Endocrine Drug Products
(HFD-510)
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

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
REC'D
MAR 16 1998
HFD-510
EVALUATION AND RESEARCH

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
PRIOR APPROVAL SUPPLEMENT
S-002

Dear Dr. Sobel:

Enclosed please find the following for the above referenced supplement:

1) Debarment Certification.
3) Amaryl Patent Information. (submitted to NDA May 30, 1997)
2) Environmental Categorical Exclusion request:

Pursuant to 21 CFR 25.31 (b), Hoechst Marion Roussel Inc. requests a categorical exclusion for the supplement, as the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

If you have any questions or need additional information, please contact me at 816-966-7796 (FAX 816-966-6794)

Sincerely,

Dan Henry, RPH
Manager, US Regulatory Affairs, Marketed Products
Hoechst Marion Roussel

Enclosures: Debarment Certification
Amaryl Patent Information (submitted to NDA May 30, 1997)

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

Hoechst Marion Roussel

November 12, 1998

ORIGINAL

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

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 6413[illegible]
Telephone (816) 96[illegible]000
U.S. Web site: ww[illegible]hmri.com

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 13 1998
HFD-510

NDA SUPP AMEND
SE1-002
BM

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496/Supplement 002
Supporting safety data for Amaryl used concomitantly with metformin

Dear Dr. Sobel:

Please find enclosed supporting safety data for the French abstract titled "Addition of Glimepiride Significantly Improves Glycaemic Control in Type 2 Diabetic Patients Insufficiently Controlled on Metformin" (*Diabetes*, volume 47, supp. 1, page A351, abstract 1355) submitted to the FDA on August 25, 1998. This response is also in reference to your letter to Dr. Michael Nicholas dated August 10, 1998, and a telephone conversation with Jena Weber on October 19, 1998. Jena had requested, on your behalf, additional safety data from the study that was conducted in France to support the use of Amaryl concomitantly with metformin when diet, exercise, and Amaryl or metformin alone do not result in adequate glycemic control.

This submission includes the following tables and listing:

1. Table 1 – Number of patients per treatment and adverse event (during and after the treatment)
2. Table 2 – Number of patients per treatment and serious adverse event (during and after treatment)
3. Listing 1 – Adverse events – patient listing

Table 1 presents the incidence for all adverse events by treatment and body system while Table 2 presents the incidence of only serious adverse events by treatment and body system. Listing 1 presents all adverse events by patient and supports the data being presented in Tables 1 and 2. The abstract in *Diabetes* erroneously stated 369 patients participated in the study by excluding from the analysis three patients from the analysis who received one or two days of treatment. However, Tables 1 and 2 correctly represent 372 patients who participated in the study.

In Table 1, the incidence for asthenia and malaise was higher in the glimepiride (G) treatment group compared to the metformin + glimepiride (M+G) and metformin (M) treatment groups. The incidence of asthenia was 10% (15/150), 4.1% (6/147), and 4.0% (3/75) in the (G), (M+G), and the (M) treatment groups, respectively. The incidence of malaise was 8.0% (12/150), 7.5% (11/147), and 4.0% (3/75) in the

(G), (M+G), and the (M) treatment groups, respectively. The incidence for asthenia in the (G) treatment group is higher than what is reported in the current prescribing information (1.6% of 746 patients). This might be explained by the smaller sample size in the French study (n=150 for glimepiride treatment group) compared to the sample size stated in the prescribing information (n=746 for the glimepiride treatment group). In addition, the patients experiencing asthenia in the (G) treatment group generally experienced hypoglycemia and the investigators assessed the asthenia as possibly related to study medication.

In Tables 1 and 2, 0.7% (1/147) of (M+G) treated patients were noted to have atrial flutter, tachycardia, and nodal tachycardia. The investigators assessed these adverse events as not related to study medication. None of the patients in the (G) and (M) treatment groups experienced these cardiovascular events. As shown in Table 1, the incidence of left heart failure and palpitation was slightly higher in the (M+G) treatment group (0.7%, 1/147; 1.4%, 2/147, respectively) compared to the (G) treatment group (0%, 0/150; 0.7%, 1/150, respectively) and the (M) treatment group (0%, 0/75; 1.3%, 1/75, respectively). For two patients experiencing palpitations, 1 (M+G) treated patient and 1 (M) treated patient, the investigators assessed the adverse events as possibly related to study medication. The investigators, for the remaining three patients in the (M+G) and (G) treatment groups, assessed the adverse events of palpitation and left heart failure as not related to study. Of these remaining three patients, only one patient from the (M+G) treatment group experienced a serious adverse event of palpitation (see Table 2).

There was a slightly higher incidence of increased appetite in the (M+G) treatment group (6.8%, 10/147) compared to both the (G) (4.0%, 6/150) and (M) (4.0%, 3/75) treatment groups (see Table 1). The (M+G) treated patients experiencing increased appetite generally also experienced hypoglycemia, malaise, and/or sweating increased.

Hypoglycemia occurred in 22.4% (33/147), 13.3% (20/150), and 12.0% (9/75) of the (M+G), (G), and (M) treated patients, respectively (see Table 1). Only one of the 33 (M+G) treated patients experienced a serious adverse event of hypoglycemia in which the study medication was discontinued and the adverse event subsided (see Table 2).

As shown in Table 1, the incidence of sweating increased and tremor was higher in the (M+G) treatment group (12.9%, 19/147; 6.1%, 9/147, respectively) compared to the (G) (6.7%, 10/150; 2.0%, 3/150, respectively) and (M) (4.0%, 3/75; 1.3%, 1/75, respectively) treatment groups. Again, the patients in the (M+G) treatment group experiencing sweating increased and tremor also generally experienced hypoglycemia, malaise, and/or asthenia.

The incidence of bronchitis was reported in 3.4% (5/147), 6.0% (9/150), and 4.0% (3/75) of patients in the (M+G), (G), and (M) treatment groups, respectively. The incidence of pharyngitis was reported in 2.0% (3/147), 2.0% (3/150), and 1.3% (1/75) of patients in the (M+G), (G), and (M) treatment groups. And finally, the incidence of rhinitis was reported in 4.1% (6/147), 2.7% (4/150), and 1.3% (1/75) of patients in the (M+G), (G), and (M) treatment groups, respectively. The investigators assessed these adverse events for patients in all three treatment groups as not related to study medication.

In summary, the most notable incidence difference for adverse events in the (M+G) treatment group was with hypoglycemia. In the draft prescribing information sent to the FDA by Dan Henry, RPh on November 3, 1997, the potential for hypoglycemia when glimepiride is used with metformin is stated both under the **PRECAUTIONS** section, as well as, the **DOSAGE AND ADMINISTRATION: AMARYL®-Metformin combination Therapy** section. Please refer to this November 3, 1997 submission for specific wording on the potential for hypoglycemia.

This entire packet of information is being faxed, as well as, a hard copy being sent via UPS to you today, November 12, 1998. I appreciate your prompt assistance with this submission, as this additional indication for Amaryl® is quite important to Hoechst Marion Roussel, Inc. Please contact me at (816) 966-5381 if you have further questions.

Sincerely,

Carol Childers

Carol Childers, PharmD
Associate Regulatory Analyst
US Regulatory Affairs, Marketed Products
HOECHST MARION ROUSSEL, INC.
(816) 966-5381
Fax: (816) 966-6794

Enclosures:

1. Table 1 – Number of patients per treatment and adverse event (during and after the treatment); 6 pages
2. Table 2 – Number of patients per treatment and serious adverse event (during and after treatment); 3 pages
3. Listing 1 – Adverse events – patient listing; 23 pages

2/22/99
Letter reviewed and concur that this will give added support to the approval of the combination of metformin and amaryl. - ISI

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES STUDY DRUG	COUNTERMEASURES OTHER	OUTCOME
GLIMEPIRIDE														
103	320	47	F	Db trt	Anxiety	2	EXAC	29	0	Moderate	None	No change	Medicament	Subsided
107	3	48	F	Db trt	Burning sensation skin	6	OTH	86	14	Severe	None	No change	Medicament	Subsided
118	479	69	M	Db trt	Hypertension	-	EXAC	21	16	Moderate	Possible	Perm. discont	Medicament	Subsided
				Db trt	Hyperglycemia	-	EXAC	21	16	Moderate	Possible	Perm. discont	Medicament	Subsided
				Db trt	Nausea	-	ADR	21	5	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Dizziness	-	ADR	21	3	Moderate	Possible	Perm. discont	None	Subsided
[illegible]	[illegible]	[illegible]	[illegible]	Db trt	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Severe	Possible	Perm. discont	None	Subsided
[illegible]	[illegible]	[illegible]	[illegible]	Db trt	Depression	[illegible]	ADR	24	[illegible]	Severe	Possible	Perm. discont	None	Still present
122	475	46	M	Db trt	Asthenia	1	ADR	14	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	ADR	14	0	Mild	Possible	No change	None	Subsided
				Db trt	Rhinitis	6	NII	126	4	Mild	None	No change	Medicament	Subsided
123	438	61	F	Db trt	Abdominal pain	6	NII	138	-	Mild	None	No change	Medicament	Still present
				Db trt	Nervousness	6	NII	138	-	Mild	None	No change	Medicament	Still present
203	13	52	F	Db trt	Bronchitis	6	NII	97	23	Moderate	None	No change	Medicament	Subsided
204	312	61	F	Db trt	Bronchitis	6	NII	88	5	Moderate	None	No change	Medicament	Subsided
207	11	65	F	Db trt	Vertigo	2	EXAC	37	6	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Back pain	4	EXAC	63	23	Severe	None	No change	Medicament	Subsided
				Db trt	Asthenia	6	OTH	77	-	Mild	None	No change	None	Still present
211	23	70	F	Db trt	Hypertension	2	EXAC	22	20	Moderate	None	No change	Medicament	Subsided
212	86	66	M	Db trt	Urinary tract infection	6	OTH	69	10	Severe	None	No change	Both	Subsided
217	22	57	F	Db trt	Hyperglycemia	2	OTH	29	6	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Dizziness	-	OTH	29	4	Severe	Possible	Perm. discont	None	Subsided
				Db trt	Headache	-	OTH	29	4	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Malaise	-	OTH	29	4	Moderate	Possible	Perm. discont	None	Subsided
301	467	67	M	Db trt	Anxiety	2	NII	38	-	Moderate	None	No change	Medicament	Still present
304	31	57	M	Db trt	Sore throat	-	NII	-3	7	Moderate	None	No change	Medicament	Subsided
				Db trt	Tenosynovitis	2	NII	38	2	Mild	None	No change	Medicament	Subsided
				Db trt	Insomnia	4	NII	62	4	Mild	None	No change	Medicament	Subsided

Note : Shading denotes a serious adverse event
a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other
b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.
c Investigator's assessment: mild, moderate, severe
d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
												STUDY DRUG	OTHER	
				Db trt	Chest pain substernal	4	NII	63	0	Moderate	None	No change	None	Subsided
367	[illegible]	[illegible]	M	[illegible]	Back pain	6	EXAC	73	7	Severe	None	No change	Both	Subsided
309	28	44	F	Db trt	Upper respiratory infection	1	NII	14	8	Moderate	None	No change	Medicament	Subsided
				Db trt	Depression	6	NII	110	25	Moderate	None	No change	Medicament	Subsided
				Db trt	Vaginitis	6	NII	120	7	Mild	None	No change	Medicament	Subsided
				Db trt	Photosensitivity reaction	6	NII	122	5	Moderate	None	No change	Medicament	Subsided
505	304	59	M	Db trt	Pharyngitis	1	NII	5	10	Moderate	None	No change	Medicament	Subsided
701	254	50	F	Db trt	Asthenia	-	EXAC	11	59	Moderate	None	No change	Medicament	Subsided
				Db trt	Asthenia	-	EXAC	11	59	Moderate	None	No change	Medicament	Subsided
704	252	49	M	Db trt	Malaise	2	ADR	41	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Stupor	2	ADR	41	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Malaise	2	ADR	41	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	41	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	41	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	41	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Malaise	2	ADR	42	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Malaise	2	ADR	42	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Malaise	2	ADR	42	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	42	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	42	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	42	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Sweating increased	2	ADR	46	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Nausea	2	ADR	46	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	46	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	46	0	Moderate	Possible	Dosage reduced	Other	Subsided
711	464	67	M	Db trt	Abnormal vision	4	OTH	28	7	Moderate	None	No change	None	Subsided
				Db trt	Abnormal vision	-	OTH	28	7	Moderate	None	No change	None	Subsided
715	259	63	F	Db trt	Sweating increased	1	ADR	38	0	Mild	Possible	No change	Other	Subsided
				Db trt	Asthenia	1	ADR	38	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	38	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	38	0	Mild	Possible	No change	Other	Subsided
				Db trt	Pruritus	1	NII	52	2	Mild	None	No change	Medicament	Subsided
				Db trt	Asthenia	4	ADR	114	1	Severe	Possible	Perm. discont	Both	Subsided
				Db trt	Hypoglycemia	4	ADR	114	1	Severe	Possible	Perm. discont	Both	Subsided

Note : Shading denotes a serious adverse event

a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other

b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
												STUDY DRUG	OTHER	
801	340	57	M	Db trt	Flu syndrome	1	NII	6	4	Moderate	None	No change	Medicament	Subsided
				Db trt	Gastritis	2	EXAC	43	78	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Increased appetite	4	ADR	112	-	Moderate	Possible	No change	None	Still present
810	183	62	F	Db trt	Dizziness	0	ADR	1	0	Severe	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	1	0	Severe	Possible	No change	Other	Subsided
				Db trt	Asthenia	0	ADR	2	0	Moderate	Possible	Temp. discont	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	2	0	Moderate	Possible	Temp. discont	Other	Subsided
				Db trt	Sweating increased	0	ADR	3	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	3	0	Mild	Possible	No change	Other	Subsided
				Db trt	Malaise	0	ADR	55	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	55	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypertension	0	EXAC	64	72	Moderate	None	No change	Medicament	Subsided
				Db trt	Neuralgia	0	NII	83	9	Mild	None	No change	Medicament	Subsided
				Db trt	Asthenia	0	ADR	119	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	119	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	0	ADR	131	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	131	0	Moderate	Possible	No change	Other	Subsided
815	354	58	M	Db trt	Tremor	2	ADR	27	0	Severe	Possible	No change	Other	Subsided
				Db trt	Tremor	2	ADR	27	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	27	0	Severe	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	27	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Increased appetite	1	ADR	55	0	Mild	Possible	No change	Other	Subsided
				Db trt	Malaise	1	ADR	55	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	55	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	55	0	Mild	Possible	No change	Other	Subsided
				Db trt	Tremor	0	ADR	62	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Tremor	0	ADR	62	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Voice alteration	0	ADR	62	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	62	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	62	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	62	0	Moderate	Possible	No change	Other	Subsided
815	357	51	M	Db trt	Asthenia	4	ADR	59	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Malaise	4	ADR	59	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	59	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	59	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	60	0	Mild	Possible	No change	None	Subsided
903	224	67	M	Db trt	Maculopapular rash	0	ADR	6	-	Moderate	Possible	Perm. discont	Medicament	Still present
				Db trt	Hot flashes	-	ADR	6	-	Mild	Possible	Perm. discont	None	Still present

Note : Shading denotes a serious adverse event

a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other

b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTENSITY[c]	CAUSALITY[d]	COUNTERMEASURES STUDY DRUG	COUNTERMEASURES OTHER	OUTCOME
909	228	51	M	Db trt	Hot flashes	6	ADR	86	58	Mild	Possible	No change	None	Subsided
				Db trt	Rhinitis	6	NII	105	5	Mild	None	No change	Medicament	Subsided
910	411	62	M	Db trt	Hypercholesterolemia	6	NII	140	213	Mild	None	No change	Other	Subsided
1003	344	55	F	Db trt	Neuralgia	2	EXAC	103	-	Severe	None	No change	Medicament	Still present
1010	103	53	F	Db trt	Paresthesia	4	OTH	68	39	Mild	None	No change	None	Subsided
				Db trt	Myalgia	6	ADR	128	-	Moderate	Possible	Perm. discont	None	Still present
				Db trt	Myasthenia	6	ADR	128	-	Moderate	Possible	Perm. discont	None	Still present
1011	215	64	F	Db trt	Hypoglycemia	4	ADR	63	0	Mild	Possible	Dosage reduced	None	Subsided
1011	219	59	M	Db trt	Malaise	4	ADR	128	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	128	0	Moderate	Possible	No change	None	Subsided
				Db trt	Malaise	4	ADR	129	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	129	0	Moderate	Possible	No change	None	Subsided
				Db trt	Malaise	4	ADR	130	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	4	ADR	130	0	Moderate	Possible	Dosage reduced	None	Subsided
1023	461	52	M	Db trt	Herpes zoster	6	NII	126	15	Moderate	None	No change	Medicament	Subsided
1101	168	63	F	Db trt	Cough increased	2	NII	22	11	Mild	None	No change	Medicament	Subsided
				Db trt	Rhinitis	2	NII	22	11	Mild	None	No change	Medicament	Subsided
				Db trt	Bronchitis	6	NII	113	10	Moderate	None	No change	Medicament	Subsided
				Db trt	Sinusitis	6	NII	134	8	Moderate	None	No change	Medicament	Subsided
1103	175	59	M	Db trt	Rhinitis	1	NII	23	10	Mild	None	No change	Medicament	Subsided
				Db trt	Pharyngitis	6	NII	70	14	Mild	None	No change	Medicament	Subsided
				Db trt	Dizziness	6	NII	97	36	Mild	None	No change	None	Subsided
				Db trt	Nausea	6	ADR	97	11	Mild	None	No change	Medicament	Subsided
				Db trt	Tremor	6	ADR	97	9	Mild	None	No change	None	Subsided
				Db trt	Constipation	6	NII	104	59	Mild	None	No change	Medicament	Subsided
				Db trt	Anxiety	6	NII	125	8	Mild	None	No change	Medicament	Subsided
1209	261	60	M	Db trt	Gynecomastia	6	ADR	122	-	Moderate	Possible	No change	None	Still present
1301	155	35	M	Db trt	Sweating increased	2	ADR	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Malaise	2	ADR	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Increased appetite	2	ADR	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	20	0	Mild	Possible	No change	None	Subsided

Note : Shading denotes a serious adverse event

a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other

b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTENSITY[c]	CAUSALITY[d]	COUNTERMEASURES STUDY DRUG	COUNTERMEASURES OTHER	OUTCOME
				Db trt	Hypoglycemia	2	ADR	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Sweating increased	2	ADR	21	0	Mild	Possible	No change	None	Subsided
				Db trt	Malaise	2	ADR	21	0	Mild	Possible	No change	None	Subsided
				Db trt	Increased appetite	2	ADR	21	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	21	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	21	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	21	0	Mild	Possible	No change	None	Subsided
				Db trt	Sweating increased	2	ADR	28	0	Mild	Possible	No change	None	Subsided
				Db trt	Malaise	2	ADR	28	0	Mild	Possible	No change	None	Subsided
				Db trt	Increased appetite	2	ADR	28	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	28	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	28	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	28	0	Mild	Possible	No change	None	Subsided
				Db trt	Neuralgia	1	EXAC	141	-	Moderate	None	No change	Medicament	Still present
1305	154	53	M	Db trt	Asthenia	1	ADR	4	-	Moderate	Possible	No change	None	Still present
				Db trt	Sweating increased	1	ADR	23	0	Mild	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	23	0	Mild	Possible	Dosage reduced	Other	Subsided
1505	243	52	M	Db trt	Dizziness	4	ADR	48	3	Mild	Possible	No change	None	Subsided
1606	401	62	F	Db trt	Angina pectoris	1	EXAC	15	4	Moderate	None	No change	Medicament	Subsided
				Db trt	Flu syndrome	6	NII	71	10	Moderate	None	No change	Medicament	Subsided
1611	159	58	M	Db trt	Bronchitis	4	NII	93	8	Moderate	None	No change	Medicament	Subsided
1701	238	49	M	Db trt	Neuralgia	1	NII	9	39	Moderate	None	No change	Medicament	Subsided
				Db trt	Dizziness	2	NII	21	27	Mild	None	No change	None	Subsided
				Db trt	Dry mouth	4	NII	48	21	Mild	None	No change	None	Subsided
				Db trt	Hyperlipemia	6	EXAC	138	-	Moderate	None	No change	Medicament	Still present
1701	239	38	F	Db trt	Sweating increased	6	ADR	107	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Vomiting	6	ADR	107	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	6	ADR	107	0	Severe	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	107	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	107	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	107	0	Severe	Possible	No change	Other	Subsided
				Db trt	Sweating increased	6	ADR	110	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Vomiting	6	ADR	110	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	6	ADR	110	0	Severe	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	110	0	Moderate	Possible	No change	Other	Subsided

Note : Shading denotes a serious adverse event
a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other
b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.
c Investigator's assessment: mild, moderate, severe
d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES STUDY DRUG	COUNTERMEASURES OTHER	OUTCOME
				Db trt	Hypoglycemia	6	ADR	110	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	110	0	Severe	Possible	No change	Other	Subsided
1701	273	54	F	Db trt	Bronchitis	6	NII	85	4	Mild	None	No change	Medicament	Subsided
				Db trt	Weight gain	6	EXAC	131	-	Severe	Possible	No change	Other	Still present
1701	275	62	M	Db trt	Nausea	1	ADR	64	67	Mild	Possible	Perm. discont	None	Subsided
				Db trt	Flu syndrome	0	NII	124	7	Moderate	None	No change	Medicament	Subsided
1701	367	57	M	Db trt	Edema	2	EXAC	42	47	Mild	None	No change	None	Subsided
				Db trt	Asthenia	6	NII	81	24	Mild	Possible	No change	None	Subsided
				Db trt	Anxiety	6	NII	84	173	Mild	None	No change	Medicament	Subsided
				Db trt	Dizziness	6	ADR	138	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	138	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Dizziness	6	ADR	139	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	139	0	Moderate	Possible	No change	Other	Subsided
[illegible]	[illegible]	[illegible]	[illegible]	Db trt	[illegible]	[illegible]	EXAC	[illegible]	[illegible]	[illegible]	[illegible]	No change	Medicament	Subsided
1703	369	53	M	Db trt	Hypoglycemia	1	ADR	10	0	Mild	Possible	No change	None	Subsided
				Db trt	Asthenia	1	NII	22	50	Moderate	None	Temp. discont	None	Subsided
				Db trt	Neoplasm of the mouth	4	NII	48	10	Mild	None	No change	Other	Subsided
1716	382	65	F	Db trt	Asthenia	1	ADR	4	0	Mild	Possible	No change	Other	Subsided
				Db trt	Sweating increased	1	ADR	4	0	Mild	Possible	No change	Other	Subsided
				Db trt	Gastritis	1	ADR	4	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Mild	Possible	No change	Other	Subsided
				Db trt	Infection	2	NII	25	8	Moderate	None	No change	Medicament	Subsided
				Db trt	Sweating increased	4	ADR	52	0	Moderate	Possible	No change	None	Subsided
				Db trt	Malaise	4	ADR	52	0	Moderate	Possible	No change	None	Subsided
				Db trt	Asthenia	4	ADR	52	0	Moderate	Possible	No change	None	Subsided
1804	458	57	M	Db trt	Bronchitis	4	NII	109	8	Severe	None	No change	Medicament	Subsided
1808	484	61	M	Db trt	Increased appetite	1	ADR	7	0	Moderate	Possible	No change	None	Subsided
				Db trt	Malaise	1	ADR	7	0	Moderate	Possible	No change	None	Subsided
				Db trt	Sweating increased	1	ADR	7	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	ADR	7	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	ADR	7	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	ADR	7	0	Moderate	Possible	No change	None	Subsided

Note : Shading denotes a serious adverse event

a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other

b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTENSITY[c]	CAUSALITY[d]	COUNTERMEASURES STUDY DRUG	COUNTERMEASURES OTHER	OUTCOME
				Db trt	Increased appetite	2	ADR	97	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Malaise	2	ADR	97	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypoglycemia	2	ADR	97	0	Moderate	Possible	No change	Other	Subsided
5101	108	50	M	Db trt	Urinary tract infection	1	OTH	5	12	Moderate	None	No change	Medicament	Subsided
5101	418	46	M	Db trt	Urinary tract infection	1	NII	7	13	Moderate	None	No change	Medicament	Subsided
5201	112	39	M	Db trt	Asthenia	1	OTH	19	-	Severe	Possible	Dosage reduced	None	Still present
				Db trt	Excessive thirst	1	OTH	19	-	Moderate	Possible	Dosage reduced	None	Still present
				Db trt	Increased urinary frequency	1	OTH	19	-	Moderate	Possible	Dosage reduced	None	Still present
				Db trt	Hyperglycemia	4	OTH	42	-	Severe	Possible	Perm. discont	Medicament	Still present
				Db trt	Movement disorder	4	OTH	61	-	Moderate	None	No change	None	Still present
5201	114	58	F	Db trt	Hyperglycemia	6	OTH	63	-	Moderate	Possible	Perm. discont	None	Still present
5201	276	60	F	Db trt	Malaise	1	ADR	10	0	Moderate	None	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	10	0	Moderate	None	No change	Other	Subsided
				Db trt	Palpitation	4	OTH	80	0	Moderate	None	No change	Medicament	Subsided
				Db trt	Palpitation	4	OTH	81	0	Moderate	None	No change	Medicament	Subsided
				Db trt	Anemia	6	NII	144	-	Moderate	Possible	No change	Medicament	Still present
5201	279	48	M	Db trt	Urinary tract infection	1	NII	4	15	Mild	None	No change	Medicament	Subsided
				Db trt	Bone fracture (not spontaneous)	1	OTH	11	34	Severe	None	No change	Other	Subsided
5401	77	60	F	Db trt	Constipation	4	ADR	6	-	Mild	Possible	No change	Medicament	Still present
				Db trt	Constipation	-	ADR	6	-	Mild	Possible	No change	Medicament	Still present
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Hyperglycemia	[illegible]	EXAC	[illegible]	[illegible]	Severe	None	No change	Other	Subsided
5501	191	45	F	Db trt	Bronchitis	4	NII	82	8	Moderate	None	No change	Medicament	Subsided
5501	194	35	F	Db trt	Sore throat	6	NII	152	8	Moderate	None	No change	Medicament	Subsided
5501	480	60	M	Db trt	Pharyngitis	4	NII	5	7	Mild	None	No change	None	Subsided
				Db trt	Pharyngitis	-	NII	5	7	Mild	None	No change	None	Subsided
5901	81	47	F	Db trt	Hypoglycemia	6	ADR	106	0	Mild	Possible	Dosage reduced	None	Subsided
6401	490	59	F	Db trt	Headache	6	OTH	85	-	Severe	Possible	Perm. discont	Medicament	Still present
				Db trt	Thorax pain	6	OTH	85	-	Severe	Possible	Perm. discont	Medicament	Still present
				Db trt	Asthenia	6	OTH	85	-	Severe	Possible	Perm. discont	Medicament	Still present

Note : Shading denotes a serious adverse event

a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other

b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

BEST POSSIBLE COPY

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES STUDY DRUG	COUNTERMEASURES OTHER	OUTCOME
				Db trt	Polyuria	6	OTH	85	-	Severe	Possible	Perm. discont	Medicament	Still present
6501	135	36	F	Db trt	Headache	-	ADR	1	3	Moderate	Possible	No change	None	Subsided
				Db trt	Headache	-	ADR	1	3	Moderate	Possible	No change	None	Subsided
6601	136	62	M	Db trt	Prostatic disorder	1	NII	4	20	Mild	None	No change	Medicament	Subsided
				Db trt	Diarrhea	6	ADR	120	-	Severe	Possible	Perm. discont	None	
6701	435	54	M	Db trt	Bronchitis	1	NII	13	10	Moderate	None	No change	Medicament	Subsided
				Db trt	Laryngitis	4	NII	84	8	Mild	None	No change	Medicament	Subsided
				Db trt	Peripheral edema	4	NII	88	39	Mild	None	No change	Medicament	Subsided
				Db trt	Tremor	6	ADR	91	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	91	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Bronchitis	6	NII	130	8	Moderate	None	No change	Medicament	Subsided
6701	446	64	M	Db trt	Asthenia	0	ADR	15	0	Mild	Possible	No change	Other	Subsided
				Db trt	Nervousness	-	ADR	15	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	-	ADR	15	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	-	ADR	15	0	Mild	Possible	No change	Other	Subsided
				Db trt	Flu syndrome	-	NII	18	-	Moderate	None	No change	Medicament	Still present
				Db trt	Sweating increased	-	ADR	20	-	Mild	Possible	No change	None	Still present
				Db trt	Weight loss	-	ADR	20	-	Moderate	Possible	No change	None	Still present
				Db trt	Sleep disorder	-	ADR	20	-	Moderate	Possible	No change	None	Still present
				Db trt	Bronchitis	-	NII	30	-	Severe	None	No change	Medicament	Still present
				Db trt	Hypoglycemia	-	ADR	[illegible]	[illegible]	Severe	None	No change	Other	Subsided
				Db trt	Tremor	-	ADR	31	[illegible]					
6901	143	50	M	Db trt	Sweating increased	1	ADR	1	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Malaise	1	ADR	1	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Increased appetite	1	ADR	1	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	1	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	1	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	1	0	Moderate	Possible	No change	Other	Subsided
7201	119	51	M	Db trt	Increased appetite	1	ADR	2	62	Moderate	Possible	No change	Other	Subsided

Note : Shading denotes a serious adverse event

a EXAC=exacerb. of pre-existing cond., NII=new intercurrente illness, ADR=potential adv. reaction, OTH=other

b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

BEST POSSIBLE COPY