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NDA 20-496

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964-02 VDA

LABECCING

Approved 11/30/95

AMARYL (Glimepiride Tablets, HOE 490) NDA 20,496
Item 2.A - Final Package Insert - Revisions Implemented 11/30/95

A.1

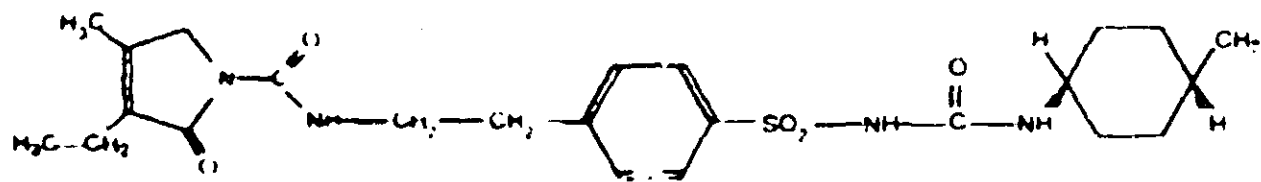
AMARYL® (GLIMEPIRIDE TABLETS)

1, 2, and 4 mg

DESCRIPTION

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

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



• Molecular Formula $C_{24}H_{34}N_4O_4S$

Molecular Weight 490.62

Glimepiride is practically insoluble in water

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In

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

PHARMACODYNAMICS

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

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

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

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

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

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

PHARMACOKINETICS

Absorption

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

Distribution

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

Metabolism

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

Excretion

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

Pharmacokinetic Parameters

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

	Volunteers	Patients with NIDDM	
	Single Dose Mean ± SD	Single Dose (Day 1) Mean ± SD	Multiple Dose (Day 10) Mean ± SD
C_{max} (ng/mL)			
1 mg	103 ± 34 (12)	—	—
2 mg	177 ± 44 (12)	—	—
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	557 ± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
T_{max} (h)	2.4 ± 0.8 (48)	2.5 ± 1.2 (26)	2.8 ± 2.2 (23)
CL _T (mL/min)	52.1 ± 16.0 (48)	48.5 ± 29.3 (26)	52.7 ± 40.3 (23)
V _d (L)	21.8 ± 13.9 (48)	19.8 ± 12.7 (26)	37.1 ± 18.2 (23)
$T_{1/2}$ (h)	5.3 ± 4.1 (48)	5.0 ± 2.5 (26)	9.2 ± 3.6 (23)

() - No. of subjects
 CL_T = Total body clearance after oral dosing
 V_d = Volume of distribution calculated after oral dosing

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

Variability

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

SPECIAL POPULATIONS

Geriatric

Comparison of glimepiride pharmacokinetics in NIDDM patients ≤ 65 years and those > 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean

AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Pediatric

No studies were performed in pediatric patients.

Gender

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

Race

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

Renal Insufficiency

A single-dose, open label study was conducted in 15 patients with renal impairment. AMARYL (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CL_{cr}). (Group I, CL_{cr} = 77.7 ml/min, n = 5), (Group II, CL_{cr} = 27.7 ml/min, n = 3), and (Group III, CL_{cr} = 9.4 ml/min, n = 7) ml/min. AMARYL was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M₁ and M₂ serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life (T_{1/2}) for glimepiride did not change, while the half-lives for M₁ and M₂ increased as renal function decreased. Mean urinary excretion of M₁ plus M₂ as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).

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

Hepatic Insufficiency

No studies were performed in patients with hepatic insufficiency.

Other Populations

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

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

Drug Interactions

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

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

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

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

Concomitant administration of propranolol (40 mg tid) and AMARYL significantly increased C_{max}, AUC, and T_{1/2} of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL_T by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

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

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

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

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

INDICATIONS AND USAGE:

AMARYL is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

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

In initiating treatment for noninsulin dependent diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of AMARYL must be viewed by both the physician and patient as a treatment in addition to diet and exercise, and not as a substitute for diet and exercise, or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of AMARYL.

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

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

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CONTRAINDICATIONS

AMARYL is contraindicated in patients with

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

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of AMARYL, and of alternative modes of therapy.

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

PRECAUTIONS

GENERAL

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

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with AMARYL or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including AMARYL, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with AMARYL monotherapy, AMARYL-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

INFORMATION FOR PATIENTS

Patients should be informed of the potential risks and advantages of AMARYL and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

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

LABORATORY TESTS

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

DRUG INTERACTIONS

(See CLINICAL PHARMACOLOGY, Drug Interactions)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46.54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 6 mg once daily based on surface area.

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

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

PREGNANCY

Teratogenic Effects

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

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

Nonteratogenic Effects

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

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half lives. Patients who are planning a

pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

NURSING MOTHERS

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

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of hypoglycemia with AMARYL, as documented by blood glucose values < 60 mg/dl., ranged from 0.9-1.7% in two large, well controlled, 1-year studies. (See

WARNINGS and PRECAUTIONS)

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

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

Adverse Events Occurring in $\geq 1\%$ AMARYL Patients

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

GASTROINTESTINAL REACTIONS

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

DERMATOLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

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

METABOLIC REACTIONS

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has

been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OTHER REACTIONS

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with AMARYL or any other hypoglycemic agent. The patient's fasting blood glucose and HbA_{1c} must be measured periodically to determine the minimum effective dose for the patient, to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and to

detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

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

USUAL STARTING DOSE

The usual starting dose of AMARYL as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See

PRECAUTIONS Section for patients at increased risk).

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

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

USUAL MAINTENANCE DOSE

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

AMARYL-INSULIN COMBINATION THERAPY

Combination therapy with AMARYL and insulin may be used in secondary failure patients. The fasting glucose level for insulinary combination therapy is in the range of > 150 mg/dL in plasma or serum depending on the patient. The recommended AMARYL dose is 8 mg once

daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA_{1c} levels.

SPECIFIC PATIENT POPULATIONS

AMARYL is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **CLINICAL PHARMACOLOGY**, **SPECIAL POPULATIONS** and **PRECAUTIONS, GENERAL**)

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

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

HOW SUPPLIED

AMARYL[™] (glimepiride) tablets are available in the following strengths and package sizes:

1 mg (pink, flat faced, oblong with notched sides at double bisect, imprinted with "AMARYL" on one side and the Hoechst logo on both sides of the bisect on the other side)

Bottles of 100	NDC 0039 0221 10
Unit Dose Cartons (100)	NDC 0039 0221 11

2 mg (green, flat faced, oblong with notched sides at double bisect, imprinted with "AMARYL" on one side and the Hoechst logo on both sides of the bisect on the other side)

Bottles of 100	NDC 0039 0222-10
Unit Dose Cartons (100)	NDC 0039 0222 11

AMARYL (Glimepiride Tablets, HOE 490) NDA 20,496
Item 2.A - Final Package Insert - Revisions Implemented 11/30/95

A.21

4 mg (blue, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side and the Hoechst logo on both sides of the bisect on the other side)

Bottles of 100 NDC 0039-0223-10

Unit Dose Cartons (100) NDC 0039-0223-11

Store at 59° - 86°F (15° - 30°C)

Dispense in well-closed containers with safety closures.

Caution: Federal law prohibits dispensing without a prescription.

AMARYL™ is a trademark of Hoechst-Roussel Pharmaceuticals Inc

ANIMAL TOXICOLOGY

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

HUMAN OPHTHALMOLOGY DATA

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

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

Glimpiride (HOE 490 Amaryl™) Tablets
NDA 20-496

Bottle Labels - 100's: 1, 2, 4 mg

7/11-1995
Submission

General Correspondence:
Labels - Response to May 17, 1995 letter
from FDA

1

Volume Contents

Unit Dose Push-Thru Foil: 1, 2, 4 mg

Volume 1 of 1

2

Unit Dose Pack: 1, 2, 4 mg

3

Samples 2, 4 mg

4

Sample Cartons 2, 4 mg

5

NDC 0039-0271-10

Amaryl
gabapentin

1 mg

Caution:
Federal law prohibits dispensing
without prescription. Do not use
if bottle cap is broken.

100 Tablets



Keep out of reach of children.
Store at 20° to 25° (68° to 77° F).
See USP Controlled Room Temperature
definition. Excursions permitted to 15° to 30° (59° to 86° F).
See USP definitions for USP Storage Temperature.

027110-506

Small Quantity: See insert for full prescribing
information. Contains 100 white, round, uncoated
tablets. Each contains 1 mg of gabapentin and 100 mg of
lactose. Store between 68° and 77° F.
Keep this and all medications out of the reach
of children. Amaryl 1 mg H02CB01 AG
Hoechst Pharmaceuticals Inc.
Somerville, NJ 08876
NDC 0039-0271-10
US Patent 4,370,785

NDC 0221-0222-10

Amaryl™
ginsenosides

2 mg

Tablets

Keep out of reach of children. Do not use if bottle cap is broken or missing.

100 Tablets

Keep out of reach of children.
Do not use if bottle cap is broken or missing.

Lot: 02210-001
Exp: 08/2005
02210-006



Keep out of reach of children.
Do not use if bottle cap is broken or missing.
Amaryl™ (ginsenosides) is a registered trademark of H. Lundbeck A/S, Denmark. © 2005 H. Lundbeck A/S. All rights reserved. US Patent 4,379,789

NDO 0223-0223-10

Lot
Exp. Date
NDC 0223-10-0223-10
100 Tablets

Amaryl
glimepiride tablets

4 mg

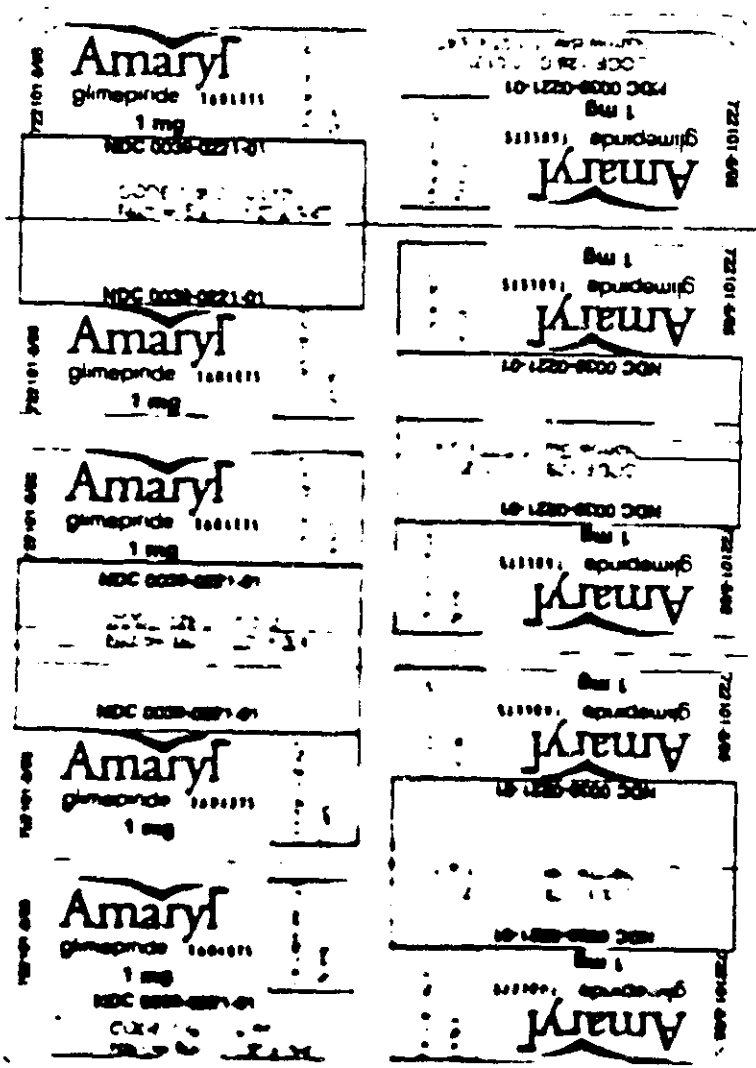
Caution
Federal law prohibits dispensing
without prescription. Do not use
if bottle shows signs of tampering.

100 Tablets

Information Ask a Pharmacist
Lot
Exp. Date
NDC 0223-10-0223-10
022310-606

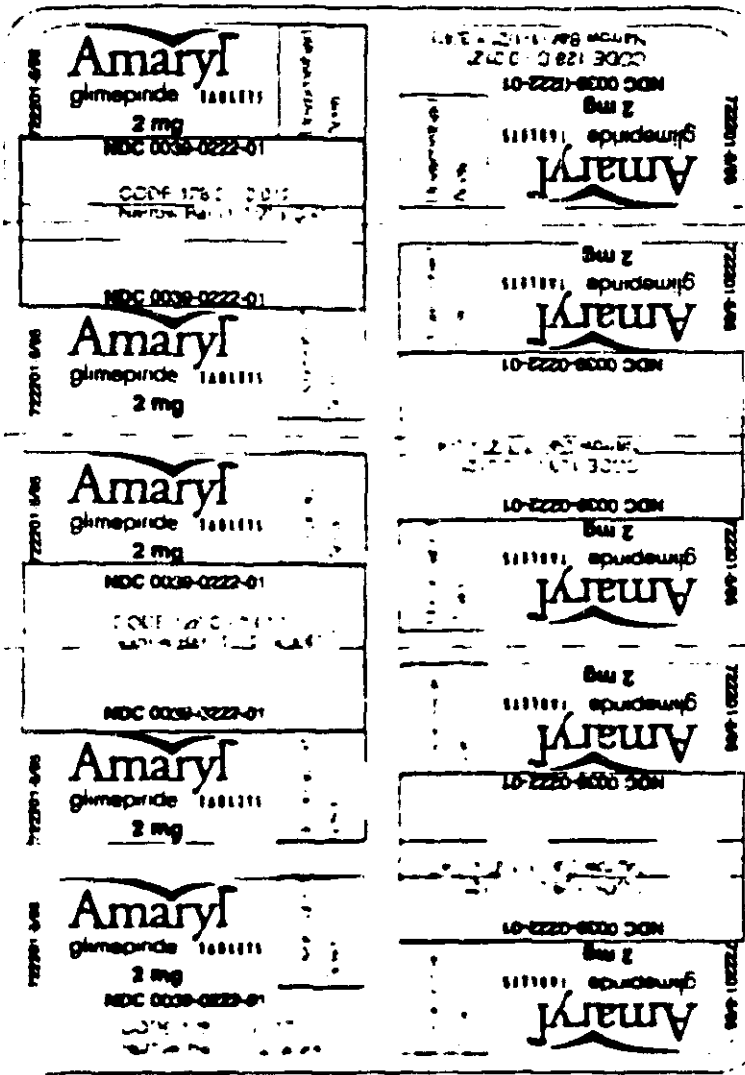


See insert for full prescribing
information. Contains 100 tablets
in a white, round, film-coated
tablet. Each tablet contains 4 mg
of glimepiride and 100 mg of
lactose. Amaryl (TM) NDC 0223-10-
0223-10 is a registered trademark of
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07927, USA
© 2003 Novartis
100 Tablets 4.379.780



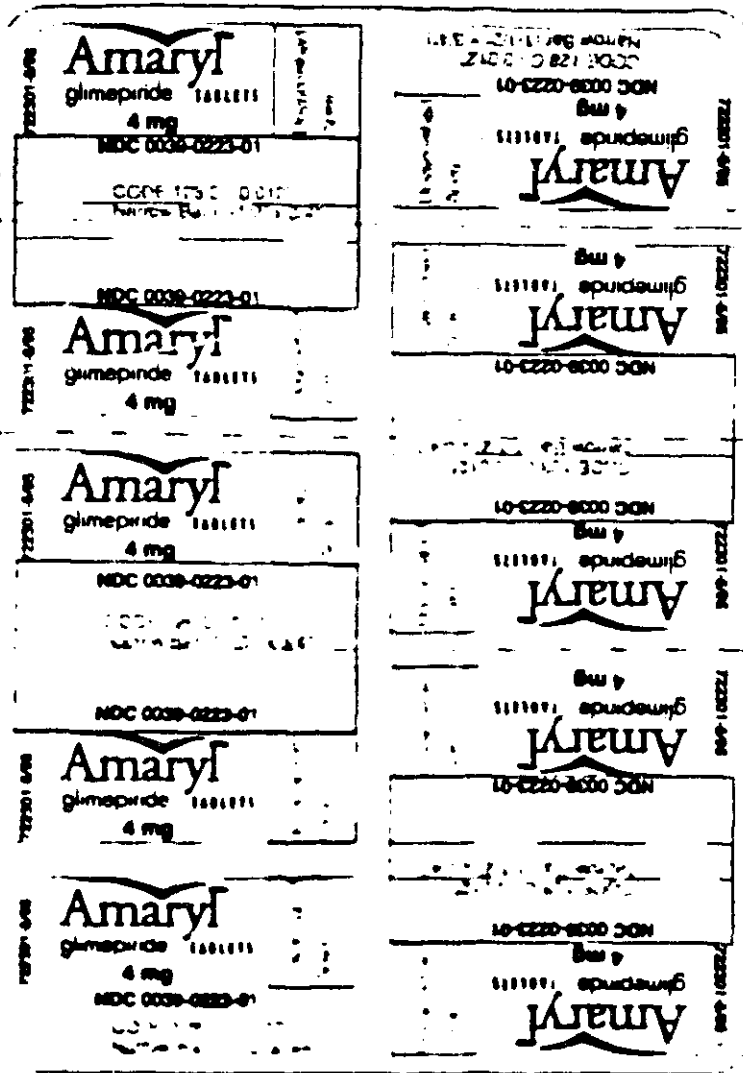
1 mg Unit Dose Push-Thru Foil

All Copy Black



2 mg Unit Dose Push-Thru Foil

All Copy Black



4 mg Unit Dose Push-Thru Fol

All Copy Black

NDC 0039-0221-11

Amaryl™

glimepiride TABLETS

Amaryl™ HOECHST AG

Initial Dosage:
See package insert for full
prescribing information.

Age between 59 and
64 years.

Caution: Federal law prohibits
dispensing without prescription.

Keep this and all
other medications out of the
reach of children.

100 Tablets

1 mg

UNIT DOSE PACK



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

© 1995 Hoechst AG



4022111-5/95

Unvarnished area
3-1/2 x 1-5/16

Unit Dose Pack

100 Tablets

glimepiride
AmarylTM

NDC 0039-0221-11

NDC 0039-0221-11

NDC UPC Barcode
0 0039-0221-11 8
1 1/2 x 100%

AmarylTM
glimepiride TABLETS

Usual Dosage:
See package in:
prescribing infor

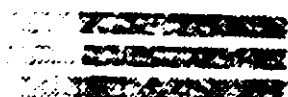
Store between 5
86° F.

Keep this and
medication out
reach of childr

100 Tablets

1 mg

UNIT DOSE PACK



NDC 0039-0222-11

AmarylTM
glimepiride TABLETS

AmarylTM HOECHST AG

Usual Dosage:
See package insert for full
prescribing information.

Store between 59 and
77° F.

Keep this and all
medication out of the
reach of children.

Caution: Federal law prohibits
dispensing without prescription.

100 Tablets

2 mg

UNIT DOSE PACK



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

HOECHST AG

4022211-5/95

Unvarnished area
3-1/2 x 1-5/64

Unit Dose Pack 100 Tablets

AmarylTM
glimepiride tablets

NDC 0039-0222-11

NDC 0039-0222-11

NDC/UPC Barcode
3 0039-0222-11 3
1 2 x 100%

AmarylTM
glimepiride TABLETS

100 Tablets 2 mg

UNIT DOSE PACK



Usual
See p
prescr

Store t
86° F.

Keep
medic
reach

NDC 0039-0223-11

AmarylTM
glimepiride TABLETS

Amaryl TM HOECHST AG

Usual Dosage:
See package insert for full
prescribing information.

Store between 59 and
F.

Keep this and all
medication out of the
reach of children.

4 mg

Caution: Federal law prohibits
dispensing without prescription.

100 Tablets

4 mg

UNIT DOSE PACK

 **HOECHST-ROUSSEL**
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258
HOECHST-ROUSSEL AG



4022311-5/95

Unvarnished area
3-1/2 x 1-5/64

100 Tablets 4 mg Unit Dose Pack

AmarylTM
glimepiride TABLETS

NDC 0039-0223-11

NDC 0039-0223-11

NDC/UPC Barcode
3 0039-0223-11 0
1/2 x 100%

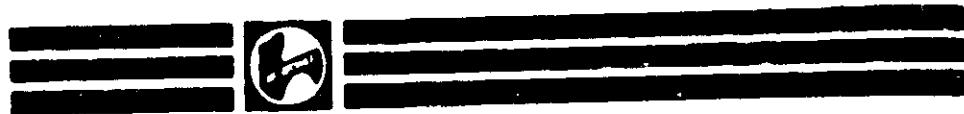
AmarylTM
glimepiride TABLETS

4 mg

100 Tablets

4 mg

UNIT DOSE PACK



Usual
See p
prescr

Store
86° F.

Keep
medic
reach

Amaryl[™]
glimepiride

2 mg Scored Tablets

**BLISTER SIDE
(2 mg Tablets)**

Amaryl[™] Professional
Sample
glimepiride

2 mg Scored Tablets



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

REG TM HOECHST AG
Amaryl TM HOECHST AG

922244-5/95

**FOIL SIDE
(2 mg Tablets)**

Amaryl
glimepiride

4 mg Scored Tablets

**BLISTER SIDE
(4 mg Tablets)**

AmarylTM Professional
Sample
glimepiride

4 mg Scored Tablets

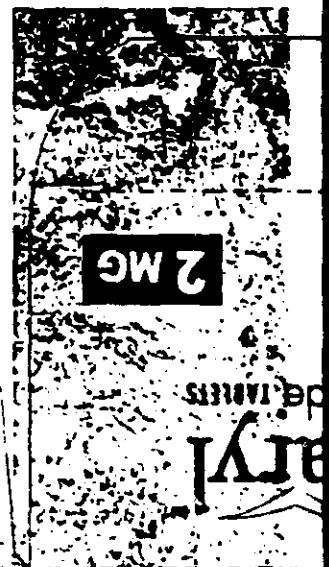
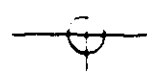


HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258
REG TM HOECHST AG
Amaryl TM HOECHST AG

822344-5/85

**FOIL SIDE
(4 mg Tablets)**

4 mg Sample Push-Thru Foil



For ease in opening
1. Puncture top
2. Push dome to
remove tablet

Amaryl
glimepiride TABLETS

Amaryl
glimepiride TABLETS

Amaryl
glimepiride TABLETS

Ama
glimepiride



PROFESSIONAL
SAMPLE

2 mg
Scored Tablets

2 MG

PROFESSIONAL
SAMPLE

8 Tablets
2 mg Scored Tablets

2 blister cards
4 tablets each

Contains tablets and blister
cards in separate packages

2 MG

PROFESSIONAL
SAMPLE

2 mg
Scored Tablets

2 MG

 **HOECHST-ROUSSEL**
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258
Amaryl is a registered trademark of Hoechst-Roussel Pharmaceuticals Inc.
© 1997 Hoechst-Roussel Pharmaceuticals Inc.

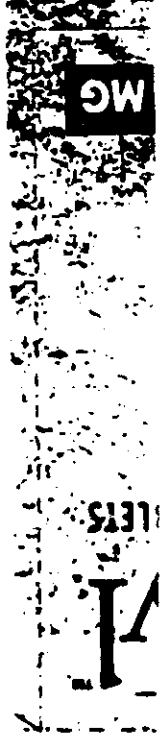
PROFESSIONAL
SAMPLE

2 mg
Scored Tablets
8 Tablets

Usual Dosage:
See insert for full
prescribing information.
Package not child resistant.
Keep this and all
medication out of
the reach of children.
Store between 59°
and 86°

Amaryl **2 MG**
glimepiride tablets





MG

LET'S

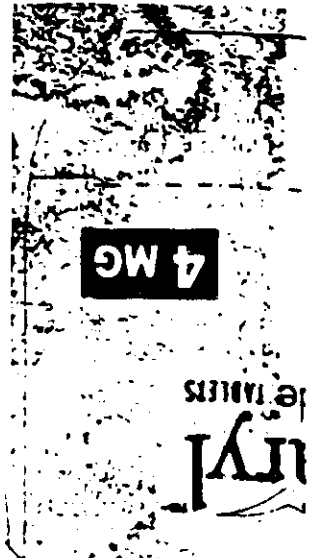
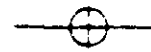
4

A

glir

PROFES
SAMPLE

2 mg
Scorec



For ease in opening:
1. Puncture top.
2. Push dome to
remove tablet.

Amaryl
glimepiride TABLETS

Amaryl
glimepiride TABLETS

Amaryl
glimepiride TABLETS

Ama
glimepirid



PROFESSIONAL SAMPLE

4 mg
Scored Tablets

4 MG

PROFESSIONAL SAMPLE

8 Tablets

Usual Dosage:
See insert for full
prescribing information.
Package not child resistant.

Keep this and all
medication out of
the reach of children.
Store between 59°
and 86°

4 MG

PROFESSIONAL SAMPLE

4 mg
Scored Tablets

4 MG

HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1252

HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1252

PROFESSIONAL SAMPLE

4 mg
Scored Tablets
8 Tablets

Usual Dosage:
See insert for full
prescribing information.
Package not child resistant.
Keep this and all
medication out of
the reach of children.
Store between 59°
and 86°

Amaryl **4 MG**
glimepiride TABLETS



4 mg
Scored Tabl

PROFESSIONAL
SAMPLE
glimer

An

yl

TABLETS

+

⊕

4 MG

○

f

NDA 20496

Bio/Pk

1

NDAA 20496

B10 PR

JUN 23 1995

NDA: 20-496

SUBMISSION DATE:

Glimepiride 1, 2, and 4 mg tablets

08/30/94

04/13/95

BRAND NAME: Amaryl

12/21/94

04/19/95 (2)

01/10/95

04/21/95

02/02/95

04/26/95

02/21/95

05/23/95

03/28/95

06/02/95

04/07/95

06/12/95

SPONSOR: Hoechst-Roussel
Pharmaceutical Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original New Drug Application (1S) for an NME

TITLE: "Review of Human Pharmacokinetics and Bioavailability Studies Submitted to NDA 20-496 (Amaryl; glimepiride 1, 2, and 4 mg Tablets)"

SYNOPSIS:

On 08/30/94, Hoechst-Roussel (HR) submitted NDA 20-496 (Amaryl; glimepiride tablets) to the Agency for review. It was classified as an NME (with a 1S status) for treating Non-Insulin Dependent Diabetes Mellitus (NIDDM). HR wants approval for Amaryl 1, 2, and 4 mg tablet strengths which are compositionally the same, but not proportionally similar across the tablet dosage strength. In its proposed package insert (PI), Amaryl is to be indicated i) as an adjunct to diet to lower the blood glucose in patients with NIDDM and ii) for use in combination with insulin to lower blood glucose in patients whose hyperglycemia can not be controlled by diet in conjunction with an oral hypoglycemic agent. The sponsor indicates that there is no fixed dosage regimen for Amaryl tablets. The usual starting dose as initial therapy is 1 to 2 mg QD administered with breakfast or the first main meal. The maximum recommended dose is 8 mg QD and the usual maintenance dose is 1 to 8 mg QD.

Under the NDA's Human Pharmacokinetics (PK) and Bioavailability (Bio) section, there were 38 study reports submitted. All the studies except two used _____ which is the form for the to-be-marketed Amaryl tablets. Two pilot studies which used both glimepiride _____ were therefore not reviewed. Twenty three out of 36 studies have been identified as pivotal PK and Bio studies. For glimepiride, studied in healthy volunteers were i) single-dose IV (intravenous) and oral administration for absolute bioavailability (F_{abs}), ii) three bioequivalence (BE) studies in which two compared the clinically tested and to-be-marketed tablets that were made at different sites and one compared the clinically tested tablets that were manufactured from bulk drug with different specific surface areas (SSAs), iii) metabolism of ^{14}C -glimepiride, iv) dose proportionality, v) inter- and

intra-subject variability, and vi) food effect. Studied in patients with NIDDM for glimepiride were i) single- and multiple-dose PK and ii) single- and/or multiple-dose PK in special populations (young vs. elderly, male vs. female, normal body weight vs. morbidly obesity, and normal renal function vs. renal impairment). Studied also were i) glimepiride PK in healthy volunteers identified as either extensive (a phenotype of hydroxylation) or poor metabolizers using a test compound, sparteine and ii) drug-drug interactions, i.e., concomitant administration with aspirin, cimetidine, ranitidine, ramipril, propranolol, or warfarin. In most of the above reviewed studies, blood glucose and/or serum insulin and C-peptide levels were reported, but no analyses of PK/PD (pharmacodynamic) relationships for glimepiride were conducted except for one study. In this NDA, i) plasma protein binding of glimepiride, ii) PK of a glimepiride oral solution in healthy volunteers, and iii) PK of the glimepiride metabolite, M1, given by IV administration to healthy volunteers were also studied. Please see the PK summary section below for details.

For this NDA, although the sponsor has attempted to carry out a study, no information on the oral administration of glimepiride tablets to individuals with hepatic impairment was available due to study recruitment problems. Analyses of PK/PD relationship for glimepiride were attempted using NONMEM and SAS programs for one study. However, the dose used was too high (16 mg BID and 32 mg QD) and the PD responses had already reached the "plateau region". In addition, there were no PK/Bio studies to support the second indication, i.e., Amaryl tablet(s) given with concomitant subcutaneous (SC) administration of insulin. In an internal meeting dated 02/28/95, HFD-510 indicated that no PK/Bio studies will be needed to support the second indication. Please see the meeting minutes for details.

Upon the Agency's request, additional in vitro dissolution profile data were submitted for the three strengths of the to-be-marketed tablets that were manufactured from bulk drug with SSAs between 5 and 8 m²/g, i.e., in simulated gastric fluid (SGF) without enzymes and simulated intestinal fluid (SIF) without enzymes using the USP method II (paddle) of 50 rpm as well as 75 rpm. Additionally, in vitro metabolism studies using human hepatic cytochrome P-450 isozymes were also conducted and submitted. Finally, the HPLC methods used for determining glimepiride and its metabolites in serum, and metabolites in urine were validated and they are found acceptable.

RECOMMENDATION:

The Division of Biopharmaceutics (HFD-420) has reviewed the Human PK and Bio section of NDA 20-496 for Amaryl (glimepiride) tablets that was submitted to the Agency on 08/30/94. HFD-420 is of the opinion that the submitted human PK/Bio studies are overall acceptable for meeting the Agency's bio-regulations to support the approval of NDA's proposed first indication.

The reviewing medical officer should review the General Comments and Labelling Comment (page No. 33) and General Comment No. 2 should be communicated to the sponsor and addressed by the sponsor as appropriate. The following dissolution method and specification should be sent to the sponsor.

900 ml of simulated intestinal fluid without enzymes (pH 7.50) at 37°C
USP Apparatus II (paddle) at 50 rpm
Q ≥ in 20 min

Tien Mien Chen

06/09/95

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch II

Biopharm Day on 06/21/95 (Drs. Collins, Ludden, Malinowski, M. Chen, Fleischer, Hussain, and W. Gillespie and Mr. Hunt)

RD initialed by John Hunt JPH 06/12/95

FT initialed by John Hunt J. Hunt 6/22/95

cc: NDA 20-496, HFD-510, Medical Officer (Gueriguian), CSO (Short), HFD-426 (Fleischer), HFD-427 (M. Chen, T. Chen), HFD-340 (Viswanathan), Chron, Drug, Reviewer, G, F, DI, FOI (HFD-19).

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I. Background	5
II. Summary of PK and Bio Studies	6
III. General Comments (No. 2 needs to be sent to the sponsor)	33
IV. Labelling Comment (Needs NOT to be sent to the sponsor)	33

Appendix 1 (Study Summary of 23 Pivotal Studies):

Item	Description	Study No.	Page
1.	Single-dose absolute bioavailability study in healthy volunteers.	1/A/114.....	34
2.	Single-dose safety, tolerability and PK of glimepiride in healthy volunteers after IV administration.	1/A/111..... 1/A/113.....	38 41
3.	Single-dose BE studies between clinically tested and to-be-marketed tablet formulations using healthy volunteers.	1/US/120..... 1/US/121..... 1/A/124.....	45 49 52
4.	Single-dose PK and metabolism of ¹⁴ C-glimepiride after oral administration to healthy volunteers.	1/ZA/101.....	57
5.	Single-dose dose proportionality study in healthy volunteers.	1/A/118.....	61
6.	Inter- and intra-subject variability in PK and PD of glimepiride after single oral doses to healthy volunteers.	1/A/122.....	66
7.	Food effect study in healthy volunteers.	8/US/103.....	72
8.	Single- and multiple-dose safety and PK studies in patients.	8/US/108/DM..... 8/US/105/DM.....	76 80
9.	PK, safety and/or efficacy of glimepiride in NIDDM patients with renal impairment.	1/YU/201/NI..... 1/B/203/NI.....	83 86
10.	PK of glimepiride in male and female patients.	8/US/114/DM.....	91
11.	Multiple-dose PK and PD study of glimepiride given QD orally to young and elderly patients.	8/US/206/DM.....	94
12.	PK of glimepiride in patients with normal weight and in patients who were morbidly obese.	8/US/112/DM.....	100

13. Drug-drug interaction studies in healthy volunteers.	1/D/115.....	103
	1/A/116.....	107
	1/A/123.....	110
	1/A/115.....	113
	8/US/118.....	116
	8/US/119.....	120

Appendix 2:

Appendix 2 contains detailed information on the pH solubility profile of glimepiride substance and tablet SSAs, content uniformities, and dissolution data/profiles.

Appendix 3:

Appendix 3 contains detailed information such as assay validation reports for i) the methods used for determining glimepiride and its metabolites in serum and/or urine, ii) the interday precision for the above assays used, iii) the assay methods for glucose in blood and insulin and C-peptide in serum, etc..

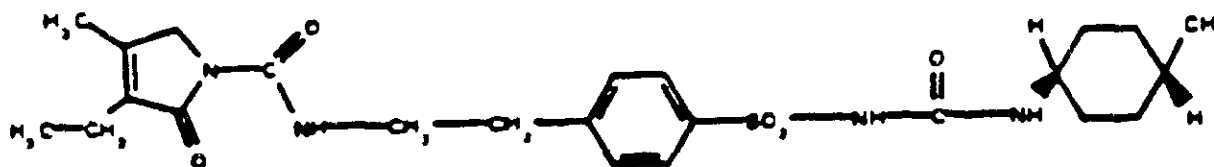
Appendix 4:

Appendix 4 contains additional information such as the PI, Dr. Gary Barnette's bioreview for the 05/19/95 supplement, plasma protein binding, the results of statistical and PK analyses, an updated PK Section of the PI, and the study summary of each non-pivotal study.

Appendices 2 to 4 are being retained in HFD-420. For PK and/or PD raw data, they are stored on diskettes and also being retained in HFD-420. They can be obtained upon request.

I. BACKGROUND:

Glimepiride is a white to yellowish-white crystalline, odorless to practically odorless powder with a molecular weight of 490.62. It is a weak acid with a pK_a of 6.2 and it is practically insoluble in water. Glimepiride does not possess a chiral center and its SSA of the bulk drug for the to-be-marketed tablets will be in the range of 5 to 8 m^2/g (by BET method). As indicated by the reviewing chemist of HFD-510, $\geq 50\%$ of particles are $\leq 2.5 \mu m$ and $\geq 99\%$ are $\leq 10 \mu m$ by using a laser granulometry). Its chemical structure is shown below:



Glimepiride is a new oral blood glucose-lowering drug of the sulfonylurea class. It appears to stimulate the release of insulin from the pancreas, an effect that depends on functioning beta cells in the pancreatic islets. However, extrapancreatic effects might be involved. The sponsor reported that glimepiride binds with high affinity to a 65 kD ATP-sensitive potassium channel which is different from that (a 140 kD) of conventional sulfonylurea. The sponsor claims that glimepiride lowers blood glucose levels with less insulin both acutely and chronically to a greater extent than that of other sulfonylureas. It also has a significantly less effect on the cardiovascular system than do other sulfonylureas.

II. SUMMARY OF PHARMACOKINETICS, BIOAVAILABILITY, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

1. PHARMACOKINETICS/BIOAVAILABILITY:

Single doses of glimepiride (1, 1.25, and 1.5 mg) were given IV to healthy volunteers (Study Nos. 1/A/114, 1/A/111, and 1/A/113, respectively). In Study No. 1/A/114, an oral dose of 1 x 1 mg tablet was also given for studying the F_{∞} value. Typical mean PK parameters for glimepiride and its metabolite, M1, in serum after the 1 mg IV and oral doses are given in Table 1 below. Due to the very small dose given no PK parameters for M2 in serum were calculated. Mean serum profiles for glimepiride and its metabolite are shown in Figure 1 attached.

Similar AUC values with no significant differences obtained after IV and oral doses indicates that glimepiride is completely absorbed after oral administration ($F_{\infty} = 1$). The mean total body clearance (CL) values for glimepiride calculated as CL/f for oral or IV dose (f assumed to be 1) were, therefore, very similar.

No parent drug was found in urine after either 1 mg oral or IV doses. Under the assumptions that i) the orally administered parent drug entirely traverses the GI wall (i.e., completely absorbed as unaltered parent drug) and ii) only hepatic metabolism occurs, the hepatic extraction ratio for glimepiride passing through the liver each time could be estimated to be around 6%. The above assumptions appear to be valid because the fraction of dose converted to metabolite M1 and further metabolized to M2, is seemingly independent of the route of administration.

The mean amounts of metabolite M1 excreted in urine were 0.366 ($\pm$ 0.060) and 0.381 ($\pm$ 0.098) mg after the IV and oral doses, respectively, and those for M2 were 0.169 ($\pm$ 0.053) and 0.143 ($\pm$ 0.060) mg, respectively. The ratio of M1/M2 was around 2 for both IV and oral doses. No significant differences in urinary recovery for the metabolites M1 and M2, as well as for M1 + M2, after IV (51%) and oral (50%) doses suggest complete absorption of the glimepiride tablets (Table 1). Attached Figure 2 shows a typical mean profile of urinary recovery of M1 + M2. Finally, the PK data/parameters

Table 1 Mean ($\pm$ SD) Pharmacokinetic Parameters for Glimepiride and M1

	Trt IV	Trt Oral Glimepiride	Trt IV	Trt Oral M1
C_{max} (ng/ml)	----	87.9 ^a (21.1) [24%]	24.4 (5.3) [22%]	20.3 (5.7) [28%]
T_{max} (hr)	----	2.7 (1.4)	1.6 (0.4)	3.9 (1.9)
AUC_{0-12h} (ng-hr/ml)	371 ^b (161) [43%]	412 (233) [57%]	68 (33) [49%]	80. (40.) [50%]
$AUC_{0-\infty}$ (ng-hr/ml)	412 ^b (184) [45%]	449 (248) [55%]	115 (39) [34%]	134 (46) [34%]
CL/f (ml/min)	47.8 ^c (19.7)	44.9 (16.3)	-----	-----
$T_{1/2}$ (hr)	3.4 (2.0)	3.1 (1.2)	2.7 (1.0)	3.3 (1.2)
Ae_{0-48h} ^d (% dose)	----	----	51.0	50.0

- ^a. Mean ($\pm$ SD) and [CV in %] calculated as SD/Mean x 100%.
- ^b. ANOVA: $p > 0.05$ for glimepiride AUCs between IV and Oral.
- ^c. For glimepiride after IV or Oral, the f value was assumed to be 1.
- ^d. M1 plus M2 as percent of dose excreted in urine after correction for molecular weight.

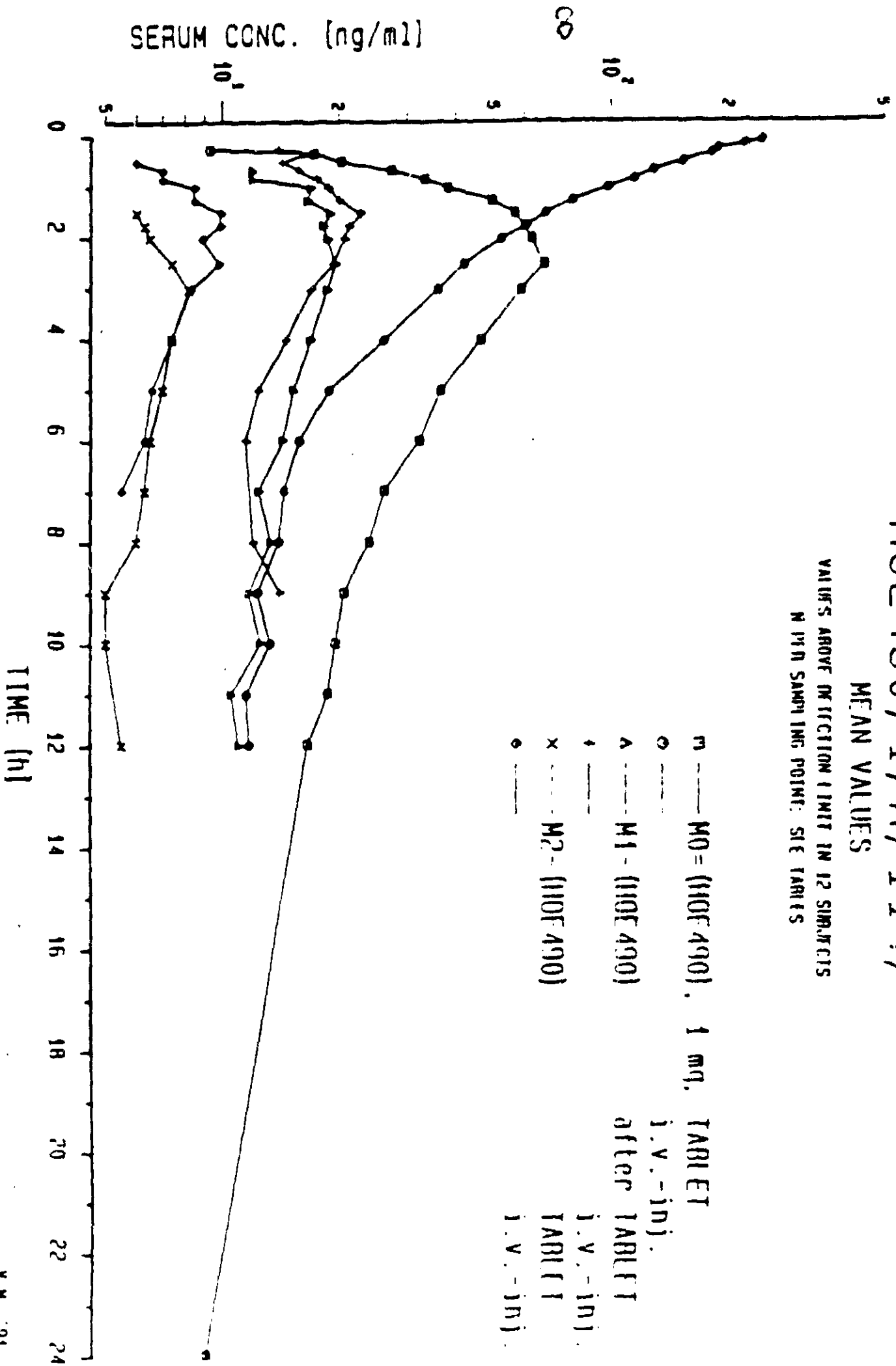
Figure 1

HOE490/1/A/114/-

MEAN VALUES

VALUES ABOVE DETECTION LIMIT IN 12 SUBJECTS
N IN SAMPLING POINT: SEE TABLES

- — M0 = (HOE490), 1 mg, TABLET
i.v.-inj.
- △ — M1 = (HOE490)
after TABLET
i.v.-inj.
- × — M2 = (HOE490)
TABLET
i.v.-inj.
- ◆ — — — — —
i.v.-inj.

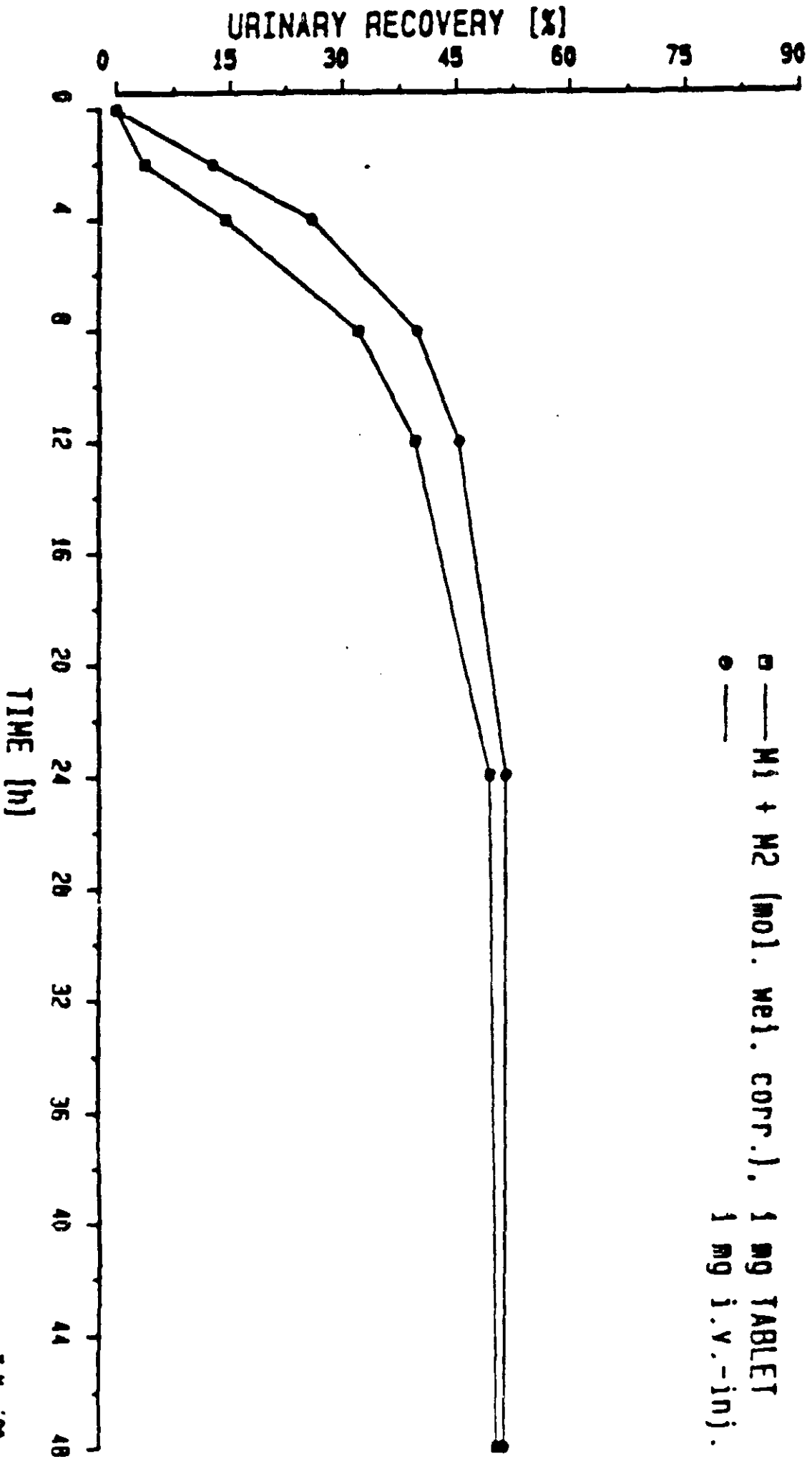


6

Figure 2

HOE 490/1/A/114/-

MEAN VALUES (n=12)



obtained from the other two IV studies (Nos. 1/A/111 and 1/A/113) all showed similar results as those obtained from Study No. 1/A/114. Please see individual study details in Appendix 1. Several non-pivotal studies were conducted; i) oral administration of glimepiride solution (Study Nos. 1/A/110 and 1/A/112), ii) IV administration of glimepiride to patients with biliary T-drainage (No. 1/BG/201/NI), and iii) IV administration of M1 metabolite (Study Nos. M1/1/A/102 and M1/1/A/103).

The results obtained from Study Nos. 1/A/110 and 1/A/112 (oral administration of 1 and 1.5 mg glimepiride solution) showed that the PK performance of glimepiride in solution is similar to that for tablets except that glimepiride solution had a higher C_{max} (peak concentration) value with a smaller T_{max} (time to reach the C_{max}) value as might be expected. In Study No. 1/BG/201/NI, 1 mg glimepiride was given IV to 5 patients who had a surgical procedure requiring biliary T-drainage. The amounts of M1 and M2 recovered in urine were 0.28 ± 0.11 mg ($n=3$) and 0.19 ± 0.12 mg ($n=3$), respectively, and the total recovery of M1 + M2 after 24 hr postdose (Ae_{0-24}) as % of glimepiride dose was around 47%. Further incubation of urine with glucuronidase/sulfatase did not change the (free) M1 levels in urine considerably. It was reported that in the bile, i) no parent drug could be detected, ii) M1 was excreted to a minor extent; 0.023 ± 0.016 mg ($n=4$), and iii) M2 could not be measured due to assay interferences.

In Study No. M1/1/A/102 a single dose of 1.5 mg of M1 was given IV to healthy volunteers and the results of the study are briefly summarized below in Table 2. The mean amounts of M1 and M2 excreted in urine were 0.853 (± 0.117) mg and 0.200 (± 0.033) mg, respectively. The ratio of M1/M2 was > 4 . The renal clearance (CL) for M1 and M2 were 43.8 ml/min and 41.8 ml/min, respectively. The urinary recovery (Ae_{0-24}) of M1 + M2 as % of glimepiride dose was 69.9 (± 7.4) % which was higher than that (50.0%) obtained from Study No. 1/A/113 where a 1.5 mg of parent drug, glimepiride, was given IV to healthy volunteers. The study results may indicate that after the IV administration of 1.5 mg M1 metabolite, M1 is less available for hepatic biotransformation as compared to its parent drug and different PK data/parameters for M1 obtained from the above two IV studies could be as expected. The results obtained from another M1 study (3 mg given IV to healthy volunteers; Study No. M1/1/A/103) showed similar PK performance of M1 metabolite in normal volunteers. The M1 and M2 amounts excreted in urine were 1.31 (± 0.27) and 0.412 (± 0.076) mg, respectively, and the M1 + M2 as % of glimepiride dose was 57 (± 8.9) %.

Table 2 Mean ($\pm$ SD) Pharmacokinetic Parameters for Metabolites M1 and M2

Metabolite	M1	M2
C_{max} (ng/ml)	-----	16.2 (3.4) [21%]
T_{max} (hr)	-----	1.5 (0.7)
$AUC_{0-\infty}$ (ng-hr/ml)	349 (110) [32%]	90 (40) [44%]
CL/f (ml/min)	78.3 ^b (24.3)	-----
$T_{1/2}$ (hr)	1.2 (0.4)	2.8 (1.1)
CL (ml/min)	43.8 (15.9)	41.8 (15.7)
Ae_{0-24} ^c (% dose)		69.9 (7.4)

^a. Mean ($\pm$ SD) and [CV in %] calculated as SD/Mean x 100%.

^b. The CL/f for M1 was calculated as dose (M1)/ $AUC_{0-\infty}$ (M1).

^c. M1 plus M2 as % of dose excreted in urine after correction for molecular weight.

2. BIOEQUIVALENCE:

Three BE studies (Nos. 1/US/120, 1/US/121, and 1/A/124) were conducted. The to-be-marketed tablets and clinically tested tablets are compositionally and proportionally the same within a tablet dosage strength except that the to-be-marketed tablets were made with dye and the clinically tested tablets were made without dye plus there were some differences in i) bulk drug SSAs and ii) shape, i.e., to-be-marketed tablet has score on its surface but the clinically tested tablet does not. Tablet lots used in the first two BE studies were i) clinically tested 1 and 4 mg tablets with an SSA of 6.0 m²/g that were manufactured by HRPI, Germany and ii) the US manufactured to-be-marketed 1 and 4 mg tablets with an SSA of 5.8 m²/g. Please see the formulations and the SSAs of tablets used in Appendix 2 for details.

Study No. 1/US/120 was a single dose, open label, 3-way crossover study with a washout period of 7 days. Twenty four healthy male volunteers received i) 1 x 4 mg clinically tested tablet with an SSA of 6.0 m²/g, ii) 1 x 4 mg to-be-marketed tablet with an SSA of 5.8 m²/g, and iii) 1 x 4 mg to-be-marketed tablet with an SSA of 8.9 m²/g under fasting conditions. The results of the 2-1-sided tests with 90% CIs (confidence intervals) for the clinically tested tablets (SSA: 6.0 m²/g as the reference product; R) and to-be-marketed tablets (SSA: 5.8 m²/g as the test product; T) showed bioequivalence based on log-transformed C_{max} (97%-118%) and AUC (98%-108%).

Since the bulk drug powder with an SSA range between 5.0 and 8.0 m²/g will be used for manufacturing the commercial tablets, the comparison between the to-be-marketed tablets with an SSA of 8.9 m²/g and the clinically tested tablets with an SSA of 6.0 m²/g is less of a concern. For this comparison, however, the 4 mg tablets with an SSA of 8.9 m²/g were found to be more bioavailable (in terms of C_{max}) than the clinically tested 4 mg tablets with an SSA: 6.0 m²/g. The results obtained from a non-pivotal study No. 8/US/110 also showed the similar trend that tablets with a higher SSA, 8.9 m² as compared to the 6.0 m²/g, tended to be more bioavailable (in terms of C_{max} and/or AUCs) as anticipated. Please see the individual study details in Appendix 1.

Study No. 1/US/121 that was submitted on 02/02/95 was a single dose, open label, 2-way crossover design using 24 healthy male volunteers who received i) 1 x 1 mg clinically tested tablet with an SSA of 6.0 m²/g and ii) 1 x 1 mg to-be-marketed tablet with an SSA of 5.8 m²/g under fasting conditions. The results of the 2-1-sided tests with 90% CIs for the clinically tested tablets (SSA: 6.0 m²/g as R) and to-be-marketed tablets (SSA: 5.8 m²/g as T) also showed bioequivalence based on log-transformed C_{max} (102%-124%) and AUC (97%-108%). However, the C_{max} of the 1 mg to-be-marketed tablet was 11% higher than that of the reference and it was statistically significantly different (p < 0.001).

In order to cover the SSA range of 5 and 8 m²/g, an additional BE study was conducted. Study No. 1/A/124 was a single dose, double-blind, 3-way crossover design using 24 healthy male volunteers who received 1 x 2 mg clinically tested tablet manufactured from bulk drug with SSAs of 7.9 (batch No. 90; Treatment A), 5.7 (batch No. 89; Treatment B), and 4.9 m²/g (batch No. 88; Treatment C) under fasting conditions. The 2 mg clinically tested tablets were all manufactured as pilot scale batches (4% of the full-scale production size batch) with three different SSAs and they were all bioequivalent to one another as shown below:

Table 3 Results of the 2-1-sided Tests with 90% CIs

90% CIs:	B/A	C/A	C/B
C _{max}	85-102%*	84-101%	90-109%
AUC _{0-12h}	98-122%	88-109%	80-99%
AUC _{0-∞}	99-122%	88-109%	80-99%

*. 90% CIs based on the 2-1-sided tests for log-transformed C_{max} or AUCs.

Urinary excretion of M1 and M2 was obtained only for study No. 1/A/124 and the Ae₀₋₂₄ values for M1 + M2 were 50.3 (± 7.7)%, 46.5 (± 6.3)%, and 47.5 (± 6.8)% for the 2 mg tablets with SSAs of 7.9, 5.7, and 4.9 m²/g, respectively. The mean Cl_r values were 42.1 ± 12.7, 36.9 ± 9.3, and 40.4 ± 12.5 ml/min, respectively. For mean blood glucose levels and mean serum insulin and C-peptide levels, there were no significant differences found among tablet batches for each PD parameter.

3. INTER- AND INTRA-SUBJECT VARIABILITY:

Inter- and intra- subject variability assessments were obtained in Study No. 1/A/122 where a single dose of 1 x 2 mg glimepiride tablet was given repeatedly to 12 healthy volunteers under fasting conditions on three occasions (Days 1, 2, and 3) with a washout period of 7 days between treatments. The results showed that i) for mean C_{max} values, the overall CV% was 32.7% and the CV% values of inter- and intra-subject variability were calculated to be 24.5% and 22.5%, respectively, and ii) for mean AUC_{0-∞} values, the overall CV% was 29.1% and those for the inter- and intra-subject variability were calculated to be 29.4% and 16.9%, respectively. The sponsor reported that i) based on the 2-1-sided tests with 90% CIs for log-transformed C_{max} and AUC, Day 1 and Day 2 are BE, but Day 3 was not equivalent to either Day 1 or Day 2 in terms of log-transformed C_{max} (79% - 110%) and ii) the urinary recovery (Ae₀₋₂₄) for M1 + M2 showed no differences among the treatments; 46.7 (± 4.6)%, 49.8 (± 4.5)%, and 51.4 (± 4.0)% for Days 1, 2, and 3, respectively. The CL_r values for M1 metabolite were calculated to be 41.9 (± 12.4), 40.9 (± 10.2), and 42.4 (±

10.4) ml/min, respectively, and they were all consistent with those reported previously. The overall CV% and the CV% values for inter- and intra-subject variability for blood glucose and serum insulin and C-peptide were also calculated. They were smaller than or similar to those obtained for PK parameters. Please see individual study details in Appendix 1.

4. METABOLISM:

The PK and metabolism of glimepiride after oral administration of ~ 1.0 mg of ¹⁴C-glimepiride in capsules was investigated in a pilot study using 3 healthy volunteers (Study No. 1/ZA/101). Typical profiles of radioactivity in blood and serum are shown in Figure 3. The serum levels of total radioactivity increased slowly and reached the C_{max} between 3 and 5 hr postdose and then its disappearance in serum exhibited a two-exponential decay with a predominant mean T_{1/2} of 4.2 ± 0.5 hr and a terminal mean T_{1/2} (about 18.4 ± 2 hr). In whole blood, C_{max} values of radioactivity were found at 4 to 5 hr postdose and the mean glimepiride blood levels were generally about half those in serum indicating that there was no appreciable binding of radioactivity to red blood cells. Due to the assay detection limit, only the predominant phase of decay in whole blood up to 24 hr postdose was obtained with a T_{1/2} of 3.3 ± 0.4 hr. The radio-chromatograms showed 3 major radioactive zones corresponding to parent drug, the hydroxymethyl metabolite, M1 (predominant), and the carboxy metabolite, M2 (further metabolism of M1) in serum.

It is reported that in 7 study days, around 55 to 63% of the orally administered radioactivity were excreted via kidneys with more than 98% being recovered in 3 days. M1 and M2 were identified as the main metabolites accounting for 80-90% of the total radioactivity recovered in urine and the remainder was distributed among numerous, quantitatively insignificant, but not yet identified compounds. No unchanged parent drug was detected in all the urine samples. The T_{1/2} values for the decay of radioactivity in urine were estimated to be 4.9 ± 0.2 hr (predominant phase) and 17.2 ± 3.1 hr (terminal phase). Based on the above study results it indicates that at least one compound may be responsible for the very long terminal T_{1/2} value for the radioactivity measured.

Within 7 days postdose, the % of radiolabelled dose recovered in feces varied to a greater extent among the 3 subjects (24 to 45 %). More than 95% of the total radioactivity found in feces was recovered in 3 days. The main metabolite found in the feces was M2 representing around 45-50% of that recovered in feces. M1 was the second main metabolite found representing > 20% of that recovered in feces. A small fraction of dose (1-2%) was recovered in feces as the parent drug. Therefore, the total radioactivities recovered in 7 days (urine + feces) were 99.0 %, 78.8%, and 99.8 % for volunteers 1 to 3, respectively.

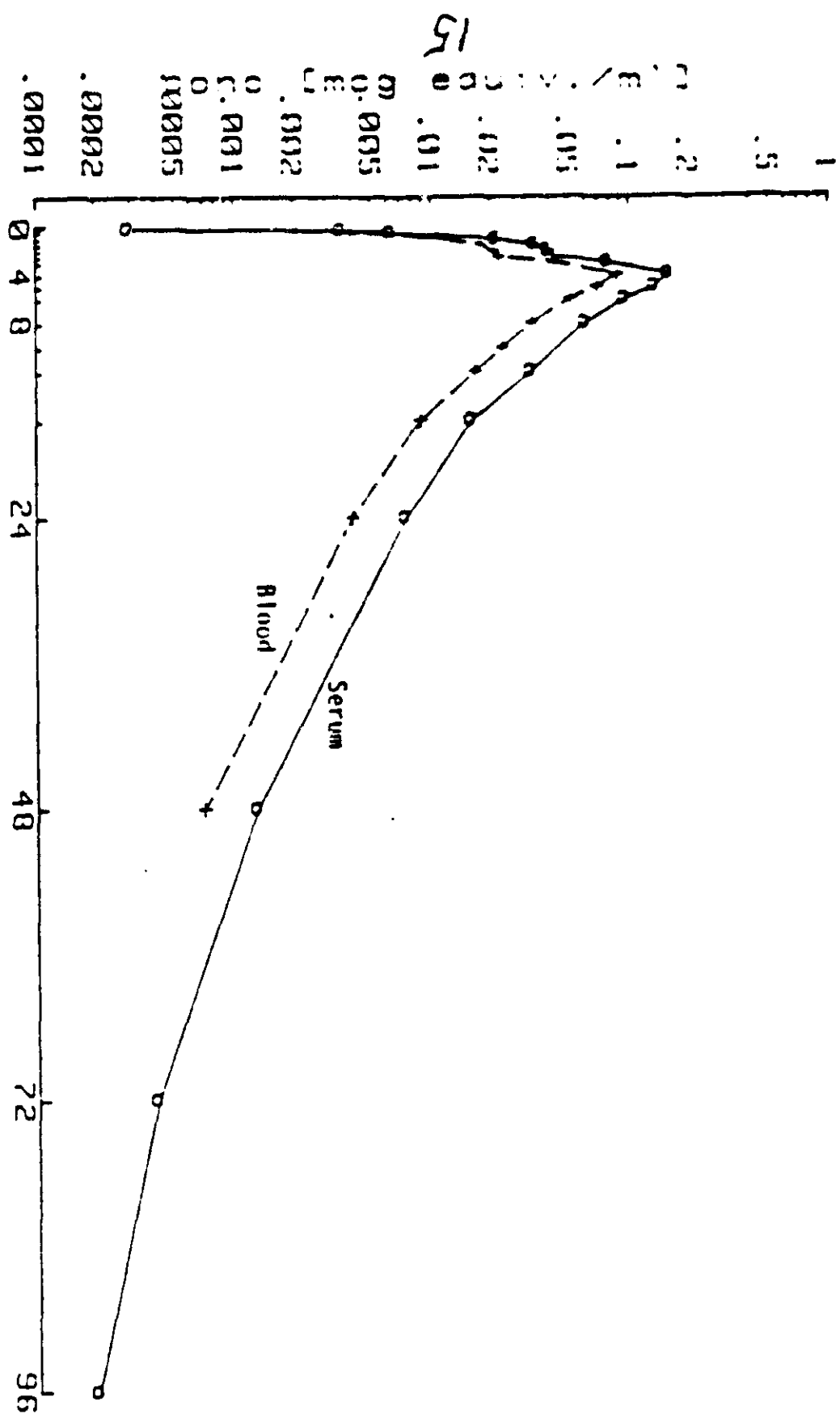


Fig. 3: Serum and blood levels after oral administration of approx. 1 mg ¹⁴C-Hoe 490 to healthy male subject 2

Abteilung: RADIOCHEMISCHES LABORATORIUM
 Verfasser: Dr. Eckert
 KLINISCHE PHARMAKOLOGIE
 Dr. Badian
 DEPT. OF PHARM. BLOEMFONTEIN
 Prof. Dr. B. Meyer, Prof. Dr. F. O. Muller

Calculation: 26.05.1987
 Bench: 01-242-0805-87
 Size: 18
 Dr. Et/su 194-204



Results of an additional in vitro metabolism study were submitted on 05/19/95. This study was conducted in order to identify the hepatic isozyme(s) which is/are responsible for the metabolism of glimepiride. The 05/19/95 submission has been reviewed by Dr. Gary Barnette of HFD-420. Please see Dr. Barnette's review in Appendix 4 for details. The metabolic pathway was proposed by the sponsor and shown below:

Scheme 1

5. DOSE PROPORTIONALITY:

Two studies were conducted. Study No. 1/A/118 was a single-dose study using a double-blind, randomized design with a washout period of at least 7 days. It was conducted in 12 healthy male volunteers where 1 x 1 mg, 2 x 1 mg, 1 x 4 mg, and 2 x 4 mg tablet doses were given. The above doses covered the recommended dose range (1 to 8 mg). The results of glimepiride PK performance, including the results of the 2-1-sided tests with 90% CIs, are summarized in Table 4.

The study results show that a less than dose-proportional increase in C_{max} values for normal healthy volunteers was observed, which was statistically significant ($p < 0.05$). Despite the differences in C_{max} , both AUC_{0-12hr} and $AUC_{0-\infty}$ over the 4 oral dose levels showed proportional dose linearity with $p > 0.05$. Only very small fractions of glimepiride oral doses were found in urine (mainly between 2 and 4 hr postdose).

Table 4 Mean ($\pm$ SD) Pharmacokinetic Parameters for Glimepiride

Dose	1 mg	2 mg	4 mg	8 mg
C_{max} (ng/ml)	103 ^a (34) [33%]	177 (44) [25%]	308 (69) [22%]	551 (152) [28%]
C_{max}^b (ng/ml)	825 ^a (275)	707 (176)	616 (139)	551 (152)
90% CIs:	(130-170%) ^d	(109-148%)	(92-131%)	Reference
T_{max} (hr)	2.3 (0.5)	2.4 (0.5)	2.1 (0.6)	2.8 (1.2)
AUC_{0-last} (ng-hr/ml)	315 (96) [30%]	649 (170.) [26%]	1280. (300.) [23%]	2613 (882) [34%]
AUC_{0-last}^b (ng-hr/ml)	2520 (768)	2596 (678)	2560. (600.)	2613 (882)
90% CIs:	(86-108%)	(89-111%)	(87-109%)	Reference
AUC_{∞} (ng-hr/ml)	326 (97) [30%]	668 (178) [27%]	1297 (303) [23%]	2633 (890.) [34%]
AUC_{∞}^b (ng-hr/ml)	2608 (776)	2672 (712)	2594 (606)	2633 (890)
90% CIs:	(91-113%)	(93-115%)	(88-111%)	Reference
CL/f (ml/min)	55.3 (16.3)	53.5 (15.5)	53.6 (10.6)	56.5 (21.1)
$T_{1/2}$ (hr)	1.2 (0.5)	1.3 (0.4)	1.5 (0.5)	1.5 (0.5)
Ae_{0-48}^f (% dose)	----	0.2	0.11 (0.08)	0.11 (0.08)

- ^a Mean ($\pm$ SD) and [CV in %] calculated as SD/Mean x 100%.
- ^b Normalized to the highest dose (8 mg).
- ^c ANOVA: $p < 0.05$ for glimepiride C_{max} values among doses while $p > 0.05$ for AUC values.
- ^d 90% CIs based on 2-t-sided tests for log-transformed C_{max} or AUCs.
- ^e The CL/f for parent drug was calculated as dose (parent drug)/AUC_∞ (parent drug).
- ^f Glimepiride as % of dose excreted in urine 48 hr postdose.

The PK parameters for M1 in serum were also obtained and they are summarized in Table 5.

Table 5 Mean ($\pm$ SD) Pharmacokinetic Parameters for Glimepiride Metabolite M1

Dose	1 mg	2 mg	4 mg	8 mg
C_{max} (ng/ml)	24.0 ^a (5.7) [28%]	42.1 (9.6) [23%]	76.7 (19.9) [26%]	135.9 (40.2) [30%]
T_{max} (hr)	2.8 (0.8)	2.8 (0.7)	3.3 (0.7)	3.2 (1.1)
AUC_{0-12hr} (ng-hr/ml)	79.1 (36.3) [46%]	157 (48) [31%]	423 (160.) [38%]	786 (249) [32%]
$AUC_{0-\infty}$ (ng-hr/ml)	133 (48) [36%]	210. (55.7) [27%]	479 (172) [36%]	853 (250.) [29%]
$T_{1/2}$ (hr)	3.4 (2.0)	3.1 (1.2)	2.7 (1.0)	3.3 (1.2)
Ae_{0-48}^b (% dose)	45.9 (6.7)	50.7 (6.5)	48.6 (7.7)	46.0 (7.0)

^a. Mean ($\pm$ SD) and [CV in %] calculated as SD/Mean x 100%.

^b. M1 plus M2 as % of dose excreted in urine after correction for molecular weight.

Less than dose-proportional increases in both mean C_{max} and AUC values for M1 were also observed. Nevertheless, the urinary recoveries of M1 + M2 as % of glimepiride dose (Ae_{0-48}) were very similar and were all close to those reported previously. The mean ratios of M1/M2 ranged from 1.87 to 1.94.

Study No. 8/US/108/DM was an open-label, "parallel group" study using 36 patients with NIDDM to assess both single- and multiple-dose dose proportionality (1 x 4 mg, 2 x 4 mg, and 4 x 4 mg tablet doses). After an initial single-dose treatment, a 3-day washout period was followed by 7 days of multiple dosing. The results obtained from this study are summarized in attached Table 6. It was concluded that i) linear PK of glimepiride is supported by the similarities between the single-dose $AUC_{0-\infty}$ and steady-state AUC_{0-24} values for each dosage group and ii) no significant accumulation was

Table 6

Single Dose Pharmacokinetic Values (Means ± SDs) for Glimperide, Metabolite I, and Metabolite II in Serum

	C_{max} (ng/ml)	t_{max} (hours)	AUC ₀₋₂₄ (hours x ng/ml)	AUC _{0-∞} (hours x ng/ml)	Normal C _{1/2α} (hour/1.73 m ²)	Normal V _{1/2α} (L/1.73 m ²)	$t_{1/2}$ (hours)
Glimperide							
Normal	547 ± 218 <i>F</i> $\frac{537}{537}$	2.89 ± 0.90	3210 ± 1030 <i>F</i> $\frac{3244}{1035}$	4000 ± 1320 <i>F</i> $\frac{3796}{1156}$	2.10 ± 0.75	32.9 ± 22.1	12.6 ± 12.8 ^b
Morbidly Obese	410 ± 124 <i>F</i> $\frac{410}{124}$	2.90 ± 0.89	2820 ± 1110 <i>F</i> $\frac{2820}{1110}$	3280 ± 1360 <i>F</i> $\frac{3280}{1360}$	2.12 ± 0.93	26.0 ± 15.4	8.89 ± 3.91
P-value ^c	0.0807	0.9916	0.2609	0.1275	0.9647	0.3501	0.3076
Stand. 90% C.I. ^d	102 to 164 <i>F</i> $\frac{102}{164}$	80.0 to 120%	93 to 147% <i>F</i> $\frac{93}{147}$	98 to 160% <i>F</i> $\frac{98}{160}$	74 to 125%	7.9 to 17.4%	7.3 to 21.1%
Metabolite I							
Normal	180 ± 63	4.50 ± 0.78	1510 ± 570	1890 ± 750	NA	NA	9.76 ± 3.24
Morbidly Obese	135 ± 52	4.33 ± 0.82	1250 ± 340	1690 ± 480	NA	NA	11.6 ± 5.2
P-value ^c	0.0416	0.5714	0.1745	0.5137	NA	NA	0.2780
Stand. 90% C.I. ^d	106 to 173%	92 to 116%	96 to 145%	87 to 136%	NA	NA	6.0 to 10.8%
Metabolite II							
Normal	50.3 ± 15.7	5.00 ± 1.14	454 ± 130	549 ± 212	NA	NA	7.09 ± 3.89
Morbidly Obese	36.5 ± 14.7	5.36 ± 1.45	316 ± 119	383 ± 211	NA	NA	6.37 ± 4.87
P-value ^c	0.0119	0.4731	0.0072	0.0251	NA	NA	0.6715
Stand. 90% C.I. ^d	114 to 179%	78 to 109%	117 to 183%	112 to 197%	NA	NA	6.7 to 15.6%

- (a) For each group and each parameter, n = 14 subjects
- (b) Normalized by body surface area
- (c) When two outliers are excluded, the mean and standard deviation of $t_{1/2}$ is 8.46 ± 2.87 hours
- (d) P-value from the two sample t-test (ANOVA)
- (e) Standardized 90% confidence interval from the two one-sided tests procedure

found after steady state was achieved, i.e., 0.95-1.2 was for glimepiride and those for M1 and M2 in serum were slightly higher, i.e., 1.1-1.2 and 1.5-1.6, respectively.

The mean amount of glimepiride in the body at steady state (Amt_{ss}) based on the last dose on Day 10 for each dose level was estimated by this reviewer. It represents $18 \pm 15\%$, $12 \pm 5\%$, and $29 \pm 18\%$ of the respective daily 4, 8, and 16 mg doses on Day 10. The steady-state volume of distribution (Vd_{ss}) values for glimepiride were, therefore, estimated to be 12.6 ± 9.4 liters, 7.2 ± 3.5 liters, and 18.9 ± 7.2 liters, respectively. The relatively small Vd_{ss} values as compared to total body water indicate that glimepiride has a limited distribution space which is consistent with its high protein binding characteristics ($> 99.5\%$).

Although the same assay method for determining glimepiride and its metabolites in serum was used, mean $T_{1/2}$ values obtained from Study No. 1/A/118 (1.2 to 1.5 hr, Table 4) were found to be smaller to those obtained from Study No. 8/US/108. The sponsor indicated that it could be due to a different PK program used in Europe to calculate individual $T_{1/2}$ values for Study No. 1/A/118. After recalculation of $T_{1/2}$ values for the study using the PCNONLIN program as that used in the US studies, the mean $T_{1/2}$ value for the 4 dose levels ($n=48$) was found to be 5.3 ± 4.1 hr which is close to those reported in Study No. 8/US/108. For M1 and M2 excreted in urine as the % of glimepiride dose i) the Ae_{0-72} values for the single doses were consistent with those reported previously for healthy normal volunteers (around 45 to 50 %) and ii) after multiple doses, Ae_{0-24} at steady state remained unchanged as compared to the Ae_{0-72} after single doses. The mean ratios of M1/M2 ranged from 1.36 to 1.42 (single doses) and those for multiple doses ranged from 1.32 to 1.43. The ratios were similar between single and multiple doses, however, it was noted that they were slightly smaller than those reported previously for healthy volunteers (about 1.5 to 2.0). The mean CL, ranged from 26 to 36 ml/min for M1 and 59 to 96 ml/min for M2 with no differences between single and multiple doses.

6. FOOD EFFECT:

In a 2-way crossover study No. 8/US/103, 1 x 2 mg glimepiride tablet was taken either with 100 ml unsweetened decaffeinated coffee or tea immediately after a standard breakfast (150 ml low-fat milk, 100 ml orange juice, 1 boiled egg, 2 slices of toasted bread, 5 gm of margarine, 20 gm of marmalade, and 20 gm of cheese) or under fasting conditions.

The relative bioavailability estimates for the clinically tested tablets given under fed conditions, as compared to fasting conditions show "equivalence" based on log-transformed C_{max} (0.94), AUC_{0-24} (0.93), and AUC_{0-72} (0.94). No differences between treatments were found in terms of the urinary excretion of M1 + M2 (Ae_{0-24}) as the % of glimepiride dose given (39% under fasting

and 40% under fed conditions). Therefore, the influence of food on the PK performance of glimepiride in vivo (C_{max} being 7% lower, AUCs being 9% lower, and T_{max} being 3% larger under fed conditions) is not considered to be significant when the tablet was given immediately following a standardized breakfast to the healthy volunteers.

7. PROTEIN BINDING:

Protein binding in % (f_b) of glimepiride was extensively studied using equilibrium dialysis and the results are summarized below: i) the f_b values for ^{14}C -glimepiride in serum albumin, α_1 -acid glycoprotein, β -globulin, and γ -globulin in physiological concentrations were 99.5%, 94%, ~90%, and ~95%, respectively, ii) those for ^{14}C -glimepiride to human serum against water (buffer) only or in the presence of aspirin, sodium salicylate, or glucose were all within a very narrow range of 99.7 to 99.9%, iii) the f_b values were fairly constant when using serum obtained from normal healthy volunteers or patients with renal insufficiency, iv) the f_b values were not changed appreciably in the presence of aspirin, sodium salicylate, or glucose when using serum of patients with renal insufficiency, and v) in the range of 0.01 to 10 $\mu g/ml$, the f_b values for human, dog, and rabbit were very similar (99.4%, 99.0%, and 99.2%, respectively). In addition, the f_b values for M1 and M2 were studied using ultrafiltration and they were > 98% and 96%, respectively. Please see Appendix 4 for details.

8. SPECIAL POPULATIONS:

A: Renal Impairment:

Single and multiple PK studies (Nos. 1/YU/201/NI and 1/B/203/NI) were conducted in NIDDM patients with various degrees of renal impairment. In Study No. 1/YU/201/NI, 15 patients were studied in three groups, i.e., Group I with CL_{cr} (serum creatinine clearance) of > 50 ml/min ($n = 5$), Group II with CL_{cr} between 20-50 ml/min ($n = 3$), and Group III with CL_{cr} of < 20 ml/min ($n = 7$). The results of the study show i) CL/f of glimepiride tended to increase with a decrease of CL_{cr} , ii) CL/f of M1 and M2 tended to decrease with a decrease of CL_{cr} , and iii) the elimination of M1 and M2 in urine was impaired in the patients with kidney disease.

Study No. 1/B/203/NI was an open, multiple-dose, dose titration study for 3 months with an initial dose of 1 mg. Two patients had CL_{cr} > 60 ml/min, 5 had CL_{cr} between 30 and 60 ml/min, 5 had CL_{cr} between 10 and 30 ml/min and 4 had CL_{cr} < 10 ml/min. It was also reported by the sponsor that CL/f of glimepiride tended to increase in patients with severe kidney disease and a decrease of CL or CL/f with the decrease of CL_{cr} was also reported for M1 and for M2 ($p < 0.01$) by the sponsor.

An alteration of f_e in these patients was suspected by the sponsor. However, this may not be the case since it has been shown in the above Section that almost no changes in f_e were found. A reduction of F_{abs} of glimepiride in these patients may be speculated and it is seemingly consistent with the fact that the excretion of M1 and M2 in urine was impaired in these patients with kidney disease. Based on the PD outcome, the sponsor concluded that the patients with renal impairment, as well as those without renal impairment, should be clinically dose-titrated and the safety should be carefully and closely evaluated. For its PD results, please see PK/PD Section (page No. 24) for details.

B: Hepatic Impairment:

No studies were conducted for NIDDM patients with hepatic impairment. However, the sponsor indicated that they attempted a study but were unable to recruit patients.

C: Obese Patients:

Study No. 8/US/112/DM was a single dose, open label, parallel group design using 28 NIDDM patients (14 M + 14 F). Prior to normalization for body weight or surface area, the mean C_{max} and AUC values for glimepiride and also for M1 and M2 were, on average, lower in the obese patients (7 M + 7 F), as compared to those in the patients with normal weight (7 M + 7 F). There were, however, no significant differences detected for the PK parameters for glimepiride. Some significant differences were found for M1 and M2 between two groups, i) the mean amounts of M1 excreted in urine (Ae_{0-24}) were significantly different between patients who were not overweight and who were obese, i.e., $16.4 \pm 4.5\%$ and $21.2 \pm 7.2\%$, respectively, ($p=0.043$) and ii) the same was true for M2, i.e., $11.9 \pm 3.5\%$ and $16.3 \pm 4.0\%$, respectively, $p=0.0051$. Mean normalized CL values for M1 between patients who were not overweight and who were obese were similar, i.e., 12.3 ± 5.2 and 13.2 ± 5.8 ml/min/1.73 m², respectively, ($p=0.654$), while those for M2 were significantly different, i.e., 32.1 ± 16.8 and 50.9 ± 23.8 ml/min, respectively, ($p=0.0235$).

Gender differences in some PK parameters for M1 and M2 were found and they existed for both patient groups, i.e., patients who were not overweight (males being heavier than females) and patients who were obese (males and females had matched body weight). After a closer look into each glimepiride PK parameter for each patient group, seemingly no gender differences were observed. Therefore, the reasons for the gender differences found in mean C_{max} and AUC values for M1 and M2 in both groups were not known. Please see individual study details in Appendix 1.

E: Elderly patients:

Study No. 8/US/206/DM was a multicenter, randomized, double-blind, crossover study of 15 weeks duration. The PK and PD of glimepiride for the young and the elderly patients were analyzed for a 6 mg QD dosing regimen. None of the PK parameters were significantly different between the young and the elderly patients for glimepiride and its M1 metabolite. Only M2 showed significant differences between the two age groups in C_{max} , AUC_{0-24} and CL/f values. However, it could be less of a concern. The results of the PD analyses show that no significant differences between the young and the elderly patients were found for all the PD parameters (blood glucose and serum insulin and C-peptide) studied.

F: Others:

Study No. 1/D/115 was a single dose, open label, "parallel group" design. After receiving a single dose of the test drug, sparteine (a marker for cytochrome P-450 IID6 enzyme which is responsible for hydroxylation metabolism), 12 healthy subjects were selected and divided in two groups for this study, i.e., 6 extensive metabolizers and 6 poor metabolizers. One x 1 mg glimepiride tablet was taken with a small portion of breakfast tea immediately before breakfast (3 slices of toast, 30 gm of butter, 25 gm of jam, 300 ml of peppermint tea, and 2 sugar cubes).

The study showed that there were no relevant nor statistically significant differences in the PK of glimepiride and its metabolites, M1 and M2, between the poor metabolizers and the extensive metabolizers. Urinary recoveries (Ae_{0-48}) of M1 + M2 as % of glimepiride oral dose were 39.2% and 39.1% for the extensive and poor metabolizers, respectively, and there were no significant different.

9. PEDIATRICS:

Glimepiride is not intended for pediatric use.

10. GENDER:

Study No. 8/US/114/DM was conducted to investigate gender differences in glimepiride PK. This was a single dose, single period, open label, "parallel group" design using 14 M and 14 F patients with NIDDM. Minor differences between genders for mean AUC_{0-24} and $AUC_{0-∞}$ values were observed but they were not statistically significant. A statistically significant difference between genders was seen for C_{max} : 423 ng/ml (32% ↑) for females as compared to 287 ng/ml for males ($p = 0.025$) which could be partly due to a difference in body weight (102 ± 13 kg for male and 83.2 ± 13.6 kg for females). No statistically significant gender differences were found for any other glimepiride PK parameters, as well as for the PK parameters obtained for M1 and M2 in

serum. The urinary excretion ($Ae_{0,24}$) of M1 + M2 as the % of glimepiride dose was similar for males (42.5%) and females (43.2%) and no gender differences were found. The mean ratios of M1/M2 were also similar for male patients (1.4) and female patients (1.3).

11. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

A PK/PD study (No. 8/US/106/DM) was conducted and the NONMEM and SAS programs were used to analyze the relationships of PK/PD for glimepiride. However, the dose used in this study was too high; 32 mg/day given either by 32 mg QD or 16 mg BID. After a joint review with Dr. Raymond Miller of HFD-420, it was found that i) the PD responses had already reached the "plateau region" and ii) the PK/PD model employed was incomplete and questionable. Therefore, it was concluded that the PK/PD data obtained from this study are not worthy for reanalysis since it is impossible to gain insight into the PK/PD relationship of this drug due to the too high dose used. For this reason, the study was viewed as a non-pivotal study. Please see individual study detail in Appendix 1.

No additional PK/PD analyses were conducted by the sponsor for oral administration of glimepiride in healthy volunteers or in NIDDM patients. From the preliminary studies of IV administration of 1, 1.25, and 1.5 mg glimepiride to normal healthy volunteers (Study No. 1/A/114, 1/A/111, and 1/A/113), it can be seen that blood glucose decreased rather sharply, i.e., i) mean blood glucose C_{min} level was reached at around 1 hr post IV administration, as compared to that (around 2 to 3 hr) post oral tablet administration and ii) the maximum increases in mean serum insulin and C-peptide levels occurred at around 0.5 hr after IV administration, as compared to around 2 hr after oral tablet administration. However, no additional statistical analysis was performed. Serum insulin and C-peptide levels seemingly responded more extensively to the food intake.

An inter-study comparison of the PD responses was briefly conducted for IV solution (A), oral solution (B), and oral tablets (C) of glimepiride given to healthy volunteers under fasting conditions. It shows that seemingly there is a PK/PD relationship between serum glimepiride levels (PK) and serum insulin and C-peptide levels and blood glucose levels (PD), i.e., i) the mean C_{max} of serum insulin and C-peptide levels occurred in a sequence of A (the earliest) < B < C (the latest) and ii) the mean blood glucose C_{min} levels occurred also in a sequence of A (the sharpest and earliest) < B < C (the mildest and latest).

It was reported by the sponsor that the results obtained from the single-dose dose proportionality study (1, 2, 4, and 8 mg; Study No. 1/A/118), where only blood glucose levels were obtained, showed a dose response in terms of blood glucose lowering effect, but no additional statistical analysis for blood lowering effects was employed.

It was further reported by the sponsor that blood glucose and serum insulin and C-peptide data obtained from Study No. 1/B/203/NI (dose-titration: glimepiride 1-8 mg QD orally to patients with renal impairment) showed that i) there were no relevant differences in PD observed after steady state was reached and ii) comparable controls in blood glucose levels between Days 1 and 35 were achieved. It is of interest to note that no difference was found between the Hemoglobin A_{1c} levels that were determined before the first medication and 1, 2, and 3 months thereafter. The sponsor indicated that it could be explained by the fact that all patients were rather well controlled before the study.

12. DRUG-DRUG INTERACTION: Please see the study description for each individual study in Appendix 1 for details.

A: Concomitant Administration With Propranolol:

Study No. 1/A/116 was a double-blind, 2-way crossover study with a washout period of 14 days. Propranolol (40 mg TID for 5 days) and placebo treatments were employed. On day 4, a single 1 x 2 mg tablet dose of glimepiride was given under fasting conditions. Under concomitant treatment C_{max}, AUC, and T_{max} values of glimepiride increased by 23%, 22%, and 15%, respectively, and they were significantly different from the placebo control (p < 0.05).

No differences were found in the mean baseline levels of the PD variables between propranolol and placebo treatments prior to glimepiride administration on Day 4. In addition, no differences were found for these PD parameters except that with the propranolol treatment, there was a 6% decrease (p < 0.05) for the average blood glucose levels during 4 to 10 hr post glimepiride dosing, as compared to placebo control.

B: Concomitant Administration With Ramipril:

Study No. 1/A/123 was a double-blind, 2-way crossover design with a washout period of 28 days. Ramipril (5 mg QD for 5 days) and placebo were employed. On Day 5, a single 1 x 2 mg tablet dose of glimepiride was given under fasting conditions. No blood samples were collected for assessing the PK of glimepiride nor were urinary data for M1 and M2 reported. It was reported by the sponsor that no significant differences were found among the PD parameters under concomitant administration of ramipril, as compared to placebo control.

C: Concomitant Administration With Aspirin:

Study No. 1/A/115 was a double-blind, 2-way crossover design with a washout period of 14 days. Aspirin (1 gm TID for 5 days) or placebo were employed. On Day 4, 1 x 1 mg tablet dose of glimepiride was given

immediately after breakfast (3 slices of toast, 30 g butter, 25 g jam, 300 ml fruit tea, and two sugar cubes). Only AUC_{0-24} (34% ↓) and CL/f (34% ↑) values of glimepiride were significantly different for aspirin treatment as compared to placebo control. The amounts of M1 + M2 excreted in urine as % of glimepiride dose ($42.3 \pm 7.8\%$ for placebo control and $40.9 \pm 7.4\%$ for aspirin treatment) were not different. Furthermore, PD data/parameters of glimepiride seemingly were not changed.

D: Concomitant Administration With Cimetidine and Ranitidine:

Study No. 8/US/118 was an open-label, randomized, 3-way crossover design with a 14-day washout period. Placebo (Treatment A), 800 mg cimetidine QD (Treatment B), and 150 mg ranitidine BID (Treatment C) were employed for 4 days. On Day 4 of each treatment period (Treatment A, B, or C), a single 1 x 4 mg glimepiride tablet dose was given under fasting conditions. A 3-hr oral glucose tolerance test (GTT; 75 gm of glucose) was conducted on Days 2, 3, and 4.

No significant differences were found in glimepiride PK parameters (i.e., mean C_{max} and AUC) among the three treatments except T_{max} value being decreased by 33% and 12% for Treatments B and C, respectively, ($p=0.0393$), as compared to Treatment A. For some glimepiride mean serum levels, significant differences for Treatment B or C, as compared to Treatment A were found. A double peaking at around 5 hr postdose was found.

For the PK of metabolite M1, significant differences were found, i) Treatments B and C had higher mean AUC values (7% and 11% ↑, respectively, $p=0.0135$), as compared to Treatment A and ii) Treatment C had a significantly higher (25% ↑) mean C_{max} value, as compared to Treatment A ($p=0.001$). Some significantly higher M1 mean serum levels were found for Treatment B or C as compared to Treatment A. Similarly, some significant differences were found among treatments for M2, i.e., i) mean C_{max} and T_{max} values and ii) mean serum levels. However, for amounts of M1 + M2 excreted in urine (Ae_{0-24}), they were almost the same; 42.6%, 42.3% and 44.2% for Treatments A to C, respectively.

Since M1 is reported to possess about 1/3 of the pharmacological activity of the parent drug in animal studies, the higher mean AUC_{0-24} and C_{max} values of M1 could be of clinical relevance. However, it was shown in the study that for serum insulin PD data/parameters, Treatments B and C had similar AUC_{0-3} and C_{max} values while for blood glucose, Treatments B and C had smaller mean AUC_{0-3} and C_{max} values, as compared to Treatment A. Therefore, it is not clear as to whether the contribution of M1 to the total pharmacologic activity after an oral administration of glimepiride is clinically relevant or not.

The PD parameters for blood glucose levels after the GTT on Day 3, i.e., baseline (denoted as Treatment D), with cimetidine only (Treatment E), and

with ranitidine only (Treatment F) and those with the addition of glimepiride (Treatments A to C on Day 4) were obtained. For blood glucose parameters, no differences among Treatments D, E, and F, nor among Treatments A, B, and C were found except for mean AUC_{0-1} values, being marginally different with $p = 0.0509$ between Treatments A and B (7% ↓). For serum insulin parameters, no significant differences among Treatments D, E, and F nor among Treatments A, B, and C were found. For mean blood glucose and serum insulin levels, some significant differences were found among Treatments A to C and/or among Treatments D to F. The concomitant administration of either cimetidine (800 mg QD in the evening) or ranitidine (150 mg BID) did not seemingly affect the PK and PD response to a single oral dose of glimepiride.

E: Concomitant Administration With Warfarin:

Study No. 8/US/119 was an open-label, non-randomized design. Each treatment period consisted of 11 days. A washout period of 14 days separated the two single-dose administrations of 5 x 5 mg warfarin tablets; Period I without glimepiride and period II with glimepiride 1 x 4 mg tablet dose QD for 10 days. Warfarin alone or given with glimepiride were all taken 30 min before breakfast. A prothrombin time (PT) was measured in both Periods.

No significant differences in PK of either R-warfarin or S-warfarin were observed between administration of warfarin alone and with concomitant administration of glimepiride. In addition, no significant changes in plasma protein binding were found. Finally, only the mean trough serum levels of glimepiride and M1 were presented and there were no significant differences found for glimepiride or M1. Statistically significant decreases in the PD responses to warfarin in terms of mean AUC_{0-168} and C_{max} values of PT were found. The magnitude of the reductions was very small. However, since this study was conducted in normal volunteers, the extrapolation of the study results to patients must be performed with caution.

In summary, i) coadministration of aspirin (1 gm TID) and glimepiride (1 mg) leads to a 34% decrease in the mean glimepiride AUC and the mean C_{max} decreased by 4% and blood glucose and serum C-peptide levels were unaffected, ii) coadministration of either cimetidine (800 mg QD) or ranitidine (150 mg BID) with glimepiride (4 mg) did not significantly alter the absorption and disposition of glimepiride and no differences were seen in hypoglycemic symptomatology, iii) concomitant administration of propranolol (40 mg TID) and glimepiride significantly increased C_{max} , AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15% respectively, and CL/f decreased by 18%, however, PD responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo, iv) concomitant administration of glimepiride (4 mg QD) did not alter the PK of R- and S-warfarin enantiomers (a single dose of 25 mg (racemate), and vi) the responses of serum glucose, insulin, C-peptide and

plasma glucagon to a 2 mg glimepiride were unaffected by coadministration of ramipril (5 mg QD) in normal subjects and no hypoglycemic symptoms were reported.

13. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

Amaryl 1, 2, and 4 mg (glimepiride) tablet strengths are compositionally the same, but not proportionally similar across the tablet dosage strength (Table 7). For dosage and administration, please see the PK summary Section as well as individual study reports in Appendix 1 for details. For the pH solubility profile of glimepiride substance, and the tablet batch Nos., SSAs, please see Appendix 2 for details.

14. DISSOLUTION AND CONTENT UNIFORMITY:

The sponsor provided information on the content uniformities and dissolution test results for tablets using 900 ml of pH 7.8 phosphate buffer at 37°C with USP Apparatus II (paddle) at 75 rpm which was used in the international stability studies. Please see Appendix 2 for details.

Additional dissolution data/profiles using the proposed method and specification (pH 7.8 buffer), plus SGF and SIF at 75 rpm as well as at 50 rpm were requested. They were submitted on 12/21/94. The tablets lots used (with SSA of 5 to 8 m²/g) are shown below in Table 8. Please see the Appendix 2 for details.

Table 8 Tablet Lots Used in the Additional Dissolution Tests

Batch No.	Strength	SSA (m ² /g)	Scale	Site of Manufacture
RP10602 (To-be-marketed) ^a	1 mg	5.8	Production	USA
RP10814 (To-be-marketed) ^b	1 mg	7.9	Production	
88 (Clinically Tested) ^c	2 mg	4.9	Pilot (	ts)
99 (To-be-marketed) ^d	2 mg	7.6	Production	
RP10560 (To-be-marketed) ^e	4 mg	5.8	Production	USA
RP10815 (To-be-marketed) ^f	4 mg	7.7	Production	

- ^a. The lot was used in the BE study No. 8/US/121.
- ^b. The lot was used in the international stability study.
- ^c. The lot was used in the BE study No. 1/A/124.
- ^d. The lot was used in the international stability study.
- ^e. The lot was used in the BE study No. 8/US/121.
- ^f. The lot was used in the international stability study.

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The average percentages of glimepiride dissolved in SGF without enzymes were 2 to 8% for the 1, 2, and 4 mg tablets and in SIF they were 69 to 95%. The dissolution (also provided in Appendix 2) showed that the highest tablet strength, 4 mg, i) could only meet the dissolution specification of $Q \geq$ in 15 min in a medium with a pH $\geq$ 7.8 at a paddle speed of either 50 or 75 rpm and ii) could be dissolved with $Q \geq$ in 20 min at a paddle speed of 50 rpm in SIF without enzymes. Therefore, the following dissolution method and specification are recommended:

900 ml of simulated intestinal fluid without enzymes (pH 7.50) at 37°C
USP Apparatus II (paddle) at 50 rpm
 $Q \geq$ in 20 min

Please see the content uniformity of the tablet lots in Appendix 2 for details.

15. SAMPLE COLLECTION:

Please see blood sample collection and treatment for details in each study report in Appendix 1.

16. ASSAY:

Determinations of serum glimepiride and its metabolites and urinary glimepiride metabolites were all performed by HPLC methods. Most of the assay methods used were the same as those detailed in the method validation report Nos. 01-L42-0550-88 and 01-L42-0550-89 for serum and urinary samples, respectively. The HPLC methods are acceptable for this NDA. The assay specifications are summarized below. Please see the results of the assay validation and the interday precision for the assay used in Appendix 4 for details.

A. Serum Samples:

i. Glimepiride:

-
- a. Standard curves:
 - b. Detection limit and limit of quantitation:
 - c. Absolute Recovery:
 - d. Accuracy:

e. Precision:

ii. M1

a. Standard curves:

b. Detection limit and
limit of quantitation:

c. Absolute Recovery:

d. Accuracy:

e. Precision:

iii. M2

a. Standard curves:

b. Detection limit and
limit of quantitation:

c. Absolute Recovery:

d. Accuracy:

e. Precision:

B. Urinary Samples:

i. M1

- a. Standard curves:
- b. Detection limit and limit of quantitation:
- c. Absolute Recovery:
- d. Accuracy:

e. Precision:

ii. M2

-
- a. Standard curves:
 - b. Detection limit and limit of quantitation:
 - c. Absolute Recovery:
 - d. Accuracy:

e. Precision:

For detailed assay validation for blood glucose and serum insulin and C-peptide levels, please see their assay validation reports in Appendix 3.

17. DATA ANALYSIS:

Noncompartmental methods were used for calculating the PK parameters for glimepiride and its metabolites in serum for each subject. For M1 and M2 excreted in urine, recoveries as the absolute amounts of M1 and M2 as well as the % of glimepiride dose excreted were calculated. ANOVA was also used.

18. OTHERS:

For the non-pivotal studies submitted, they all showed similar PK results and/or PD outcome.

III. GENERAL COMMENTS: (No. 2 needs to be sent to the sponsor)

1. The clinically tested 2 mg tablet formulation with three different SSAs (Lot Nos. 88, 89, and 90) that was used in Study No. 1/A/124 was made as pilot scale batches. Since

- these tablets were all bioequivalent to one another,
- one of the batches (Lot No. 88 with an SSA of 4.9 m²/g) showed similar dissolution data/profiles as compared to a full-scale production size batch (Lot No. 99 with an SSA of 7.6 m²/g) using various recommended dissolution media with paddle speeds of 50 and 75 rpms,
- the to-be-marketed and the clinically tested tablets are compositionally the same within each tablet strength except the former was made with dye and the latter was made without dye, and
- BE has been shown between the respective to-be-marketed and the clinically tested 1 and 4 mg tablets.

the to-be-marketed tablets can be considered to be "equivalent" to the clinically tested tablets that are manufactured with SSAs between 5 and 8 m²/g for each tablet strength of 1, 2, or 4 mg.

2. No information on glimepiride in patients with hepatic impairment was provided. Therefore, it is recommended to

- i) determine if any patients enrolled in any of the completed clinical efficacy and safety studies had liver function tests that were outside normal ranges and
- ii) determine whether these patients had any unexpected efficacy and/or adverse effect findings.

In addition, such data/information should be monitored from a postmarketing perspective. Finally, the package insert should be updated accordingly based on the results of the above data analyses.

IV. LABELLING COMMENT: (Needs NOT to be sent to the sponsor)

Previously, a format recommended for the PK Section of the PI had been sent to the sponsor and the PK section was revised accordingly by the sponsor. It has been submitted to the Agency for review. The Agency's comments with the revised PK Section after its review was sent to the sponsor on 06/08/95.

NOV 3 1995

NDA: 20-496

SUBMISSION DATE: 10/05/95

Glimepiride 1, 2, and 4 mg tablets

BRAND NAME: Amaryl

SPONSOR: Hoechst-Roussel
Pharmaceutical Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Amendments For An NME (1S) New Drug Application

TITLE: "Firm's Responses To The Agency's Letter Dated September 29, 1995"

BACKGROUND:

Glimepiride is a white to yellowish-white crystalline, odorless to practically odorless powder with a molecular weight of 490.62. It is a new oral blood glucose-lowering drug of the sulfonylurea class and it was classified as an NME (with a 1S status) for treating Non-Insulin Dependent Diabetes Mellitus (NIDDM). On 08/30/94, Hoechst-Roussel Pharmaceutical Inc. (HR) submitted NDA 20-496 to the Agency for review for Amaryl (glimepiride) 1, 2, and 4 mg tablet strengths. In its proposed package insert (PI), Amaryl is to be indicated i) as an adjunct to diet to lower the blood glucose in patients with NIDDM and ii) for use in combination with insulin to lower blood glucose in patients whose hyperglycemia can not be controlled by diet in conjunction with an oral hypoglycemic agent. The sponsor indicates that there is no fixed dosage regimen for Amaryl tablets. The usual starting dose as initial therapy is 1 to 2 mg QD administered with breakfast or the first main meal. The maximum recommended dose is 8 mg QD and the usual maintenance dose is 1 to 8 mg QD.

SYNOPSIS:

NDA 20-496 was reviewed by the Division of Biopharmaceutics (HFD-420) on 06/23/95. It was found to be acceptable for supporting the first indication, however, several comments/recommendations were communicated to the firm after the bioreview. Two comments were sent to the firm on 09/29/95 regarding i) the report for study No. HOE490/1/YU/201/LI for investigating safety, pharmacokinetics (PK) and Feasibility Efficacy of multiple doses of Amaryl in patients with liver impairment and ii) additional in vivo inhibition studies for glimepiride with various concentrations of phenytoin, diclofenac, ibuprofen, naproxen, mefenamic acid and S-warfarin.

On 10/05/95, the firm submitted its responses to the Agency for Amaryl's NDA 20-496 (glimepiride tablets) in response to the Agency's 09/29/95 letter. The firm agreed that once the above study reports become available, they will be submitted to the Agency for review.

Notes:

1. Previously, HFD-420 indicated to the firm and HFD-510 that a lack of PK data to support the second indication (Amaryl 8 mg QD in combination with insulin given subcutaneously). HFD-510, however, indicated on 02/28/95 in an internal status meeting that no PK studies would be needed to support the second indication. As presented by the firm in a meeting on 06/23/95, the only clinical trial conducted to support the second indication used Amaryl 8 mg BID plus insulin. The Division of Pharmaceutical Evaluation II (HFD-870, formerly HFD-420) was informed later by the CSO that the second indication would be granted for approval also by HFD-510. However, as indicated by the medical officer, a Phase IV commitment for conducting PK study(ies) by the firm in support of the second indication would be requested.

2. Upon the medical officer's request, minor modification for the PK section in the PI was made by HFD-870 regarding the patients with renal insufficiency.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the firm's responses that were submitted on 10/05/95 in response to the Agency's letter dated 09/29/95 for NDA 20-496 (Amaryl tablets). The firm's responses are acceptable and HFD-870 is looking forward to reviewing the study reports in the near future.



10/27/95

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by John Hunt JPH 11/03/95

FT initialed by John Hunt [Signature] 11/3/95

cc: NDA 20-496, HFD-510 (Copy), HFD-510 (MO, CSO), HFD-870 (M. Chen, T. Chen, G. Barnette), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), FOI (HFD-19).

SEP 22 1995

NDA: 20-496

SUBMISSION DATE: 08/28/95

Glimepiride 1, 2, and 4 mg tablets

BRAND NAME: Amaryl

SPONSOR: Hoechst-Roussel
Pharmaceutical Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Amendments For An NME (1S) New Drug Application

TITLE: "Firm's Responses To The Agency's Letter Dated July 12, 1995"

BACKGROUND:

Glimepiride is a white to yellowish-white crystalline, odorless to practically odorless powder with a molecular weight of 490.62. It is a new oral blood glucose-lowering drug of the sulfonylurea class and it was classified as an NME (with a 1S status) for treating Non-Insulin Dependent Diabetes Mellitus (NIDDM). On 08/30/94, Hoechst-Roussel Pharmaceutical Inc. (HR) submitted NDA 20-496 to the Agency for review for Amaryl (glimepiride) 1, 2, and 4 mg tablet strengths. In its proposed package insert (PI), Amaryl is to be indicated i) as an adjunct to diet to lower the blood glucose in patients with NIDDM and ii) for use in combination with insulin to lower blood glucose in patients whose hyperglycemia can not be controlled by diet in conjunction with an oral hypoglycemic agent. The sponsor indicates that there is no fixed dosage regimen for Amaryl tablets. The usual starting dose as initial therapy is 1 to 2 mg QD administered with breakfast or the first main meal. The maximum recommended dose is 8 mg QD and the usual maintenance dose is 1 to 8 mg QD.

A concern was raised to HFD-510 and to HR by the Division of Biopharmaceutics (HFD-420) soon after the initiation of the bioreview that there were no pharmacokinetic (PK)/bioavailability (Bio) studies to support the second indication, i.e., Amaryl tablet(s) given with concomitant subcutaneous (SC) administration of insulin. In an internal meeting held on 02/28/95, HFD-510 indicated that no PK/Bio studies would be needed to support the second indication. Please see the meeting minutes for details. A meeting between HR and the Agency was held on 06/21/95 to discuss labelling issues of the PI as well as the second indication, i.e., using the only available clinical data for a dosing regimen of 8 mg BID (Study No. 305) to support the second indication with a dosing regimen of 8 mg QD. HFD-510 indicated that it would be discussed internally.

*Comments
concerned to
from - letter
dated 9/29/95.*

*HRBI response
dated 10/5/95.
Review 11/3/95*

The firm proposed its in vitro dissolution method and specification for the Amaryl tablets as follows:

900 ml of phosphate buffer pH 7.8 at 37°C
USP Apparatus II (paddle) at 75 rpm
Q ≥ in 15 min

The firm also submitted dissolution data for Amaryl 1, 2, and 4 mg tablets using the above proposed method. On 06/23/95, HFD-420 completed its bio-review for NDA 20-496 for Amaryl tablets. HFD-420 concluded that the submitted human PK/Bio studies were overall acceptable for meeting the Agency's bio-regulations to support the approval of NDA's proposed first indication. However, HFD-420 recommended changing the firm's proposed dissolution method and specification as follows:

900 ml of simulated intestinal fluid without enzymes (pH 7.50) at 37°C
USP Apparatus II (paddle) at 50 rpm
Q ≥ in 20 min

An Agency letter was sent to the firm on 07/12/95. Please see the Agency's letter in HFD-420 drug review file for details.

SYNOPSIS:

On 08/28/95, the firm submitted its responses to the Agency for Amaryl's NDA 20-496 (glimepiride tablets) regarding the Agency's comments/recommendations that were sent to them on 07/12/95, i.e., i) modification of the dissolution method and specification, ii) analyses of clinical efficacy and safety data for patients with hepatic impairment, and iii) in vitro metabolism study.

For the tablet dissolution testing, the firm indicated on 09/13/95 that no pH changes were found in the dissolution media at the end of the studies. Regarding the Agency's recommended dissolution method and specification changes, the firm raised that i) there are no stability data to support the Agency's recommended dissolution method and specification, ii) its originally proposed NDA's dissolution method and specification have been used in the international stability studies, iii) the firm's method and specification will meet the needs for all its dosage strengths (1 to 4 mg in the US and 1 to mg internationally) for all regulatory and pharmacopoeial concerns worldwide, and iv) the NDA's dissolution method and specification will be filed in official monographs internationally (international harmonization). Please see Attachment 1 for details.

The firm further indicated in a telecon on 09/18/95 that for the international mg tablet strength, i) no dissolution testing was conducted using the Agency's proposed dissolution method and specification and ii) sink conditions could not be maintained using the Agency's proposed dissolution method based on the information on the solubility of glimepiride.

Note: The sink conditions being maintained is "defined" by the USP and FDA as when completely dissolved in a pH buffered dissolution medium, the tested article gives a concentration which is $\leq 1/3$ of its saturated solution at that pH, e.g., for a 2 mg tablet completely dissolved in 900 ml pH 7.5 dissolution medium, 2 mg in 900 ml gives 2.22 mg/liter which is ≤ 2.53 mg/liter ($1/3$ of its saturated solution at pH 7.5, = 7.6 mg/liter). For a 4 mg tablet in 900 ml pH 7.5 dissolution medium (i.e., 4.44 mg/liter), the sink conditions could not be maintained "theoretically".

Finally, the firm requested that no changes for the original NDA's dissolution method and specification be made. HFD-420 is now of the opinion that since i) the firm's responses are reasonable and ii) the dissolution data for the lots employed in the PK/Bio and clinical studies using the original NDA's proposed dissolution method were previously submitted and reviewed, no change in the original NDA's dissolution method and specification is needed at this time.

For the analyses of clinical efficacy and safety data for patients with hepatic impairment, the results showed that there were no apparent differences between patients with and without hepatic impairment (Tables 1 to 5). Updated clinical safety information also showed no differences. The firm's analyses appear to be acceptable. However, the medical staff should review all this information/data. Lastly, the firm indicated that an additional study in patients with hepatic impairment entitled "Safety, PK and Feasibility Efficacy Study of Multiple Doses of Glimepiride in Type II-Diabetic Patients with Liver Impairment" (Study No. 1/YU/201/LI) was initiated on 05/27/93 in Europe. However, no study report is available yet at this time. Please see the attached protocol in Attachment 2 for details.

Note: The efficacy data for patients with hepatic impairment were obtained from Vol. Nos. 1.354 and 1.355 and those for safety data were obtained from Vol. Nos. 1.357 and 1.360. The safety update (12/29/94) is found in Vol. Nos. 2.1 and 2.2. Therefore, they are not attached to this bioreview.

Regarding the firm's responses to the Agency's comments on the in vitro metabolism study for glimepiride (Attachment 3), Dr. Gary Barnette of HFD-420 indicated that the firm's responses are acceptable except that there is one comment which should be sent to the firm. Please see the Comment No. 2 below for details.

RECOMMENDATION:

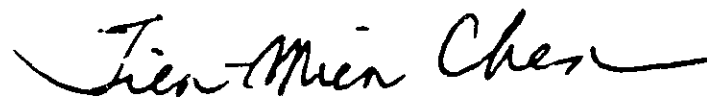
The Division of Biopharmaceutics (HFD-420) has reviewed the firm's responses to the Agency's requests for NDA 20-496 (Amaryl tablets) that were submitted in the NDA amendment dated 08/28/95. The responses were submitted in response to the Agency's letter dated 07/12/95 and they appear to be acceptable. The reviewing medical staff of HFD-510 should review i) the clinical data noted above and ii) the Comments below. The following dissolution method and specification that were originally proposed by the firm are recommended for NDA 20-496 (Amaryl tablets):

900 ml of phosphate buffer pH 7.8 at 37°C
USP Apparatus II (paddle) at 75 rpm
Q ≥ ; in 15 min

The above Recommendation as appropriate and the Comments below should be sent to the firm. The Comments should be appropriately addressed by the firm.

COMMENTS: (Need to be sent to the firm)

1. You indicated that Study No. 1/YU/201/LI entitled "Safety, PK and Feasibility Efficacy Study of Multiple Doses of Glimepiride in Type II-Diabetic Patients with Liver Impairment" was initiated on 05/27/93 in Europe but the study report is not available at this time. It is recommended that once it becomes available, the study report be submitted to the Agency for review.
2. It is recommended that *in vitro* inhibition studies be carried out with various concentrations of phenytoin, diclofenac, ibuprofen, naproxen, mefenamic acid and S-warfarin (i.e., sources of potential interaction due to metabolism by CYP2C9 reported in the labelling). It is acknowledged that if microsomes are utilized in these proposed studies, the presence of an interaction *in vitro* may not translate to a clinically significant interaction due to factors such as cellular transportation of the compounds in question. However, the absence of observed *in vitro* interaction would allow for more proof that an *in vivo* interaction is unlikely and the package labelling could be updated to indicate such. If further assistance is necessary concerning these studies, please contact the Division of Biopharmaceutics.



09/18/95

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt JPH 09/21/95

FT initialed by John Hunt J. T. Hunt 9/22/95

cc: NDA 20-496, HFD-510 (Copy), HFD-510 (MO, CSO), HFD-426 (Fleischer), HFD-427 (M. Chen, T. Chen, G. Barnette), HFD-340 (Viswanathan), Chron, Drug, Reviewer, FOI (HFD-19).

Median Change from Baseline in Efficacy Variables by Hepatic Abnormality

Table 1

Variable	Disease	Glimepiride		Placebo	
		N	Change	N	Change
FPG (mg/dl)	Present	177	-56.0	78	15.0
	Absent	497	-56.0	183	6.0
FPG (mg/dl)	Present	153	-73.0	66	4.0
	Absent	466	-82.0	155	0.0
HbA1c (%)	Present	155	-0.6	68	0.7
	Absent	454	-0.6	156	0.6

Table 2
Safety data

Hepatic Abnormality - US Subjects				
	Yes		No	
	N	%	N	%
No of Subjects	389	100.0	1130	100.0
No. with TESS	270	69.4	794	70.3
No. with DDOS	31	8.0	103	9.1
5% TESS*	None			
2% DDOS*	None			
5% PCAs*				
SGGT - Inc	33/356	9.3	23/1043	2.7
Alk Phosphatase - Inc	29/357	7.3	24/1043	2.3
2% LPCAs*				
SGGT - Inc	21/356	5.9	16/1043	1.5
SGPT - Inc	12/355	3.4	10/1040	1.0
Alk Phosphatase - Inc	16/357	4.5	14/1043	1.3

*Individual adverse events or laboratory variables for which the rates differed by the specified percentage.

Table 3
Safety data

Hepatic Abnormality - European Subjects				
	Yes		No	
	N	%	N	%
No of Subjects	571	100.0	901	100.0
No. with TESS	268	46.9	422	46.8
No. with DDOS	82	14.4	142	15.8
5% TESS*	None			
2% DDOS*	None			
5% PCA*				
SGGT - Inc	75/484	15.5	44/717	6.1
Alk Phosphatase - Inc	72/519	13.9	63/622	7.7
2% LPCA*				
SGGT - Inc	33/484	8.1	15/717	2.1
Alk Phosphatase - Inc	28/519	5.4	21/622	2.6
2% CNLAs*	None			

*Individual adverse events or laboratory variables for which the rates differed by the specified percentage.

SUMMARY OF CLINICALLY NOTEWORTHY LABORATORY VALUES

Table 4

BY HEPATIC ABNORMALITY

US TRIALS
DRUG-DISEASE INTERACTION: GLIMEPIRIDE SUBJECTS

VARIABLE	YES		NO		ALL SUBJ	
	n/N	%	n/N	%	n/N	%
HEMOGLOBIN	0/ 346	0.0	3/1026	0.3	3/1372	0.2
HEMATOCRIT	0/ 346	0.0	3/1026	0.3	3/1372	0.2
PLTS - COUNT	0/ 340	0.0	0/1023	0.0	0/1363	0.0
WBC COUNT	0/ 346	0.0	1/1026	0.1	1/1372	0.1
EOSINOPHILS	1/ 338	0.3	4/1009	0.4	5/1347	0.4
SGOT	2/ 355	0.6	0/1037	0.0	2/1392	0.1
SGPT	2/ 355	0.6	0/1040	0.0	2/1395	0.1
SERUM GGT	0/ 355	0.0	0/1043	0.0	0/1399	0.0
S ALK PHOS	0/ 357	0.0	0/1043	0.0	0/1400	0.0
S T BILI	0/ 357	0.0	0/1042	0.0	0/1399	0.0
BLOOD UREA	0/ 356	0.0	0/1043	0.0	0/1399	0.0
S CREATININE	0/ 356	0.0	0/1045	0.0	0/1402	0.0

Table 5

EUROPEAN TRIALS
DRUG-DISEASE INTERACTION: GLIMEPIRIDE SUBJECTS

VARIABLE	YES		NO		ALL SUBJ	
	n/N	%	n/N	%	n/N	%
HEMOGLOBIN	6/ 522	1.1	8/ 836	1.0	14/1358	1.0
HEMATOCRIT	2/ 454	0.4	5/ 677	0.7	7/1131	0.6
PLTS - COUNT	4/ 519	0.8	1/ 831	0.1	5/1350	0.4
WBC COUNT	3/ 522	0.6	1/ 836	0.1	4/1358	0.3
EOSINOPHILS	7/ 443	1.6	8/ 716	1.1	15/1159	1.3
SGOT	3/ 496	0.6	1/ 766	0.1	4/1262	0.3
SGPT	5/ 480	1.0	1/ 734	0.1	6/1214	0.5
SERUM GGT	8/ 485	1.6	0/ 729	0.0	8/1214	0.7
S ALK PHOS	1/ 520	0.2	0/ 825	0.0	1/1345	0.1
S T BILI	3/ 521	0.6	0/ 825	0.0	3/1346	0.2
BLOOD UREA	2/ 495	0.4	0/ 760	0.0	2/1255	0.2
S CREATININE	0/ 521	0.0	1/ 835	0.1	1/1356	0.1
SERUM CA	0/ 460	0.0	1/ 700	0.1	1/1160	0.1
SERUM K	1/ 514	0.2	1/ 806	0.1	2/1320	0.2

SEP 19 1995

NDA: 20-496

SUBMISSION DATE:

06/07/95

Glimepiride 1, 2, and 4 mg tablets

06/15/95

06/22/95

BRAND NAME: Amaryl

SPONSOR: Hoechst-Roussel
Pharmaceutical Inc.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Amendments For An NME (1S) New Drug Application

TITLE: "Firm's Responses To A Biopharm Review For A New Drug Application (1S)"

BACKGROUND:

Glimepiride is a white to yellowish-white crystalline, odorless to practically odorless powder with a molecular weight of 490.62. It is practically insoluble in water and its specific surface area (SSA) of the bulk drug for the to-be-marketed tablets will be in the range of 5 to 8 m²/g (by BET method). As indicated by the reviewing chemist of HFD-510, $\geq 50\%$ of particles are $\leq 2.5 \mu\text{m}$ and $\geq 99\%$ are $\leq 10 \mu\text{m}$ by using a laser granulometry.

Glimepiride is a new oral blood glucose-lowering drug of the sulfonylurea class. It appears to stimulate the release of insulin from the pancreas, an effect that depends on functioning beta cells in the pancreatic islets. The sponsor claims that glimepiride lowers blood glucose levels with less insulin both acutely and chronically to a greater extent than that of other sulfonylureas. It also has a significantly less effect on the cardiovascular system than do other sulfonylureas.

On 08/30/94, Hoechst-Roussel (HR) submitted NDA 20-496 (Amaryl; glimepiride tablets) to the Agency for review. It was classified as an NME (with a 1S status) for treating Non-Insulin Dependent Diabetes Mellitus (NIDDM). HR wants approval for Amaryl 1, 2, and 4 mg tablet strengths. In its proposed package insert (PI), Amaryl is to be indicated i) as an adjunct to diet to lower the blood glucose in patients with NIDDM and ii) for use in combination with insulin to lower blood glucose in patients whose hyperglycemia can not be controlled by diet in conjunction with an oral hypoglycemic agent. The sponsor indicates that there is no fixed dosage regimen for Amaryl tablets. The usual starting dose as initial therapy is 1 to 2 mg QD administered with breakfast or the first main meal. The maximum recommended dose is 8 mg QD and the usual maintenance dose is 1 to 8 mg QD.

A concern was raised to HFD-510 and to HR by the Division of Biopharmaceutics (HFD-420) soon after the initiation of the bioreview that there were no pharmacokinetics

NAI

(PK)/bioavailability (Bio) studies to support the second indication, i.e., Amaryl tablet(s) given with concomitant subcutaneous (SC) administration of insulin. In an internal meeting held on 02/28/95, HFD-510 indicated that no PK/Bio studies would be needed to support the second indication. Please see the meeting minutes for details.

A meeting between HR and the Agency was held on 06/21/95 to discuss labelling issues of the PI. In that meeting, HR presented clinical data for a dosing regimen of 8 mg BID which was to be used to support the second indication and a dosing regimen of 8 mg QD. This reviewer raised a concern as to whether the clinical data for a dosing regimen of 8 mg BID could support the second indication with a dosing regimen of 8 mg QD. HFD-510 indicated that it would be discussed internally.

On 06/23/95, HFD-420 completed its bio-review for NDA 20-496 for Amaryl tablets. HFD-420 concluded that the submitted human PK/Bio studies were overall acceptable for meeting the Agency's bio-regulations to support the approval of the NDA's proposed first indication.

SYNOPSIS:

On 06/07, 06/15, and 06/22/95, HR formally submitted three additional NDA amendments. The 06/07/95 amendment provided analyses of pharmacodynamic data comparing young and elderly patients receiving Amaryl 6 mg QD. The 06/15/95 amendment provided information on batch Nos, sizes, and content uniformity, etc.. All this information had been previously faxed to HFD-420 and was reviewed prior to the 06/23/95 bio-review. Therefore, it will not be reviewed again here.

The 06/22/95 amendment provided information on the control of SSA and/or the particle size distribution of glimepiride bulk drug substance. The above information was faxed to HFD-420 on 06/22/95. It provided *additional information on the methodology used in the SSA determination for glimepiride bulk drug substance.* Please see Appendix 1 for details. Although there is no further detailed information on the particle size distribution of glimepiride bulk drug substance, the validation report of SSA determination for this drug substance is acceptable.

COMMENDATION:

The additional NDA amendments that were formally submitted by HR on 06/07/95 and 06/15/95 were previously faxed to and reviewed by HFD-420. Therefore, they do not need to be reviewed again. Another NDA amendment dated 06/22/95 provided additional information on the control of specific surface area of glimepiride bulk drug substance and it is acceptable.

Tien-Mien Chen

09/08/95

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt JPH 09/17/95

FT initialed by John Hunt J. Hunt 9/18/95

cc: NDA 20-496, HFD-510 (Copy), HFD-510 (Gueriguian, Short), HFD-426 (Fleischer), HFD-427 (M. Chen, T. Chen), HFD-340 (Viswanathan), Chron, Drug, Reviewer, FOI (HFD-19).

JUN 1 1995

NDA: 20,496
Compound: Glimepiride Tablets (Amaryl™)
Submission Date: 5/19/95
Sponsor: Hoechst-Roussel Pharmaceuticals, Inc.
Type of Submission: NDA Amendments
Reviewer: K. Gary Barnette, Ph.D.

Background: HOE 490 is an antidiabetic agent from the class of sulfonylureas. In vivo metabolism studies indicated that the compound is extensively metabolized in man. Only small amounts of unchanged HOE 490 were excreted (<1%), while two major metabolites (M I and M II) accounted for about 80% of the administered dose. Therefore a closer investigation of the metabolic degradation of glimepiride would entail identification and characterization of the enzymes responsible for the formation of M I and M II.

*Comments -
1-6 included
in the STA
7/12/95 (modified
by circulatory Dept).
(See Review dated 6/3/95)*

Study Title: Investigations on the Enzymes Responsible for the Main Metabolic Routes of Biodegradation of Glimepiride (HOE 490) in Man

Objective: The purpose of this study is to determine the enzymes responsible for the elimination of this extensively metabolized compound.

Results: see Attachment #1

Conclusions:
The results of this study indicate that the isofamily is the predominant enzyme family responsible for the metabolism of Glimepiride in man, in particular

Comments:

1. The _____ that have been tested and reported herein are

However, it is unclear why _____ was not included in this study. It is a _____ of _____ in the liver of man and should have been included in this study to rule out the possibility of its role in the metabolism of this compound.

2. The sponsor should be cautioned that along with the possible drug interactions listed on page 17 of this submission (phenytoin, diclofenac, ibuprofen, naproxen, mefenamic acid and S-warfarin), an interaction between glimepiride and ethinylestradiol (also metabolized by _____) should be tested.
3. It has been reported that _____) and _____ (a marker for substrate for _____ metabolism is highly variable between human livers. Therefore, the metabolism of glimepiride is probably highly variable as well and appropriate and cautious dose titration should be executed.
4. Due to the relatively long incubation time and the known degradation of NADPH when in solution, it is unclear why a NADPH regenerating system was not employed instead of the addition of large amounts (1.2 mM) of NADPH.
5. Similarly, the stability of the _____ during a 3 h incubation is a concern.
6. It is apparent that 20-25% of the dose is unaccounted for by the formation of M I and M II. Metabolism of glimepiride by other _____ is the probable fate of this fraction of the dose. To completely characterize the metabolic pathways of this compound these metabolites should ideally be identified and quantitated.

Recommendation:

Due to the lack of specificity of chemical and immunoinhibitors as well as the difficulty to separate and purify _____ identification of the particular _____ responsible for the metabolism of any compound is a formidable task. However, the sponsor appears to have employed state of the

art technology in identifying
as the predominant involved in the metabolism of
glimepiride. The above comments (#1-6) should be forwarded to
the company for response and/or action.

K. Gary Barnette, Ph.D.
Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt, Section Head, JPH 5/31/95

FT signed by John Hunt, Section Head, *J. Hunt 6/1/95*

cc: NDA 20,496, HFD-510, HFD-510 (Gueriguian, Short), HFD-
426 (Fleischer), HFD-427 (M.Chen, A.Chen, Barnette), HFD-
340 (Viswanathan), Drug file, Chron. file, review, FOI (HFD-
19)

JUN 30, 1995

NDA: 20,496 (Addendum to review dated 1 June 1995)
Compound: Glimepiride Tablets (Amaryl®)
Submission Date: 7/19/95
Sponsor: Hoechst-Roussel Pharmaceuticals, Inc.
Type of Submission: NDA Amendments
Reviewer: K. Gary Barnette, Ph.D.

Background:

This is an addendum to my review dated 6/1/95 of the in vitro metabolism studies of glimepiride submitted to NDA 20,496 on 5/19/95. These additional comments were inspired by suggestions made during the Biopharm Day for Glimepiride tablets held on 6/21/95 by Dr. Tien-Mein Chen (primary reviewer).

Study Title:

Investigations on the Enzymes Responsible for the Main Metabolic Routes of Biodegradation of Glimepiride (HOE 490) in Man

Objective:

The purpose of this study is to determine the enzymes responsible for the elimination of this extensively metabolized compound.

Additional Comments:

1. It was determined that Ca^{2+} extensively inhibited the formation of metabolite I of glimepiride in microsomal human liver fractions 10^{-6} M, further indicating that Ca^{2+} in the formation of this metabolite of glimepiride.
2. Similarly, the influence of glimepiride on Ca^{2+} in microsomal human liver fractions was tested. No change in activity was seen, suggesting that Ca^{2+} plays a minor role, if any, in the metabolic fate of glimepiride.
3. It is noted that a thorough study of the in vitro metabolism of glimepiride was submitted

*Approved
in letter to firm
dated 7/12/95*

and it is commendable that it was done in such a short time frame. Ideally, in the future, such studies should be included in the original submission, as these studies are essential to understanding the pharmacokinetics and safety concerns associated with a given xenobiotic and/or formulation.

Recommendation:

Comment #3 should be communicated to the sponsor in addition to the comments identified in the 6/1/95 Biopharm review that are also to be sent.

K. Gary Barnette, Ph.D.
Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt, Section Head, JPH 6/23/95

FT signed by John Hunt, Section Head, J. Hunt 6/23/95

cc: NDA 20,496, HFD-510, HFD-510 (Gueriguian, Short), HFD-426 (Fleischer), HFD-427 (M.Chen, A.Chen, Barnette), HFD-340 (Viswanathan), Drug file, Chron. file, Review, FOI (HFD-19)

NDA 20496

1 OF 6

VDA 20.496

AP LETTER



NDA 20-496

Food and Drug Administration
Rockville MD 20857

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
P.O. Box 25000
SOMERVILLE NJ 08876-1258

NOV 30 1995

Dear Dr. Reit:

Please refer to your August 30, 1994, new drug application 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 amendments dated October 14 (2), November 10, and December 21 and 29, 1994; and January 10, February 2 and 21, March 28 and 30, April 7, 10, 13, 19 (2), 21 (3), and 26, May 10, 19, and 23, June 2, 7, 12, 15, 20 (2), 22, and 26, July 10, 12, 17, and 20, August 9, 10, 15, 16, 17, and 28, September 11, 13, and 25, October 5, 6, 9, 16, and 20, and November 30, 1995. Your July 10, 1995 submission extended the user fee goal date to November 30, 1995.

This new drug application as amended provides for the use of Amaryl:

- 1) as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone, and
- 2) in combination with insulin to lower the blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent.

We have completed the review of this application, 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 draft labeling in the submissions dated July 12, 1995 (carton and container labels), and November 30, 1995 (package insert). Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 12, 1995 (carton and container labels), and November 30, 1995 (package insert). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen 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 "FINAL PRINTED LABELING" for approved NDA 20-496. Approval of this labeling by FDA is not required before it is used.

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

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,



James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ODE I/II ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA# 20-496 Drug Amaryl (glimepiride) Tablets 1/24 mg

Applicant Hoechst-Roussel Pharmaceuticals, Inc CSO SHORT /phone x33510

Arrange package in the following order

		Check or Comment
1	ACTION LETTER with supervisory signatures	AP ☒ AE ☐ NA ☐
2	~~ACTION PACKAGE TRACKING FORM~~	
3	Completed copy of this CHECKLIST in package	Chem/Ther Types <u>1S</u>
4	LABELING (package insert and labels) (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx PI and HFD-210 reviews will be used as SBA equivalent.)	Draft ☒ Final ☐ Revised Draft ☐
5	SUMMARY BASIS OF APPROVAL (Copy of previous version with ODE's comment as well as disk. FPL and sign-off sheet must accompany revised of final version. If no SBA, include memo stating what reviews will be used as SBA equivalent.)	SBA ☐ Revised SBA ☐ SBA Note ☒
6	PATENT INFORMATION ☒ EXCLUSIVITY CHECKLIST ☒	
7	Debarment Certification (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992)	-----X-----
8	DIVISION DIRECTOR'S MEMO If more than 1 review	-----X-----
	GROUP LEADER'S MEMO If for any 1 discipline	-----X-----
	PEDIATRIC PAGE Separate reviews with	-----X-----
	MEDICAL REVIEW In a sheet of colored paper	-----X-----
	SAFETY UPDATE REVIEW Any conflicts between	-----X-----
	STATISTICAL REVIEW reviews must have	-----X-----
	BIOPHARMACEUTICS REVIEW resolution documented	-----X-----
	PHARMACOLOGY REVIEW (Include pertinent IND reviews)	-----X-----
	Statistical Review of Carcinogenicity Study(ies)	-----X-----
	CHEMISTRY REVIEW	-----X-----
	Date EER completed <u>8/30/95</u> (attach signed form or CIRTS printout). FUR needed ☒ requested	OK ☒ NO ☐
	Have the methods been validated? <u>(Sent E-Mail reminder 10/14/95)</u>	Yes (attach) ☐ No ☒
	Environmental Assessment Review	-----X-----
	MICROBIOLOGY REVIEW	-----N/A-----
	Has the monograph been approved?	Yes ☐ No ☐
9	Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed Attach a COMIS printout of DSI status	--Gus says that investigations will be -----completed by 11/30/95-----
10	CORRESPONDENCE and MEMOS OF TELECONS	-----X-----
11	MINUTES OF MEETING	-----X-----
	Date of End-of-Phase II Meeting <u>NONE</u>	
	Date of pre-NDA Meeting <u>7/7/93</u>	
12	ADVISORY COMMITTEE MEETING MINUTES or, if not available 48-Hour Info Alert or pertinent section of transcript	Minutes ☐ Info Alert ☐ Transcript ☐ No mtg ☒
13	FEDERAL REGISTER NOTICES, OTC or DESI DOCUMENTS	-----N/A-----
14	If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ☐ No ☐ Yes documentation attached ☐ No, included in AP ltr ☒
15	Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes ☒ No ☐ -----
16	Integrated Summary of Safety	-----X-----
17	NDA (especially Medical/Statistical) Summary	-----X-----

SBA

SBA or

SBA EQUIVALENT

ARE NO LONGER NECESSARY

PATENT &

EXCLUSIVITY INFO

Amaryl

PATENT & EXCLUSIVITY INFORMATION

ACTIVE INGREDIENT: glimepiride ←

TRADEMARK: Amaryl®

DOSAGE FORM: Tablets

ROUTE OF ADMINISTRATION: Oral

APPLICANT FIRM: Hoechst-Roussel Pharmaceuticals Inc.

PATENT HOLDER: Hoechst-Roussel Pharmaceuticals Inc.

U.S. PATENT NUMBER: 4,379,785 (issue date: 4/12/83)

TYPE OF PATENT CLAIMS:

1. compound
2. composition
3. method of lowering blood sugar level

EXPIRATION DATE: 4/12/2000

As provided under Section 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, Hoechst-Roussel Pharmaceuticals Inc. requests an exclusivity period of five (5) years.

EXCLUSIVITY SUMMARY for NDA # 20-496 SUPPL # N/A

Trade Name Amaryl Tabs 1,2,4 mg Generic Name glimepiride tablets

Applicant Name Hoechst-Roussel Pharmaceuticals, 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 / X / NO / /

b) Is it an effectiveness supplement? YES / / NO / X /

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

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 / X / NO / /

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

5 years (see patent info.)

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?

YES / / NO / X /

If yes, NDA # _____ Drug Name _____

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 / X /

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 /X/

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

NDA # _____
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.

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 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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/
Investigation #3	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 /___/
Investigation #3	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 #__, Study # _____

Investigation #__, Study # _____

Investigation #__, 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: _____

John R. Short
Signature John R. Short
Title: Consumer Safety Officer

10/23/95
Date

[Signature]
Signature of Division Director

11/12/95
Date

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

LABELING

Approved 11/30/95

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A.1

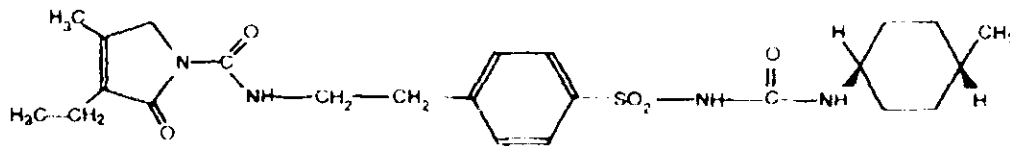
AMARYL® (GLIMEPIRIDE TABLETS)

1, 2, and 4 mg

DESCRIPTION

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

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



Molecular Formula: $C_{24}H_{34}N_4O_5S$

Molecular Weight: 490.62

Glimepiride is practically insoluble in water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In

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

PHARMACODYNAMICS

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

In larger dose-ranging studies, blood glucose and HbA1c were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of AMARYL. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of AMARYL up to 8 mg once daily. No difference in response was found when AMARYL was administered once or twice daily.

In two 14-week, placebo-controlled studies in 720 subjects, the average net reduction in HbA1c for AMARYL patients treated with 8 mg once daily was 2.0% in absolute units compared with placebo-treated patients. In a long-term, randomized, placebo-controlled study of NIDDM patients unresponsive to dietary management, AMARYL therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA1c. Efficacy results were not affected by age, gender, weight, or race.

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

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

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

PHARMACOKINETICS

Absorption

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

Distribution

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

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Metabolism

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

Excretion

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

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Pharmacokinetic Parameters

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

	Volunteers	Patients with NIDDM	
	Single Dose Mean ± SD	Single Dose (Day 1) Mean ± SD	Multiple Dose (Day 10) Mean ± SD
C_{max} (ng/mL)			
1 mg	103 ± 34 (12)	---	---
2 mg	177 ± 44 (12)	---	---
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	557 ± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
T_{max} (h)	2.4 ± 0.8 (48)	2.5 ± 1.2 (26)	2.8 ± 2.2 (23)
CL _T (mL/min)	52.1 ± 16.0 (48)	48.5 ± 29.3 (26)	52.7 ± 40.3 (23)
V _d (L)	21.8 ± 13.9 (48)	19.8 ± 12.7 (26)	37.1 ± 18.2 (23)
$T_{1/2}$ (h)	5.3 ± 4.1 (48)	5.0 ± 2.5 (26)	9.2 ± 3.6 (23)

() No. of subjects

CL_T = Total body clearance after oral dosing

V_d = Volume of distribution calculated after oral dosing

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

Variability

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

SPECIAL POPULATIONS

Geriatric

Comparison of glimepiride pharmacokinetics in NIDDM patients < 65 years and those > 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean

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AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Pediatric

No studies were performed in pediatric patients.

Gender

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

Race

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

Renal Insufficiency

A single-dose, open label study was conducted in 15 patients with renal impairment. AMARYL (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CL_{cr}): (Group I, CL_{cr} = 77.7 mL/min, n = 5), (Group II, CL_{cr} = 27.7 mL/min, n = 3), and (Group III, CL_{cr} = 9.4 mL/min, n = 7) mL/min. AMARYL was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{1/2}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III)

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

Hepatic Insufficiency

No studies were performed in patients with hepatic insufficiency.

Other Populations

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

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

Drug Interactions

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

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

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

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

Concomitant administration of propranolol (40 mg tid) and AMARYL significantly increased C_{max} , AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta blockers. However, if beta blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

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

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

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

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

INDICATIONS AND USAGE

AMARYL is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

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

In initiating treatment for noninsulin dependent diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of AMARYL must be viewed by both the physician and patient as a treatment in addition to diet and exercise, and not as a substitute for diet and exercise, or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short term administration of AMARYL.

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

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

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CONTRAINDICATIONS

AMARYL is contraindicated in patients with

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

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WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of AMARYL and of alternative modes of therapy.

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

AMARYL (Glimperide Tablets, HOE 490) NDA 20,496
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A.13

PRECAUTIONS

GENERAL

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

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with AMARYL or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including AMARYL, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as *secondary failure*, to distinguish it from *primary failure* in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with AMARYL monotherapy, AMARYL-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

INFORMATION FOR PATIENTS

Patients should be informed of the potential risks and advantages of AMARYL and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

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

LABORATORY TESTS

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

DRUG INTERACTIONS

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

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

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

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

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

AMARYL (Glimpiride Tablets, HOE 490) NDA 20,496

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PREGNANCY

Teratogenic Effects

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

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

Nonteratogenic Effects

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

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a

AMARYL (Glimepiride Tablets, HOE 490) NDA 20,496
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pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

NURSING MOTHERS

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

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of hypoglycemia with AMARYL, as documented by blood glucose values < 60 mg/dL, ranged from 0.9-1.7% in two large, well controlled, 1-year studies. (See

WARNINGS and PRECAUTIONS)

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

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

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Adverse Events Occurring in > 1% AMARYL Patients

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

GASTROINTESTINAL REACTIONS

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

DERMATOLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

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

METABOLIC REACTIONS

Hepatic porphyria reactions and disulfiram like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has

AMARYL (Glimepiride Tablets, HOE 490) NDA 20,496
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been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OTHER REACTIONS

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with AMARYL or any other hypoglycemic agent. The patient's fasting blood glucose and HbA_{1c} must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to

AMARYL (Glibenclamide Tablets, HOE 490) NDA 20,496
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detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

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

USUAL STARTING DOSE

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

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

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

USUAL MAINTENANCE DOSE

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

AMARYL-INSULIN COMBINATION THERAPY

Combination therapy with AMARYL and insulin may be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of > 150 mg/dL in plasma or serum depending on the patient. The recommended AMARYL dose is 8 mg once

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daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA_{1c} levels.

SPECIFIC PATIENT POPULATIONS

AMARYL is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS** and **PRECAUTIONS, GENERAL**).

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

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

HOW SUPPLIED

AMARYL™ (glimepiride) tablets are available in the following strengths and package sizes:

1 mg (pink, flat-faced, oblong with notched sides at double bisect, imprinted with "AMARYL" on one side and the Hoechst logo on both sides of the bisect on the other side)
Bottles of 100 NDC 0039 0221 10
Unit Dose Cartons (100) NDC 0039 0221 11

2 mg (green, flat faced, oblong with notched sides at double bisect, imprinted with "AMARYL" on one side and the Hoechst logo on both sides of the bisect on the other side)
Bottles of 100 NDC 0039 0222-10
Unit Dose Cartons (100) NDC 0039 0222 11

AMARYL (Glimepiride Tablets, HOP 490) NDA 20,496
Item 2.A - Final Package Insert - Revisions Implemented 11/30/95

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4 mg (blue, flat-faced, oblong with notched sides at double bisect, imprinted with "AMARYL" on one side and the Hoechst logo on both sides of the bisect on the other side)

Bottles of 100

NDC 0039-0223-10

Unit Dose Cartons (100)

NDC 0039-0223-11

Store at 59° - 86°F (15° - 30°C).

Dispense in well-closed containers with safety closures.

Caution: Federal law prohibits dispensing without a prescription.

AMARYL™ is a trademark of Hoechst-Roussel Pharmaceuticals Inc.

ANIMAL TOXICOLOGY

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

HUMAN OPHTHALMOLOGY DATA

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

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

Glinepiride (HOE 490 Amaryl™) Tablets
NDA 20-496

Bottle Labels - 100's: 1, 2, 4 mg

7/11/95
~~8/26/95~~

General Correspondence:
Labels - Response to May 17, 1995 letter
from FDA

1

Volume Contents

Unit Dose Push-Thru Foil: 1, 2, 4 mg

Volume 1 of 1

2

Unit Dose Pack: 1, 2, 4 mg

3

Samples: 2, 4 mg

4

Sample Cartons: 2, 4 mg

5

UNAPPROVED FOR SALE
IN CANADA BY
LAWSON'S
PHARMACEUTICALS

UNAPPROVED FOR SALE
(U.S. & CANADA)

UNAPPROVED FOR SALE IN CANADA
BY LAWSON'S PHARMACEUTICALS

Exp: (M) x (Y)

622110-695

NDC 0039-0221-10

Amaryl™
gimepiride

1 mg

Caution:
Federal Law prohibits dispensing
without prescription. Do not use
if bottle closure seal is broken.

100 Tablets



Usual Dosage: See insert for full prescribing
information. Dispense in well-child container
with safety closure. Store between 20 and 25°C
(68 and 77°F) in original container. For full
prescribing information, see the full prescribing
information. **Lawson's Pharmaceuticals Inc.**
Lawson's Pharmaceuticals Inc.
10000 16th Street SE
Bellevue, WA 98008-4378
U.S. Patent 4,379,785

NDC 0039-0222-10

UNPROTECTED AND
1 CONTAINS 100
TABLETS
See all other labels

Unprotected Area
(12 x 1.187)

Amaryl™
glimepiride TABLETS

2 mg

Caution:

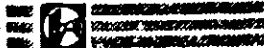
Federal law prohibits dispensing
without prescription. Do not use
if bottle closure seal is broken.

100 Tablets

UNPROTECTED AREA IS THAT
OF SEAL. Dispense without
seal.

Exp: (M x YYY)

622210-595



UNPROTECTED AREA IS THAT OF SEAL. Dispense without seal. See insert for full prescribing information. Dispense in well-closed container with readily observable. Store between 20 and 25°C (68 and 77°F). Keep this and all medications out of the reach of children. Amaryl™ THE HOECHST AG. Hoffmann-La Roche, Inc. 340 Kings Highway East, New Jersey 07002, USA. US Patent 4,379,785

NDC 0039-0223-10

Unpackaged Amaryl
NDC 0039-0223-10
100 Tablets
Net Wt. 10.0g (0.35oz)

Unpackaged Amaryl
(100 x 4mg)

Amaryl™
glimepiride tablets

4 mg

Caution:
Federal law prohibits dispensing
without prescription. Do not use
if bottle closure seal is broken.

100 Tablets

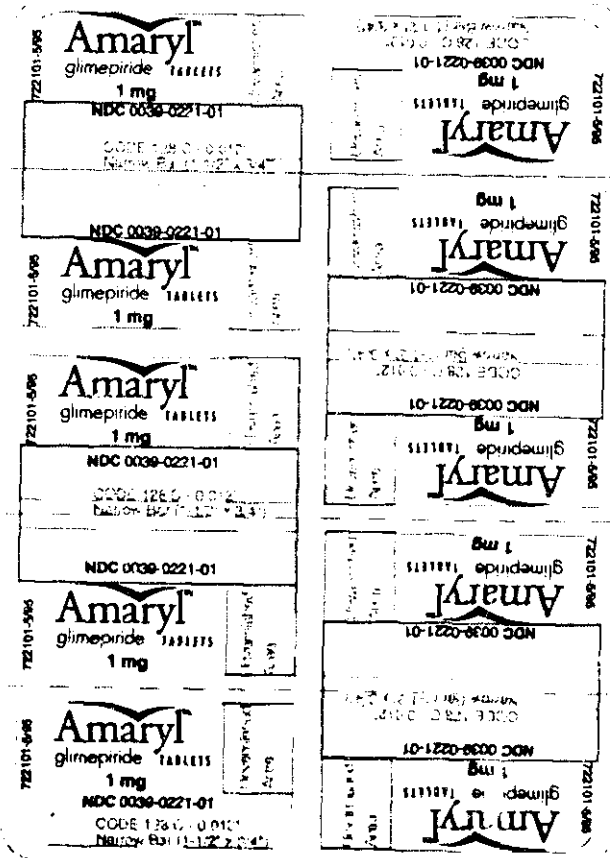
Unpackaged Amaryl in form
of 100 tablets. Contains 100 tablets.
Exp. (M & M)

622310-596



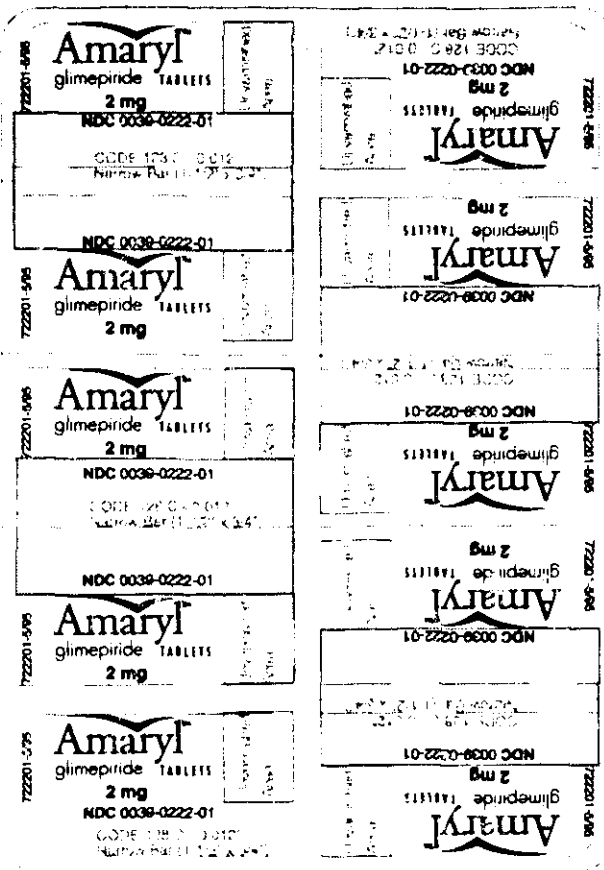
Unpackaged Amaryl. See insert for full prescribing
information. Dispense in child-resistant container.
Keep out of reach of children. See also the insert
of Amaryl, Amaryl™ HCOBIST AG
Amaryl, Amaryl™, and Amaryl HCOBIST AG
are registered trademarks of
Hoechst AG, Germany.

U.S. Patent 4,379,729



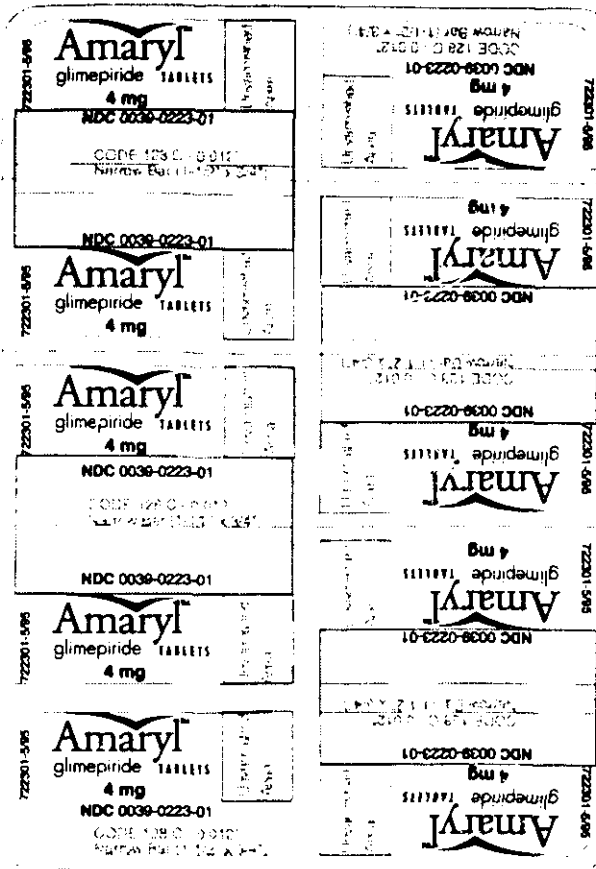
1 mg Unit Dose Push-Thru Foil

All Copy Black



2 mg Unit Dose Push-Thru Foil

All Copy Black



4 mg Unit Dose Push-Thru Foil

All Copy Black

NDC 0039-0221-11

AmarylTM
glimepiride TABLETS

Amaryl TM HOECHST AG

Initial Dosage:
See package insert for full
prescribing information.

Use between 59 and
65 F.

Caution: Federal law prohibits
dispensing without prescription.

Keep this and all
medications out of the
reach of children.

100 Tablets

1 mg

UNIT DOSE PACK



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

REG TM HOECHST AG



Unvarnished area
3-1/2 x 1-5/6"

Unit Dose Pack

100 Tablets

AmarylTM
glimepiride TABLETS
NDC 0039-0221-11

NDC 0039-0221-11

NDC UPC Barcode
0039-0221-11 8
3-1/2 x 1-5/6"

AmarylTM
glimepiride TABLETS

Usual Dosage:
See package insert
prescribing information

Store between 59°
and 86° F.

100 Tablets

1 mg

UNIT DOSE PACK

Keep this and all
medication out of
reach of children



NDC 0039-0222-11

AmarylTM
glimepiride TABLETS

Amaryl TM HOECHST AG

Usual Dosage:
See package insert for full
prescribing information.

Store between 59 and
86° F.

Caution: Federal law prohibits
dispensing without prescription.

Keep this and all
medication out of the
reach of children.

100 Tablets 2 mg
UNIT DOSE PACK



 **HOECHST-ROUSSEL**
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258
REG TM HOECHST AG

4022211-5/95

Unvarnished area
3-1/2 x 1-5/8

Unit Dose Pack

100 Tablets

glimepiride
AmarylTM
NDC 0039-0222-11

NDC 0039-0222-11

NDC/UPC Barcode
3 0039-0222-11 3
1.2 x 100%

AmarylTM
glimepiride TABLETS

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Store t
86° F.

Keep t
medic
reach

100 Tablets

2 mg

UNIT DOSE PACK



NDC 0039-0223-11

AmarylTM
glimepiride TABLETS

Amaryl TM HOECHST AG

Initial Dosage:
See package insert for full
prescribing information.

Use between 59 and
65 F.

Keep this and all
other medication out of the
reach of children.

4 mg

Caution: Federal law prohibits
dispensing without prescription.

100 Tablets

4 mg

UNIT DOSE PACK



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

REG. TM HOECHST AG



4022311-5/95

Unvarnished area
3-1/2 x 1-5/64

100 Tablets
4 mg
Unit Dose Pack
AmarylTM
glimepiride tablets
NDC 0039-0223-11

NDC 0039-0223-11

NDC/UPC Barcode
3 0039-0223-11 0
1/2 x 100%

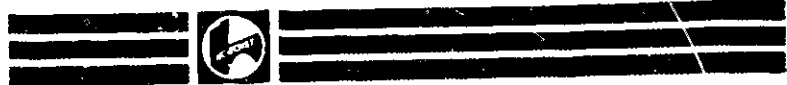
AmarylTM
glimepiride TABLETS

4 mg

100 Tablets

4 mg

UNIT DOSE PACK



Usual
See pa
prescri

Store t
86° F.

Keep t
medic
reach

Amaryl™
glimepiride

2 mg Scored Tablets

BLISTER SIDE
(2 mg Tablets)

Amaryl™ Professional
Sample
glimepiride

2 mg Scored Tablets



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

REG TM HOECHST AG
Amaryl TM HOECHST AG

922244-5/95

FOIL SIDE
(2 mg Tablets)

Amaryl[™]
glimepiride

4 mg Scored Tablets

BLISTER SIDE
(4 mg Tablets)

Amaryl[™] Professional
Sample
glimepiride

4 mg Scored Tablets



HOECHST-ROUSSEL
Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

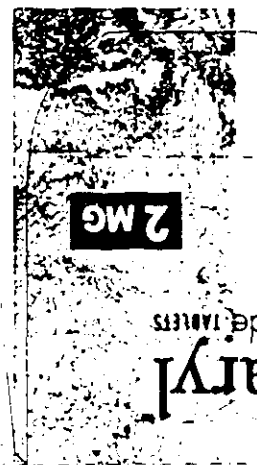
REG TM HOECHST AG

Amaryl TM HOECHST AG

922344-5/95

FOIL SIDE
(4 mg Tablets)

4 mg Sample Push-Thru Foll



For ease in opening:
1. Puncture top.
2. Push dome to
remove tablet.

Amaryl™
glimepiride TABLETS

Amaryl™
glimepiride TABLETS

Amaryl™
glimepiride TABLETS

Ama
glimepirid

PROFESSIONAL
SAMPLE

2 mg
Scored Tablets

2 MG

PROFESSIONAL
SAMPLE

8 Tablets
2 mg Scored Tablets

2 Blister Cards
x 4 Tablets each

Caution: Federal law prohibits
dispensing without prescription.

2 MG

PROFESSIONAL
SAMPLE

2 mg
Scored Tablets

2 MG



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Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

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Amaryl™ is a registered
trademark of Hoechst-Roussel

422281-1-85

PROFESSIONAL
SAMPLE

2 mg
Scored Tablets

8 Tablets

Usual Dosage:
See insert for full
prescribing information.
Package not child resistant.
**Keep this and all
medication out of
the reach of children.**
Store between 59°
and 86°F

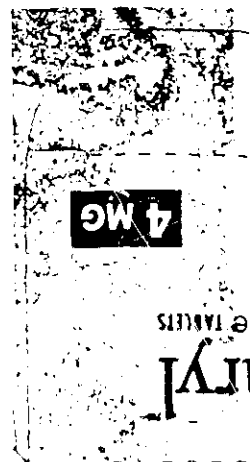
Amaryl™ **2 MG**
glimepiride TABLETS



A

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PROFESS
SAMPLE

2 mg
Scored



Amaryl
glimepiride TABLETS

Amaryl
glimepiride TABLETS

Amaryl
glimepiride TABLETS

Ama
glimepirid

PROFESSIONAL
SAMPLE

4 mg
Scored Tablets

4 MG

PROFESSIONAL
SAMPLE

8 Tablets
4 mg Scored Tablets

2 Blister Cards
x 4 Tablets each

Caution: Federal law prohibits
dispensing without prescription

4 MG

PROFESSIONAL
SAMPLE

4 mg
Scored Tablets

4 MG



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Pharmaceuticals Incorporated
Somerville, NJ 08876-1258

© 1997 Hoechst-Roussel
Pharmaceuticals, Inc.

PROFESSIONAL
SAMPLE

4 mg
Scored Tablets
8 Tablets

Usual Dosage:
See insert for full
prescribing information.
Package not child resistant.
**Keep this and all
medication out of
the reach of children.**
Store between 59°
and 86°F

Amaryl **4 MG**
glimepiride TABLETS

Scored Tabl

PROFESSIONAL

glimer

An

yl™

TABLETS

4 MG



Handwritten comments
in form revision on 6/14
7 J.L., D.T., J.S. Page
.. (Hector) A.2, A.10, A.5.
J. Hunt
6/14/95

REVISIONS of PI submitted 1/10/95 - AS PER FDA INTERNAL MEETING HELD
JUNE 6, 1995.

LEGEND:

COMMENTS = in *italics* and preceded by the word "COMMENT"

DELETIONS = ~~strikeout~~ material

ADDITIONS = redline material

(COMMENT: The dosage form should immediately follow the established name throughout the PI. Previously communicated in letter of May 17, 1995.)

AMARYL

(GLIMEPIRIDE, HOE 490)

ITEM 2.A.1

ANNOTATED PACKAGE INSERT

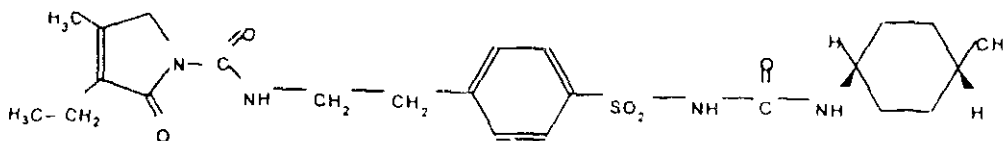
**AMARYL™ (GLIMEPIRIDE)
1, 2, and 4 mg Tablets**

DESCRIPTION

AMARYL™ (glimepiride) is an oral blood glucose-lowering drug of the sulfonylurea class. It is a white to yellowish-white crystalline, odorless to practically odorless, powder formulated into tablets of 1 mg, 2 mg, and 4 mg strengths for oral administration.

AMARYL tablets contain the active ingredient glimepiride and the following inactive ingredients: lactose (hydrous), sodium starch glycolate, povidone, microcrystalline cellulose, and magnesium stearate. In addition, AMARYL 1 mg tablets contain Ferric Oxide Red, AMARYL 2 mg tablets contain Ferric Oxide Yellow and FD&C Blue #2 Aluminum Lake, and AMARYL 4 mg tablets contain FD&C Blue #2 Aluminum Lake.

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



Molecular Formula $C_{24}H_{34}N_4O_5S$

Molecular Weight 490.62

Glimepiride is practically insoluble in water.

Approved at
6/14/95
JTB, AF, JS

CLINICAL PHARMACOLOGY:

(Comment: All the animal studies cited in this section and any wording suggesting either extrapancreatic effects of the drug or putative superiority of this sulfonylurea over others should be deleted.)

OK to summarize

will correct other

MECHANISM OF ACTION

Like all sulfonylureas, glimepiride appears to lower blood glucose by stimulating the release of insulin from the pancreas¹, an effect dependent on functioning beta cells in the pancreatic islets.

However, in normal, fasted animals, glimepiride lowers blood glucose levels with less insulin both acutely² and chronically³ to an extent greater than that of other sulfonylureas. This suggests extrapancreatic effects might be involved. In isolated adipocytes and diaphragm, glimepiride stimulates glucose transport more than glyburide⁴. However, glimepiride has no effect on blood glucose in totally insulin deficient animals^{5,6}. This suggests that the extrapancreatic effects of glimepiride are due to an insulin sensitizing mechanism.

Glimepiride has significantly less effect on the cardiovascular system than do other sulfonylureas. In contrast to glyburide and glipizide, glimepiride did not produce

1. Geisen K. Blood glucose and plasma insulin after oral administration of single doses of glimepiride, glibenclamide, glipizide and gliclazide as clear, aqueous sodium salt solutions in fasted dogs. Document No. 013017 (Vol 1 20/36)

2. Geisen K. Blood glucose and plasma insulin in fasted dogs after a single oral dose of glimepiride and glibenclamide and subsequently given repeatedly an oral glucose load. Document No. 013063 (Vol 1 20/39)

3. Sarah Y. et al. A novel sulfonylurea, glimepiride, exhibits hypoglycemic effect caused by its extrapancreatic action in genetically diabetic KK-Ay mice. Document No. 013020 (Vol 1 20/42)

4. Muller G. et al. Stimulation of glucose utilization in 3T3 adipocytes and rat diaphragm in vitro by the sulfonylureas, glimepiride and glibenclamide is correlated with modulations of cAMP regulatory cascade. Document No. 013026 (Vol 1 20/131)

5. Geisen K. Blood glucose in streptozotocin-diabetic rats during a five-day oral treatment with high doses of HOE 490 and HB 419. Special Pharmacology Report L (Vol 1 20/214)

6. Geisen K. Blood glucose in pancreatectomized and chemically diabetic dogs during an eight-day oral treatment with high doses of glimepiride and glibenclamide. Special Pharmacology Report M (Vol 1 20/217)

vasoconstriction in a hypoxic lactic acidosis model in dogs⁷. Glimepiride has also been shown to produce less alteration in coronary flow/resistance in dogs compared to glyburide or gliclazide⁸. These *in vivo* observations may be explained by the specific nature of glimepiride's interaction with the binding protein of the ATP-sensitive potassium channel. *In vitro* studies have demonstrated that glimepiride inhibits ATP sensitive potassium channels in cardiomyocytes 3-times less than glyburide^{9,10}. This might be due to the ATP-sensitive potassium channel associated binding protein of glimepiride differing from that of conventional sulfonylureas. In beta cell membranes, it was shown that glyburide binds with high affinity to a 140 kD ATP-sensitive potassium channel associated protein while glimepiride binds with lower affinity to a 65 kD membrane protein¹¹.

Glimepiride also demonstrates a significant anti-atherogenic activity in rabbits fed a high cholesterol diet¹². In addition, glimepiride selectively inhibits human platelet cyclooxygenase *in vitro*¹³.

Diuretic, anti-inflammatory, analgesic, muscle relaxant, antidepressant, anesthetic or neuroleptic activities were found to be absent or minimal.

PHARMACODYNAMICS

A mild glucose-lowering effect first appeared following single oral doses as low as 0.5-

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7. Landry, D.W. et al. The ATP sensitive K⁺ channel mediates hypotension in endotoxemia and hypoxic lactic acidosis in dog. *J Clin Invest* 89: 2071-2074, 1992. Document No. 013032 (Vol 1.21/13)
 8. Papp, J.G. Report on the cardiovascular effects of glibenclamide, glimepiride (HOE 490) and gliclazide in anesthetized open chest dogs. Document No. 013132 (Vol 1.21/17)
 9. Gögelein, H. Inhibition of HOE 234-activated K(ATP) currents by glibenclamide and glimepiride in isolated rat ventricular cardiomyocytes. Document No. 013002 (11) (Vol 1.21/16J)
 10. Makiejski, J.C. et al. Effects of HOE 490 (Glimepiride) on cardiac ATP. Document No. 013728 (Vol 1.21/171)
 11. Müller, G. et al. Differential interaction of glimepiride and glibenclamide with the B-cell sulfonylurea receptor. Document No. 013012 (Vol 1.19/218)
 12. Satoh, Y. et al. A novel sulfonylurea, glimepiride, inhibits atherogenesis without changing serum lipid levels in cholesterol-fed rabbits. Document No. 013113 (Vol 1.21/215)
 13. Ozaki, T. et al. Effects of oral hypoglycemic agents on platelet functions. *Biochim Pharmacol* 44: 687-691 (1992). Document No. 013114 (Vol 1.21/262)

0.6 mg in healthy subjects¹⁴. The time required to reach the maximum effect [i.e., minimum blood glucose level (T_{min})] was about 2 to 3 hours. In NIDDM patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg qd) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours.¹⁵ Higher doses (up to 32 mg) of glimepiride ~~did not present any serious safety issues but~~ did not appear to offer additional benefit¹⁶.

In larger dose-ranging studies¹⁷, blood glucose and HbA_{1c} were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of Amaryl. Some patients, particularly those with higher HbA_{1c} levels, may benefit from doses of Amaryl up to 8 mg/day. No difference in response was found when Amaryl was administered once daily or bid.

(COMMENT: The next sentence should be revised also to provide the average net reduction in HbA_{1c} values.) The results of 14-week, double-blind, parallel trials in previously-treated NIDDM patients demonstrated a maximal net reduction in median HbA_{1c} for Amaryl treated patients of 2.2% in absolute units compared to placebo treated patients. Efficacy results were not affected by age, gender, weight, or race.¹⁸

In long-term extension trials with previously-treated patients, no meaningful deterioration

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- 14 R/J101/ Pharmacokinetics and Pharmacodynamics of HOE 490 After Single Oral Administration in Healthy Volunteers (Vol 1 112/166)
1/A/102/ Pharmacodynamics of HOE 490 To Determine The Minimum Effective Dose (Vol 1 6-V1)
- 15 8/USA/104/DM Dose-Response Study of HOE 490 in Patients with Non-Insulin Dependent Diabetes Mellitus (Vol 1 173/A)
- 16 8/USA/105/DM Evaluation of Safety, Tolerance and Pharmacodynamic Effect of Multiple Doses of 8 mg, 16 mg and 32 mg Glimepiride (HOE 490) in Patients with Non-Insulin-Dependent Diabetes Mellitus (Vol 1 117/a)
- 8/USA/06/DM Evaluation of Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple-Dose Administration of Glimepiride (HOE 490) in Patients with Non-Insulin Dependent Diabetes Mellitus (Vol 1 119/A)
- 17 8/USA/201/DM A dose-dependent study of HOE 490 (glimepiride) in subjects with noninsulin-dependent diabetes mellitus (NIDDM) who have previously received sulfonylurea agents (Vol 1 196/A)
- 8/USA/205/DM Comparison of bid vs qd regimen of glimepiride (HOE 490) in subjects with noninsulin-dependent diabetes mellitus (NIDDM) who have previously received sulfonylurea agents (Vol 1 203/a)
- 18 8/USA/201/DM A dose-dependent study of HOE 490 (glimepiride) in subjects with noninsulin-dependent diabetes mellitus (NIDDM) who have previously received sulfonylurea agents (Vol 1 196/A)
- 8/USA/205/DM Comparison of bid vs qd regimen of glimepiride (HOE 490) in subjects with noninsulin-dependent diabetes mellitus (NIDDM) who have previously received sulfonylurea agents (Vol 1 203/a)

in mean fasting blood glucose (FBG) or HbA1c levels was seen after 2½ years of Amaryl therapy.¹⁹

516 mg/dl is reason for deleting this 19

~~Amaryl reduced FPG promptly and safely compared with other sulfonylureas. In a controlled trial vs. glipizide, Amaryl resulted in a significantly greater decrease in FPG within the first treatment month (Amaryl: 51.5 mg/dl, Glipizide: 32 mg/dl) in conjunction with a comparable incidence of hypoglycemia (Amaryl: 3.0%, Glipizide: 2.8%). This trend continued throughout the 3-month treatment period. In a controlled trial vs. glyburide, FPG reduction was similar for the two drugs during the first month of treatment (Amaryl and Glyburide: 46 mg/dl), but significantly less hypoglycemia occurred with Amaryl (Amaryl: 1.7%, Glyburide: 5.6%). This trend continued throughout the study.²⁰~~

~~Combination therapy with Amaryl and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose ideal body weight (IBW) was $\geq 130\%$. Initially 5-10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined fasting plasma glucose (FPG) values. Both groups in this double-blind study achieved similar reductions in FPG levels but the Amaryl/insulin therapy group used approximately 38% less insulin.²¹ (COMMENT: This paragraph is deleted because the indication of glimepiride in combination with insulin is not being allowed.)~~

19. 2MN/301/DM Multicenter Clinical Trial to Study the Effects of Glimepiride During Long-Term Treatment of Type II Diabetic Patients. Double-Blind, Parallel Group Comparison of Glimepiride and Diaonil (Nonmicronized Glibenclamide). (Vol 1, 254/1)
- 2MN/302/DM Follow-up Study to Multicenter Clinical Trial to Study the Effects of Glimepiride During Long-Term Treatment of Type II Diabetic Patients. Double-Blind, Parallel Group Comparison of Glimepiride and Diaonil (Nonmicronized Glibenclamide). (Vol 1, 31,3/1)
- 2MN/311/DM Multicenter Clinical Trial to Study the Effects of Glimepiride During Long-Term Treatment of Type II Diabetic Patients. Double-Blind, Parallel Group Comparison of Glimepiride and Euglucon N (Micronized Glibenclamide). (Vol 1, 275/1)
- 2MN/312/DM Follow-up Study to Multicenter Clinical Trial to Study the Effects of Glimepiride During Long-Term Treatment of Type II Diabetic Patients. Double-Blind, Parallel Group Comparison of Glimepiride and Euglucon N (Micronized Glibenclamide). (Vol 1, 319/1)
20. 8USA/301/DM Randomized comparative evaluation of the efficacy and safety of glimepiride (HOE 490) versus glipizide in patients with noninsulin-dependent diabetes mellitus. (Vol 3, 2/1)
- M52200001 Randomized, double-blind, parallel group study comparing the efficacy and safety of glimepiride (HOE 490) and glyburide in the treatment of subjects with noninsulin-dependent diabetes mellitus. (1, 228/1)
21. 8USA/305/DM Randomized Comparative Evaluation of Glimepiride (HOE 490) Combined With Insulin Versus Insulin Combined With Placebo in the Treatment of Patients With Noninsulin-Dependent Diabetes Mellitus. (Vol 1, 3,2/1)

In a long-term, randomized, placebo-controlled trial, Amaryl therapy improved postprandial insulin/C-peptide responses and overall ~~produced good~~ glycemic control ~~without producing any clinically meaningful increases in fasting insulin/C-peptide levels.~~ The ~~postprandial insulin/C-peptide responses, however, were enhanced with Amaryl therapy~~²².

In a controlled study, Amaryl-treated NIDDM patients demonstrated a greater decrease in C-peptide concentration during acute exercise than under non-exercise conditions compared to glyburide-treated patients. ~~Under these conditions, both treatment groups had comparable reductions in blood glucose. The results imply suggest the possibility that Amaryl therapy, compared with equivalent glyburide therapy, induces a more physiologic response to acute exercise. is seen with Amaryl than glyburide.~~²³

*During Amaryl therapy, a mild trend in decreasing total and LDL cholesterol levels was sometimes seen when compared to placebo-treated patients. there were some significant differences from placebo in Total cholesterol and LDL cholesterol, with the trend in the glimepiride group always being in the medically beneficial direction. In two active-controlled studies, triglycerides were reduced by approximately 10% in the Amaryl groups; triglycerides increased approximately 4% in the glipizide group and did not change in the glyburide group.*²⁴

PHARMACOKINETICS

22 8/USA/202/DM A placebo controlled, dose titration study of HOE 490 in patients with noninsulin-dependent diabetes mellitus (NIDDM) (Vol 1, 212/a)
23 2/MN/202/DM Effects of physical exercise on metabolic control in Type II diabetic patients treated with glimepiride (HOE 490) and glibenclamide (IB 419) (Vol 1, 300/A)
24 8/USA/301/DM Randomized, comparative evaluation of the efficacy and safety of glimepiride (HOE 490) versus glipizide in patients with noninsulin-dependent diabetes mellitus (Vol 3, 2/1)
M:52200001 Randomized, double-blind, parallel group study comparing the efficacy and safety of glimepiride (HOE 490) and glyburide in the treatment of subjects with noninsulin-dependent diabetes mellitus (Vol 1, 228/1)

(COMMENT: This subsection and the Special Populations subsection were revised in your amendment dated June 2, 1995, and subsequently revised by our Biopharmaceutics staff. A copy of their revised version (not showing changes) is attached at the end of this PI.)

After oral administration, glimepiride is absorbed rapidly and completely from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with NIDDM have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2 to 3 hours. When glimepiride was given after meals, the rate of absorption (T_{max}) was slightly decreased, but the extent of absorption (AUC) was unaffected²⁵. After multiple dosing with 4 mg qd in NIDDM patients,²⁶ the apparent terminal half life ($t_{1/2}$) was about 8 hours.

The pharmacokinetics of glimepiride were linear in a single-dose study in normal subjects using doses of 1 to 8 mg/day and in a multiple-dose study in patients using doses of 4 to 16 mg/day. There were no differences in pharmacokinetics between normal subjects and patients with NIDDM.²⁷ At steady state, mean peak concentrations of glimepiride (C_{max}) after 4 mg and 8 mg oral doses were approximately 300 ng/ml and 600 ng/ml, respectively. Glimepiride did not accumulate in plasma with repeated qd or bid oral dosing. Protein binding was greater than 99%²⁸. After intravenous dosing in normal subjects, the volume of distribution was 8.8 L (113 ml/kg), and the total body clearance was 47.8 ml/min²⁹.

As estimated by the coefficient of variation (CV%), the intraindividual variabilities in C_{max} , the area under the serum concentration-time curve (AUC), and the relative total body

25. BUSA/103/ The Effect of Food On The Pharmacokinetics of a Single Oral Dose of HOE 490 in Healthy Men. (Vol 1, 137/A)

26. BUSA/108/DM Single and Multiple Dose Pharmacokinetics of HOE 490 in Patients with Non-Insulin Dependent Diabetes Mellitus. (Vol 1, 113/1)

27. BUSA/108/DM Single and Multiple Dose Pharmacokinetics of HOE 490 in Patients with Non-Insulin Dependent Diabetes Mellitus. (Vol 1, 113/1)

17A/118/ Dose Linearity Study of Glimepiride (HOE 490) Tablets in Healthy Volunteers. (Vol 1, 99/1)

28. Report No. 949 Protein Binding of HOE 490. (Vol 1, 157/25)

29. 1A/114/ Absolute Bioavailability Study of a 1.0 mg Glimepiride (HOE 490) Tablet in Healthy Volunteers. (Vol 1, 82/A)

clearance (CL/f) for glimepiride were 23%, 17%, and 15%, respectively; these are smaller than the interindividual variabilities (25%, 29%, and 24%)³⁰.

Glimepiride is completely metabolized. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). M1 is further metabolized to M2. When ¹⁴C-glimepiride was given orally, approximately 60% of the radioactivity was recovered in the urine and 40% in feces. No parent drug was recovered from urine or feces³¹. No significant biliary excretion of glimepiride or its M1 or M2 metabolites has been observed³². M1 and M2 contribute no clinically meaningful glucose-lowering effect³³.

SPECIAL POPULATIONS

A single-dose, open-label study was conducted in 15 patients with renal impairment³⁴. Amaryl (3 mg) was administered to 3 groups of patients with different levels of creatinine clearance (CL_{Cr}). Group I had 5 patients with a mean CL_{Cr} of 77.7 ml/min; Group II had 3 patients with a mean CL_{Cr} of 27.7 ml/min, and Group III had 7 patients with a mean CL_{Cr} of 9.4 ml/min. Amaryl was found to be well-tolerated in all 3 groups. The results showed that the CL/f and V/f of glimepiride increased as CL_{Cr} decreased, while the apparent t_{1/2} did not change. These differences may be due to a decrease in binding to plasma proteins by glimepiride resulting in a larger volume of distribution. Mean urinary excretion of M1 and

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30. 1/A/122/- Investigation of Inter- and Intra-individual Variability in Pharmacokinetics and Pharmacodynamics After Single Oral Doses of 2 mg Glimepiride (HOE 490) in Healthy Volunteers (Vol 1.102/A)
31. 1/Z/A/101/- Pharmacokinetics and Metabolism of ¹⁴C-HOE 490 Following Oral Administration of 1.0 mg (100 mcg) of ¹⁴C to Three Healthy Male Volunteers: Pharmacokinetics after single oral dose 1 mg ¹⁴C HOE 490 (HOE 490-¹⁴C (S 80 B490) Glimepiride) metabolism in man after oral administration of 1 mg (Vol 1.76/92)
32. 1/B/G/20111- Pharmacokinetics of Glimepiride (HOE 490) in Patients with Biliary T. Drain (Vol 1.136/A)
33. M1/A/101/- Safety and Tolerability of a Single Intravenous Dose of 1 mg Metabolite M1 in Healthy Volunteers (Vol 1.190/A)
M1/A/102/- Pharmacokinetics of Single Doses of 1.5 mg HOE 490 Metabolite M1 I.V. and a Comparison with Placebo in Healthy Volunteers (Vol 1.191/A)
M1/A/103/- Safety and Tolerability of a Single Intravenous Dose of 3 mg HOE 490 Metabolite M1 in Healthy Volunteers (Vol 1.194/A)
34. 1/Y/U/201/N1- Pharmacokinetics of Glimepiride (HOE 490) in Patients with Renal Impairment (Vol 1.180/A)

M2 as a percent of dose was 44.4% for Group I, 21.9% for Group II, and 9.3% for Group III.

A multiple-dose titration study was also conducted in 16 NIDDM patients with renal impairment using doses ranging from 1-8 mg for 3 months³⁵. CL/f of glimepiride increased and renal excretion of M1 and M2 decreased in these patients as CL_{cr} decreased, which was consistent with the results observed after a single dose. The pharmacokinetic characteristics of glimepiride did not change throughout the duration of the study, implying that there is no accumulation of glimepiride in these patients. All patients with a CL_{cr} less than 22 ml/min had adequate control of their glucose levels with a dosage regimen of only 1 mg qd. The results from this study suggested that a starting dose of 1 mg Amaryl may be given to NIDDM patients with kidney disease, and a dose titration may then be performed as appropriate on the basis of fasting blood glucose levels.

Comparison of glimepiride pharmacokinetics in young (≤ 65 years) and elderly (> 65 years) NIDDM patients was performed in a crossover study comparing a dose of 3 mg bid with a dose of 6 mg qd³⁶. The mean AUC at steady state was 2748 ng $\cdot$ h/ml for the young and 2586 ng $\cdot$ h/ml for the elderly. The mean weight-adjusted clearance was 0.556 ml/min/kg for the young patients and 0.557 ml/min/kg for the elderly patients. These results indicate that there are no significant differences in glimepiride pharmacokinetics between young and elderly NIDDM patients.

There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight³⁷. There were no important

35. 1/B/203/N1 - Pharmacokinetics and Pilot Efficacy of HOE 490 in Patients with Renal Impairment (1 mg Multiple Dose) (Vol. 1, 154/38)

36. M5/203/XXX/3 - Pharmacokinetics of HOE 490 in Young and Elderly NIDDM Patients (SUSAN/203) (Vol. 1, 123A)

37. SUSAN/114/D1 - Pharmacokinetics of Glimepiride Tablets 4.0 mg in Male and Female Subjects With Non-Insulin-Dependent Diabetes Mellitus (NIDDM) (Vol. 1, 121A/01)

differences in glimepiride metabolism between subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine³⁸.

The pharmacokinetics of glimepiride in the morbidly obese patients were similar to those in the normal weight group, except for a lower C_{max} and AUC. However, since neither C_{max} nor AUC values were normalized for body surface area, the lower values of C_{max} and AUC for the obese patients were the result of their excess weight³⁹ and not due to a difference in the kinetics of glimepiride.

✓ Same company of glimepiride
pages of PLG's insert to
be chat.

INDICATIONS AND USAGE:

(COMMENT: Delete all reference to the combination treatment of glimepiride with insulin in this Section and throughout the PI.)

Amaryl is indicated as an adjunct to diet to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet alone.

Amaryl is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet in conjunction with an oral hypoglycemic agent.

(COMMENT: The words "and exercise" should follow all references to use with diet.) In initiating treatment for noninsulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood

glucose and symptoms of hyperglycemia. ~~The importance of~~ In addition to regular physical activity, ~~should also be stressed, and~~ cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of Amaryl must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring ^vonly short-term administration of Amaryl.

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

The Diabetes Control and Complications Trial (DCCT) demonstrated that control of HbA1c and glucose was associated with a decrease in retinopathy, neuropathy, and nephropathy for insulin-dependent diabetic (IDDM) patients. In considering the use of Amaryl in asymptomatic patients, it should be recognized that blood glucose control in NIDDM has not definitely been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes. ~~However, seventy-five percent of NIDDM patients unresponsive to dietary management achieved and maintained control of blood glucose and HbA1c on Amaryl40.~~

CONTRAINDICATIONS:

Amaryl is contraindicated in patients with:

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

WARNINGS:

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2): 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show

an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of Amaryl and of alternative modes of therapy.

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

PRECAUTIONS

GENERAL

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal insufficiency may cause elevated blood levels of glimepiride or its metabolites and increase the risk of serious hypoglycemic reactions. Debilitated or malnourished patients, and those with adrenal, pituitary or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with Amaryl or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including Amaryl, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. In such cases, institution of a course of Amaryl-insulin combination therapy is recommended.

INFORMATION FOR PATIENTS

Patients should be informed of the potential risks and advantages of Amaryl and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

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

LABORATORY TESTS

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

DRUG INTERACTIONS

(COMMENT: This section should be deleted. Most of the text has already been incorporated in revised Pharmacokinetics and Special Populations subsections of the CLINICAL PHARMACOLOGY Section as per your amendment dated June 2, 1995. Those subsections have been subsequently revised by our Biopharmaceutics staff, and a revised version is attached at the end of this PI. In addition, please include the first two paragraphs of this Drug Interactions subsection at the beginning of the Drug-Drug Interactions subsection attached.)

(COMMENT: Expressions such as "well tolerated" should be replaced by "did not result in any visible ill effects". This also applies of the attached revision by the Biopharmaceutics staff.)

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

these drugs are withdrawn from a patient receiving Amaryl, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. (calcium channel blockers omitted).⁴¹ When these drugs are administered to a patient receiving Amaryl, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving Amaryl, the patient should be observed closely for hypoglycemia.

Coadministration of aspirin and Amaryl leads to a decrease in the glimepiride AUC and a 34% increase in CL/f. These changes may be due to a decrease in protein binding. However, blood glucose, insulin, and C-peptide concentrations were unaffected⁴². No hypoglycemic symptoms were reported and the drugs were well tolerated. Pooled data from clinical trials showed that uncontrolled concurrent administration of aspirin and other salicylates with Amaryl was well tolerated.⁴³

Coadministration of either cimetidine or ranitidine with a single 4 mg oral dose of Amaryl did not alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology⁴⁴. Pooled data from clinical trials showed that uncontrolled concurrent administration of H₂-receptor antagonists with Amaryl was well tolerated⁴⁵.

41. *Meyler's Side Effects of Drugs*, Twelfth Edition - ed. MNG Dukes, Elsevier 1992 p. 450

Integrated Summary of Safety - Drug-Drug-Interactions (Vol 1 357/232)

42. 1/A/115/- Interaction of Glimepiride (HOE 490) and Aspirin in Healthy Volunteers (Vol 1 139/a)

43. Integrated Summary of Safety - Drug-Drug Interactions (Vol 1 357/232)

44. BAUSA/116/- The Effects of Cimetidine and Ranitidine on Glimepiride Pharmacokinetics and Pharmacodynamics in Normal Subjects (Vol 1 144/1)

45. Integrated Summary of Safety - Drug-Drug Interactions (Vol 1 357/232)

Concomitant administration of propranolol and Amaryl increased the C_{max} , AUC, and $t_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively. It also decreased the CL/f by 18%. The recovery of M1 and M2 in the urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo⁴⁶. Pooled data from clinical trials in patients with NIDDM showed that uncontrolled concurrent administration of beta-blockers with Amaryl was well-tolerated⁴⁷. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of Amaryl (4 mg qd) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Amaryl treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the PT-time curve and maximum PT values during Amaryl treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important⁴⁸.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

46. N/A116r. Interaction Study of Glimepiride (HOE 490) and Propranolol in Healthy Volunteers. (Vol 1, 146/001)

47. Integrated Summary of Safety - Drug-Drug Interactions. (Vol 1, 157/232)

48. NUSA/119r. Influence of Multiple-Dose Glimepiride on the Pharmacokinetics and Pharmacodynamics of Racemic Warfarin in Healthy Volunteers. (Vol 1, 143/1)

The responses of serum glucose, insulin, C-peptide and plasma glucagon to 2 mg Amaryl were unaffected by coadministration of 5 mg ramipril (an ACE inhibitor) in normal subjects. No hypoglycemic symptoms were reported and the drugs were well tolerated⁴⁹.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of: calcium-channel blockers, ACE inhibitors, estrogens, fibrates, NSAIDs, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone⁵⁰. (*COMMENT: Why were "sympathomimetics" deleted?*)

SENSITIZATION STUDIES

Glimepiride was not found to be antigenic in mice, rats, or guinea pigs⁵¹.

(COMMENT: Drug exposure comparisons between preclinical and clinical doses should be based on plasma concentration, e.g., AUC, rather than on mg/kg. If plasma concentrations of the drug are not known, exposure comparison should be based on surface area (mg/m²). This comment was included in our 5/17/95 letter, but in that letter it pertained only to the Pregnancy subsection of the PRECAUTIONS Section. It should have pertained from THIS point forward in the PRECAUTIONS Section.)

(COMMENT: The following is not a Section. It should be made equivalent to other subsections of the PRECAUTIONS Section.)

49 1/A/123/ Interaction of Glimepiride (HOE 490) and Ramipril in Healthy Volunteers (Vol 1:156/A)
50 Integrated Summary of Safety - Drug-Drug Interactions (Vol 1:357/232)
Safety Update (Vol 2:1/1)
51 Mouse and Rat Antigenicity Study (Doc. No. 11827 (Vol 1:59/12))
Guinea Pig Antigenicity Study (Doc. No. 11739 (Vol 1:59/123))

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

GLIMEPIRIDE IS NON-MUTAGENIC IN A BATTERY OF ~~IN-VITRO~~ *IN VITRO* AND ~~IN-VIVO~~ *IN VIVO* MUTAGENICITY STUDIES (AMES TEST, SOMATIC CELL MUTATION, CHROMOSOMAL ABERRATION, UNSCHEDULED DNA SYNTHESIS, MOUSE MICRONUCLEUS TEST)⁵². STUDIES IN RAT AT DOSES OF UP TO 5000 PPM IN COMPLETE FEED (100-2156 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE) FOR 30 MONTHS SHOWED NO EVIDENCE OF CARCINOGENESIS⁵³. IN MICE, ADMINISTRATION OF GLIMEPIRIDE FOR 24 MONTHS RESULTED IN AN INCREASE IN BENIGN PANCREATIC ADENOMA FORMATION WHICH WAS DOSE-RELATED⁵⁴. THESE ADENOMAS ARE THOUGHT TO BE THE RESULT OF CHRONIC PANCREATIC STIMULATION. THE NO-EFFECT DOSE FOR ADENOMA FORMATION IN MICE IN THIS STUDY WAS 320 PPM IN COMPLETE FEED, OR 46-54 MG/KG BODY WEIGHT/DAY. THIS IS ABOUT 300 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE (8 MG/DAY). ~~NO EVIDENCE OF TUMOR FORMATION WAS OBSERVED IN BEAGLE DOGS EXPOSED TO CONCENTRATIONS OF GLIMEPIRIDE UP TO 320 MG/KG BODY WEIGHT/DAY FOR 12 MONTHS (—2000 TIMES THE MAXIMUM HUMAN DOSE—8 MG/DAY)~~⁵⁵. (*COMMENT: THE DOG IS NOT THE PROPER MODEL IN WHICH TO MAKE THIS DETERMINATION.*)

THERE WAS NO EFFECT OF GLIMEPIRIDE ON MALE MOUSE FERTILITY, IN ANIMALS EXPOSED UP TO 2500 MG/KG BODY WEIGHT (> 15,000 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE)⁵⁶.

GLIMEPIRIDE HAD NO EFFECT ON THE FERTILITY OF MALE AND FEMALE RATS ADMINISTERED UP TO 4000 MG/KG BODY WEIGHT (> 24,000 TIMES THE MAXIMUM HUMAN DOSE)⁵⁷.

52 Ames Test - Doc. No. 4944 (Vol. 1 72/1)
Somatic Cell Mutation Test - Doc. No. 7265 (Vol. 172/118)
Chromosomal Aberration Test - Doc. No. 9938 (Vol. 1 72/193)
Unscheduled DNA Synthesis Test - Doc. No. 7490 (Vol. 1 72/140)
Mouse Micronucleus Test - Doc. No. 5684 (Vol. 1 72/227)
53 Rat Carcinogenicity Test - Doc. Nos. 9620 and 11894 (Vols. 1 52/1 and 1 51/246)
54 Mouse Carcinogenicity Test - Doc. No. 9619 (Vol. 1 38/068)
55 Dog Repeated dose (12 Month) Oral Toxicity Study - Doc. No. 8577 (Vol. 1 34/001)
56 Mouse Male Fertility Study - Doc. No. 8251 (Vol. 1 59/162)
57 Rat Reproduction Study - Doc. No. 8281 (Vol. 1 60/1)

(COMMENT: The following is not a Section. It should be made equivalent to other subsections of the PRECAUTIONS Section.)

PREGNANCY

TERATOGENIC EFFECTS

Pregnancy Category C. Glimepiride did not produce teratological effects in rats^{58,59} exposed orally up to 4000 mg/kg body weight (> 24,000 times the maximum recommended human dose) or in rabbits⁶⁰ exposed up to 32 mg/kg body weight (~200 times the maximum human dose). In some studies, however, a high rate of intrauterine fetal death was observed which may have been associated with maternal hypoglycemia⁶¹.

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

NONTERATOGENIC EFFECTS

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period⁶². Significant concentrations of glimepiride were observed in

58 Rat Reproduction Study - Doc. No. 8281 (Vol 160/1)
59 Rat Reproduction Study - Doc. No. 6520 (Vol 163/1)
60 Rabbit Teratology Study - Doc. No. 6589 (Vol 1 71/1 and 5)
61 Rat Teratology Study - Doc. No. 9623 (Vol 1 63/113)
Rabbit Teratology Study - Doc. No. 6589 (Vol 1 71/1 and 5)
Rabbit Teratology Study - Doc. No. 8986 (Vol 1 71/122)
62 Rat Reproduction Study - Doc. No. 8281 (Vol 160/1)
Rat Teratology Study - Doc. No. 9623 (Vol 1 63/113)

the serum and breast milk of the dams as well as in the serum of the pups⁶³. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride⁶⁴.

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

NURSING MOTHERS

In rat reproduction studies significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups⁶⁵. Although it is not known whether Amaryl is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, Amaryl should be discontinued in nursing mothers. If Amaryl is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

63 Rat Lactation Study, Doc. No. 11670 (Vol. 1 64/278)
64 Rat Reproduction Study, Doc. No. 12029 (Vol. 1 65/1)
65 Rat Lactation Study, Doc. No. 11670 (Vol. 1 64/278)

ADVERSE REACTIONS

HYPOGLYCEMIA (SEE PRECAUTIONS AND WARNINGS)

All available blood glucose values were reviewed and subjects in US controlled trials who had at least one documented value below 60 mg/dl were identified.

No. of Patients with Blood Glucose Levels < 60 mg/dl

	No. with <60 mg/dl	No. Studied	%
Amaryl	11	746	1.5
Placebo	0	294	0
Amaryl	5	289	1.7
Glyburide	7	288	2.4
Amaryl	5	537	0.9
Glipizide	3	257	1.2

The number of subjects with one or more signs or symptoms of hypoglycemia was higher than the number of subjects with documented hypoglycemia. In controlled, comparative studies with placebo and active control agents, the following results were seen:

No. of Patients with Hypoglycemic
 Signs/Symptoms

	No. with <u>Symptoms</u>	No. <u>Studied</u>	%
Amaryl	104	746	13.9
Placebo	6	294	2.0
Amaryl	29	289	10.0
Glyburide	47	288	16.3
Amaryl	115	543	21.2
Glipizide	53	258	20.6

~~These results from dose response and dose titration studies demonstrate that the incidence of clinically relevant hypoglycemia is likely to be low. Combined use of glimepiride and insulin may result in increased frequency of hypoglycemic episodes and weight gain.~~

ADVERSE EVENTS

Amaryl has been evaluated for safety in over 4,500 patients with NIDDM. Of these, 2,013 were studied in US controlled trials, and 1,551 were studied in foreign controlled trials. More than 1650 of these patients were treated for at least 1 year. In placebo-controlled trials, the overall incidence of adverse events was low, but was higher in Amaryl than in placebo patients. The most commonly reported adverse events (possibly or probably related to Amaryl) were hypoglycemia (based on symptomatology), dizziness, asthenia, headache,

and nausea⁶⁷.

Treatment emergent signs and symptoms (TESS) other than hypoglycemia (see above - **Hypoglycemia**) considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with Amaryl are shown below.

TESS Occurring in $\geq$ 1% Amaryl Patients

	Placebo		Amaryl	
	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>
Total Treated	294	100.0	746	100.0
Dizziness	1	0.3	13	1.7
Asthenia	3	1.0	12	1.6
Headache	4	1.4	11	1.5
Nausea	0	0.0	8	1.1

GASTROINTESTINAL REACTIONS

Gastrointestinal disturbances, e.g., (*COMMENT: As written, this means "that is"; is that correct?*) nausea and GI fullness, occur occasionally. Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in controlled trials was similar to that of placebo. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

DERMATOLOGIC REACTIONS

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or

maculopapular eruptions occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of Amaryl; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

HEMATOLOGIC REACTIONS

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

METABOLIC REACTIONS

Hepatic porphyria reactions have been reported with sulfonylureas; however, no cases have yet been reported with Amaryl. Disulfiram-like reactions have not been reported with Amaryl. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OTHER REACTIONS

Changes in accommodation and/or blurred vision may occur with the use of Amaryl. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may

actually be reduced by treatment. In placebo-controlled trials of Amaryl, the incidence of blurred vision was: placebo - 0.7%, Amaryl - 0.4%

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

(COMMENT: Delete all references to use of glimepiride in combination with insulin.)

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

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

USUAL STARTING DOSE

The usual starting dose of Amaryl as initial therapy is 1-2 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg daily, and should be titrated carefully. (See PRECAUTIONS Section for patients at increased risk). *(COMMENT: Move to here the last 2 sentences of the Usual Maintenance Dose subsection.)* Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Some Type II diabetic patients previously treated with insulin may respond satisfactorily to

Amaryl.

USUAL MAINTENANCE DOSE

The usual maintenance dose is 1 to 8 4 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored with HbA1c measurements performed, on average, every 3 to 6 months.

No exact dosage relationship exists between Amaryl and the other oral hypoglycemic agents. The maximum starting dose of Amaryl should be no more than 2 mg. *(COMMENT: Move the last 2 sentences of this subsection to the Usual Starting Dose subsection -- as indicated.)*

MAXIMUM DOSE

The maximum recommended dose is 8 mg qd.

DOSAGE INTERVAL

In controlled clinical trials, Amaryl has been shown to effectively control blood glucose when given once daily.

COMBINATION OF AMARYL AND INSULIN IN PATIENTS WITH SECONDARY FAILURE.

Combination therapy with Amaryl and insulin is indicated in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of ≥ 150 mg/dl in plasma or serum depending on the patient. The recommended Amaryl dose is 8 mg qd administered with the first main meal. After starting with low-dose insulin, upward

adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose levels⁶⁸.

SPECIFIC PATIENT POPULATIONS.

Amaryl is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See Precautions).

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

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

HOW SUPPLIED

AMARYL™ (glimepiride) tablets are available in the following strengths and package sizes:

1 mg (pink, figure-8 shape, monogrammed, scored)

Bottles of 100 NDC 0039-0221-10

2 mg (green, figure-8 shape, monogrammed, scored)

Bottles of 100 NDC 0039-0222-10

Bottles of 500 NDC 0039-0222-50

Unit Dose Cartons (100) NDC 0039-0222-11

4 mg (blue, figure-8 shape, monogrammed, scored)

Bottles of 100 NDC 0039-0223-10

Bottles of 500 NDC 0039-0223-50

Unit Dose Cartons (100) NDC 0039-0223-11

Store at controlled room temperature (59° - 86° F; 15° - 30° C).

Dispense in well-closed containers with safety closures.

Caution: Federal law prohibits dispensing without a prescription.

AMARYL™ is a trademark of Hoechst-Roussel Pharmaceuticals Inc.

ANIMAL TOXICOLOGY

Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to 320 mg glimepiride/kg/day for 12 months (approximately 2,000 times the recommended human dose). One female and one male dog developed bilateral subcapsular cataracts⁶⁹. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation⁷⁰. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative, and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture⁷¹.

HUMAN OPHTHALMOLOGY DATA

Ophthalmic examinations were carried out in over 500 subjects during long-term studies using the methodology of Taylor and West⁷² and Laties et al.⁷³. No significant differences were seen between Amaryl and glyburide in the number of subjects with clinically important changes in visual acuity, intra-ocular tension, or in any of the five lens-related variables examined⁷⁴.

Ophthalmic examinations were carried out during long-term studies using the method of Chylack et al.⁷⁵ No significant or clinically meaningful differences were seen between

69 1 year dog study. "Repeated-Dose (12-month) Oral Toxicity Study of HOE 490 (S 80 8490) in Dogs" (Study No. 88 1262 Report No. 90 0280 by R. Brunk, et al. Hoechst AG, Frankfurt, Federal Republic of Germany, June 12, 1990, Document No. 008577) (Vol 1, 34/001)

70 Cataract formation study. "In Vitro Investigations of the Effects of HOE 490 on Bovine Lenses" (Study No. 92 1203 by O. Hockwin and W. Brexipohl, University of Bonn, Federal Republic of Germany, December 1, 1992, Document No. 012322) (Vol 1, 59/1)

71 Co-cataractogenic Potential Study. "Study to Test the Possible Cocataractogenic Potential of Anti-diabetic Compound HOE 490 (Glimepiride) in Experimental Cataract Models in Rats" (Study No. 92-03 by K. Sasaki, et al., Kanazawa Medical University, Ishikawa, Japan, June/July 1993, Document No. 013126) (Vol 1, 59/28)

72 Taylor, H.R. and West, S.K. A simple system for the clinical grading of lens opacities. *Lens Res* 1988; 5: 175-182

73 Laties, A., et al. Field test reliability of a new lens opacity rating system utilizing slit-lamp examination. *Lens and Eye Tox Res* 1989; 6: 443-464

74 Protocol 8/USA/302DM. Evaluation of the Efficacy and Safety of Glimepiride versus Glyburide in Subjects with Noninsulin-Dependent Diabetes Mellitus. (Vol 1, 228/1)

75 Chylack, L.T. et al. Lens Opacities Classification System II (LOCS II). *Arch Ophthalmol* 1989; 107: 991-997

Chylack, L.T. et al. Quantitating cataract and nuclear brunescence: the Harvard and LOCS systems. *Optom Vis Sci* 1993; 70: 886-95

Amaryl and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination.

PHARMACOKINETICS

Absorption

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

Distribution

After intravenous (IV) dosing in normal subjects, the volume of distribution (V_d) was 8.8 L (113 ml/kg), and the total body clearance (CL) was 47.8 ml/min². Protein binding was greater than 99.5%³.

Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes⁴. M1 but not M2 possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model, however, whether the glucose lowering effect of M1 is clinically meaningful is not clear⁵.

Excretion

When ¹⁴C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the

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- ¹ 8/USA/103/- The Effect of Food On The Pharmacokinetics of a Single Oral Dose of HOE 490 in Healthy Men. (Vol 1.137/A)
 - ² 1/A/114/- Absolute Bioavailability Study of a 1.0 mg Glimepiride HOE 490 Tablet in Healthy Volunteers. (Vol 1.82/A)
 - ³ Report No. 999 Protein Binding of HOE 490. (Vol 1.157/25)
 - ⁴ Doc. No. 014755 Investigations of enzymes responsible for the main metabolic routes of biodegradation of glimepiride in man.
 - ⁵ MI/1/A/101/- Safety and Tolerability of a Single Intravenous Dose of 1 mg, Metabolite M1 In Healthy Volunteers. (Vol 1.190/A)
MI/1/A/102/- Pharmacokinetics of Single Doses of 1.5 mg HOE 490 Metabolite M1, I.V. and a Comparison with Placebo in Healthy Volunteers. (Vol 1.191/A)
MI/1/A/103/- Safety and Tolerability of a Single Intravenous Dose of 3 mg HOE 490 Metabolite M1 in Healthy Volunteers. (Vol 1.194/A)

total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces⁶. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed⁷.

Other

In normal healthy volunteers, the intraindividual variabilities of C_{max} , AUC, and CL/f for glimepiride were 23%, 17%, and 15%, respectively, and the interindividual variabilities were 25%, 29%, and 24%, respectively. Following oral once daily dosing, glimepiride did not have unexpected accumulation in serum and over glimepiride's dosage range, AUC is proportional to dose in patients with NIDDM.

SPECIAL POPULATIONS

Geriatric

Comparison of glimepiride pharmacokinetics in young (≤ 65 years) and elderly (> 65 years) NIDDM patients was performed in a study using a dosing regimen of 6 mg qd⁸. The mean AUC at steady state for the elderly patients was about 13% lower than that for the young patients. The mean weight-adjusted clearance for the elderly patients was about 11% higher than that for the young patients. These results indicate that there are no significant differences in glimepiride pharmacokinetics between young and elderly NIDDM patients.

Pediatric

No studies were performed in pediatric patients.

⁶ 1/ZA/101/- Pharmacokinetics and Metabolism of ¹⁴C-HOE 490 Following Oral Administration of 1.0 mg (100 mCi of ¹⁴C) to Three Healthy Male Volunteers
Pharmacokinetics after single oral dose 1 mg ¹⁴C-HOE 490
HOE 490-14C (S 80 8490, Glimepiride) metabolism in man after oral administration of 1 mg.
(Vol 1.76/92)

⁷ 1/BG/201/LI Pharmacokinetics of Glimepiride (HOE 490) in Patients with Biliary T-Drain. (Vol 1.136/A)

⁸ M/5200/0003/ Pharmacokinetics of HOE 490 in Young and Elderly NIDDM Patients (8/USA/206). (Vol 1.123/A)

Gender

There were no significant differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight⁹.

Race

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

Renal Insufficiency

A single-dose, open-label study was conducted in 15 patients with renal impairment¹⁰. AMARYL (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLcr); 77.7 (n = 5), 27.7 (n = 3), and 9.4 (n = 7) ml/min. AMARYL was found to be well-tolerated in all 3 groups. The results showed that CL/f and Vd/f of glimepiride increased as CLcr decreased, while the apparent terminal half-life ($T_{1/2}$) did not change. Mean urinary excretion of M1 plus M2 as percent of dose were 44.4%, 21.9%, and 9.3% for Groups I to III, respectively.

A multiple-dose titration study was also conducted in 16 NIDDM patients with renal impairment using doses ranging from 1-8 mg qd for 3 months¹¹. CL/f of glimepiride increased and renal excretion of M1 and M2 decreased in these patients as CLcr decreased, which was consistent with the results observed after a single dose. All patients with a CLcr less than 22 ml/min had adequate control of their glucose levels with a dosage regimen of only 1 mg qd. The results from this study suggested that a starting dose of 1 mg AMARYL may be given to NIDDM patients with kidney disease, and a dose titration may then be performed as appropriate on the basis of fasting blood glucose levels.

Hepatic Insufficiency

No studies were performed in patients with hepatic insufficiency.

⁹ 8/USA/114/DM Pharmacokinetics of Glimepiride Tablets 4.0 mg in Male and Female Subjects With Non-Insulin Dependent Diabetes Mellitus (NIDDM). (Vol 1.121/001)

¹⁰ 1/YU/201/NI Pharmacokinetics of Glimepiride (HOE 490) in Patients with Renal Impairment. (Vol 1.130/A)

¹¹ 1/B/203/NI Pharmacokinetics and Pilot Efficacy of HOE 490 in Patients with Renal Impairment (1 mg Multiple Dose). (Vol 1.159/38)

Other Populations

There were no important differences in glimepiride metabolism between subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine¹².

The pharmacokinetics of glimepiride in the morbidly obese patients were similar to those in the normal weight group, except for a lower C_{max} and AUC. However, since neither C_{max} nor AUC values were normalized for body surface area, the lower values of C_{max} and AUC for the obese patients were likely the result of their excess weight¹³ and not due to a difference in the kinetics of glimepiride.

Drug-Drug Interactions

Coadministration of aspirin (1 gm tid) and AMARYL leads to a 34% decrease in the mean glimepiride AUC and therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported and the drugs were well tolerated¹⁴. Pooled data from clinical trials showed that uncontrolled concurrent administration of aspirin and other salicylates with AMARYL was well tolerated.¹⁵

Coadministration of either cimetidine (800 mg qd) or ranitidine (150 mg bid) with a single 4 mg oral dose of AMARYL did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology¹⁶. Pooled data from clinical trials showed that uncontrolled concurrent administration of H₂-receptor antagonists with AMARYL was well tolerated¹⁷.

Concomitant administration of propranolol (40 mg tid) and AMARYL significantly increased C_{max} , AUC, and $T_{1/2}$ of glimepiride by 23%, 22%, and 15% respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 in the urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo¹⁸. Pooled data from clinical trials in patients

¹² 1/D/115/- Influence of the Hydroxylation Phenotype on the Pharmacokinetics of Glimepiride (HOE 490). (Vol 1.132/A)

¹³ 8/USA/112/DM The Pharmacokinetics of Glimepiride (HOE 490) in Normal Weight and Morbidly Obese Type II Diabetic Subjects. (Vol 1.134/A)

¹⁴ 1/A/115/- Interaction of Glimepiride (HOE 490) and Aspirin in Healthy Volunteers. (Vol 1.139/a)

¹⁵ Integrated Summary of Safety - Drug-Drug Interactions. (Vol 1.357/232)

¹⁶ 8/USA/118/- The Effects of Cimetidine and Ranitidine on Glimepiride Pharmacokinetics and Pharmacodynamics in Normal Subjects. (Vol 1.144/1)

¹⁷ Integrated Summary of Safety - Drug-Drug Interactions. (Vol 1.357/232)

¹⁸ 1/A/116/- Interaction Study of Glimepiride (HOE 490) and Propranolol in Healthy Volunteers. (Vol 1.146/001)

with NIDDM showed that uncontrolled concurrent administration of beta-blockers with AMARYL was well-tolerated¹⁹. However, if beta-blockers are used caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of AMARYL (4 mg qd) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. AMARYL treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the PT-time curve and maximum PT values during AMARYL treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important²⁰.

The responses of serum glucose, insulin, C-peptide and plasma glucagon to 2 mg AMARYL were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg qd in normal subjects. No hypoglycemic symptoms were reported and the drugs were well tolerated²¹.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.²²

Pharmacokinetic Parameters

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

-
- ¹⁹ Integrated Summary of Safety - Drug-Drug Interactions. (Vol 1.357/232)
²⁰ 8/USA/119/- Influence of Multiple Dose Glimepiride on the Pharmacokinetics and Pharmacodynamics of Racemic Warfarin in Healthy Volunteers. (Vol 1.143/1)
²¹ /A/123/- Interaction of Glimepiride (HOE 490) and Ramipril in Healthy Volunteers. (Vol 1.150/A)
²² Doc. No. 014755 Investigations of enzymes responsible for the main metabolic routes of biodegradation of glimepiride in man.

	Volunteers	Patients with NIDDM	
	Single Dose	Single Dose (Day 1)	Multiple Dose (Day 10)
C_{max} (ng/ml)			
1 mg	103 ± 34 (12) ¹		
2 mg	177 ± 44 (12)		
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	557 ± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
T_{max} (hr)	2.4 ± 0.8 (48)	2.5 ± 1.2 (26)	2.8 ± 2.2 (23)
CL/f (ml/min)	54.7 ± 15.8 (48)	48.5 ± 29.3 (26)	52.7 ± 40.3 (23)
Vd/f (L)	14.9 ± 6.0 (48)	19.8 ± 12.7 (26)	37.1 ± 18.2 (23)
$T_{1/2}$ (hr)	1.4 ± 0.5 (48)	5.0 ± 2.5 (26)	9.2 ± 3.6 (23)

¹. (): Number of subjects.

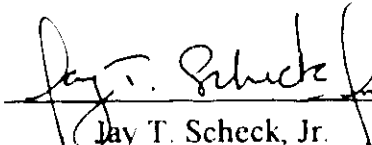
Direct dial number (908) 231-2794

Jay T. Scheck, Jr.
Secretary & General Counsel

NDA 20-496

Amaryl™ (glimepiride) Tablets

In accordance with the requirement of section 306(k) of the Federal Food, Drug, and Cosmetic Act, Hoechst-Roussel certifies that, to the best of Hoechst-Roussel's knowledge, Hoechst-Roussel has not and will not use any person debarred under subsections (a) or (b) of Section 306 in any capacity in connection with this NDA.


Jay T. Scheck, Jr.

REVIEW

MEDICAL HISTORY

NDA 20496

2 OF 6

OCT - 5 1995

Group Leader Review¹ of an NDA

Amaryl™ (glimiperide)

Oral hypoglycemic

September 27, 1995

This oral hypoglycemic is the latest on a long list of other sulfonylurea drug products. Is it substantially any different than other agents in its subclass? That is largely the theme of this review and the common thread among all remaining labeling issues.

I will recommend some modifications of the primary reviewer's recommendations with what I hope is sufficient justification. It is important to point out that these issues involve substantial policy considerations. I welcome a process of continued debate so that our ultimate decisions will be as sound as possible.

Issue #1 Should the new indication (and it would be the first for any SU) for combination insulin and Amaryl be approved?

I believe that it is a close call, but yes, the indication is supported by the data. First some background: There was a time when DMEDP was actively encouraging SU developers to pursue novel hypotheses and trial designs. One idea that we accepted was that exogenous "insulin sparing" could itself be considered a benefit of SU therapy. Of course, that notion is somewhat debatable since we know that the SUs work primarily by stimulating endogenous insulin secretion. The hope is that because of its splanchnic bed location, endogenous insulin secretion is better than exogenous insulin injection particularly in suppressing hepatic glucose output. This remains a hope, but not an entirely unreasonable one.

In our discussion with the company, we accepted that if glycemic control was equal or better when used in combination with insulin injections, and if the amount of insulin injected was significantly reduced, this would be sufficient to justify the indication. What we did not say explicitly, but is always implicit in our decision making is that the overall risk/benefit relationship should be acceptable just as for any other indication.

Dr. John Gueriguian, the primary reviewer, astutely identified a significantly higher incidence of

¹Material reviewed: Dr. Gueriguian's medical review, tabulated data from all patients with hypoglycemic symptoms, case report forms of patients with hypoglycemic symptoms, excerpts from the NDA and subsequent data presented during the meeting of 6/23/95 (see attachments).

hypoglycemia among patients on Amaryl+insulin than in patients on insulin alone. As he correctly pointed out to the sponsor, it does not matter that the difference was not large, or that on second look by the company, that there seemed to be fewer patients on combination therapy who experienced "more than mild" symptoms than was seen with insulin alone. [Note that we are talking largely about symptoms. Home glucose monitoring was performed, but inconsistently. Certainly there are no laboratory determined values.]

Dr. Gueriguian's logic is sound. A statistically significant signal from a trial, though perhaps modest on an absolute scale, can be expected to be amplified with marketed use. Since we know that roughly the same proportion of patients die of SU-induced hypoglycemia as from metformin-induced lactic acidosis, we would be foolish to ignore even small increases in hypoglycemic potential that could translate ultimately into additional deaths.

I also quickly realized that it did no good to review the case report forms of all patients who had developed hypoglycemic during the trial, or to consider the various post hoc analyses presented by the company. All these efforts are after the fact, and nothing could come out of these efforts except hypothesis generation. I came to two conclusions:

First, the outcome could have been anticipated. An oral, long acting hypoglycemic is inherently more likely to cause hypoglycemia in NIDDM patients than insulin itself. Clearly, the pharmacokinetic profile of the oral hypoglycemic cannot like insulin be adjusted during the course of the day to more closely fit the patient's eating and activity schedule. The pill gives a one size fits all profile. Insulin allows more individualization. This does not excuse the hypoglycemia issue, but perhaps does explain its existence. The fact that the combination treated patients experienced more rapid improvement during the first eight weeks of therapy is also important. It was during this period that differences occurred in incidence of hypoglycemia. Furthermore, the combination patients ended up with better control by .5 %units HbA1c. So the combo treated patients had more rapid onset of improved control and ended up with better control than insulin only treated patients. The overall risk/benefit for combo and insulin monotherapy may therefore turn out to be about the same when the increase in hypoglycemia is adjusted for the increase in glycaemic control and the rate at which it was achieved.

Secondly, combo-treated patients did significantly reduce their total insulin used but also the number of daily injections required. This was not a huge effect, but one that could translate into some patients getting by with less insulin injections.

In summary, the sponsor did the study that we reviewed and approved. By the criteria we explicitly accepted, they proved the combination therapy to be effective. There did appear to be a difference in risk/benefit between combo and monotherapy, but without resorting to any post hoc analysis, this appears to diminish or even evaporate if adjustments are made for differences in efficacy. An additional small, but tangible benefit was also demonstrated. This would be the first of any additional indication allowed for SU drug products. Undoubtedly, we should be prepared to defend it if that be our decision.

Recommendation: Approve the indication with labeling modification as described below.

#2 Is there such a thing as an extrapancreatic effect of SU therapy in general and of glimiperide in particular?

I don't think any of us believe that there is much of such an effect, i.e. SUs acting to increase insulin sensitivity as opposed to stimulating insulin release. The company has made much of this effect and wishes to suggest that Amaryl is better than any other SU in this respect largely because of animal model data. Dr. Gueriguian appropriately called them out on this, and asked that they remove all references to extrapancreatic in the labeling. Unfortunately, we later learned that other SU labels already contained this word. We can't do any less for the sponsor though it is one of those things we should take another look at when we re-do class labeling. The company does make a very strong case that glimiperide has such an effect in rats. This is, however, CDER - not CVM, and I don't think this should count for too much, certainly not in the labeling.

Recommendation:

Allow some references to the extrapancreatic effect, but trim the proposed labeling on this point.

#3 Should the combination of glimiperide with metformin therapy be allowed some mention in the labeling?

This is a complicated issue produced by the arrival of metformin. It involves all the other SUs as well. The short answer is fortunately no. Mention need not be made in the initial labeling because the company has accepted our decision to defer any kind of mention of metformin in their product labeling until we have arrived at a policy for the drug class. I discuss this issue here because Dr. Gueriguian recommended that we allow an indication for glimiperide/metformin therapy consistent with a recommendation that he made sometime ago, i.e. we approve such an indication for all SU's as a kind of class labeling action. His reasoning is sound, but the administrative and policy considerations make the granting of this indication to this sponsor impossible to implement fairly by without further discussions.

Metformin (MF) was approved with an indication for use in combination with sulfonylurea drugs. Lipha had conducted a pivotal study with glyburide and no other SU to show synergism with MF in improving glycemic control. We concluded as mentioned above that the results could reasonably be expected with all other SU drug products, and, therefore, accepted the drug class language. Some data are available to support this conclusion though no studies comparable to Lipha's study of glyburide have been conducted.

Since the metformin approval, two SU marketers have asked to add the combination indication so that they will be on the same footing as Hoechst and Upjohn, marketers of glyburide. Data to support each of the other SUs range from next to nothing to published results from relatively small, short term studies. Though the overall benefit/risk of each combination of SU with MF might vary slightly from one to another, any differences are likely to be driven by the SU, not a variable contribution from the MF component. The approach to adding MF to any SU therapy could not differ from the stated recommendation in the metformin labeling, i.e., done under close monitoring, etc.

Dr. Gueriguan recommended that we grant the combination indication to all SUs without requiring clinical data to be submitted, basically for the same reason that we allowed the drug class language in the metformin label. If we require data to be submitted, most if not all marketers would have to conduct studies. These studies could not reasonably be required to be powered to detect the small anticipated differences in the risk/benefit of the various combinations. In effect, they would be pro forma.

Another approach would be to allow all companies to include mention of the general and specific experience with combination therapy in the CLINICAL PHARMACOLOGY section. This might placate most of the SU marketers for now, but they would presumably still have to do a clinical study to get into the INDICATION section. Putting this information in the C.P. section is also the pusillanimous approach that we are attempting to avoid in order to prevent the creation of de facto indications.

Should we grant this new indication to all SU marketers without requiring any data at all? Or, should we require of each company the submission of all data available to support the individual and/or the drug class effect? Or, do we require all companies to do additional studies. Humorously, _____, one of the glyburide marketers, has already submitted a supplement for the combination indication. They asked the UF to be waived because the data had already been reviewed by us. Their supplement contained no data, and they had no data themselves. They opined that we must have already seen convincing data when we reviewed the metformin NDA!

4. Are there convincing data to support differences in efficacy and/or safety between glimiperide and other sulfonylurea agents?

In the 301 study, the sponsor found that Amaryl resulted in somewhat more rapid improvement of glycemic control than did glipizide during the first month of therapy, but there was no difference in HbA1c group averages by the end of treatment at one year. Rates of hypoglycemia for the two groups were comparable. On the other hand, in study 302, Amaryl treatment was associated with somewhat less hypoglycemia during the first month than that with glyburide despite comparable rates of glycemic control during the entire 12 month treatment period. The sponsor had originally proposed to put these data in the C.P. section, but withdrew them at our request.

Clearly they are not convincing of substantial differences among these members of the same drug class. More rapid achievement of improved glycemic control during the first month, for example, could easily result from different potencies in the tablets used in that trial. The glyburide data have since appeared in the ADVERSE EVENTS section as, in effect, a claim of superiority. These data are inappropriate in the C.P. section and even more out of place in the ADVERSE EVENTS section.

Recommendations (NDA 20-496):

The NDA should be approved for the indications of adjunct to diet and exercise to lower the blood glucose in patients with NIDDM, and for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Approval of the indication for use with metformin should be withheld until a class labeling approach is finalized, or data have been submitted by the company that directly support the indication.

The most recently submitted version of the labeling (June 20, 1995) should be modified as suggested below:

1. Delete lines 9-15, p.A.2.

Comment: The clinical significance of these findings remains to be determined.

2. Delete lines 12-21, p. A.3

Comment: The clinical significance of these differences among drug products is highly questionable particularly in the context of treating individual patients

3. Delete lines 1-5, p. A.4

Comment: Same as in 2.

4. Add the following sentence, or words to the effect, after the sentence concluding on line 11, p. A.10:

Additional caution is warranted with the used of combined insulin and Amaryl therapy because of an increased potential for hypoglycemia compared with insulin therapy alone.

Comment: There is sufficient evidence from the controlled study to warrant this caution.

- 5. Delete the sentence beginning on line 26, p.A.10 and all subsequent references to combined metformin-Amaryl therapy.

Comment: The Agency is in the process of developing appropriate class labeling for this combination therapy. Data supporting the combination of metformin and glimipiride were not submitted as part of the NDA and can be reviewed only as a supplement to the approved NDA.

- 6. Add a sentence similar to that described under 4. following the sentence concluding on line 22, p. A.13.

- 7. Delete line 15, p. A.16 through line 8, p. A.17.

Comment: The ADVERSE REACTIONS section is not intended as an opportunity for making comparative claims. Appropriate information on this subject is provide under the PRECAUTIONS section.

Handwritten notes:
 (a) ...
 ... FAX
 ... 4/29/05.
 ...

Signature: Alexander Fleming
 10/05/95

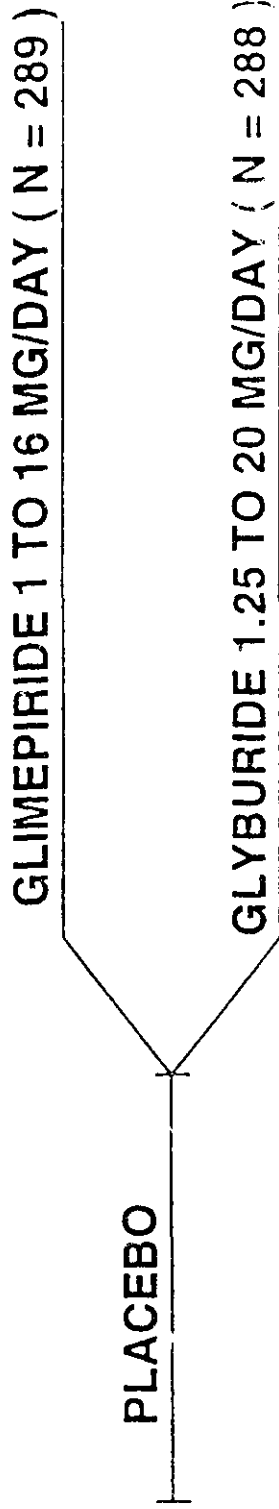
Alexander Fleming, M.D.

cc:
 /HFD 510
 /NDA 20-496
 /Gueriguian

STUDY DESIGN - 8/USA/302

SCREENING PHASE

RANDOMIZATION PHASE



Hoechst-Roussel Pharmaceuticals Inc.

Hoechst



Figure 8 Means for FPG Over Time

Fasting Plasma Glucose (mg/dL)
Means at Each Time Point (with 1 SE)

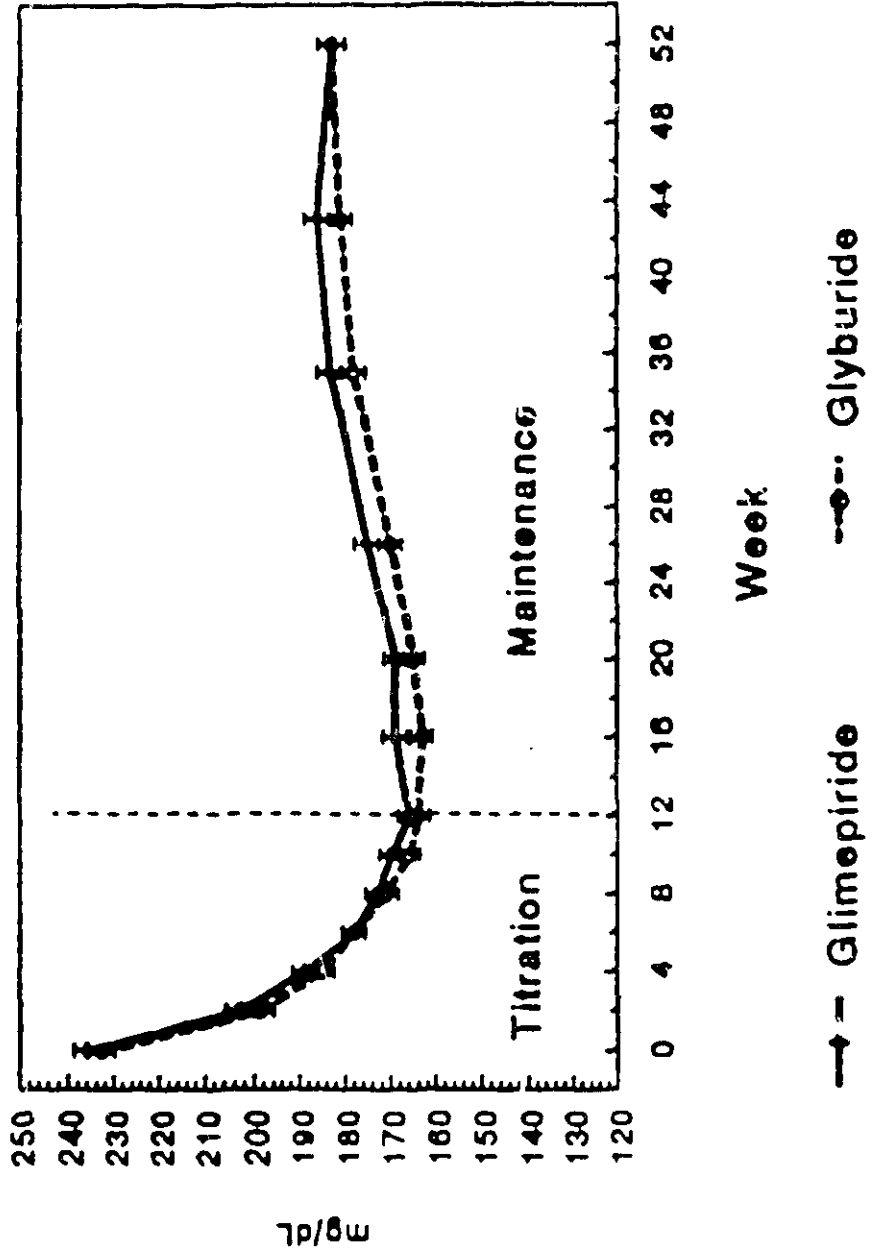
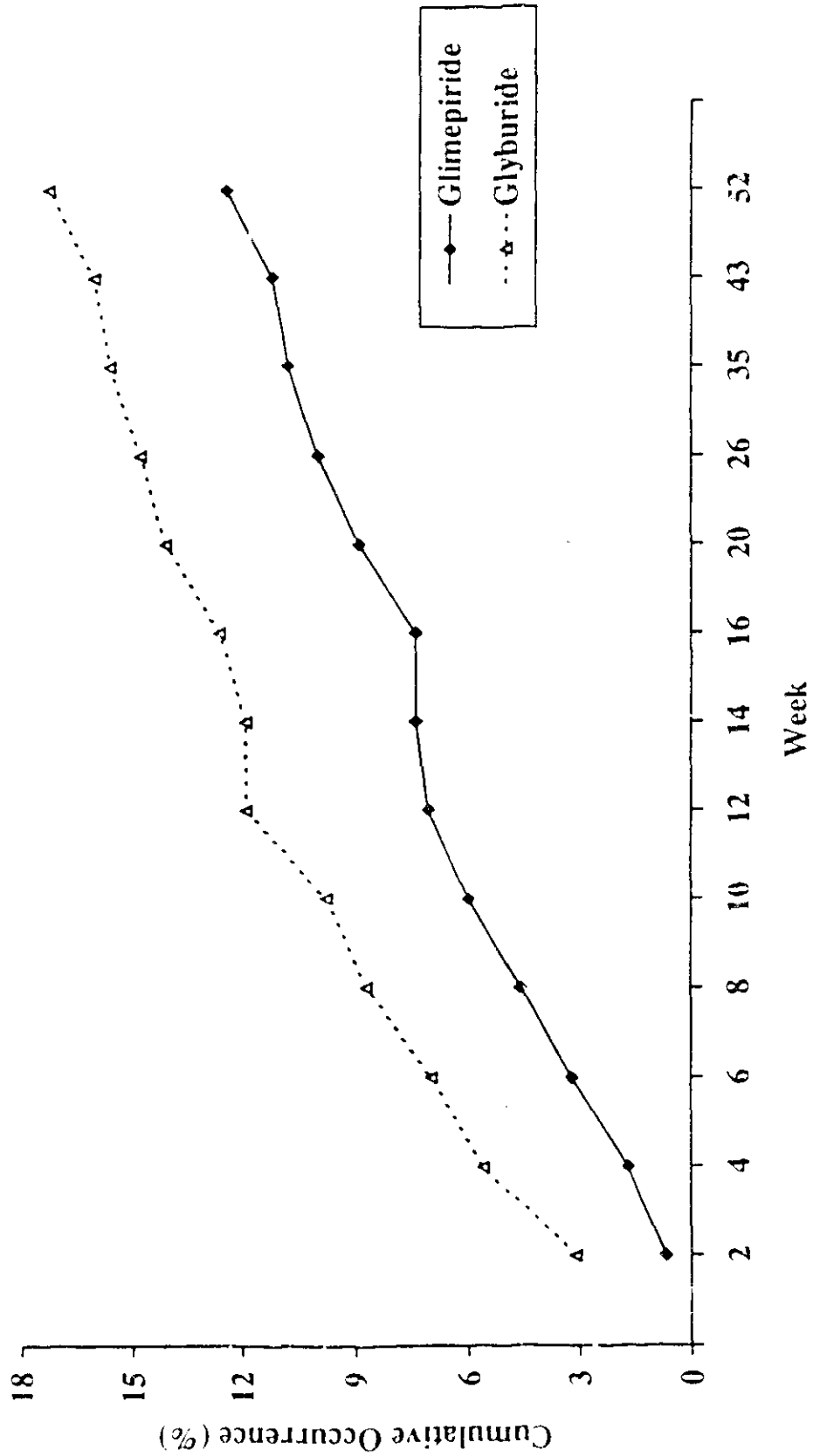


Figure 9
Time To First Occurrence of Hypoglycemia



Amaryl™ Tablets, NDA 20-496

**TIME TO FIRST OCCURRENCE OF HYPOGLYCEMIA (FIRST MONTH) -
8/USA/302**

<u>DAYS IN STUDY</u>	<u>GLIMEPIRIDE</u>			<u>GLYBURIDE</u>			<u>P-VALUE</u>	
	<u>NO. OF SUBJ AT RISK</u>	<u>WITH EVENT</u>	<u>CUM. OCC. %</u>	<u>NO. OF SUBJ AT RISK</u>	<u>WITH EVENT</u>	<u>CUM. OCC. %</u>	<u>LOG- RANK</u>	<u>WIL- COXON</u>
1 - 7	289	2	0.7	288	6	2.1	0.015	0.014
8 - 14	285	0	0.7	282	3	3.1		
15 - 28	284	3	1.7	279	7	5.6		
> = 29	280	0	-	271	0	-		

Cumulative % occurrence are estimated using the life table method.

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Amaryl™ Tablets, NDA 20-496

COMPARATIVE PHARMACODYNAMICS

8/USA/302

Comparison with glyburide

Randomized, double-blind, 1-year trial

N = 577

Equivalent efficacy during titration and at EP

Less hypoglycemia (signs and symptoms) during titration with
glimepiride ($p < 0.05$)

Trend toward less hypoglycemic symptoms throughout study ($p < 0.09$)

Hoechst-Roussel Pharmaceuticals Inc.

Hoechst



Amaryl™ Tablets, NDA 20-496

COMPARATIVE PHARMACODYNAMICS

8/USA/302

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Hoechst-Roussel Pharmaceuticals Inc.



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Amaryl™ Tablets, NDA 20-496

STUDY DESIGN - 8/USA/301

OBJECTIVE: SAFETY, EFFICACY

TARGET POPULATION: PATIENTS WITH NIDDM - DIETARY NON-RESPONDERS;
ORAL AGENT USERS
FBG: 160-300 OFF MEDS

NO. OF SUBJECTS: 802

PRIMARY EFFICACY VARIABLES: FBG
Hgb A1c

SPECIAL ASPECTS: 1. QUALITY OF LIFE
2. EYE AMENDMENT - SEVERAL SITES



STUDY DESIGN - 8/USA/301

SCREENING PHASE

RANDOMIZATION PHASE

PLACEBO

GLIMEPIRIDE 1 TO 16 MG/DAY (N = 544)

GLIPIZIDE 2.5 TO 40 MG/DAY (N = 258)

← 3 WEEKS →

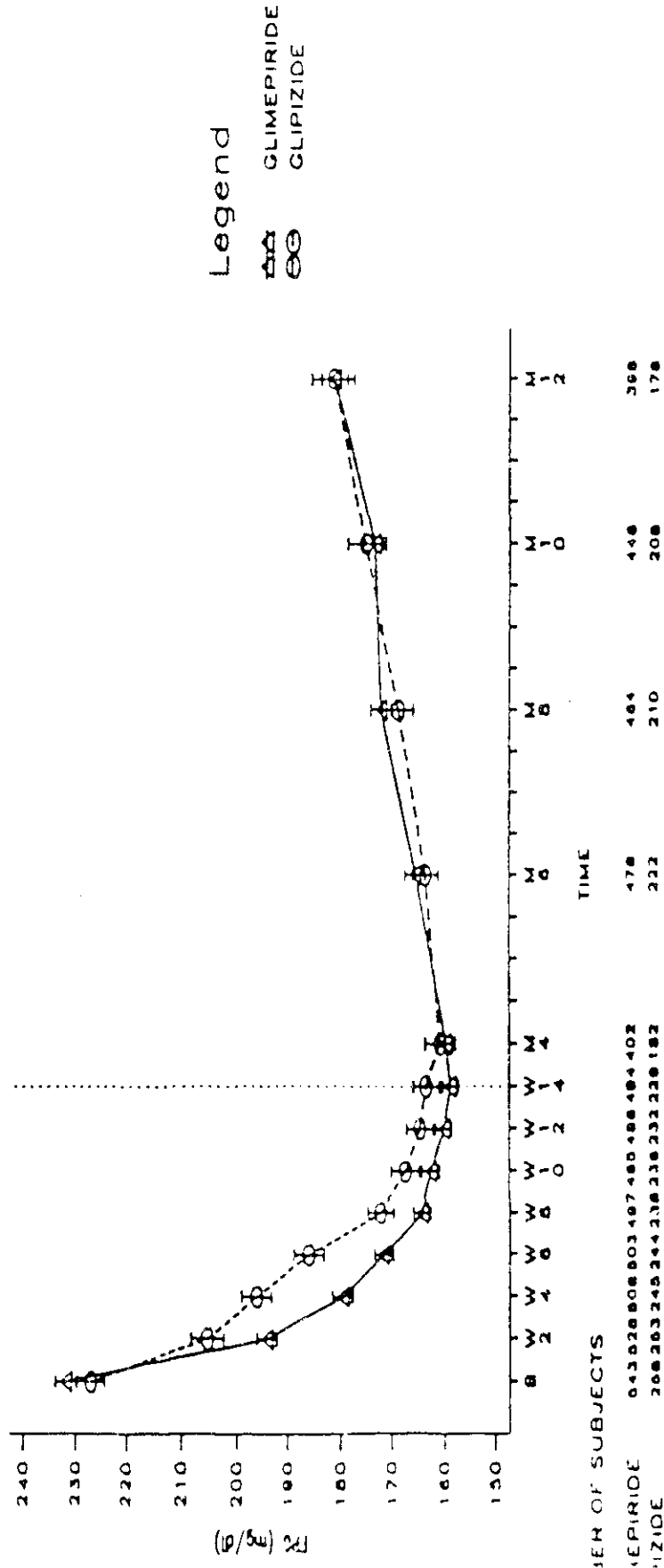
← 1 YEAR →

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Figure 10
 MEAN FASTING PLASMA GLUCOSE (mg/dl) OVER TIME WITH 1 STANDARD ERROR—
 ALL SUBJECTS



Amaryl™ Tablets, NDA 20-496

MEAN FASTING PLASMA GLUCOSE FPG (mg/dl) - 8/USA/301

<u>VISIT</u>	<u>GLIMEPIRIDE</u>		<u>GLIPIZIDE</u>		<u>BETWEEN TREATMENT</u>			
	<u>N</u>	<u>MEAN</u>	<u>CHG</u>	<u>N</u>	<u>MEAN</u>	<u>CHG</u>	<u>DIFF</u>	<u>P-VALUE</u>
Baseline	532	231.4	-	255	277.0	-	- 4.4	0.832
Week 2	527	194.1	- 37.2	253	205.4	- 21.9	15.3	< 0.001 ***
Week 4	508	179.7	- 51.5	245	196.3	- 32.1	19.5	< 0.001 ***

N = No. of subjects, Chg = Mean change from baseline, - Not applicable.

P-values are from Linear Models Analysis.

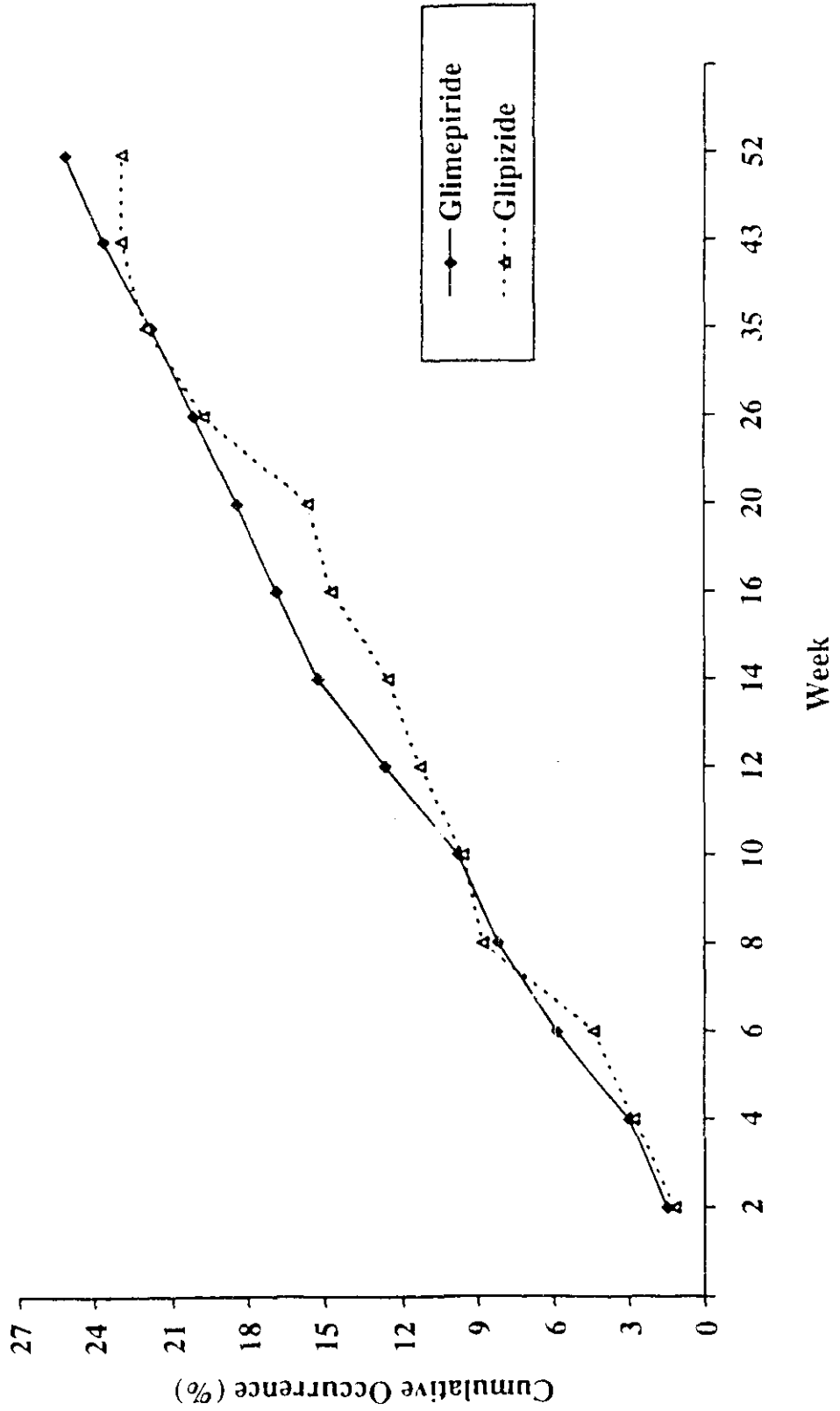
* p ≤ 0.050, *** p ≤ 0.001.



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Figure 11
Time To First Occurrence of Hypoglycemia



Amaryl™ Tablets, NDA 20-496

COMPARATIVE PHARMACODYNAMICS

8/USA/301

Comparison with glipizide

Randomized, double-blind, 1-year trial

N = 802

Glimepiride and glipizide had equivalent safety (hypoglycemic symptoms)

Faster reduction of FPG during titration ($p < 0.05$) with glimepiride

Equivalent efficacy during maintenance



BENEFITS OF RAPID GLYCEMIC CONTROL DURING TITRATION

The faster initial glycemic response and lower initial rate of hypoglycemia may:

- Encourage patients starting treatment to continue treatment
- Encourage compliance with diet, exercise, and medicinal therapy
- Facilitate the management of patients switching from other agents or initiating sulfonylurea therapy

12 In a 1-year controlled trial vs. glyburide, glycemic control was comparable for the two drugs
13 throughout the 12-month period. However, significantly less hypoglycemia occurred with
14 AMARYL (AMARYL: 1.7%, glyburide: 5.6%) during the first month of treatment. Adjusting for
15 dropout rates, the cumulative percent occurrence of hypoglycemia at the end of the study was
16 12.4% for AMARYL and 17.2% for glyburide.

17 In a 1-year controlled trial vs. glipizide, the incidence of hypoglycemia adjusted for dropout
18 rates was comparable throughout the study (AMARYL: 25%; glipizide: 23%). However, there
19 was a significantly greater decrease in fasting plasma glucose (FPG) in the AMARYL treatment
20 group during the first month (AMARYL 51.5 mg/dl, glipizide: 32.1 mg/dl). At study endpoint,
21 glycemic control was comparable for the two drugs.

ADVANTAGES OF COMBINATION THERAPY - LITERATURE

- Allows sulfonylurea secondary failures to achieve better glycemic control
- Nighttime insulin suppresses hepatic glucose production and sulfonylurea covers meal related insulin requirements
- More convenient than complex insulin regimens
- Provides a transition between oral therapy and complex insulin regimens
- Provides better glucose reduction than oral agent combinations. Additionally, not everyone is a suitable candidate for metformin (i.e., renal/hepatic dysfunction)
- More glycemic stability (due to lower within subject variability) demonstrated with combination therapy vs. insulin alone
- Previous studies have demonstrated decreased insulin dose and/or decreased Hb A1c with combination therapy vs. insulin alone



Amaryl™ Tablets, NDA 20-496

FDA AGREEMENT FOR POSITIVE PROTOCOL 305 STUDY

Similar HbA1c values for both groups
and
Significantly less exogenous insulin in combination group

OR

Significant HbA1c reduction in combination group
and
Similar exogenous insulin requirements

Hoechst-Roussel Pharmaceuticals Inc.



Hoechst

STUDY DESIGN - 8/USA/305

OBJECTIVE: COMPARE EFFICACY AND SAFETY
OF COMBINATION THERAPY OF
HOE 490 PLUS INSULIN VS. INSULIN
ALONE

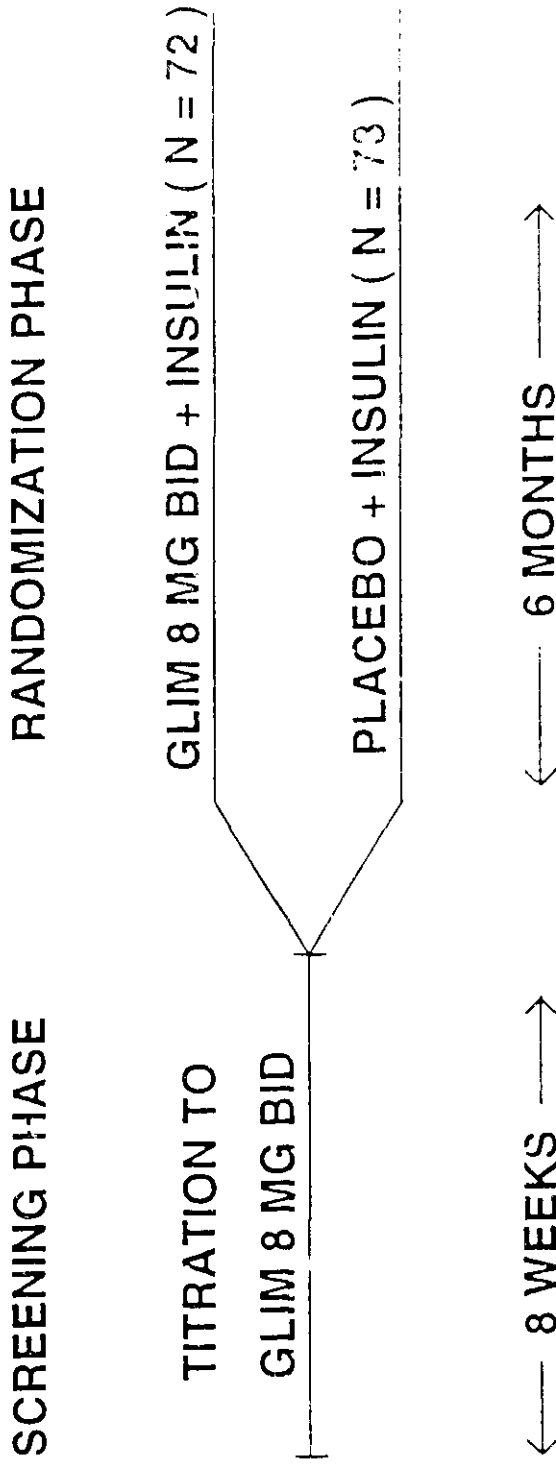
**TARGET
POPULATION:** PATIENTS WITH NIDDM - SECONDARY
FAILURES ON ORAL SULFONYLUREA
FBG: > 180 MG/DL ON ORAL AGENT

**NO. OF
SUBJECTS:** 145

**PRIMARY EFFICACY
VARIABLES:** INSULIN DOSE
Hgb A1c



STUDY DESIGN - 8/USA/305



Hoechst-Roussel Pharmaceuticals Inc.



Hoechst

Amaryl™ Tablets, NDA 20-496

ADVANTAGES OF COMBINATION THERAPY - 8/USA/305

Fewer patients require 2 injections/day of insulin (> 100 Units/Day)

<u>Glimepiride/Insulin</u>	<u>Placebo/Insulin</u>
<u>N (%)</u>	<u>N (%)</u>
4 (6)	10 (14)

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Amaryl™ Tablets, NDA 20-496

ADVANTAGES OF COMBINATION THERAPY - 8/USA/305

Similar HbA1c decrease with significantly less insulin ($p < 0.001$)

<u>Treatment</u>	<u>N</u>	<u>Mean HbA1c (%)</u>		<u>Change</u>	<u>Insulin Dose</u> <u>(Units)</u>
		<u>Baseline</u>	<u>Endpoint</u>		
Glimepiride/Insulin	69	9.7	7.6	- 2.2	48.5
Placebo/Insulin	66	9.9	7.9	- 2.0	77.9

Hoechst-Roussel Pharmaceuticals Inc.



Hoechst

Amaryl™ Tablets, NDA 20-496

ADVANTAGES OF COMBINATION THERAPY - 8/USA/305

Similar HbA1c decrease with significantly less insulin ($p < 0.001$)

<u>Treatment</u>	<u>N</u>	<u>Mean HbA1c (%)</u>		<u>Change</u>	<u>Insulin Dose (Units)</u>
		<u>Baseline</u>	<u>Endpoint</u>		
Glimepiride/Insulin	69	9.7	7.6	- 2.2	48.5
Placebo/Insulin	66	9.9	7.9	- 2.0	77.9

Hoechst-Roussel Pharmaceuticals Inc.



Hoechst

Amaryl™ Tablets, NDA 20-496

ADVANTAGES OF COMBINATION THERAPY - 8/USA/305

Less within subject FPG variability

<u>Standard Deviation</u>	<u>Glimepiride/Insulin</u> (N = 53)	<u>Placebo/Insulin</u> (N = 42)
Median	20.8	25.0
Minimum	4.0	1.7
Maximum	44.0	85.9

Hoechst-Roussel Pharmaceuticals Inc.

Hoechst



Amaryl™ Tablets, NDA 20-496

ADVANTAGES OF COMBINATION THERAPY - 8/USA/305

Significant difference in FPG at Week 2 ($p < 0.001$)

<u>Treatment</u>	<u>N</u>	<u>Mean FPG (mg/dl)</u>		
		<u>Baseline</u>	<u>Week 2</u>	<u>Change</u>
Glimepiride/Insulin ^a	69	250.2	204.7	-45.5
Placebo/Insulin ^a	67	259.3	266.0	+6.7

^a Patients received approximately 10 units of insulin daily

Hoechst-Roussel Pharmaceuticals Inc.

Hoechst



Amaryl™ Tablets, NDA 20-496

ADVANTAGES OF COMBINATION THERAPY - 8/USA/305

Fewer total discontinuations ($p \leq 0.01$) and less discontinuations due to adverse events

	<u>Placebo + Insulin</u>	<u>Glimepiride + Insulin</u>
	<u>No. (%)</u>	<u>No. (%)</u>
No. of Subjects Treated	73 (100)	72 (100)
Did Not Complete Study	11 (15)	2 (3)
Reason For Not Completing		
Hyperglycemia	3 (4)	0 (0)
Safety	3 ^a (4)	0 (0)
Other	5 ^a (7)	2 (3)

^a Five of these 8 subjects had high glucose values.

Hoechst-Roussel Pharmaceuticals Inc.



Hoechst

DEFINITION OF HYPOGLYCEMIA

The presence of one or more signs or symptoms compatible with hypoglycemia. No confirmation by laboratory data was necessary.

Note: Our definition was broad and captured symptoms which can not be taken as a true reflection of low glucose levels (i.e., $\leq 60\text{mg/dl}$)



Amaryl™ Tablets, NDA 20-496

NUMBER OF SUBJECTS WITH HYPOGLYCEMIA - 8/USA/305

	<u>Placebo + Insulin</u> <u>No. (%)</u>	<u>Glimepiride + Insulin</u> <u>No. (%)</u>
Subjects Treated	73 (100)	72 (100)
Worst Case		
Mild	16 (22)	29 (40)
Moderate	11 (15)	8 (11)
Severe	0 (0)	0 (0)

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Amaryl™ Tablets, NDA 20-496

BENEFIT/RISK - 8/USA/305

<u>Visit</u>	<u>Placebo + Insulin</u>		<u>Glimepiride + Insulin</u>	
	<u>HbA1c</u> <u>Change</u>	<u>No. with</u> <u>Hypoglycemia</u>	<u>HbA1c</u> <u>Change</u>	<u>No. with</u> <u>Hypoglycemia</u>
Week 12	-1.2	15	-1.7	26
Week 24	-2.1	12	-2.1	11

Hoechst-Roussel Pharmaceuticals Inc.



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Amaryl™ Tablets, NDA 20-496

BENEFIT/RISK - 8/USA/305

<u>TREATMENT</u>	<u>NO. REACHED FBG TARGET</u>	<u>NO. DID NOT REACH FBG TARGET</u>
Placebo + Insulin	59 (81%)	14 (19%)
Glimepiride + Insulin	68 (94%)	4 (6%)

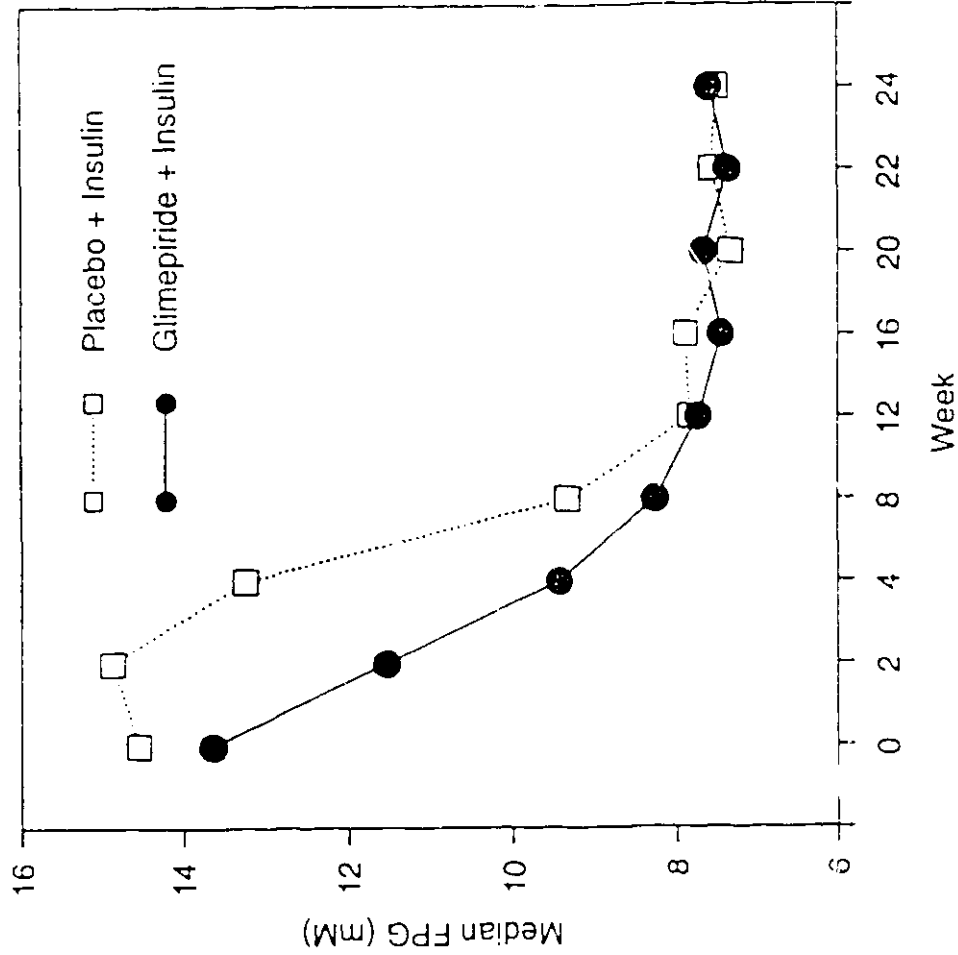
Hoechst-Roussel Pharmaceuticals Inc.

Hoechst



Amaryl™ Tablets, NDA 20-496

MEDIAN FASTING PLASMA GLUCOSE MG/DL - 8/USA/305



ADVANTAGES OF COMBINATION THERAPY - LITERATURE

- Allows sulfonylurea secondary failures to achieve better glycemic control
- Nighttime insulin suppresses hepatic glucose production and sulfonylurea covers meal related insulin requirements
- More convenient than complex insulin regimens
- Provides a transition between oral therapy and complex insulin regimens
- Provides better glucose reduction than oral agent combinations. Additionally, not everyone is a suitable candidate for metformin (i.e., renal/hepatic dysfunction)
- More glycemic stability (due to lower within subject variability) demonstrated with combination therapy vs. insulin alone
- Previous studies have demonstrated decreased insulin dose and/or decreased Hb A1c with combination therapy vs. insulin alone



DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-496

Trade (generic) names Amaryl (glimepiride) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

- 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim. *NO*
- 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&W studies in children. *NO*
 - a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
 - b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
- 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children):
 - a. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing.
 - (2) Protocols have been submitted and approved.
 - (3) Protocols have been submitted and are under review.
 - (4) If no protocol has been submitted, on the next page explain the status of discussions.
 - b. 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 do not need to be encouraged because the drug product has little potential for use in children.

b. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

[This area contains 20 horizontal lines for handwritten explanation. No text is present on these lines.]

John J. [Signature]
Signature of Preparer
in consultation w/ Mo

7/5/95
Date

cc: Orig NOA
HFD-510/Div File
NOA Action Package/KSO

NDA 20496
Sponsor: Hoechst-Roussel
Drug: Glimepiride

Received: 9/23/97
Reviewed: 10/10/98
Doct: N20496B G113

MEDICAL OFFICER'S REVIEW OF SAFETY UPDATE

Amaryl (Glimepiride) is a novel sulfonylurea with hypoglycemic activity for the treatment of type II diabetes (or NIDDM). It has been fully reviewed and deemed approvable. The Company is now sending a safety update, with data from patients who completed trial participation between September 1, 1994 (the previous cut-off date) and July 1, 1995.

This highlights of this submission are as follows: a set of data concerning a patient that died, various discontinuations for safety reasons, and other serious adverse event.

Subject 002/0215 in Protocol 490/2/MN/204/DM died of an apparent rupture of an aortic (abdominal) aneurysm after receiving a low dose of glimepiride (1 mg) for 37 days. The Company asserts, with apparent justification, that the event was not considered to be associated with the study drug.

Seventeen (17) subjects discontinued due to adverse events. Of those, nine (9) could be termed as "worst cases" and are presented in some details below (note that in a few cases, the code has not been broken yet):

(1) Protocol 490/2/MN/203/DM, subject 003/0310: After 65 days of treatment (either glimepiride or glyburide) the subject developed cholelithiasis, biliary stenosis and hyperglycemia

(2) Protocol 490/2/MN/203/DM, subject 1100/1106: Subject was involved in a traffic accident which may have been due to hypoglycemia. The Sponsor states: "Hypoglycemia was excluded as a cause of the accident because blood glucose levels had always exceeded 140 mg/dl for the 4 weeks prior to the accident." This may have been the case but is hardly conclusive evidence that hypoglycemia was not the cause of the accident. Recovered after prolonged hospitalization

(3) Protocol 490/2/MN/204, subject 002/0201: Subject was on glimepiride 2 mg. Severe hypoglycemia (43 mg/dl) resulted after receiving the drug for 36 days. Recovered without additional treatment.

(4) Protocol 490/2/MN/204, subject 002/212: Subject was on glimepiride 2 mg. Severe hypoglycemia (41 mg/dl) resulted after receiving the drug for 57 days. Recovered without additional treatment.

(5) Protocol 490/2/MN/204, subject 016/1602: After being on glimepiride for 15 days (2 mg), subject suffered a severe episode of angina pectoris that lasted for 5 minutes. At the hospital: normal EKG, release after observation.

(6) Protocol 490/2/MN/204, subject 016/0001: Subject was on glimepiride (increasing doses up to 6 mg) and metformin (2,500 mg, added later). High serum lactate levels (4.6 mmol/L) were noted 30 days after introduction of metformin, and both drugs were discontinued. Recovered.

(7) Protocol 490/2/MN/201, subject 001/0104: After a single IV dose (glimepiride 1.2 mg or glyburide 2.5 mg), the subject developed hypoglycemia (18 mg/dL) which remained low (37 mg/dL) even after glucose infusion. Subject eventually recovered. This is a puzzling case which is impossible to elucidate as to its mechanisms.

(8) Protocol 490/2/MN/201, subject 003/0308. After a single IV dose of glyburide (2.5 mg), and during an elaborate sequence of events during cardiac catheterization, the subject developed an MI. Recovery was obtained only after prolonged hospitalization. One cannot exclude two possibilities: the first, probable, that all this elaborate catheterization and drug IV injection created a bolus which then resulted in an occluded coronary; and the second, less probable, that, somehow, the intravenous glyburide contributed to the MI. Again, difficult to interpret events.

(9) Protocol 490/2/MN/302, subject 008/0186. Subject was on glyburide (1 mg) for over one year when a basal cell carcinoma was discovered on her left cheek. This rather common tumor was then excized and treated with radiation, while the study was completed.

After this review, the following comments may be useful:

(1) This safety update does not contain any information that would lead us to change our mind about the approvability of glimepiride.

(2) It would be wise, however, to state (somewhere in the labeling), that when glimepiride and metformin are used in combination, physicians should strictly adhere to the precautions listed and highlighted in the metformin labeling.

(3) I still perceive, here, faint signs of hypoglycemic propensity in this drug, more so than any other second generation sulfonylurea on the market. I recommend that the verbiage in the glimepiride labeling is strengthened in the section with talks about hypoglycemia as a frequent side-effects. I also recommend that the epidemiology of hypoglycemia due to glimepiride be pursued after the approval of the drug. This can best be achieved with a phase IV study of the type recommended by Dr. Stadel and myself.

John L. Gueriguian, M.D.
10/10/95

cc:

The File
Dr. Fleming
Dr. Stadel
Dr. Gueriguian

John L. Gueriguian, M.D.
See my letter of 10/5
10/10/95

JUN 19 1995

NDA 20496
Sponsor: Hoechst-Roussel
Drug: Glimepiride

Received: 9/23/94
Reviewed: 5/30/95
Doct: N20496A/G113

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION

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MEDICAL REVIEW PROPER

1 GENERAL INFORMATION

1.1 Drug Name and Structure

1.1.1 Generic name: Glimepiride

1.1.2 Proposed trade name: Amaryl

1.1.3 Chemical name: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-beta-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.

1.1.4 Structure: See Fig. 1 for structural formula.

1.2 Scientific Information

1.2.1 Pharmacological category

Oral hypoglycemic drug, sulfonylurea class. As is well known, a number of sulfonylureas have been introduced in the marketplace during the last two decades or so. In fact, as recently as a month ago, only hypoglycemic sulfonylureas were available for sale in the United States; though, recently, our Advisory Committee recommended the approval of 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.

It should also be added that this particular class has been under some scrutiny since the conclusion of the highly publicized and controversial UGDP study. This clinical trial, performed under the aegis of the NIH, showed that, under the particular conditions of the study, sulfonylurea users died more frequently than those on insulin. The lesson

from this situation appears to this reviewer to be as follows: We have to be careful and consider that a company has to make all reasonable efforts to bolster the safety picture of an as yet unapproved sulfonylurea, either before or after the approval of a drug belonging to that class.

1.2.2 Proposed indication(s)

The company is offering this drug for the following indications:

(1) for the lowering of glycemia in patients with non-insulin-dependent diabetes (or NIDDM, or type II), but as an adjunct to diet, provided that diet alone has not been able to control hyperglycemia. and,

(2) For use in combination with insulin to lower glycemia in patients whose hyperglycemia cannot be controlled by diet in conjunction with an oral hypoglycemic agent alone.

1.2.3 Dosage form(s): 1, 2, and 4 mg tablets.

1.2.4 Route(s) of administration: Oral.

1.3 Regulatory Information

1.3.1 Review priority rating: There are already many oral hypoglycemic agents on the market belonging to the sulfonylurea chemical family. Therefore, at first glance, there is no particular reason to assign a very high priority rating to yet another member of that family, unless there is a particular reason to do so.

1.3.2 Related drugs

As stated, numerous sulfonylurea-type oral hypoglycemics are presently in use in the United States. It is important to consider one crucial comparison parameter: Is the new member any safer than its marketed congeners?

Below, one will find a summary safety profile of the main sulfonylurea oral hypoglycemics presently on the marketplace:

(1) Chlorpropamide (Diabinese from Pfizer): severe hypoglycemia, gastro-intestinal disorders (nausea, vomiting, procto-colitis, hepatic porphyria, and cholestatic jaundice), dermatological complications (porphyria cutanea tarda, erythema multiforme and exfoliative dermatitis), hematological reactions (leukopenia, eosinophilia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia), and endocrine adverse effects (inappropriate antidiuretic hormone, ADH, secretion).

(2) Tolbutamide (Orinase from Upjohn): Essentially similar to chlorpropamide toxicity, except for an apparent lack of severity of the rare dermatological reactions, and the existence of taste alterations.

(3) Glyburide (DiaBeta from Hoechst, Glynase from Johnson, and Micronase from Upjohn): Essentially similar to chlorpropamide toxicity, except for a more diverse hepatic toxicity (liver function abnormalities and hepatitis), an apparent reduction of the severity of the dermatological reactions), and hyponatremia.

(3) Glipizide (Glucotrol from
Essentially similar to the toxicity profile of glyburide.

2 LISTING OF VOLUMES REVIEWED

The following volumes (and pages) have been particularly scrutinized during the review of this NDA, though additional volumes were cursorily glanced at, or reviewed for a punctual information, on a need basis:

Vol.1.196
Vol.1.203
Vol.1.212
Vol.1.218
Vol.1.228
Vol.1.254
Vol.1.275
Vol.1.291
Vol.1.300
Vol.1.304
Vol.1.306
Vol.1.307

Vol.1.309
Vol.1.310
Vol.1.313
Vol.1.319
Vol.1.326
Vol.1.354
Vol.1.357

3 CHEMISTRY AND MANUFACTURING CONTROLS

The submitted moiety is structurally closest to glipizide and is therefore expected to have a toxicity profile roughly similar to that drug's profile.

From a manufacturing viewpoint, our Chemists have decided that the application was approvable pending a favorable environmental impact assessment evaluation --said evaluation pending --and the Sponsor's satisfactory response to the minor deficiencies delineated in the Chemist's review.

For a more accurate description of Chemistry and Manufacturing Controls, please consult the Chemist's Review, as well as any comments by the Supervisory Chemist. Needless to say, if this NDA is recommended for approval by the reviewing M.O., our Chemists must have approved the formulation and the labeling after their usual scrutiny.

4 PRECLINICAL PHARMACOTOXICOLOGY

4.1 Pharmacodynamics & Mechanisms of Action

The drug moiety has been tested in a number of animal species (rats, rabbits, and dogs) and was found to induce hypoglycemia after oral administration. The main mechanism of action is the release of insulin from the pancreatic beta cells. It is stated that the drug possesses some extrapancreatic effect, perhaps due to an insulin sensitizing mechanism. If one compares glimepiride to glyburide, it would seem that the former produces a greater stimulation of insulin release at higher hyperglycemic

titers and, also, it produces faster and longer lasting correction of hyperglycemia than the latter, without markedly increasing insulinemia titers. It remains to be seen whether these apparent advantages (if that's what they are) are also present in humans.

If these postulates are true in humans, we would expect to see the following: (1) greater hypoglycemic efficacy than similar agents presently on the market; (2) lower insulinemia during long-term treatment of diabetics; and, (3) lowered frequency of primary or secondary failures.

4.1 Toxicology

Glimepiride is alleged to be acutely non-toxic in rats, mice, and dogs. The Sponsor states: " Pharmacologic effects of chronic administration resulted in degranulation of the pancreatic beta cells in both rodents and dogs, and pancreatic adenoma formation in mice but not in rats or dogs. Although cataracts were observed in 2 dogs after chronic exposure, additional studies suggest that this compound is unlikely to exacerbate cataract formation. Glimepiride was not antigenic in animals and was not mutagenic in a number of *in vivo* and *in vitro* mutagenicity assays. Glimepiride was not teratogenic in rats or rabbits but, like many sulfonylureas, exposure did result in increased intrauterine fetal death. Glimepiride caused skeletal anomalies in rats exposed to test compound via breast milk."

Clearly, some of the implications of the above findings are rather worrisome. For example, since diabetics do develop eye complications, the fact that, in 2 chronically exposed dogs, cataract formation was observed is hardly any solace. To the contrary, it would seem prudent to devise some measure of follow-up to see if this potential is realized in humans. This, and other, aspects of the relevance of pharmacology to the human exposure will be discussed, later, in an appropriate section of this review.

Needless to say, if this NDA is recommended for approval by the reviewing M.O., our Pharmacologists must give this NDA a positive nod from their expert viewpoint.

5 CLINICAL BACKGROUND

5.1 Direct information

5.1.1 Human pharmacodynamics

NIDDM is characterized by a diminished insulin secretion associated with a resistance to insulin. Initially at least, the pancreas can increase its secretion of insulin in order to offset the insulin-resistance. Over time, however, the insulin secretion will fail to keep pace with the increasing target-cell insulin-resistance, eventually leading to impaired glucose tolerance and, later, clear-cut and persistent hyperglycemia, i.e., overt diabetes with its known sequel of accidents and complications which increase the overall mortality of the affected population.

From a mechanistic viewpoint the following comments appear to be in order:

- (1) About 90% of all diabetics have NIDDM;
- (2) genetic predisposition appears to be more telling in NIDDM, though environmental factors continue to play some role in the physiopathological development of the disease; and,
- (3) the intake of excessive calories, and the ensuing weight gain and sometimes frank obesity, are particularly important pathogenetic factors, leading in particular to the increased insulin-resistance observed in such patients. It then follows that an effort should be always made to convince these patients to reduce their caloric intake and to increase their physical exertions.

Clearly, this strategy is unsuccessful in a great number of patients in whom, after a proper period of trial (diet and exercise) the physician will decide to introduce oral hypoglycemics in the therapeutic picture. Regardless, efforts to maintain a proper diet and exercise should continue even after the introduction of sulfonylurea therapy, inasmuch as even small increases in body weight can exacerbate glucose intolerance, at least in some patients. This is why all our labeling of such products properly introduces them as an adjunct to diet and exercise.

The sulfonylureas appear to correct glycemia by increasing insulin secretion by the pancreatic beta-cells, and can only be effective in patients with some capacity for endogenous production. In the past, experts have debated whether overdosing sulfonylureas might contribute to secondary treatment failures by "burning out" an already compromised pancreas. This reviewer feels that although such a mechanism is conceivable and possible, the data are not yet in our possession to affirm its existence. Regardless of such considerations, it is important to give the least dose that is effective to each patient. If not, providing higher doses will not increase the efficacy of therapy, yet it will certainly increase the toxicity of the product. Therefore, on the simple grounds of general pharmacology, it behooves the Sponsor to show the average least dose that is correcting effectively hyperglycemia in most patients. This will allow to correctly inform the practicing and prescribing physician as to the proper dosing of the drug and the proper titration procedure for each individual patient. In the absence of such information, the drug may be construed not to have been proven to be safe and effective as prescribed.

Thus, it is important for the Sponsor to have conducted dose-response studies to determine the least dose that is effective in most treated subjects. Such determinations can be performed with any number of efficacy end-points, e.g., FPG (fasting plasma glucose) or glycated hemoglobin (HbA1c). In any event, the chosen end-point should be measured serially, at any given dose level, till a steady-state is shown to have been achieved. Measurements made without proof of attainment of steady-state can only distort the dose-response curve and furnish wrong and misleading information. These considerations will be kept in mind while reviewing the efficacy data provided in this NDA.

There are other pharmacodynamic considerations that apply more specifically to the perceived safety of the drug. Following therapy with a sulfonylurea, measurable increases in fasting and postprandial insulin and C-peptide titers can be observed in general. One should state that fasting hyperinsulinemia is perceived by many experts as undesirable, since it is believed that it may lead, among other possible mechanisms, to untoward changes in lipid metabolism and to an atherogenic effect. Though these

postulates have not been conclusively proven, it remains that this is the current consensus in the expert community and we, at the FDA, are required by statute to take into account such a consensus.

5.1.2 Human pharmacokinetics

Glimepiride is a so-called second-generation sulfonylurea (together with glipizide and glyburide), as opposed to first-generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide and tolbutamide). The so-called second-generation moieties appear to be (mole for mole) more potent, possess a relatively longer half-life and thus have a longer duration of effect. In all probability, the lipophilic side-chain of the second-generation moieties (absent in the first-generation drugs) confers these observed differences. It is thought that the strong binding of second-generation sulfonylureas to circulating human serum albumin (HSA) is one of the factors that changes the pharmacokinetics of these compounds. If this is true, it then follows that drugs which competitively bind to HSA (e.g., warfarin and phenylbutazone) will tend to displace sulfonylureas from their binding sites and, thus, affect, their pharmacokinetic properties.

Radio-labeled drug (^{14}C -tagged glimepiride) was administered orally to humans. Two major metabolites (M1 and M2) were detected. Some 60% of the administered dose was recuperated in the urine and about 40% in the feces, where the metabolites amounted to about 85% of the radioactivity in the urine, and about 47% in the feces. These results suggests the possible existence of an enterohepatic circulation. Glimepiride and its metabolites interacted weakly with red blood cells, but more than 99% of the circulating moieties were found to be bound to HSA.

Single-dose pharmacokinetic studies were performed, using the iv (aqueous solution) and po (tablet, capsule and aqueous solution) routes, at four different dosages. The orally administered drug was completely absorbed and the pharmacokinetics remained linear in the 0.25 to 8 mg range. The mean plasma half-life was 5 to 8 hours. These studies were performed in normal volunteers as well as diabetic patients. The results were similar in both groups.

Multiple-dose pharmacokinetics in male and female diabetic patients were analyzed during 5 (five) studies. For doses ranging from 0.5 to 32 mg/d, the steady-state pharmacokinetics were found to be similar to the single-dose pharmacokinetics, thus excluding an overt accumulation of the drug or its metabolites in some covert bodily compartment. In addition, it was found that the pharmacokinetics of a 6 mg qd dose was comparable to that of a 3mg bid dose.

Regardless, I would feel much more comfortable if these studies were carefully scrutinized by our expert pharmacokineticists, in order to reassure us that the data support without ambiguity and equivocation the results that are claimed above.

5.1.3 Dose-response studies

Such studies are to be performed by choosing either a rapidly- (FPG) or slowly- equilibrating (HbA1c) pharmacodynamic endpoint. The Sponsor, not surprisingly, has chosen the least costly solution, that of measuring the FPG. The Sponsor states: "The glucose-lowering effect of glimepiride appeared at a minimum (single) dose of 0.5 mg in healthy men. In patients with mild NIDDM, glimepiride at a steady-state dose of 0.5 mg qd maintained control of serum glucose levels that had been previously provided by glyburide. The steady-state dose-response relationship of glimepiride was not delineated by the Phase I studies since the study duration (which were not more than 14 days) were insufficient to assure the achievement of pharmacodynamic steady state (including counterregulation) and there were too few subjects given the variability in the glucose measurements."

The Sponsor adds, however, that "analysis of a phase II/III study indicated that 8 mg and 16 mg qd were on a maximal plateau for the glucose-lowering effect. At daily glimepiride doses of 6 mg and above, the qd dosing regimen was as effective as the bid dosing regimen in lowering glucose levels." I take this mean to the following: That the the least dose that is maximally effective in the average patient is situated somewhere between 0.5 mg to 8 mg daily. Therefore--setting aside for a while--the task of critically assessing this statement the labelling should recommend the

a dose, determined through phase III studies, as the initial recommended dosage of the product, subject to follow-up titration in individual patients in 2-3 month intervals.

5.2 Indirect information

5.2.1 Information from foreign sources

As of August 1994, the drug was not marketed in any country. The Sponsor tells us that applications for approval of marketing have been submitted to:

Under the circumstances, we do not have any data base concerning the use of the drug outside the United States. This will force us to be a little more circumspect when assessing the safety side of the benefit-versus-risks equation.

5.2.2 Related INDs and NDAs

A number of sulfonylureas are already present on the marketplace, some of them for decades. Their IND and NDA numbers can be readily obtained from the Divisional records.

5.3 Other information

5.3.1 Regulatory background

The sulfonylureas represented, for a long period of time, the only oral hypoglycemics available on the marketplace in the United States. The first wave of sulfonylureas were approved before the so-called UGDP study. They were, by and large, more conducive to hypoglycemic episodes, some for long periods of time, than the so-called second-generation sulfonylureas. The advent of the latter group on the marketplace was considerably delayed by the controversy due to the conclusions of the UGDP study. The latter suggested that the sulfonylurea-treated group had a greater number of deaths than the other treatment groups. Others countered that since glycemia was not properly titrated in individual patients, and instead was given to all at fixed doses, this was the cause for the observed excess mortality.

Eventually, the FDA approved second-generation oral hypoglycemics of the sulfonylurea group, but with a special labelling containing words of wisdom and caution: That diet and exercise should be tried first in type II diabetes, and drugs added only when diet and exercise did not properly reduce hyperglycemia. Even then, prescribing physicians and diabetics were warned that a potential cloud obscured the therapeutic usefulness of sulfonylureas.

Meanwhile, another battle erupted on another front: That of the biguanides, another oral hypoglycemic chemical category. Phenformin was approved in the United States, then withdrawn from the marketplace by then Secretary Califano, on the ground that a number of people had died of lactic acidosis following treatment with phenformin. After this action, taken in the '70s, no biguanide was permitted to be even studied in the United States, till metformin (an apparently safer moiety than phenformin) was allowed to have an IND. Metformin was eventually approved by the FDA and introduced in the marketplace in 1995.

Therefore, and presently, a number of oral hypoglycemics are available in the United States, belonging to two chemical groups: The sulfonylureas and the biguanides.

5.3.2 Directions for use

During the last two decades, important studies, conducted worldwide, have allowed us to improve our understanding of some of the pathogenetic mechanisms of diabetes and some of the parameters of their effective correction. These studies culminated recently when the NIH published the results of a long collaborative study (DCCT) in which type I diabetics were treated aggressively to attempt to obtain euglycemia. The study showed that there is a continuous correlation between decreases in HbA1 values and decreases in morbidity and mortality. On another front, and during several public discussions -- some of them organized by the FDA -- experts advised the Agency of the following:

(1) That HbA1c value decreases of 1.00 to 1.50 % units may well be meaningful clinically; i.e., one would expect improvements of morbidity and mortality in the

presence of such results not counterbalanced by the toxicity of average antidiabetic drugs; and,

(2) That even more important than set reductions in HbA1c or HbA1 values, was the normalization or near-normalization of said values.

Based on the above considerations, one can now summarize the proper direction for use of any oral hypoglycemic agent, including the sulfonylureas:

1. Diet and exercise should always be encouraged aggressively in treated patients; they should be maintained, at any given sustainable level, even in the case of drug therapy;

2. If diet and exercise do not significantly affect glycemia, drug therapy is indicated. Therapy should be initiated only in actual diabetics, and not in patients "suffering" from novel and yet untested pathological entities, such as syndrome X and the like;

3. Drug therapy should commence with the dosage proven to be the minimal dose which has been found to effectually lower glycemia in most patients. Efficacy of therapy should be followed with FPG and HbA1 measurements, the latter beginning three months after initiation of therapy;

4. Dosing should be titrated regularly in individual patients, to reassure oneself that drug therapy (monotherapy or combination therapy) was effective in significantly correcting hyperglycemia albeit using the lowest effective dose in a given patient;

5. The advantages of drug therapy would be considered to outweigh the risks that attend any therapy only if HbA1 values are reduced to levels accepted as possessing clinical significance.

The Company gives the following directions for use: "In initiating treatment for noninsulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce

symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of Amaryl must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of Amaryl. During maintenance programs, Amaryl monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations. Secondary failures to Amaryl monotherapy can be treated with Amaryl-insulin combination therapy... The patient's FPG must be measured periodically to determine the minimum effective dose for the patient... In clinical trials, doses of 1-8 mg qd and 3,4 and 8 mg bid were found to be effective and safe... The usual starting dose of Amaryl as initial therapy is 1-2 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg daily, and should be titrated carefully... The maximum starting dose of Amaryl should be no more than 2 mg... The usual maintenance dose is 1 to 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response... The maximum recommended dose is 8 mg qd... In combination therapy, the recommended dose of Amaryl is 8 mg qd administered with the first meal. After starting with loose-dose insulin, upward adjustments of insulin can be done at weekly intervals, as guided by frequent measurements of fasting blood glucose."

With these considerations in mind, we can now study and analyze the clinical information contained in this submission.

6 CLINICAL DATA SOURCES

6.1 IND and NDA Studies

6.1.1 Type of studies

A great number of studies, of varying degrees of quality, were performed to study and test this drug. Only the phase II/III studies, performed in the US (see Table I)

and Europe (see Table II), double-blind, controlled studies, and with a minimum duration of 2 weeks will be presented and discussed here. These studies fall naturally into 3 groups: Placebo-controlled, short-term active treatment-controlled, and long-term active treatment-controlled.

Only placebo-controlled and long-term active treatment controlled studies are considered to be pivotal studies, and they will be presented and discussed as such in this review. On the other hand, all the trial universe will be used to assess, as much as can be done at this early juncture, the safety of the drug for the indications and under the conditions of use.

In addition, two precise indications have been pursued in the controlled clinical trials:

Indication I (limepiride monotherapy as adjunct to diet in patients with NIDDM); and.

Indication II (glimepiride in combination with insulin, in NIDDM patients with secondary failures to diet + glimepiride therapy).

7 PIVOTAL CLINICAL STUDIES

7.1 First pivotal study: Trial # 8/USA/201: Indication I. Placebo-controlled

7.1.1 Description of study

7.1.1.1 Title, objective and rationale

"A dose response study of HOE 490 (glimepiride) in subjects with noninsulin-dependent diabetes mellitus (NIDDM) who previously received sulfonylurea agents. The study wanted to compare the efficacy, safety, and tolerability of glimepiride versus placebo in the treatment of type II diabetics, and to determine a possible dose-response relationship.

7.1.1.2 Protocolar design

This was a 14-week, randomized, double-blind, placebo-controlled, parallel-group, fixed dose, multicenter, dose-

response study. Subjects were randomized to treatment with 1, 4, or 8 mg qd glimepiride, or an equivalent number of placebo tablets -- all medications were administered with the morning meal. All subjects began drug treatment with 1 mg qd, and were increased to their final assigned dosage by a forced titration to 4 mg after 1 week and again to 8 mg after the second week.

7.1.1.3 Demographics

Patients were men and women with NIDDM, age 30 through 75, weighing between 90% and 150% of ideal body weight.

7.1.1.4 Safety considerations

Adverse events were recorded at each visit. Laboratory evaluations, ECGs, and vital signs were recorded at scheduled times throughout the study.

7.1.1.5 Efficacy end-points

Primary efficacy end-points: FPG, HbA1c, and 2-hour postprandial glucose (PPG). Secondary efficacy variables: fasting and 1-hour post-prandial C-peptide and insulin levels in plasma, and FPG and HbA1c variability.

7.1.1.6 Statistical approaches

Linear model analyses and the Cochran-Mantel-Haenszel test were used to evaluate demographic and background data. Subject attrition caused the primary analysis to determine the response of treatment based on each subject's last treatment evaluation. For evaluating safety variables (vital signs and lipids), non-parametric analyses (Mood's, Mantel-Haenszel, and William's modification of the Shirley's test) were used because changes from baseline data at endpoint were not normally distributed. Our Statistician will evaluate the propriety of the choice of these tests and advise the Medical Officer if any problem arises.

7.1.2 Results and conclusions

7.1.2.1 Patient comparability

I cannot see any significant difference between the control-group and the treated groups, with respect to any demographic and background variable. Again, the Medical Officer needs the reassurance and confirmation of our Statistician on this point.

7.1.2.2 Patient disposition

From a total of 304 subjects that were initially randomized, the following completed the study: placebo (66%) and drug (from 80.8% to 92.1%, depending on the group).

7.1.2.3 Efficacy data

FPG: At baseline, median FPG values were similar in all four groups. At endpoint, FPG had decreased relative to placebo: in the 1 mg qd group (-43.0 mg/dl), the 4 mg qd group (-70.5 mg/dl) and the 8 mg qd group (-74.0 mg/dl). The differences between baseline and endpoint were statistically significant ($p < 0.001$). The difference was trivial between the 4 mg qd group and the 8 mg qd group.

HbA1c: At baseline, median HbA1c values were similar in all four groups. At endpoint, HbA1c values increased from baseline in the placebo and 1 mg qd groups, while they decreased in the two other treatment groups. At endpoint, HbA1c had decreased relative to placebo: -1.2% (1 mg qd), -1.8% (4 mg qd), and -1.9% (8 mg qd). The differences between baseline and endpoint were statistically significant ($p < 0.001$). The difference was trivial between the 4 mg qd group and the 8 mg qd group.

PPG: The PPG values evolved in parallel with FPG and HbA1c values, as described above. There was no difference whatsoever between 4 mg qd and 8 mg qd values.

Other endpoints: Glimepiride increased fasting and postprandial C-peptide and insulin levels significantly. At all visits, all measured lipid values (total cholesterol, HDL, LDL and triglycerides) were found to remain constant within all four groups.

7.1.2.4 Safety data

Treatment emergent signs and symptoms (TESS) were reported by 66% of placebo subjects, and 73% (1 mg qd), 78% (4 and 8 mg qd) of patients on glimepiride. Table III lists all events that occurred in more than 5% of studied subjects, regardless of diagnostic interpretation and existing or perceived causality relationship with drug treatment. Two features are worthy of note: (1) The 4 and 8 mg qd groups evidence a greater percentage of hypoglycemic episodes than the 1 mg qd group; and, (2) Conversely, the latter group showed a tremendous increase in hyperglycemic episodes (comparable to that seen in the placebo group), while the two other treatment groups showed a tremendous reduction in such episodes. No subject died during the trial and its immediate aftermath (14 days). Some 15 and 12 patients (placebo and glimepiride, respectively) quit the study for adverse events. One 8 mg qd patient had mild leucocytosis. One placebo subject had elevated liver enzyme values.

7.1.2.5 Sponsor's conclusions

"Compared with placebo, glimepiride given once daily in doses of 1, 4 and 8 mg is an effective glucose-lowering agent in Type II diabetics. Glimepiride 4 and 8 mg once-daily produced comparable effects and were significantly better than glimepiride 1 mg. The adverse events and laboratory data show that glimepiride is a safe therapy in the management of Type II diabetics."

7.1.2.6 Reviewer's conclusions

Efficacy: The proper dosage is definitely greater than 1 mg and equal to or perhaps even lower than 4 mg. Within the short span of the study and the small population studied, glimepiride didn't produce any unexpected untoward reactions.

7.2 Second pivotal study: Trial # 8/USA/202: Indication I. Placebo-controlled

7.2.1 Description of study

7.2.1.1 Title, objective and rationale

"A dose response study of HOE 490 (glimepiride) in subjects with noninsulin-dependent diabetes mellitus (NIDDM). The study wanted to compare the efficacy, safety, and tolerability of glimepiride versus placebo in the treatment of type II diabetics non-controlled by diet alone, and to determine a possible dose-response relationship."

7.2.1.2 Protocolar design

This was a 22-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed dose, dose-titration study. Subjects were randomized to treatment with 1, 2, 3, 4, 6 or 8 mg qd glimepiride, or an equivalent number of placebo tablets; all medications were administered with the morning meal. Each subject began the 10 week titration phase at the lowest dose of study drug and dosage was titrated upward or downward at 2 week intervals until FPG was 90-150 mg/dl. After 10 weeks of titration, subjects were maintained at their final dose for the remaining 12 weeks of the study drug.

7.2.1.3 Demographics

Patients were men and women with NIDDM, age 30 through 75, weighing between 90% and 150% of ideal body weight, not previously treated with oral antidiabetics, or had not received an oral antidiabetic or insulin for the last 6 months.

7.2.1.4 Safety considerations

Adverse events were recorded at each visit. Laboratory evaluations, ECGs, and vital signs were recorded at scheduled times throughout the study.

7.2.1.5 Efficacy end-points

Primary efficacy end-points: FPG, HbA1c, and 2-hour postprandial glucose (PPG). Secondary efficacy variables: fasting and 1-hour post-prandial C-peptide and insuline levels in plasma, and FPG and HbA1c variability.

7.2.1.6 Statistical approaches

Linear model analyses and the Cochran-Mantel-Haenszel test were used to evaluate demographic and background data. Subject attrition caused the primary analysis to determine the response of treatment based on each subject's last treatment evaluation. For evaluating safety variables (vital signs and lipids), non-parametric analyses (Mood's, Mantel-Haenszel, and William's modification of the Shirley's test) were used because change from baseline data at endpoint were not normally distributed. Our Statistician will evaluate the propriety of the choice of these tests and advise the Medical Officer if any problem arises.

7.2.2 Results and conclusions

7.2.2.1 Patient comparability

The two groups (placebo and glimepiride treatment groups) were not found to be different in any meaningful demographic or background variable.

7.2.2.2 Patient disposition

From the total of 249 subjects treated, 66.7% (placebo) and 84.6% (glimepiride) completed the study.

7.2.2.3 Efficacy data

All efficacy endpoints were suitably and significantly improved in the drug treatment group, as compared to the placebo group. FPG was down 46.0 mg/dl, HbA1c was reduced by 1.4 % units. No difference was seen in all the studied blood lipid parameters, except for LDL values which were significantly lower in the glimepiride group, as compared to the placebo group.

7.2.2.4 Safety data

TESS were reported by 77% of the glimepiride subjects and 72% of the placebo patients. The frequency of adverse reactions were comparable to that already provided in Table III. Symptomatic hypoglycemia occurred in 21% of glimepiride patients and in 4% of the placebo subjects, all of them termed to be mild to moderate events. Sponsor asserts that

patients who have not previously received an oral antidiabetic or have not received an oral antidiabetic or insulin therapy for at least 6 months (as the ones selected for this study) are more prone to experience hypoglycemic episodes -- hence, the abnormally high frequency for such events in this particular study among those treating with glimepiride. That is not a convincing argument since what counts here is the observed, and not surprising, difference between glimepiride and placebo-treated patients.

7.2.2.5 Sponsor's conclusions

"Glimepiride in doses of 1-8 mg once daily is an effective glucose-lowering agent compared with placebo in Type II diabetics who are dietary failures. The adverse event and laboratory data show that glimepiride is a safe therapy in the management of Type II diabetics."

7.2.2.6 Reviewer's conclusions

Naive or weaned-off diet-failure patients -- with, respectively, 180, 200, 220 and 240, mg/dl baseline FPG -- were given 1, 2, 4 and 8 mg qd of glimepiride daily, respectively. Each group had a rough reduction of baseline glycemia of about 45 mg/dl. This is a typical semi-log plot of pharmacological activity, indicating that drug dosage doubles when the parameter to correct is increased by a fixed increment. Under such conditions, the doubling of the dose would result -- at the higher end of the dosing -- with greater risks of untoward events.

The changes in HbA1c values are much less clearcut and/or systematizable. All that can be reasonably concluded is that, at the end of the study, the treated group has an advantage of 1.3% units over the placebo group.

The Sponsor's explanation as to the abnormally high hypoglycemic events in this study needs to be taken at face value but should not be explained out, as the Sponsor seems to have done. The data ought to be included, in some fashion, in the WARNINGS section of the labelling.

Our Statistician concluded: "This study has shown that glimepiride is statistically significantly superior to placebo."

7.3 Third pivotal study: Trial # 8/USA/205; Indication I.
Placebo-controlled

7.3.1 Description of study

7.3.1.1 Title, objective and rationale

"Comparison of bid versus qd dose regimen of glimepiride in patients with NIDDM who have previously received sulfonylureas." To test the efficacy, safety and tolerance of glimepiride in the treatment of NIDDM. Two dose regimens (qd & bid) at two different total daily doses (8 and 16 mg) were compared to placebo in Type II diabetics who cannot be controlled by diet alone.

7.3.1.2 Protocolar design

Fourteen-week, multicenter, randomized, placebo-controlled, parallel-group, fixed dose, double-blind study. A 3-week placebo washout preceded randomization.

7.3.1.3 Demographics

A total of 416 subjects, men and women, with NIDDM, age 30 through 80, and weighing between 90% and 150% of ideal body weight.

7.3.1.4 Safety considerations

Same general safety precautions as previous studies.

7.3.1.5 Efficacy end-points

Efficacy end-points as per previous studies.

7.3.1.6 Statistical approaches

Statistical considerations essentially similar if not identical to previous studies.

7.3.2 Results and conclusions

7.3.2.1 Patient comparability

There were no significant differences between glimepiride and placebo for any of parameters known to be significant, indicating good comparability with respect to meaningful and significant demographic and background variables.

7.3.2.2 Patient disposition

Some 54% of the subjects dropped out from the placebo group, 8% from the glimepiride 8 mg qd group, 17% from the group treated with 4 mg bid, 11% from the group treated with 16 mg qd, and 7% with the group treated with 8 mg bid. Needless to say, the dropout rate from the placebo group is excessive and may adversely affect significance computations. We should read carefully our Statistician's comments in this regard.

7.3.2.3 Efficacy data

With respect to FPG and HbA1c, the following results are to be noted: On average, FPG decreased for all doses by about 90 mg/dl, and the HbA1c values decreased for all doses by about 2.0% units. Other secondary endpoints were less clearcut but appear to have little significance. The main point to emphasize here: ALL THE TESTED DOSES APPEAR TO BE EQUIVALENT AS FAR AS THE QUANTITATIVE EFFICACY OF THE DRUG IS CONCERNED. The only logical explanation that comes to mind to this reviewer, to explain this rather curious fact is as follows: That the lowest tested daily dose (8 mg) is already in the plateau region of the dose-response curve. This is consistent with an observation made by us, above, concerning a previous study, namely that the average minimal effective dose is probably greater than 1 mg qd and equal to or lower than 4 mg qd. Also, changes in plasma lipids in the treated group existed but appears to be rather clinically inconsequential.

7.3.2.4 Safety data

The safety profile is very similar here than the one obtained during previous studies. To strengthen the commentary on efficacy made in the preceding paragraph, hyperglycemic events appeared to be constant in all

dosages/regimens (4% to 7%), and the same was also applicable to the frequency of hypoglycemic episodes. Again, the implication is clear: the doses used were clearly in the plateau region of the dose-response curve in humans.

7.3.2.5 Sponsor's conclusions

"A significantly greater proportion of glimepiride than placebo subjects completed treatment. All doses of glimepiride were significantly more effective in lowering FPG, HbA1c, and PPG than placebo. All glimepiride doses and regimens were found to be equally well tolerated and safe in the treatment of subjects with NIDDM. In general, there was [sic] no meaningful differences between the bid and qd regimens, and the 8 and 16 mg total daily doses."

7.3.2.6 Reviewer's conclusions

I wholeheartedly agree with the Sponsor's conclusion, and most emphatically with the last sentence of that conclusion (see immediately above). Our Statistician concluded: "This study has shown that all four dose-regimen combinations of glimepiride studied are statistically significant (even with multiple comparison adjustments) superior to placebo. There is a weak (not statistically significant by multiple comparison adjustments) indication that 8 mg bid regimen may be negligibly superior...to the other three dose-regimen combinations." So much for statistical acumen.

7.4 Fourth pivotal study: Trial # 8/USA/305: Indication II, Placebo-controlled

7.4.1 Description of study

7.4.1.1 Title, objective and rationale

"A randomized, comparative evaluation of glimepiride combined with insulin[,] versus placebo combined with insulin[,] in the treatment of patients with NIDDM." To evaluate the safety and efficacy of combination therapy with glimepiride and insulin in the treatment of overweight patients with NIDDM who had previously failed to respond to oral antidiabetic agents.

7.4.1.2 Protocolar design

A multicenter (17 sites) study, with an 8-wk open label evaluation of the safety of glimepiride, followed by a 24-wk, double-blind, randomized, parallel-group comparison of the efficacy and safety of combination therapy (glimepiride + insulin) versus placebo + insulin. Insulin dose was titrated to achieve and maintain FPGs between 100 to 120 mg/dl.

7.4.1.3 Demographics

A total of 208 men and women with NIDDM, with secondary failures to oral antidiabetic agents (defined as subjects with FPG greater than 180 mg/dl after 8 weeks of glimepiride therapy), 45 to 70 years old, weighing between 130% to 170% of so-called ideal weight.

7.4.1.4 Safety considerations

Safety precautions, examinations, laboratory analyses, and collection and reporting of adverse events were essentially as described in previous studies.

7.4.1.5 Efficacy end-points

The primary efficacy endpoint was the 4-wk average insulin dose at endpoint, as well as the change in HbA1c values, from baseline to endpoint. Secondary endpoints were as defined in previous studies.

7.4.1.6 Statistical approaches

As described in previous studies, see above.

7.4.2 Results and conclusions

7.4.2.1 Patient comparability

Satisfactory. All efficacy variables in the two treatment groups were similar at baseline. Also, and more importantly, the HbA1c values were, 9.9% and 9.7% (at baseline), and 7.9% and 7.6% (at endpoint) for, respectively, the glimepiride+insulin group and the

placebo+insulin group. This shows that insulin titration was successful and the degree of glycemic control achieved were very similar and, de facto, equivalent in the two groups.

7.4.2.2 Patient disposition

Of the 208 patients initially enrolled in the first stage of the study, only 145 entered the second stage, and only 132 completed the study.

7.4.2.3 Efficacy data

At endpoint, the glimepiride+insulin group required significantly less insulin (49 UC than the placebo+insulin group (78 U). Both treatments tended to decrease total cholesterol, increase HDL levels and decrease triglyceride levels.

7.4.2.4 Safety data

The TESS profile was roughly similar to than seen in previous studies. The glimepiride+insulin group had frequencies of 51% and 2% for, respectively, hypoglycemic and hyperglycemic episodes. The equivalent figures in the placebo+insulin group were, respectively, 37% and 7%.

7.4.2.5 Sponsor's conclusions

According to the Sponsor, this study showed that: "[s]ignificantly less insulin was required with combination therapy...; [t]he reduction in HbA1c from baseline to endpoint was similar with the two therapies; ... [and a] significantly greater proportion of glimepiride than placebo subjects completed treatment."

7.4.2.6 Reviewer's conclusions

The Sponsor is missing a major point. In fact, we didn't need to prove that an insulin-secreting oral hypoglycemic would spare insulin in a combination therapy. That conclusion is evident and derives from the very mechanism of action of sulfonylureas: They induce pancreatic secretion of insulin and, thus, less exogenous insulin is needed to maintain equivalent glycemic control.

The real purpose of rational and useful combination therapy using insulin is two-fold:

(1) Help correct the vicious circle created by the use of insulin alone, where insulin down-regulates the insulin-receptor response to itself, thus requiring more of the hormone to hopelessly try to correct the very defect it creates;

(2) To increase the HbA1c improvement to clinically significant thresholds; and,

(3) To improve the safety profile by reducing the frequency of the major adverse events during antidiabetic therapy, e.g., hyper- and (more importantly) hypoglycemic episodes.

Objective (1) is achieved ONLY if we use, in conjunction with insulin, oral hypoglycemics that favorably affect glycemia WITHOUT increasing internal insulin secretion (as sulfonylureas do). Specifically, we are alluding to the drug classes that affect insulin-receptor sensitivity to insulin; either directly (insulin-receptor response modifiers), or indirectly (drug with other non-insulinotropic mechanisms of action).

That the combination use of sulfonylurea+insulin may well be self-defeating is amply supported by the observation that the frequency of hypoglycemic episodes was greatly increased in the glimepiride+insulin group, as compared to the placebo+insulin group -- this, even though the baseline and endpoint HbA1c values were comparable in each group.

The only visible advantage of the sulfonylurea+insulin combination therapy is the reduction of the frequency of hyperglycemias. But this advantage can be acquired otherwise, and probably without paying the penalty that was exacted here.

Our Statistician concluded: "In this study, significantly less exogenous insulin was required with glimepiride plus insulin therapy than with placebo plus insulin therapy. The reduction of HbA1c from baseline to endpoint was similar in the two treatment groups...Statistically more weight gain in the glimepiride plus insulin treatment group than in the placebo plus insulin group, upto Week 12, if of concern." Thus, is is

clear that yet another untoward consequence is the result of glimepiride+insulin use: that of increased weight coexisting, no doubt, with still more reduced receptor sensitivity to insulin -- be it exogenous or endogenous in origin.

7.5 Fifth pivotal study: Trial # 8/USA/301: Long-term Active-controlled

7.5.1 Description of study

7.5.1.1 Title, objective and rationale

"Randomized comparative evaluation of the efficacy and safety of HOE 490 versus glipizide in patients with NIDDM." A multicenter (24 sites), study to compare the safety and tolerance of glimepiride to that of glipizide.

7.5.1.2 Protocolar design

A randomized, double-blind, unbalanced (2:1; glimepiride-glipizide) study with a 3-wk placebo washout period, followed by a 12-mo active-controlled treatment period. Daily doses of 1, 2, 3, 4, 8 and 12mg of glimepiride were compared to daily doses of 2.5, 5, 10, 20, and 40 mg of glipizide.

7.5.1.3 Demographics

Some 130 men and women with NIDDM, aged 30-80 yrs, and weighing from 90-150% of so-called ideal body weight, had been enrolled as of March 1, 1992 (86 glimepiride and 44 glipizide). At the time of the initial NDA submission, the study was reported as ongoing.

7.5.1.4 Safety considerations

Essentially similar to previous studies.

7.5.1.5 Efficacy end-points

Essentially similar to previous studies.

7.5.1.6 Statistical approaches

Essentially similar to previous studies with some variations, mostly due to the active-controlled comparative nature of the study. Consult our Statistician's report for full particulars.

7.5.2 Results and conclusions

7.5.2.1 Patient comparability

Appeared to be satisfactory.

7.5.2.2 Patient disposition

The percentage of subjects who did not complete the study were similar in glimepiride (12.8%) and glipizide (13.6%) patients.

7.5.2.3 Efficacy data

To be supplied in subsequent submissions.

7.5.2.4 Safety data

Symptomatic hypoglycemia occurred in 18.6% of glimepiride and in 15.9% of glipizide subjects. It should be noted that given the incompleteness of the study at the time of the submission of the original NDA, only an interim safety report was filed in this NDA. A complete report was promised to be included with the Safety Update package.

7.5.2.5 Sponsor's conclusions

"Overall, both glimepiride (1-16 mg/d) and glipizide (2.5-40 mg/d) were equally well tolerated and safe in the treatment of patients with NIDDM."

7.5.2.6 Reviewer's conclusions

The Reviewer agrees with the Sponsor. However, the following caveat should be added: It seems that patients on sulfonylureas seem to be having a very high incidence of upper respiratory infections. This may be comparable to general population statistics but this needs to be carefully

assessed in the future. As will be noted in the next study, the same observation was made there, i.e., a relatively high incidence of upper respiratory infections in patients treated with glimepiride and glyburide. This indicates that the aforementioned observation is not a fluke.

7.6 Sixth pivotal study: Trial # 8/USA/302: Long-term Active-controlled

7.6.1 Description of study

7.6.1.1 Title, objective and rationale

"A randomized, double-blind, parallel-group study comparing the efficacy and safety of glimepiride and glyburide in the treatment of subjects with non-insulin-dependent diabetes mellitus," to compare the relative efficacies of the new drug (in doses of 1 to 16 mg/d) and glyburide (in doses of 1.25 to 20 mg/d). This was a 12-mo US, . multicenter (30 study sites) clinical trial.

7.6.1.2 Protocolar design

A 4-wk washout period (during which no therapy was provided) preceded a 12-wk treatment period. This was an uptitrating of the dose every 2 weeks, to achieve an FPG in a targeted range (reduction of at least 25 mg/dl from baseline at week 0). After titration phase, there was a maintenance phase of no more than 40 wks.

7.6.1.3 Demographics

A total of 577 men and women with NIDDM, aged 30-80 yrs, weighing between 90% and 150% of so-called ideal body weight, with FPG values (at screening) less than 200 mg/dl for oral hypoglycemic users and at 160-300 mg/dl for diet non-responders (not on hypoglycemics). Some 491 subjects completed the study.

7.6.1.4 Safety considerations

As in previous studies.

7.6.1.5 Efficacy end-points

As in previous studies.

7.6.1.6 Statistical approaches

Basically, as in previous studies with slight variations mostly concerning the statistical analysis of adverse events. Consult our Statistician's report for full particulars of this aspect of the file.

7.6.2 Results and conclusions

7.6.2.1 Patient comparability

Comparability was satisfactory and concerned all pertinent parameters.

7.6.2.2 Patient disposition

Some 40 and 46 patients on glimepiride and glyburide, respectively, did not complete the study.

7.6.2.3 Efficacy data

The endpoint dosages were below the maximum level for 38% of glimepiride subjects and 42% of glyburide subjects. At endpoint, 4.2, 4.5, 9.8, 9.1, 10.5, and 62% of patients on glimepiride, and 3.8, 7.3, 9.0, 11.1, 10.8 and 58.0% of those on glyburide were distributed to, respectively, the 1st, 2nd, 3rd, 4th, 5th and sixth dose of oral hypoglycemic. In both arms, efficacy parameters tended to increase over time even though dose adjustments were permitted.

7.6.2.4 Safety data

Hypoglycemia was reported by 12% and 17% of, respectively, glimepiride and glyburide subjects. Symptomatic hyperglycemia was reported in 7% and 16% of, respectively, glimepiride and glyburide. The rest of the safety profile appears to be as expected for a sulfonylurea.

7.6.2.5 Sponsor's conclusions

"Glimepiride... and non-micronized glyburide... were not different in their ability to maintain metabolic control over 1 year of treatment in this group of NIDDM dietary failures."

7.6.2.6 Reviewer's conclusions

It is clear to this reviewer that glimepiride and glyburide are equally effective, almost mg for mg of administered dose. Also, over time, both drugs are less and less efficacious in controlling glycemia. At 12 mos., about 60% of the subjects are on the maximal (and excessive) dose. And yet, both average FPG and HbA1c values have steadily deteriorated to a barely acceptable level. Of course, allowance has to be made that a placebo group, if it existed, would have shown a much greater deterioration. Nevertheless, it is clear that sulfonylureas have reasonably good relative efficacy but marginal absolute efficacy in controlling the evolution of diabetes in treated patients.

Under the conditions of the present study, glimepiride appears to have a lower frequency of hypo- and hyperglycemic episodes than glyburide -- an admittedly paradoxical and difficult to explain result.

7.7 Seventh pivotal study: Trial # 2/MN/301: Long-term Active-controlled

7.7.1 Description of study

7.7.1.1 Title, objective and rationale

"Multicenter clinical trial to study the effects of glimepiride during long-term treatment of type II diabetic patients." To compare the therapeutic value of glimepiride with that of glyburide, at doses roughly comparable in hypoglycemic efficacy.

7.7.1.2 Protocolar design

This was a double-blind, parallel-group comparison of glimepiride and non-micronized glyburide. Multinational,

multicenter (49 sites), active-substance controlled study. A 2-wk open run-in phase was followed by a 1-yr randomized double-blind test phase. Initially, all subjects were put on 1 mg/d (glimepiride) or 2.5 mg/d (glyburide). Later, dose titration was implemented to a maximum of 8 mg glimepiride or 20 mg glyburide, as dictated by metabolic control results.

7.7.1.3 Demographics

Subjects (a total of 1044) were NIDDM outpatients, 40-80 yrs old, with fasting blood glucose equal or greater than 250 mg/dl, pretreated for at least 6 mos with glyburide and who had no change in dosage for at least 2 mos.

7.7.1.4 Safety considerations

As per previous studies, on the main.

7.7.1.5 Efficacy end-points

As per previous studies, with minor modifications, e.g., a 1-hr. post-prandial blood glucose as one of the tested efficacy measures. The main endpoints were FPG and HbA1c.

7.7.1.6 Statistical approaches

Consult our Statistician's review for full particulars. Per-protocol and intent-to-treat analyses were both performed, with a two-tailed test at a significance of 0.05. The minimum clinically relevant difference was defined as 0.552% HbA1c and 22.1 mg/dl FBG.

7.7.2 Results and conclusions

7.7.2.1 Patient comparability

Satisfactory, as described and defined per previous studies, inasmuch as the two groups, at baseline, were similar for all pertinent or significant known variables.

7.7.2.2 Patient disposition

Of the 1044 subjects who entered the study, some 816 completed it.

7.7.2.3 Efficacy data

At endpoint, 18.4, 10.7, 8.0, 6.3, 5.4, and 51.2% of patients on glimepiride, and 23.1, 10.8, 6.9, 7.1, 9.8 and 57.7% of those on glyburide were distributed to, respectively, the 1st, 2nd, 3rd, 4th, 5th and sixth dose of oral hypoglycemic. In both arms, efficacy parameters tended to increase over time even though dose adjustments were permitted. In both groups, FBG and K_bAlc values got worse as time went by (see Table IV). Even the Sponsor agrees that "most subjects did not achieve better metabolic control with titration to the higher dose levels." This is consistent with our long-standing contention that sulfonylurea are, by and large, overdosed in the U.S. today, i.e., most patients are prescribed doses that are very high yet no more effective than relatively lower doses. Such high dosing eschews negatively the benefit-versus-risk ratio of such drugs. The fact that a sulfonylurea becomes ineffective doesn't justify upping the dosage to levels that are still ineffective yet clearly more toxic. The labelling should reflect this most important observation and conclusion, particularly since the Sponsor agrees with them. The above data must be interpreted with the following fact kept in mind: There was no washout period of previous therapy prior to randomization of the subjects

7.7.2.4 Safety data

A total of 228 subjects withdrew: 126 (of which 33 for non-medical reasons) from glimepiride and 102 (of which 71 for non-medical reasons) from glyburide. Thus, glimepiride is, from this particular viewpoint, slightly worse than glyburide. Of the 630 subjects who had at least one adverse event, 130 (65 in each group) had a serious event, i.e., a 12.5% frequency of such events -- which is non negligible. Could this be related to the 'overdosing' of sulfonylureas, as presented and discussed above? The incidences of hypoglycemia was 2.0% in each group. The incidence of hyperglycemia were 2.9% and 2.3% for, respectively, glimepiride and glyburide. Again, upper respiratory

infections were frequent (8.6% for glyburide and 6.6% for glyburide). There were 11 glimepiride and 4 glyburide deaths. Of noteworthy adverse laboratory changes, 19 occurred in glimepiride and 26 occurred with glyburide. Still and overall, in most of the above categories, glimepiride seems to have fared, if anything, a bit worse than glyburide.

7.7.2.5 Sponsor's conclusions

"Both treatment groups tended to increase FBG [and] HbA1c... levels during the course of the study, but not by clinically meaningful amounts."

7.7.2.6 Reviewer's conclusions

The Sponsor's statement is correct in its first part. The last part bears discussion. If it is thought that any improvement in HbA1c is clinically meaningful, then it may well follow that any worsening in that same parameter is equally clinically meaningful, albeit in the negative sense this time around. On the other hand, if we agree that, practically, a certain threshold of efficacy must be attained with "ordinary" or "average" hypoglycemics (those having roughly comparable safety profiles) in order to have a clinically significant improvement of the patient, then whatever improvement below that threshold would not be deemed to be clinically significant.

Briefly stated, one can't use both arguments at the same time, in different parts of a submission, and when it suits the needs of the moment. That would be having one's cake and eating it too.

It should also be added that any improvement is offset by the price to be paid because of the toxicity of a particular drug.

7.8 Eight pivotal study: Trial # 2/MN/302: Long-term Active-controlled

7.8.1 Description of study

7.8.1.1 Title, objective and rationale

"Multicenter clinical trial to study the effects of glimepiride during long-term treatment of type II diabetic subjects [compared to] glibenclamide."

7.8.1.2 Protocolar design

Double-blind, multinational and multicenter (33 sites), parallel-group, active-controlled study, with an open extension (not reported in the original submission.) The study is intended to achieve 12 mos of treatment for all subjects entered into it. At present, not all patients have completed the study.

7.8.1.3 Demographics

A total of 457 subjects who had completed protocol 2/MN/301 (see above), were enrolled in the present study, continuing to receive their double-blind regimen from previous protocol.

7.8.1.4 Safety considerations

As per previous study, of which this study is an extention.

7.8.1.5 Efficacy end-points

Efficacy variables (principally, FBG and HbA1c values) were measured at 3-mos intervals.

7.8.1.6 Statistical approaches

As described for the immediately previous study. See our Statisticians for full particulars and possible minor differences from above.

7.8.2 Results and conclusions

7.8.2.1 Patient comparability

Since at the enpoint of the previous study, of which this study is an extension, defining parameters were

comparable, it follows that these same parameters were comparable at baseline of the present study.

7.8.2.2 Patient disposition

On the main, similar to that described for the previous study.

7.8.2.3 Efficacy data

As during the previous study, glycemic control worsened. FBG went from about 150 mg/dl at baseline to about 160 mg/dl at endpoint; however, HbA1c values showed a more convincing deterioration: from about 7.7% at baseline to 8.3% at endpoint, i.e., a 0.6% worsening. Which gives a total worsening of 1.1% during somewhat less than a full 2 yrs of treatment (since not all patients were treated for that length of time at submission.)

7.8.2.4 Safety data

Not visibly different from the observations and conclusions made during the previous study.

7.8.2.5 Sponsor's conclusions

"Both treatment groups tended to have stable FBG5/20/9..., and to increase their HbA1c levels during the course of the study, but not by clinically meaningful amounts."

7.8.2.6 Reviewer's conclusions

The most significant observation here is the dichotomy between FPG and HbA1c values during long-term treatment. Indeed, in this study, and by the Sponsor's admission, FBG remain stable during therapy whereas HbA1c deteriorate.

7.9 Ninth pivotal study: Trial # 2/MN/311-312: Long-term Active-controlled

7.9.1 Description of study

7.8.1.1 Title, objective and rationale

"Multicenter clinical trial to study the effects of glimepiride during long-term treatment of type II diabetic subjects [compared to] glyburide (micronized)."

7.8.1.2 Protocolar design

Double-blind, multinational and multicenter (74 sites), parallel-group, active-controlled study. Subjects were NIDDM outpatients aged 40-80 yrs, with FBG values equal to or greater than 180 mg/dl, who were pretreated for at least 6 mos with glyburide, and who had no dosage changes for at least 2 mos. A 2 wk open run-in phase with subjects on glyburide was followed by a 1-yr randomized, double-blind test phase. All patients were placed on the lowest dose of either drug then titrated upward as in previous studies, up to a maximum of 18 mg glimepiride and 14 mg of glyburide. Protocol 312 was a 1-yr open extension of protocol 311.

7.8.1.3 Demographics

A total of 852 subjects were randomized at the beginning of the study, Retention was similar as in previous studies, either in the first or the second leg of the study.

7.8.1.4 Safety considerations

Similar to those observed during active-controlled previous studies, except that hypoglycemic frequencies were slightly better than previously observed.

7.8.1.5 Efficacy end-points

Efficacy variables (principally, FBG and HbA1c values) were measured at 1-mo (at first) and (later) 2-mos. intervals.

7.8.1.6 Statistical approaches

As described for the immediately previous study. See our Statisticians for full particulars and possible minor differences from above.

7.8.2 Results and conclusions

7.8.2.1 Patient comparability

Comparability was satisfactory.

7.8.2.2 Patient disposition

On the main, similar to that described for the previous study.

7.8.2.3 Efficacy data

As during the previous active-controlled studies, glycemic control worsened: from 171 mg/dl to 177 mg/dl for FBG, and from 8.4% to 8.7% for HbA1c.

7.8.2.4 Safety data

Not visibly different from the observations and conclusions made during the previous study.

7.8.2.5 Sponsor's conclusions

"Glimepiride (1-8 mg qd) and micronized glyburide (1.75-14 mg daily), titrated to optimized dosages, were similarly effective in their ability to maintain metabolic control after 1 year of treatment."

7.8.2.6 Reviewer's conclusions

Again, a dichotomy is seen between FPG and HbA1c values during long-term treatment. Otherwise, this Reviewer is in broad agreement with the Sponsor's conclusions. This is particularly clear during the 1-yr extension of the trial where FBG was 163 at baseline and 168 mg/dl at endpoint, while HbA1c values were at 8.3% at baseline and at 8.7% at endpoint.

8 NON-PIVOTAL CLINICAL STUDIES

8.1 First non-pivotal study: Trial # 8/USA/206

This was a multicenter (9 sites), randomized, double-blind, clinical efficacy/pharmacodynamic, safety, and

pharmacokinetics crossover study of glimepiride given once a day and twice a day in subjects with NIDD, of 15 weeks duration. Glimepiride was given either 6 mg once daily or 3 mg bid.

Subjects were as described in previous studies with respect to entrance criteria. A 1-wk screening period was followed by a 3-wk washout period, to enter into the 4-wk double-blind treatment period. Another 3-wk placebo-washout period preceded the second double-blind 4-wk treatment period.

The primary efficacy endpoint was FBG. Statistical considerations are best retrieved in our Statistician's review. A total of 161 patients entered the study and 106 finished it. Since a significant effect was detected in the FPG data, the primary FPG analysis used data from the first test period. Our Statistician will advise us if this is acceptable. Under these conditions, however, the mean change from baseline at endpoint was not significantly different between the two regimens, although the decrease was somewhat greater with 6 mg qd, as opposed to 3 mg bid.

The Sponsor thinks that the study favored the qd dosing. This Reviewer doesn't wish to raise any objections to this conclusion, except to say that a difference, if any between them, must be very small and relatively trivial. On the other hand, their marketing people would rather have the drug prescribed once a day.

3.2 Second non-pivotal study: Trial # 2/MN/202

This was a multicenter (14 sites), parallel-group study, in 188 patient treated for 21-35 days. The objective was to compare the effects of physical exercise on blood glucose control in NIDDM patients treated with glimepiride or glyburide under outpatient conditions. All subjects, previously treated with glyburide or any other equipotent oral sulfonylurea for at least 3 mos. Subjects with FBG levels of 100-150 mg/dl entered the 7-day test phase after being randomized to sulfonylurea. Four groups were formed: 'exercise,' 'non-exercise,' at baseline and endpoint. No significant differences were seen in the groups with respect to FBG and PPBG (post-prandial blood glucose) values, but glimepiride treatment resulted in a greater decrease in the

maximum concentration of post-prandial C-peptide and insulin under conditions of acute exercise vs. non-exercise, compared with glyburide treatment -- although both treatments yielded similar glycemic control.

The Sponsor concludes that "more than 90% of subjects who had been stabilized on 10 mg non-micronized glyburide daily (or an equivalent sulfonylurea treatment) achieved similar metabolic control when switched to 3 mg of glimepiride." The conclusion is overreaching and the best that can be said about it is that a not-too-carefully performed study showed no difference between a few glycemic parameters, using glimepiride and sulfonylurea dosing assumed to be equipotent. More importantly, the so-called 21-35 days of treatment were separated into 14-28 days of "metabolic stabilization," and only 7 days of actual treating the patients and testing whatever hypothesis was assessed in this study.

8.3 Third non-pivotal study: Trial # 8/GB/203

A single center, double-blind, dose-titration, crossover study, involving 34 subjects and entailing two 28-days treatment periods. The objectives being: To compare the effect of treatment with glimepiride on cardiovascular risk factors in NIDDM outpatients; and to determine which dose is required (from the used 1, 2, 3, 4, 6 and 8 mg of glimepiride; and 2.5, 5, 7.5, 10, 15 and 20 mg of non-micronized glyburide) to achieve FBG levels of less than 126 mg/dl.

There was a significant difference in the FBG values between baseline and endpoint, with glyburide achieving a greater reduction than glimepiride (by about 18 mg/dl. No inter-group changes were seen in any of the other parameters. One wonders about the reasons for conducting such a study in the first place. Muddled committee decisions? Promotional purposes?

8.4 Fourth non-pivotal study: Trial # 2/D/221

A multicenter (5 sites), parallel-group study using 74 subjects for 28 treatment days. The objective: Whether an equivalent or better degree of metabolic control could be achieved with glimepiride, as compared to glyburide, in

NIDDM outpatients (already on either 10.5 mg micronized or 15 mg non-micronized glyburide, and in whom satisfactory metabolic control was deemed to have been achieved). Patients were randomized to either 2 mg of glimepiride or 10.5 mg micronized glyburide. Change from baseline in glycemic control parameters were followed, including HbA1c or HbA1 measurements. Inter-group patient comparability was proven satisfactorily at baseline. At endpoint, FBG values (significantly) increased by 9.6 mg/dl in the glimepiride group and decreased by 15.6 mg/dl in the glyburide group. A similar trend was observed for HbA1c or HbA1 values.

The Sponsor concludes: "[A] 2 mg daily dose of glimepiride was not enough to maintain... metabolic control in this group of subjects." This reviewer has already expressed the opinion that at least one of the pivotal studies seems to strongly indicated that the average minimal effective dose of glimepiride, in a representative population, is probably between 2 mg and 4 mg. The present study, irrespective of its well-understood limitations, enforces this perception.

8.5 Fifth non-pivotal study: Trial # 2/D/223

A single-center, parallel-group study in 24 subjects for 28 treatment days. The objective and protocol highlights: As for the previous study, except that 15 mg nonmicronized glyburide replaced 10.5 mg micronized glyburide, and 3 mg glimepiride were administered daily, as opposed to 2 mg in the previous study. Also, and unfortunately, only PPBG and HbA1c measurements were performed, since FBG could not be performed because the outpatient subjects were generally unavailable before breakfast. The Sponsor concludes: "[G]limepiride gave significantly greater reduction in 2-hour PPBG and HbA1 levels than... glyburide." Again, this otherwise limited and inconclusive study, seems to suggest that 3-4 mg of glimepiride qd is probably a good starting dose for the average patient in need of such therapy. With the same amount of time and resources, a more rigorous study could have been conducted, but one can review and weigh only that which one is supplied with.

8.6 Sixth non-pivotal study: Trial # 8/F/301

A multicenter (31 sites), double-blind, parallel-group, dose-titration study in 229 subjects, for up to 14 wks of treatment. Objective: To compare glimepiride (1, 2, 3, and 4 mg qd) to gliclazide (80, 160, 240 and 320 mg) in NIDDM patients, already metabolically stabilized to a satisfactory degree with 80-240 mg of the latter drug. Baseline inter-group comparability was proven. At endpoint, FBG levels were significantly higher in the glimepiride than in the gliclazide group, but the difference did not seem clinically meaningful to the Sponsor, which concludes: "The majority of subjects were stabilized at one of the two lowest dosages of either study drug," i.e., 1 and 2 mg glimepiride qd, or 80 and 160 mg gliclazide. Again, this otherwise limited and somewhat inconclusive study nevertheless supports this Reviewer's early contention that the average minimal effective dose of glimepiride, in a representative patient population, is somewhere between 3 to 4 gm qd, since the 2 mg dosing allowed the rise of FBG values during the treatment period, while 80 mg of gliclazide didn't. The Sponsor's further statement that "a 1 mg dose of glimepiride has nearly equivalent to an 80 mg dose of gliclazide," is a bit of indefensible posturing and a rather meaningless tongue-twisting.

9 OVERVIEW OF EFFICACY

Indication I

This is an indication for glimepiride monotherapy. It is supported by US trials 8/USA/104, 8/USA/105, 8/USA/106, **8/USA/201**, **8/USA/202**, 8/USA/205, 8/USA/206, 8/USA/301, and 8/USA/302; as well as European trials 2/D/213, 2/D/221, 2/D/223, 8/GB/203, 2/MN/202, 2/MN/301, 2/MN/302, 2/MN/311, 2/MN/312, AND 8/F/301. The underlined trials explored the 2-4 mg qd dose range, either under placebo- or active drug-controlled conditions. The **bolded** trials are placebo-controlled pivotal ones, while the *italicized* ones are active drug-controlled pivotal ones. These trials involved anywhere from 18 to 577 patients (grand total of 2745 subjects), over a period of time of between 2 wks to 12 mos.

Key efficacy variables were FPG, HbA1c (when appropriate), and 2-hour PPPG (when measured). Statistical significance was deemed to be achieved at or better than the 0.05 level.

A careful analysis of the results of dose-response relationships (either in fixed-dose, or ascending-dose studies) leads one to conclude that the average minimal dose that is effective is probably in the 2-4 mg range. Clearly, 1 mg is insufficient in most cases. Unfortunately, the 2-3 mg qd dosing range has not been studied in the fixed-dose trials. However, the following table from upward-titration study 8/USA/202, seems to indicate the correctness of the Reviewer's oft repeated statement that the average minimal dose that is effective is probably in the 2-4 mg range, 2 mg qd being effective in many patients, and being the dose that one would recommend for the initiation of therapy in most patients, excluding those that have HbA1c titers in the upper range of the abnormal (e.g., those with HbA1c values above 9.4%).

Dose (mg qd)	N	FPG (mg/dl)			HbA1c (%)		
		base	end	change	base	end	change
2	16	202	133	-69	9.5	6.9	-2.6
3	14	214	166	-47	9.2	6.7	-2.6
4	16	224	164	-60	9.2	6.7	-2.4
6	12	229	156	-74	9.5	6.6	-2.9
8	42	239	189	-51	9.8	7.7	-2.2

There is no perceptible difference in the HbA1c changes at any of the tested doses. In other words, and for all practical purposes, we are either close to or at the plateau region of the dose-response curve. Looking now at the two fixed-dose, placebo-controlled studies (8/USA/201 and 8/USA/205), we can see the following dose-response curves after 14 wks of treatment:

Dose (mg qd)	HbA1c		
	base	end	difference from placebo
1	7.8	8.0	-1.2
4	7.7	7.7	-1.8
8	7.9	7.6	-2.0
16	8.0	7.4	-2.0

Again, there is no significant difference in the improvement in HbA1c relative to placebo at 4, 8, or 16 mg. On the other hand, the 1 mg dose clearly has a lower effect on that parameter. Putting the two set of data together, we can now safely conclude:

- (1) the 1 mg dose belongs to the ascending part of the dose-response curve;
- (2) the 8-16 mg is clearly in the plateau region of the dose-response curve; and,
- (3) the 2-4 mg dose appears to be the average minimal effective dose; except for those who show highly perturbed HbA1c values, i.e., about 9.4 and above.

In the effective dose-range, the average improvement of HbA1c values is in the 1.8-2.4% range, for patients with baseline values between 7.5% and 11.2%, under optimal conditions of treatment. This is a good and clinically significant improvement, clearly militating for an approval of Indication I (i.e., monotherapy), assuming that the safety profile allows such a conclusion.

On the critical side of the ledger, it must be added that the 1.8-2.4% range of improvement of HbA1c values is slightly overstated, because the data base included results from studies with a probably insufficient initial washout period prior to sulfonylurea therapy. Under these conditions, initial HbA1c levels were not quite at real baseline. Nevertheless, we estimate the improvement in HbA1c due to treatment with glimepiride to be between 1.5 and 2.0%.

Indication II

This is a proposal to use a combination of glimepiride plus insulin in cases of secondaire failures of

sulfonylurea therapy. Study 8/USA/305 has already been reviewed under pivotal studies. It reached the following conclusions with respect to efficacy:

- Significantly less insulin was required to achieve comparable metabolic control (between the placebo +insulin and the drug+insulin groups);
- A smaller proportion of subjects receiving drug+insulin were put on 100 U insulin qd, with the practical result that fewer patients would require more than one insulin injection per day.

It should be noted, however, that glimepiride was administered at a fixed dosage of 8 mg bid in study 8/USA/305, which is outside the recommended dosage range for this compound. Thus, the support for the advantages are slightly put in question but -- to be honest -- without jeopardizing the main finding.

That finding, itself, is almost self-evident. Indeed, as observed earlier by this reviewer, it is no surprise that a sulfonylurea, such as glimepiride, would induce pancreatic secretion of insulin and, thus, lessen the dosing of exogenous insulin needed to maintain comparable glycemic control. But this does not help correct the vicious circle created by the use of exogenous insulin alone, where insulin down-regulates the sensitivity and response of its own receptors, thus increasing the need for exogenous insulin to hopelessly try to correct the very defect it creates. In fact, adding a sulfonylurea (that produces more endogenous insulin) to a reduced dose of exogenous insulin doesn't change the existence of that vicious circle.

Thus, the combined use of sulfonylurea+insulin is probably self-defeating. At any rate, as seen in the reviewed studies, it results in creating the same undesirable effects, e.g., hyperinsulinemia, weight gain and reduced insulin-receptor sensitivity to insulin, while also showing a greater frequency of hypoglycemic episodes in the glimepiride+insulin group, as compared to the placebo+insulin group.

The only visible advantage of the sulfonylurea+insulin combination therapy is the reduction of the frequency of hyperglycemias. But this advantage can be acquired

otherwise, and probably without paying the penalty that was exacted here.

Novel indication proposed by this Reviewer

Hermann LS et al. [Diabetes Care (1994) 17:1100-9] have shown that during sulfonylurea (SU) monotherapy some 36% of the treated subjects will show insufficient and worsening glycemic control within a relatively short period of time. Her also showed that the adjunction of Metformin (M) will result in near normal glycemic control, even in many cases of advanced NIDDM. The following additional recent reports of actual clinical trials also support the beneficial effect of the SU+M therapy when monotherapy with either agent eventually leads to a loss of desirable glycemic control: 1. Jeppesen J et al., Diabetes Care (1994), 17:1093-9; 2. Aguilar CA et al., Rev Invest Clin (1992) 44:71-6; 3. Trischitta V et al., Diabetes Care (1992) 15:539-42; 4. Reaven GM et al., JCEM (1992) 74:1020-6; 5. Laurenti O et al., Clin Ter (1992) 140:259-63; 6. Haupt et al., Diabete Metab (1991) 17 (pt 2):224-31; 7. Groop L & Widen E, Diabete Metab (1991) 17 (pt 2):218-23; 8. Viguerie R et al., Diabete Metab (1991) 17 (pt 2): 232-4; 9. Klein W, Diabete Metab (1991) 17 (pt 2): 235-40; and, 10. Jennings AM et al., Diabetes Care (1989) 12:203-8.

There are additional benefits when M is added to SU, either initially or during secondary failure of the SU therapy:

1. M improves glycemia by a different mechanism of action than SU. This restores the therapeutic effect of SU;
2. As the UKPDS report 13 has shown [BMJ (1995) 310:83-8], bodily weight increases significantly during SU therapy while it tends to be either constant or slightly improves during M therapy. Such an effect results in an improved sensitivity to insulin. Indeed, as shown by Groop L & Widen E [see above, ref. 7], and by Klein W [see above, ref. 9], the adjunction of M to SU improves insulin sensitivity and, for this reason, is preferred by some to the adjunction of Insulin to SU-unresponsive patients;
3. SU alone, and SU+insulin tend to result in hyperinsulinemia and hypoglycemic episodes, both undesirable developments for a variety of reasons. M tends to reduce the intensity or the frequency of such occurrences; and,

4. The addition of M to SU also improves the lipidemic picture slightly, although finitely [see Haupt et al., ref. 6, above].

For all the above reasons, it is highly desirable to encourage, whenever appropriate, the use of SU+M combination therapy, provided that dosing is carefully titrated in each patient, in order to obtain the maximal effect with the least dosing of each drug. Titration should be followed by FPG measurements, to follow short-term results of therapy; and by HbA1c measurements (done every 3 to 6 mos.) in order to assess the integrality of the euglycemic effect of therapy. 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 probability of too frequent hypoglycemic episodes.

All the above considerations should be included in the labelling of any sulfonylurea, in clear language. Finally, since all sorts of different SUs were used in the above mentioned trials, these considerations apply to all SU presently sold in the United States, even though some of them may not have been specifically tested. This because any number of studies have shown the essential comparability of all sulfonylureas in term of their overall efficacy and safety.

Since the above consideration apply to glimepiride as well, we recommend that this novel indication be approved for glimepiride, in replacement of Indication II whose approval will not be recommended by this Reviewer.

10 OVERVIEW OF SAFETY

10.1.1 Observations pertaining to all sulfonylureas

All sulfonylureas are known to result in a low yet finite incidence of severe hypoglycemic episodes. Renal insufficiency, hepatic pathology, adrenal or pituitary insufficiencies -- particularly in the elderly and the debilitated patients -- increase the risk of a hypoglycemic crisis. Other contributing factors include: insufficient caloric intake, after strenuous and long exercise,

following alcohol ingestion, and administration of other drugs with hypoglycemic side-effects.

The following discussion is important to understand the current position of the FDA regarding the approval and labelling of sulfonylurea oral hypoglycemics. It is mostly based on the University Group Diabetes Program (UGDP) study, which was a long-term prospective clinical trial, during which some 823 patients were followed to evaluate the effectiveness and safety of tolbutamide, insulin or diet. The patients were treated for 5-8 years and cardiovascular complications were tallied in each group. The tolbutamide-treated subjects had 2.5 times the rate of cardiovascular mortality of patients treated with diet alone. The conclusion that treatment with sulfonylurea increased mortality was hotly debated and became very quickly highly controversial. One of the counter-arguments that was offered, by opponents of the study, was that individual subjects were not titrated properly to make sure that they received the optimal dosing of either sulfonylurea or insulin.

The FDA found itself in a relatively difficult position. On the one hand, it could not simply ignore the facts derived from the UGDP study. On the other hand, it had to take into account the valid arguments of the opposing party. As a result, a compromise was reached: The FDA eventually approved the so-called second generation hypoglycemic sulfonylureas but required that a rather restrictive and constraining warning be added to their labeling.

Sulfonylureas are contraindicated in individuals with known hypersensitivity to any other sulfonylurea drug. Other contraindications include: diabetes complicated by ketoacidosis, with or without coma; therapy of IDDM (or type I) diabetes. Since there are no adequate studies

10.1.2 General observations pertaining to glimepiride

The primary evaluation of the general safety of glimepiride is based on 4875 subjects in trials in the US (2169 subjects in 10 trials) and Europe (2706 subjects in 10 trials) -- see Tables V and VI. Thus, the number of subjects

evaluable for safety is somewhat larger than available for its efficacy evaluation.

Total discontinuations, for all reasons, were 63/294 (21.4%) for placebo, 134/1523 (8.5%) for glimepiride, 42/307 (13.7%) for glyburide, and 7/44 (15.9%) for glipizide, for all the US trials combined. The figures for the combined European trials were 228/1489 (15.3%) for glimepiride, 214/1132 (18.9%) for glyburide, and 6/115 (5.2%) for gliclazide. The European figures are higher than the US ones, because the former included a number of subjects treated for up to 3 years.

The deaths will be now discussed (see Table VIIa as well). It should be noted that, in Table VIIa, the "causes" of death are not exactly that; rather, they represent the investigator's best clinical description of the subject at the time of death -- a cute euphemism for "I really don't know.". Thus, the total lethalties are more meaningful than the categorized ones, and all discussion of the latter should bear in mind the above mentioned limitation. Some 0/294 patients (0%) died during placebo treatment, 5/1523 (0.3%) during glimepiride treatment, and 1/307 (0.3%) during glyburide treatment in the US trials; 25/1489 (1.7%) during glimepiride treatment and 19/1132 (1.7%) during glyburide treatment in the European trials. All deaths occurred after the treatment was discontinued. As expected, most of the deaths may be ascribed to cardiovascular events, i.e., mostly myocardial infarction and cerebrovascular accidents.

Three conclusions may be hazarded at this point, the first one, rather straightforward; the second, a bit more controversial; and the third, indifferent, if anything:

- It would appear that glimepiride is no more or no less lethal than glyburide. In point of fact, a special study concerning myocardial infarctions and cardiovascular deaths pointed out that a "ad hoc analysis of such events provided some evidence that the risk of cardiovascular mortality and total mortality in glimepiride subjects was equivalent to that of other sulfonylureas."
- If we agree with the accepted dogma that correction of glycemia is unable to prevent the macrovascular complications and accidents of diabetes, then it follows that all of the deaths in the sulfonylurea treated group

may be ascribed to the toxicity of sulfonylureas -- since, no deaths were observed in the placebo treated patients.

- This doesn't mean that sulfonylureas are not improving the clinical lot of the patient. The DCCT study has shown improvement in the diabetic complications during an aggressive euglycemic efforts over long periods of time.

The conclusion to be derived from the above comments is obvious: Even though we have some idea that glycemic correction has a positive clinical benefit, the risk linked to the use of sulfonylureas is again illustrated by the observed differences in the frequency of death between placebo and sulfonylurea.

In sum, we don't know for sure, even today, that lives are saved when patients are treated with sulfonylureas, irrespective of any other benefit that they may impart to the treated subjects. In fact, some indications (even in this submission) suggest that lives may be lost, at least during certain intervals of treatment time.

With respect to non-lethal adverse events, one comment is obvious: The overwhelming impact of drug treatment on the frequency of hypoglycemic reactions (6/294, i.e., 2.0% in placebo treated patients; and 104/746, i.e., 13.9% in glimepiride treated patients -- see Table VIIf). One assumes that the 2 patients dying from "Metabolic and nutritional disorders" (2 treated with glimepiride, and 2 others with glyburide -- see Table VIIa) died most probably during a hypoglycemic episode. Other non-lethal adverse events are expected to be similar to those observed during the use of the so-called "second generation" of sulfonylureas, though future experience will confirm or deny this hypothesis. The most frequently occurring adverse events comprise the following: Upper respiratory infections (placebo, 9.5%; drug, 15.7%), and hyperglycemia (16.0% vs. 3.8%). Of course, the latter statistic highlights a benefit of the drug. The Sponsor admits: "Both hypoglycemia and upper respiratory infection occurred significantly more often in the glimepiride group than in the placebo group." Obviously, the labelling will reflect this conclusion prominently.

Another question of potential toxicity ought to be addressed now. Two dogs developed cataract when dosed

chronically with glimepiride. The dog is prone to such a toxic side-effect. Nevertheless, this fact cannot just be simply brushed aside. Lovostatin also produces cataracts in dogs and I discussed this issue with Dr. Troendle who was engaged in efforts to initiate a trial during which the propensity of lovostatin to opacify human lenses would be studied. I was told that the methodology used by the experts in the field had not been validated properly and the FDA ophthalmological consultant (Dr. W. Chambers) had dismissed the acceptability of such tenuous data set. I am specifically referring to the studies conducted by Dr. Chylack of Harvard in which a system called LOCS (Lens Opacity Classification System) was developed and found to be inadequately correlated with the natural history of the disease. Under the circumstances, therefore, it is useless to request any clinical study to evaluate the potential toxicity of the drug in humans with respect to cataract formation. On the other hand this danger cannot simply be ignored in diabetics, suffering from many complications affecting their vision. Therefore, this reviewer will recommend the inclusion in the labeling of a succinct presentation of the dog-cataract data, as provided in this NDA. Such a clear and visible statement of facts should motivate prescribing physicians to be attentive to the advent of cataracts or other visual problems in their patients. One hopes that it would encourage them to send to the Company adverse reaction reports. Such reports would be then relayed to the Agency, whose epidemiologists might then be able to assess or at least estimate such a risk, if it exists in humans. In any event, the Sponsor reports: "Eye changes seen in glimepiride subjects were similar to those seen in glyburide-treated subjects. No findings suggestive of an adverse effect related to cataract formation were seen in glimepiride subjects."

The Sponsor also concludes: "Review of the adverse events associated with study discontinuation does not reveal any pattern suggesting an important hazard... of glimepriide in the population studied." This reviewers agrees, subject to the caveats expressed above about the yet untested risk-versus-benefit ratio of the sulfonylureas.

With respect to laboratory findings, the various studies showed the following drug-linked abnormalities:

increases in SGPT, SGOT, and decreases in platelets. The labelling ought to reflect these findings.

With respect to drug-interactions, none of the some 13 drug-categories tested (alcohol, ACE inhibitors, beta-blockers, Ca-channel blockers, estrogens, fibrates, H2-receptor blockers, propionic acid derivatives, salicylic-acid derivatives, sulfonamides, sympathomimetics, thyroid hormones, and warfarin) during appropriate pharmacokinetic studies showed any significant drug-drug interactions with glimepiride. Some interactions, probably not clinically significant, were detected between glimepiride and ranitidine, cimetidine, aspirin and propranolol. The labelling should include, however, that there are some interactions possible between glimepiride and H2-receptor antagonists, salicylic acid derivatives and beta-blockers. Indeed, there is a risk associated with the use of beta-blockers in NIDDM patients, who need to be warned that, in their case, beta-blockers should be used with caution.

No abuse potential or withdrawal phenomena are expected. No pregnancies occurred during clinical trials with glimepiride and, therefore, no human reproduction data are available.

10.1.3 Safety comments pertaining to Indication I

Without discussion, this treatment will be recommended for approval, but under certain conditions to be presented and discussed later in this review. Thus, by taking the safety implications into account, and labelling the drug accordingly, we think we have an acceptable benefit-vs-risk ration for this indication.

10.1.4 Safety comments pertaining to Indication II

The Sponsor states correctly that the combination use of drug+insulin results in a diminution of the frequency of hyperglycemic episodes. However, this is more than compensated by a visible increase of the hypoglycemic episodes. Indeed, the frequency of hypoglycemic episodes was significantly increased in the glimepiride+insulin group, as compared to the placebo+insulin group; this, even though the baseline and endpoint HbA1c values were comparable in each group. Also, the weight of patients in the combined therapy

group tended to move upward -- clearly, an undesirable effect.

11 LABELING REVIEW

11.1 Drug description

Appears satisfactory. Our Chemist will review in detail, this, and other Chemistry and Manufacturing, section.

11.2 Clinical pharmacology

The principal mechanism of action is clearly detailed. All the animal studies cited in this section by the Sponsor, and the wording to suggest either extrapancreatic effects for the drug, or a putative superiority of this sulfonylurea over others, ought to be deleted. Human studies do not suggest any such superiority. Therefore, it doesn't seem permissible to adumbrate vaguely persuasive animal studies to vastly overstate the case. Besides, all these useless citations and discussions render the labelling that much heavier and less readable.

The sentence concerning the 0.5-0.6 mg dose should be modified to add the underlined word: "A mild glucose-lowering effect..."

The following sentence should be modified to ELIMINATE the underlined part: "Higher doses (up to 32 mg)... did not present any serious safety issues but did not appear to offer additional benefit."

The sentence beginning with "The results of 14 week, ..." should be modified to also provide the average net reduction in HbA1c values. The sentence beginning "Combination therapy with Amaryl and insulin..." ought to DELETED in case, as recommended, Indication II is not approved. If it is, however, a sentence should be added here to state that hypoglycemic episodes also were increased.

The sentence beginning "In long-term, randomized...", the following words should be DELETED: "without producing any clinically meaningful increases in fasting insulin/C-peptide levels."

In the section comparing glimepiride and glyburide during acute exercise, the following modification should be implemented: In the last sentence of that paragraph, REPLACE "The results imply..." by "The results suggests..."

The sentence discussing lipid effects, should read as follows: "During Amaryl therapy a mild trend in improving total and LDL cholesterol levels was sometimes seen, in comparison to placebo-treated patients."

The "Special populations" section should be greatly reduced, in order to have a more easily readable labeling. To do this, only critical data ought to be cited, together with an appropriate but brief conclusion.

11.3 Indications and usage

All words and sentences pertaining to the combined use of glimepiride and insulin ought to be eliminated.

The sentence beginning "In initiating treatment..." should include the underlined addition: "diet and exercise should be emphasized...Proper dietary management and exercise..." The last sentence in that paragraph ought to read: "In addition to stressing regular physical activity, cardiovascular risk factors..."

The procedure to follow in case of glimepiride monotherapy failure should recommend adjunction of metformin to glimepiride as an acceptable option.

11.4 Contraindications

Acceptable.

11.5 Warnings

Acceptable, inasmuch it reproduces the boiler-plate language recommended by the FDA for all oral hypoglycemics.

11.6 Precautions

11.6.1 General

Adequate.

11.6.2 Information for patients

Adequate.

11.6.3 Laboratory tests

Modify as follows: "Glycosylated hemoglobin should also be monitored, usually every three to six months, to more precisely assess long-term glycemic control."

11.6.4 Drug interactions

Adequate. Yet expressions such as "well tolerated" ought to be replaced by the more conservative "did not result in any visible ill-effect..."

11.6.5 Carcinogenesis, mutagenesis, fertility

Adequate. In any event, ought to be reviewed by our Pharmacologists.

11.6.6 Pregnancy

Adequate. Should also be reviewed by our Pharmacologists. The section entitled "Nonteratogenic Effects," ought to be consolidated under this "Pregnancy" heading, without additional title needed.

11.6.7 Labor and delivery

Laconic but correct.

11.6.8 Nursing mothers

Adequate. Our Pharmacologist ought to review and express an opinion.

11.6.9 Pediatric use

Laconic but correct.

11.7 Adverse reactions

Delete the last sentence : "These results..." Add that the combined use of glimepiride and insulin may result in increased frequency of hypoglycemic episodes and weight gain. Otherwise, adequate.

11.8 Drug abuse and dependence

Laconic but adequate.

11.9 Overdosage

Adequate.

11.10 Dosage and administration

In the first paragraph, add the underlined items: "The patient's fasting blood glucose and HbA1C value must be measured periodically..."

Correct by adding the underlined item and [deleting the bracketed item] : "The usual maintenance dose is 1 to 4 [8] mg once daily." Add the underlined part to the following sentence: " After reaching a dose of 2 mg, dosage increases... based upon the patient's blood glucose response. Long-term efficacy should be monitored with HbA1C measurements performed, on average, every 3 to 6 months."

The section on glimepiride plus insulin ought to be deleted, if the Reviewer's recommendation to eliminate Indication II is implemented. Also, if the Reveiwer's recommendation to add an indication of glimepiride plus metformin is retained, a new section ought to be added.

11.11 How supplied

To be reviewed by our Chemists.

12 CONCLUSIONS & REVIEWER'S RECOMMENDATIONS

Basically, this drug is recommended for approval, provided that certain conditions are met:

(1) As far as Indication I goes, the Reviewer recommends approval, with only some minor (and already suggested; see above) modifications to the labeling, as now briefly summarized. Basically, figs. 2 and 3 show that 4, 8 and 16 mg daily have equivalent efficacy results in the studied population and they belong to the plateau region of the dose-response curve. They also show that the 1 to 4 mg interval was not studied -- an oversight by the Sponsor, which recommends 1 mg as the recommended starting dose. This Reviewer feels, without being certain given the data base, that 2 mg ought nevertheless be the recommended starting dose. On the other hand, since upward titration is usually performed very quickly, and since some patients (e.g., renally impaired ones) may require a lower initial dosage, he will go along with the Sponsor's recommendation. Fig. 4 shows that the average efficacy of the drug, as measured by the net comparison between HbA_{1c} values (between placebo and drug-treated groups) is one considered by the experts to be of clinical significance in the treatment of diabetes -- an effect which is assumed to possess a favorable benefit-to-risk ratio. Fig. 5 shows that, by 12 weeks, HbA_{1c} values have essentially stabilized -- justifying this Reviewer's recommendation that HbA_{1c} measurements be regularly assessed every 3 to 6 months. Fig. 6, showing the high variability and (therefore) unreliability of single FPG measurements, further supports the Reviewer's recommendation to also measure HbA_{1c} values, particularly when one is trying to assess the long-term efficacy of the hypoglycemic treatment in a given individual patient.

(2) As far as Indication II is concerned, the Reviewer emphatically recommends non-approval. This recommendation has been explained in detail in the body of the review. In summary, the reasons for rejection are as follows:

(a) The simultaneous use of a sulfonylurea and insulin is not a rational one from an efficacy viewpoint, since the end-result of therapy is equivalent: A sulfonylurea will increase endogenous insulin, while administered insulin will have an equivalent effect.

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3 OF 6

(b) The main reason for avoiding insulin, from the patient's perspective, is to prevent discomforting injections. When insulin is added to sulfonylurea, the discomfort is still there, even though in reduced form (lower number of injections);

(c) In case of sulfonylurea secondary failure, adding insulin will certainly not improve the hormone-receptor sensitivity to the sulfonylurea; quite the contrary.

(d) Combined sulfonylurea and insulin therapy will probably result in more loss of insulin-receptor sensitivity and hyperinsulinemia. This would cause, in all probability, continued weight gain and further loss of glycemic control.

(e) The clinical trial presented and discussed in the NDA and this review shows a trend toward increased hypoglycemic episodes in the glimepiride plus insulin group, compared to the placebo plus insulin group. This is present even though the two groups were titrated to show comparable glycemic control. The studies also show a trend toward gaining weight in the glimepiride+insulin group.

Thus, it is clear why Indication II ought not to be approved: It doesn't offer any advantage whilst creating a number of problems and hazards.

(3) This Reviewer is recommending that a "Novel Indication" be conceded immediately to the Sponsor: The option of adding metformin to glimepiride in case of secondary failure and/or inadequate glycemic control during monotherapy. This is a highly desirable option and one which has been supported by numerous recent publication (as summarized in the body of this review). Another company has requested that such an indication be added to the labeling of their currently marketed sulfonylurea, and the Division is inclined to concede the point and ask that all sulfonylurea manufacturers be granted the same privilege.

*Not new
Along with
sulfonylurea
JMT
7/3/95*

(4) Approval of Indication I and "Novel Indication" (see above) is predicated upon a commitment by the Company to perform a Phase IV study, similar to the one that has been proposed by Dr. Bruce Stadel of this Division for Metformin, and that has already been approved in that case by our Advisory Committee. Such a study would probably be a simple and straightforward multicenter, prospective, randomized, comparative, parallel design, open-label, long

term (one year) surveillance study of serious adverse events. Eligible patients ought to be randomized to either glimepiride (glimepiride or glimepiride+metformin) or usual care (insulin and/or metformin). It should be mentioned that the feasibility of this kind of study has been proven [see Lesko SM et al., "An assessment of the safety of pediatric Ibuprofen," JAMA (1995) 273: 929-33].

Ph 4 protocol
randomizing pts to
glyburide NOT
insulin and/or
metformin

AD Fleming for JG
John L. Gueriguian
Medical Officer
5/30/95

Review
10/20/95
submission
to IND and
NDA
Did not
require
Phase 4 study

- cc.
- The File
- Dr. Sobel
- Dr. Troendle
- Dr. Fleming
- Dr. Stadel
- Dr. Gueriguian

See Group
Headline Memo
dated 10/27/95

Excellent review,
Will write a
note largely supporting
Dr Gueriguian's findings
and conclusions

AD Fleming
6/19/95

FIGURE 1

1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-βcarboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea

The structural formula is:

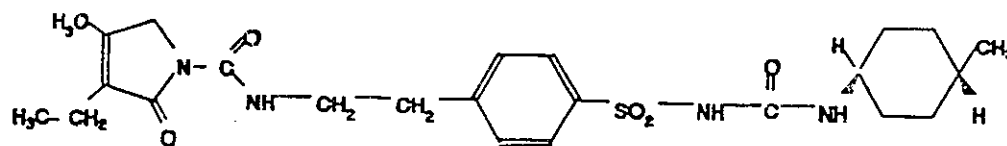
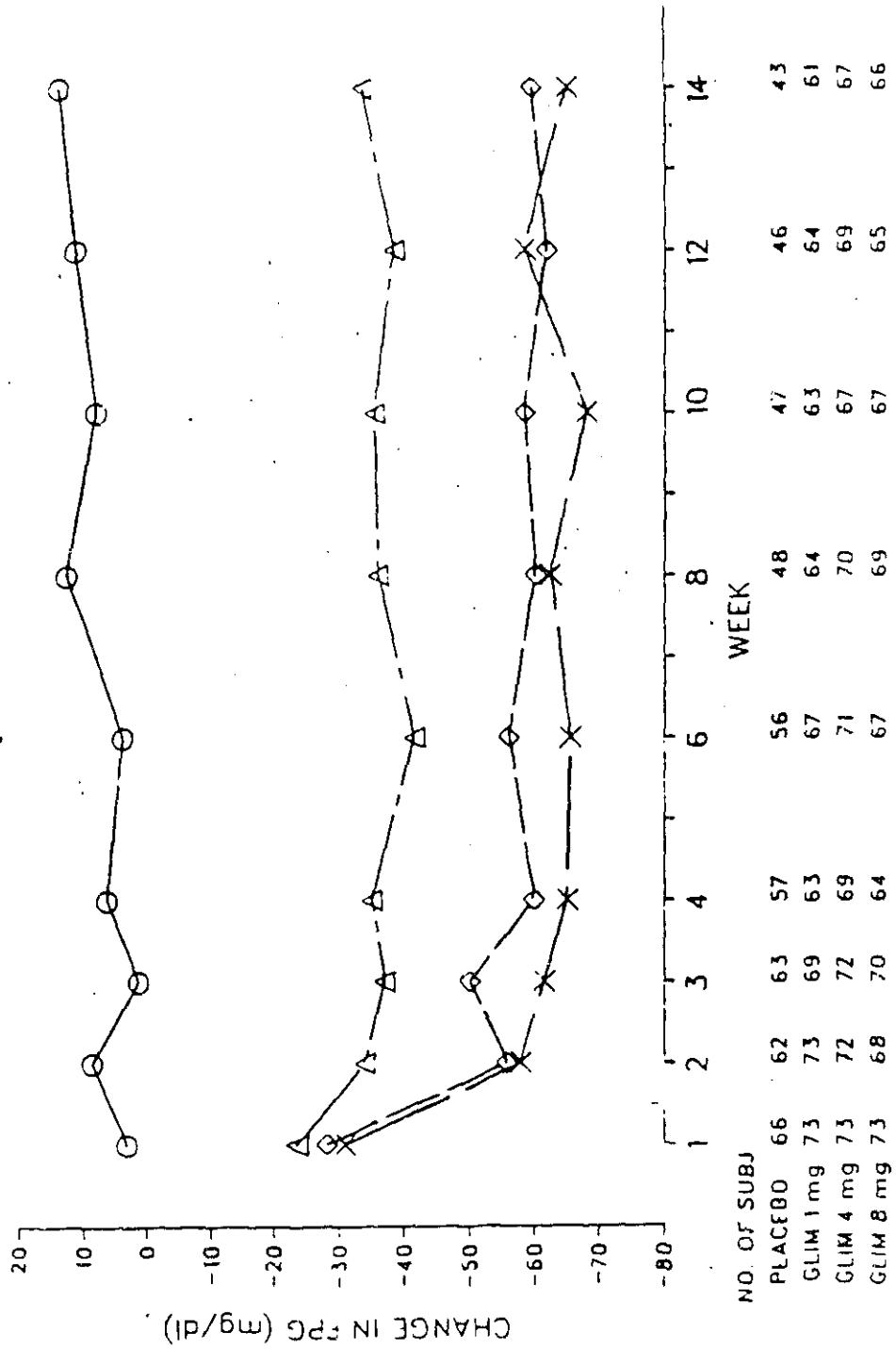


FIGURE 2

MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE

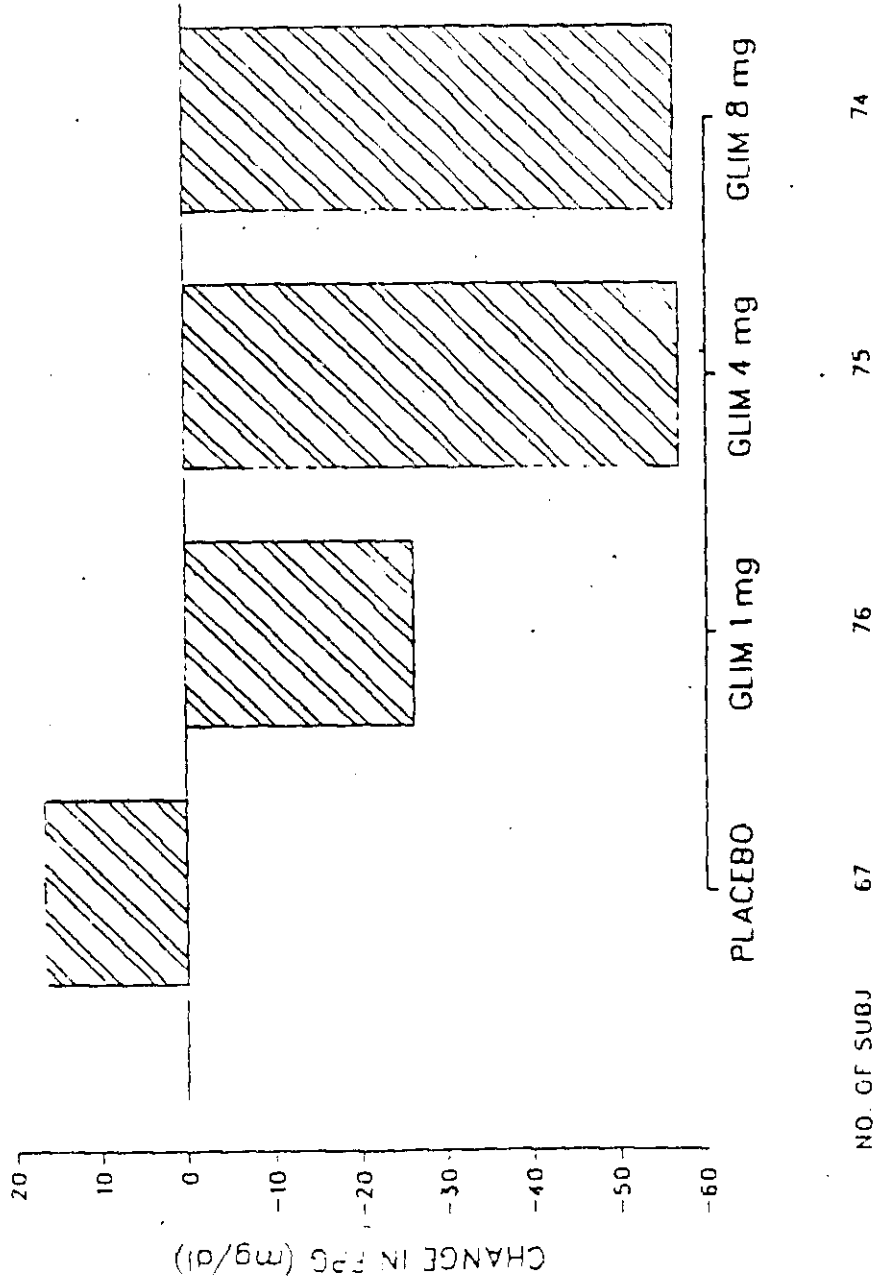


Legend
 ○ PLACEBO
 △ GLIM 1 mg
 ◇ GLIM 4 mg
 × GLIM 8 mg

NO. OF SUBJ	1	2	3	4	5	6	7	8	9	10	11	12	13	14
PLACEBO	66	62	63	57	56	48	47	46	43					
GLIM 1 mg	73	73	69	63	67	64	63	64	61					
GLIM 4 mg	73	72	72	69	71	70	67	69	67					
GLIM 8 mg	73	68	70	64	67	69	67	65	66					

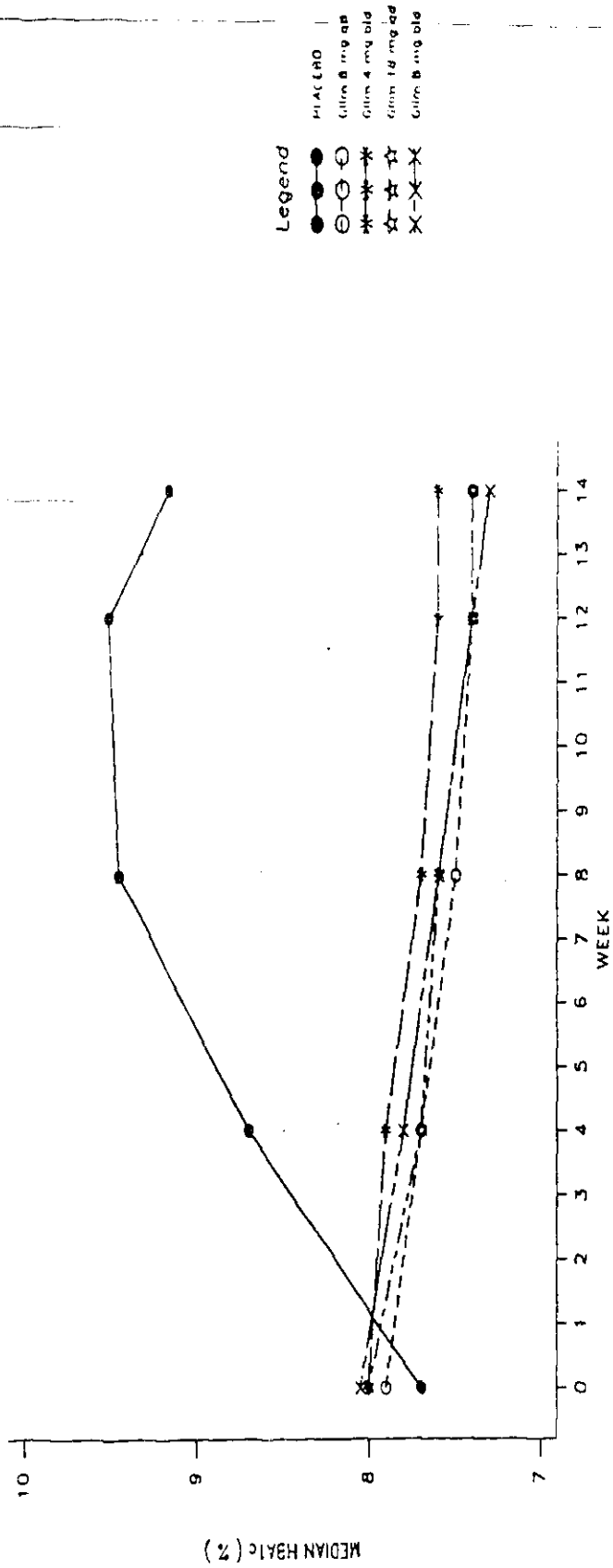
FIGURE 3

MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE AT ENDPOINT



IND 490 8/USA/205/DM - Glimepiride

FIGURE 4
 MEDIAN HbA1c (%) LEVELS BY VISIT



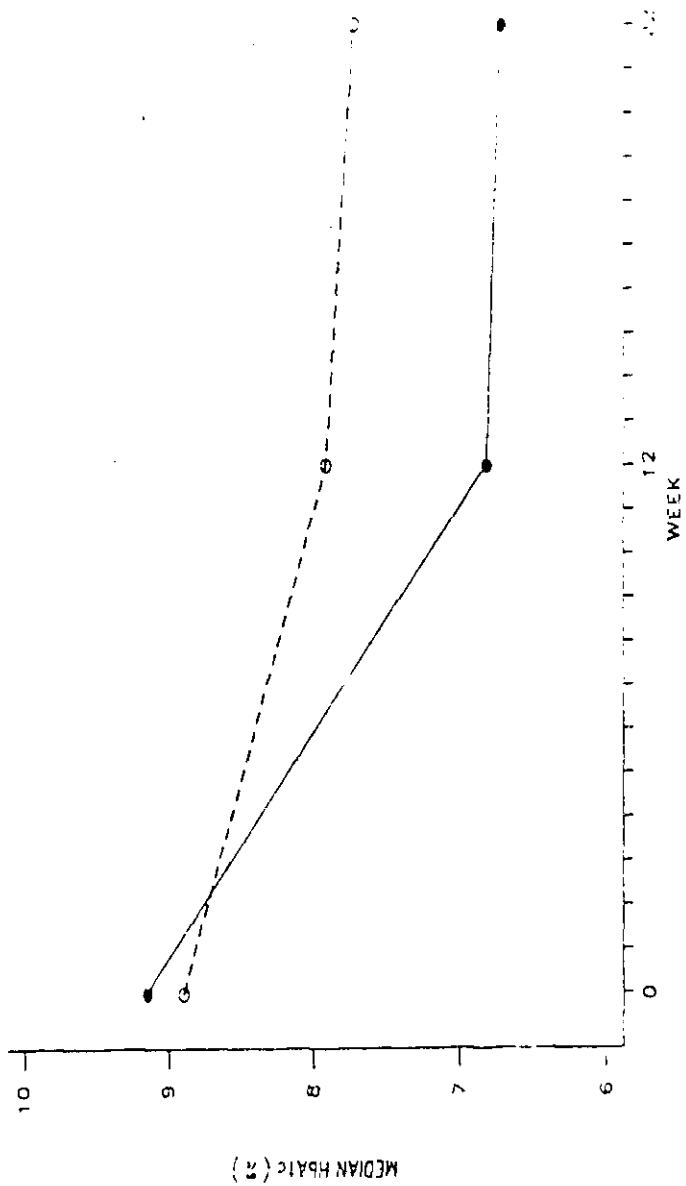
NO. OF SUBJ	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
PLACEBO	66	60	48	31	31	31	31	31	31	31	31	31	31	31	31	34
Glime 8 mg qd	76	71	73	70	71	71	71	71	71	71	71	71	71	71	71	71
Glime 4 mg bid	74	69	63	63	63	63	63	63	63	63	63	63	63	63	63	65
Glime 16 mg qd	75	73	71	66	66	66	66	66	66	66	66	66	66	66	66	66
Glime 8 mg bid	80	75	79	65	65	65	65	65	65	65	65	65	65	65	65	71

At all postbaseline visits, glimepiride lowered HbA1c more than placebo (p < 0.001).

101 490 B/USA/202/DM - Glimepiride

FIGURE 5

MEDIAN HbA1c (%) LEVELS BY VISIT



Legend
● GLIMEPIRIDE
○ PLACEBO

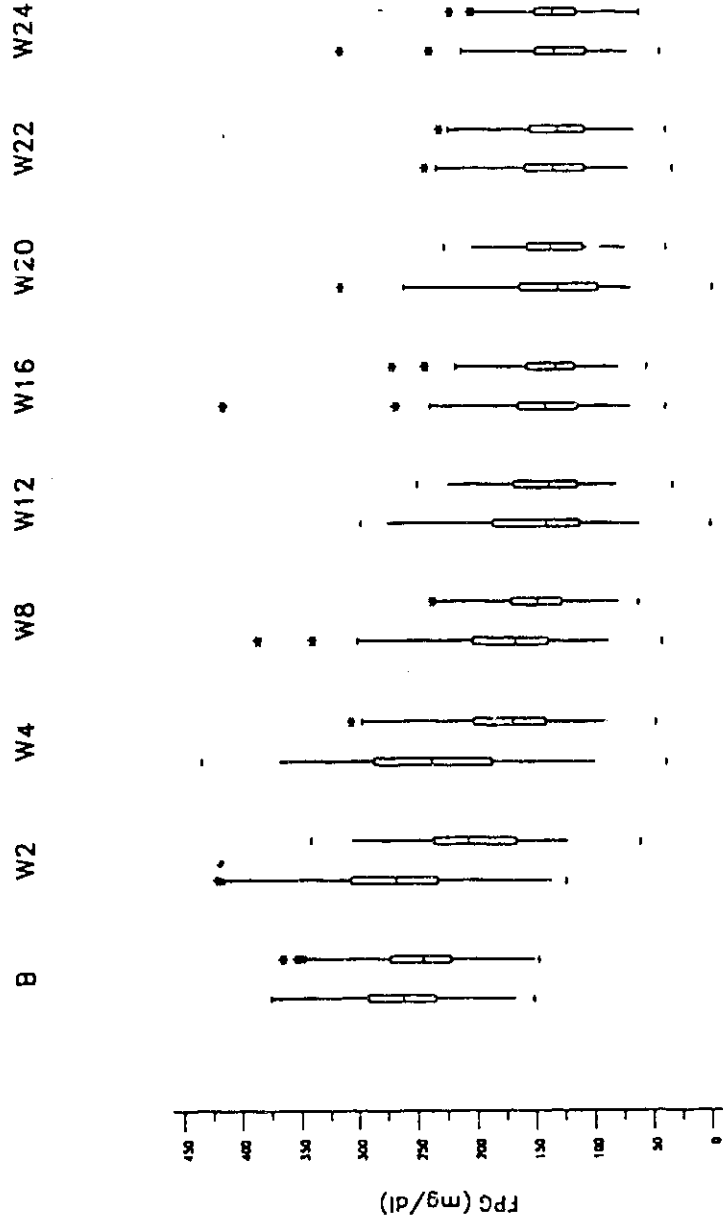
NO. OF SUBJ
GLIMEPIRIDE 106
PLACEBO 94

93
81

At both post baseline visits, glimepiride lowered HbA1c significantly more than placebo ($p < 0.001$)

FIGURE 6

BOX PLOT OF THE DISTRIBUTION OF FASTING PLASMA GLUCOSE (FPG)



N	P G	P G	P G	P G	P G	P G	P G	P G	P G	P G	P G
70 71	67 69	65 55	68 70	65 67	60 68	49 61	55 64	61 68			

WEEK

G: GLIM + INS; P: PBO + INS

STAT REVIEW

ORIGINAL

Statistical Review and Evaluation

Date:

NDA #: 20-496/ Drug Class 1S

Applicant: Hoechst-Roussel Pharmaceuticals, Inc.

Name of the Drug: Amaryl® (glimepiride) Tablets

Indication I: Treatment of Noninsulin-Dependent Diabetes Mellitus Unresponsive to Diet

Indication II: Combination Therapy With Insulin in Treatment of NIDDM Unresponsive to Diet and to Oral Sulfonylureas

Documents Reviewed: 1.1, 1.364 to 1.393, 1.528 to 1.541 dated August 31, 1994, Amendment dated November 10, 1994, Amendment Dated April 10, 1995, 4/21/95

Clinical Reviewer: John Gueriguian, M.D. (HFD-510)

Submission of 4/21 is not referred to in this review because analyses are consistent with previous analyses.
JEG
7-5-95

The issues in this review have been discussed with the reviewing Medical Officer, John Gueriguian, M.D. (HFD-510).

Various Sections of this review are:

I. Background/Introduction

II. Indication I

II.a) Clinical Studies With Comments and Conclusions on Each Separately

1. Study 8/USA/201/DM

2. Study 8/USA/205/DM

3. Study 8/USA/202/DM

II.b) Reviewer's Comments and Conclusions on Indication I

III. Indication II

4. Study 8/USA/305/DM (Comments and Conclusions on Indication Ii at the End)

IV. Reviewer's Overall Conclusions

Background/Introduction

Indication I

Data from 20 US and European clinical trials are submitted in support of the efficacy and/or safety for Indication I. Data from 2 European long-term extensions of 1-year base studies were included in both the efficacy and safety results (as separate studies for efficacy). Data from an additional 5 Japanese

trials are presented as supplementary information. A brief summary of the designs and dosage used in these trials is given in the attached Table 0.1.1

Indication II

The sponsor states that the FDA agreed at a meeting on June 9, 1992, that, were it positive, the study under protocol 8/USA/305 alone would be sufficient to support labeling for this indication. This double-blind, randomized, parallel-group study consisted of an 8-week open-label trial of glimepiride alone, followed by 24 weeks of treatment with insulin plus either glimepiride or placebo. Subjects who failed to achieve or maintain glucose control during the open-label phase were randomized to combination therapy.

Summary Information- Secondary Failure Study

<u>Protocol</u>	<u>Design</u>	<u>Doses</u>	<u>Treatment Duration</u>	<u>Glimepiride Monotherapy</u>	<u>Placebo + Insulin</u>	<u>Glimepiride + Insulin</u>
8/USA/305 OL	Dose Titration	Glim: 8, 12, 16 mg qd; 8mg bid	8 weeks	208	-	-
8/USA/305	Fixed Dose	PBC + Insulin Glim: 8mg bid + Insulin	24 weeks		73	72

Only the primary studies will be reviewed individually.

II. Indication I

II.a) Clinical Studies (With Comments and Conclusions on Each Separately) :

1. Study 8/USA/201/DM (Placebo-Controlled U.S. Study)

A. Objective

The study objectives were:

1. To determine if Amaryl is better than placebo in Type II diabetic subjects.
2. To determine if there is a dose response.
3. To compare the safety and tolerance of 3 doses of Amaryl (1, 4, and 8 mg) with placebo.

B. Design and Conduct of the Trial

This was a double-blind, 14-weeks double blind duration, 32-investigators, randomized (stratified), placebo controlled, parallel-groups (0, 1, 4, and 8 mg/day), dose response study in patients with Type II or noninsulin-dependent diabetes mellitus (NIDDM) who previously received sulfonylurea agents.

Patients eligible for inclusion in this study were men and women with NIDDM, age 30 through 75, and weighing between 90% and 150% of ideal body weight as specified by Metropolitan Life Insurance tables. Subjects discontinued their oral sulfonylurea medication at the beginning of the washout phase. On Day -21, subjects had to have a fasting plasma glucose (FPG) level no greater than 180 mg/dl to enter the 3-week single-blind placebo washout period. On Day -7 and Day -3, a subject's value had to increase by at least 25 mg/dl from the Day -21 value. On Day -3, the FPG value had to differ no more than 50 mg/dl from the Day -7 value, and had to be

180-300 mg/dl. Subjects with FPG values below 150 mg/dl at Baseline were to be dropped from the study after the FPG results were known and before the subjects had any post baseline FPG data. Before randomization, qualifying subjects were stratified to low and high groups based on Day -3 FPG values (low=180 to 240 mg/dl, high=241 to 300 mg/dl).

The starting dose of medication for all subjects was glimepiride 1 mg/day or placebo. For subjects randomized to 4 mg and 8 mg, the dose was to be increased at weekly intervals, first to 4 mg and then to 8 mg, as long as the dose was well-tolerated, until the randomized dose was reached. Once the randomized dose level was reached, subjects were to be maintained at that dose until week 14.

The schedule of observations is attached as Table 1.1.1¹. Efficacy measures were taken at baseline and throughout the study. Primary efficacy variables were fasting plasma glucose, 2-hour postprandial plasma glucose, and hemoglobin A1c (HbA1c). Two fasting samples were taken at each visit, one about 30 minutes before and one immediately before drug was administered; the mean of these values was used in the analyses of FPG. Secondary efficacy variables were fasting and 2-hour postprandial C-peptide and insulin levels, and FPG and HbA1c variability.

The number of patients in the centers varied from 1 to 21. The sponsor states that the blind was not broken by any of the investigators or by any personnel of the sponsor during the conduct of this study.

C. Study Completion Status

One subject was randomized to placebo but never received study drug, and is excluded from all tables and listings. A total of 304 patients were treated. The percentages of patients continuing at different weeks are provided in the attached Figure 1.1.2² by treatment. The dropouts at different time-intervals can be seen from the attached Table 1.1.3 of Duration of Treatment. Percentages of dropouts due to different reasons are in the attached Table 1.1.4.

Most of the dropouts were from the placebo and the 1 mg groups. In each of the 4 and 8 mg groups, 92.1% patients completed the study.

D. Data Sets Analyzed

The sponsor stated, "No protocol violation warranted the exclusion of a subject's data from any analysis. Since only 14 of the 294 subjects evaluated for efficacy had major violations, a separate per protocol analysis was not done." The intent-to-treat patient sample was identified to consist of 294 patients with 69, 76, 75, and 74 in the placebo and, 1, 4, and 8 mg glimepiride groups, respectively. Exclusion was as usual (efficacy analyses were based on all patients randomized who received at least one dose of assigned drug and provided efficacy data at baseline and at least one follow-up evaluation). No protocol-correct set was considered.

¹ In the Table number i j k, i is the code for the study number and equals 1,2,3,and 4, respectively, for studies 8/USA/201/DM, 8/USA/205/DM, 8/USA/202/DM, and 8/USA/305/DM, j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

² No separate numbering system has been followed for Figures. In the same numbering system, some are called Tables and some Figures as appropriate.

In addition to the end-point analysis, visit-wise analyses of observed data for the intent-to-treat patients were done.

A set of day ranges or "windows" were defined for analysis purposes, which were different for different efficacy variables (NDA Vol. 1,365, p 14-15). In the event that a patient had more than one measurement in any one window, the last measurement within that day range was analyzed.

E. Sponsor's Analysis Methods

Efficacy Data

The sponsor stated, "For evaluating efficacy and safety variables, nonparametric instead of parametric analyses were used because the change from baseline data at Endpoint were not normally distributed. Since these data were skewed, medians were used to describe the data."

Considering only the primary efficacy variables, the Williams' modification of Shirley's test was used to determine if glimepiride is better than placebo, if a dose response relationship was present, and if so, to determine the minimum effective dose of glimepiride.

For all efficacy variables, the extended Mantel-Haenszel test adjusting for baseline Fasting Plasma Glucose (FPG) stratum effects was used to determine if glimepiride is different from placebo. The same procedure was used to determine if there are differences between the glimepiride groups. The p-values were not adjusted for multiple comparisons.

Since 18 out of 32 investigators enrolled fewer than 10 subjects, centers were combined into regions based on geographic area. To justify that the data from different regions can be pooled in this multicenter study, the region and the treatment-by-region interaction effects on the primary efficacy variables were examined using the General Linear Models (GLM) analysis with treatment, region, baseline FPG stratum, and 2-way interactions included in the model.

Demographic and Background Characteristics

Demographic and background variables were summarized with descriptive statistics. Homogeneity in these variables was assessed using GLM analyses for age, height at baseline, and HbA1c and FPG at admission, and the Cochran-Mantel-Haenszel (CMH) test for sex, race, duration of diabetes, and FPG stratum. Baseline FPG stratum was included in both tests.

F. Comparability of Treatment Groups

The sponsor states that no statistically significant differences were detected among the treatment groups on any demographic or background characteristics. This statement refers to comparison of all treatment groups together. Significant p-values for pairwise comparisons are discussed below.

Demographic and Background Characteristics

Some demographic information follows:

	Placebo	Glimepiride		
		1mg	4mg	8mg
Mean Age (yr)	60.4	58.9	57.8	59.6
No. of Males	48(65%)	56(72%)	41(54%)	43(57%)
No. of Females	26(35%)	22(28%)	35(46%)	33(43%)
Mean Weight	186.9	184.5	189.4	187.8
White (Race)	60(81%)	65(83%)	60(79%)	64(84%)
Mean Dur. of Diab.(yr)	8.5	8.5	6.7	7.9

Proportion of males in the 1 mg glimepiride group differed significantly (p-value=0.16) from that in the 4 mg group and almost significantly (p-value=.053) from the 8 mg group. Subjects in the glimepiride 8 mg group had a significantly longer duration of diabetes compared with the 4 mg group. The sponsor states that no other characteristics were significantly different between any 2 of the treatment groups.

The sponsor provided analysis of covariance with "gender" as a covariate, which showed overall treatment effect. The sponsor did not consider pairwise comparisons in this analysis of covariance. However, since there were no imbalances compared with the placebo group, all the above imbalances are of no concern with regards to the efficacy of glimepiride (vs placebo).

Concomitant medication

The sponsor states that the use of concomitant medications that are known to affect blood glucose levels and that were started 30 days before study drug or during randomization were examined. The number of subjects who were treated with NSAIDs and salicylates (Placebo-7, 1mg-10, 4mg-12, 8mg-11), diuretics, thyroid products, and estrogens was similar in each treatment group.

Dose and Duration of Treatment

Percentages of subjects receiving study drug for at least 84 days are 66.2%, 82.1%, 92.1%, and 92.1%, respectively, for placebo, 1 mg, 4 mg, and 8 mg of glimepiride.

G. Efficacy Results (Sponsor's Analyses)

As mentioned under "Sponsor's analysis Methods," nonparametric instead of parametric analyses were used because the change from baseline data at Endpoint were not normally distributed. It was mentioned in the protocol, "If the assumptions of normality and homogeneous error variances are not satisfied, alternative analyses may be applied to assess efficacy." However, no specific nonparametric method was mentioned in the protocol.

Determination of dose response was indeed mentioned as an objective in the protocol; however, the specific test for dose response was not mentioned. The Williams' modification of Shirley's nonparametric procedure [Williams, D.A.(1986). "A Note on Shirley's Nonparametric Test for Comparing Several Dose Levels With a Zero-Dose Control," *Biometrics* 42, 187-190] has been used to determine the lowest (among the 3 doses studied) effective dose. Except that the method was not pre-specified, this reviewer does not see anything wrong with the

Williams' modification of Shirley's nonparametric method.³

This reviewer will discuss the sponsor's comparisons with placebo, making multiple comparison adjustments as relevant (the sponsor did not make any such adjustments).

Hemoglobin A1c

According to the protocol, the change from baseline was to be considered. The detailed analysis results are attached as Table 1.2.1. The Figures for comparing the doses are attached as Figures⁴ 1.2.2 (Median, Visit-Wise) and 1.2.3 (Mean, LOCF).

We see that at endpoint and at all (planned) timepoints, all the three doses of glimepiride are statistically highly significantly superior to placebo, even with multiple comparison adjustments. Four and 8 mg doses are statistically significantly superior to 1 mg dose. However, 4 and 8 mg doses are not statistically significantly different from each other.

At endpoint, the median superiority of 1, 4, and 8 mg glimepiride over placebo is 1.2, 1.8, and 1.9⁵ respectively.

Fasting Plasma Glucose (FPG)

Same comments as with respect to HbA1c apply. The detailed analysis results are attached as Table 1.3.1.

At endpoint, the median superiority of 1, 4, and 8 mg glimepiride over placebo is 43.0, 70.5, and 74 respectively.

The Figures for comparing the treatment groups, with respect to change from baseline, are attached as Figures 1.3.2 (Visit-wise) and 1.3.3 (Endpoint). The differences of the glimepiride groups with the placebo group are highly pronounced.

2-hour Postprandial Plasma Glucose (PPG)

In the subset of subjects who had 2-hour postprandial glucose data (collected at Weeks 0, 8, and 14), both "2-hour postprandial glucose" and "Fasting Plasma Glucose" were examined. However, we shall not discuss about

³ This is a sequential test procedure, in which the highest dose group is compared to placebo (observations in all dose groups are included in ranking). The lower dose groups are compared to placebo in sequence if and only if the previous comparison (immediately higher dose vs placebo) was significant. This procedure gives the experimentwise control over the Type I error rate. To carry out this test, one has to re-rank observations at each stage of the sequential test procedure, after excluding all observations at those higher dose levels at which significant evidence of an effect has already been established.

⁴ No separate numbering system has been followed for Figures. In the same numbering system, some are called Tables and some Figures as appropriate.

⁵ These estimates are based on the "Hodges-Lehmann estimate". This estimate has superior statistical properties to the simple difference in treatment group medians. Note that this estimate may not necessarily be the same as the simple difference in treatment group medians. For example, in Table 1.2.1 for Endpoint (last page), the simple difference between placebo and 1mg group medians is -1.50; whereas, the "Difference From" placebo is given to be -1.20

the FPG here. FPG has been discussed above and this subset does not show anything of interest.

Same comments as with respect to HbA1c and FPG apply, except that, at Week 14 and Endpoint, superiority of 4 and 8 mg doses over the 1 mg dose is not clear-cut (either not highly significant or not significant in view of the multiple comparison adjustments, and one p-value is .055). The detailed analysis results are attached as Table 1.4.1.

At endpoint, the median superiority with respect to PPG of 1, 4, and 8 mg glimepiride over placebo is 63.0, 91.5, and 93 respectively.

Dose Response

By Williams' modification of Shirley's nonparametric test, with respect to all the above three primary efficacy variables, 1 mg is the minimum effective dose (among the three doses considered).

As we saw in previous analyses, all three doses of glimepiride are statistically efficacious. Glimepiride 4 and 8 mg doses are comparable and better than 1 mg dose. The sponsor states, "In general, it has been difficult to demonstrate a dose-response relationship with sulfonylurea."

H. Reviewer's Comments and Conclusions on Study 8/USA/201/DM

This study has shown that all the three (1, 4, and 8 mg) doses studied are statistically efficacious. Glimepiride 4 and 8 mg doses are comparable and better than 1 mg (statistically), with respect to efficacy.

The reviewer performed some statistical analyses (simple pairwise comparisons vs placebo) independently. Provided the data supplied by the sponsor on the diskette are reliable, no clues were found to raise any concern against the efficacy of glimepiride.

2. Study 8/USA/205/DM (Placebo-Controlled U.S. Study)

A. Objective

The study objectives were:

1. To determine if Amaryl is better than placebo in Type II diabetic subjects
2. To compare 2 dose regimens bid vs qd
3. To compare the safety and tolerance of 2 doses of Amaryl (8 and 16 mg) with placebo.

B. Design and Conduct of the Trial

This was a double-blind, 14-weeks double blind duration, 38-investigators, randomized (stratified), placebo controlled, parallel-groups (0, 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid) study in patients with Type II or noninsulin-dependent diabetes mellitus (NIDDM) who previously received sulfonylurea.

Patients eligible for inclusion in this study were men and women with NIDDM, age 30 through 80.

Other details are same as in the previous study.

Those subjects randomized to 16 mg qd (or 8 mg bid), received 8 mg qd (or 4 mg bid, respectively) during the first week. If this lower dose was well-tolerated, then at the beginning of the second week the subjects received the higher dose to which they had been assigned. Once the randomized dose level was reached, subjects were to be maintained at that dose until week 14.

The schedule of observations is attached as Table 2.1.1⁶. Efficacy measures were taken at baseline and throughout the study. Primary efficacy variables were fasting plasma glucose, 2-hour postprandial plasma glucose, and hemoglobin A1c (HbA1c). Secondary efficacy variables were fasting and 2-hour postprandial C-peptide and insulin levels, and FPG and HbA1c variability.

The number of patients in the centers varied from 1 to 27. The blind was broken for one patient in this study because of serious adverse event.

C. Study Completion Status

A total of 417 patients were randomized and 416 patients were treated; one subject randomized to glimepiride 4 mg bid never took study drug.

The percentages of patients continuing at different weeks are provided in the attached Figure 2.1.2 by treatment. The dropouts at different time-intervals can be seen from the attached Table 2.1.3 of Duration of Treatment. Percentages of dropouts due to different reasons are in the attached Table 2.1.4.

Most of the dropouts were from the placebo group (54%, with 40.5% due to Safety/Lack of Efficacy: Hyperglycemia). In each of the 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid groups, respectively, 92%, 83%, 89%, and 93% patients completed the study.

D. Data Sets Analyzed

The sponsor stated, "No protocol violation warranted the exclusion of a subject's data from any analysis. ... Since only 13 out of the 408 (3.2%) subjects evaluated for efficacy had major violations, a separate per protocol analysis was not done." The intent-to-treat patient sample was identified to consist of 408 patients with 76, 87, 80, 82 and 83 in the placebo, 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid glimepiride groups, respectively. Exclusion was as usual (efficacy analyses were based on all patients randomized who received at least one dose of assigned drug and provided efficacy data at baseline and at least one follow-up evaluation). No protocol-correct set was considered.

In addition to the end-point analysis, visit-wise analyses of observed data for the intent-to-treat patients were done.

⁶ In the Table number i.j.k, i is the code for the study number and equals 1,2,3 and 4, respectively, for studies 8/USA/201/DM, 8/USA/205/DM, 8/USA/202/DM, and 8/USA/305/DM, j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

A set of day ranges or "windows" were defined for analysis purposes, which were different for different efficacy variables (NDA Vol. 1.374, p.15). In the event that a patient had more than one measurement in any one window, the last measurement within that day range was analyzed.

E. Sponsor's Analysis Methods

Efficacy Data

The sponsor states, "For evaluating efficacy and safety variables, nonparametric instead of parametric analyses were used because the change from baseline data at Endpoint were not normally distributed for most variables. Both medians and means were used to describe the data."

For primary efficacy variables, the extended Mantel-Haenszel test was used to determine if there was an interaction between dose level and dose regimen.

For all efficacy variables, the extended Mantel-Haenszel test adjusting for baseline Fasting Plasma Glucose (FPG) stratum effects was used to determine if glimepiride is different from placebo. The same procedure was used to determine if there are differences between the glimepiride groups. The p-values were not adjusted for multiple testings (there is no justification for not adjusting for multiple comparisons in this study).

Since 28 out of 38 investigators enrolled fewer than 15 subjects, centers were combined into regions based on geographic area. To justify that the data from different regions can be pooled in this multicenter study, the region and the treatment-by-region interaction effects on the primary efficacy variables were examined using the General Linear Models (GLM) analysis with treatment, region, baseline FPG stratum, and 2-way interactions included in the model.

Demographic and Background Characteristics

Demographic and background variables were summarized with descriptive statistics. Homogeneity in these variables was assessed using GLM analyses for age, height, and weight at baseline, and HbA1c and FPG at admission, and the Cochran-Mantel-Haenszel (CMH) test for sex, race, duration of diabetes, tobacco and alcohol consumption, and FPG stratum. Baseline FPG stratum was included in both tests.

F. Comparability of Treatment Groups

The sponsor states, "There were no significant differences across all treatment groups for the overall homogeneity test. As expected in multiple comparisons, 5% of the differences were significant between treatment groups for the pairwise comparisons. However, these differences did not affect the results of the primary efficacy analyses."

Demographic and Background Characteristics

Some demographic information follows:

	<u>Placebo</u>	<u>Glimepiride</u>			
		<u>8mg qd</u>	<u>4mg bid</u>	<u>16mg qd</u>	<u>8mg bid</u>
Mean Age (yr)	61.1	61.8*	58.8*	59.6	61.7
No. of Males	53(67%)	65(74%)	57(70%)	55(66%)	61(72%)
No. of Females	26(33%)	23(26%)	24(30%)	28(34%)	24(28%)
Mean Weight	190.9	184.2	191.8	187.1	192.9
White (Race)	62(79%)	73(83%)	68(84%)	65(78%)	70(82.4%)
Mean Dur.of Diab.(yr)	7.7	9.5	7.6	6.9*	9.3*

* A significant difference was found between these groups ($p \leq .05$).

None of the glimepiride dose vs placebo imbalances found in baseline disease history or status were statistically significant by multiple comparison adjustments.

Concomitant medication

The sponsor states that the use of concomitant medications that are known to affect blood glucose levels and that were started 30 days before study drug or during randomization were examined. The number of subjects who were treated with NSAIDS/salicylates are : Placebo-14, 8mg qd-12, 4mg bid-19, 16mg qd-15, and 8mg bid-18.

Dose and Duration of Treatment

Percentages of subjects receiving study drug for at least 84 days were 45.6%, 92.0%, 86.4%, 88.0%, and 92.9%, respectively, for placebo, 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid of glimepiride.

G. Efficacy Results (Sponsor's Analyses)

As mentioned under "Sponsor's analysis Methods," nonparametric instead of parametric analyses were used because the change from baseline data at Endpoint were not normally distributed. It was mentioned in the protocol, "If the assumptions of normality and homogeneous error variances are not satisfied, alternative analyses may be applied to assess efficacy." However, no specific nonparametric method was mentioned in the protocol.

Because of the post-hoc nature of the decision on the statistical method, this reviewer will consider multiple comparison adjustments for the comparisons with placebo, where the sponsor did not make any such adjustments.

Hemoglobin A1c

According to the protocol, the change from baseline was to be considered. The detailed analysis results are attached as Tables 2.2.1 . We see that at endpoint and at all (planned) timepoints, all the dose-and-regimen combinations of glimepiride are statistically highly significantly superior to placebo, even with multiple comparison adjustments.

At endpoint, the median superiority of 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid glimepiride over placebo is 2.0, 2.0, 1.9, and 2.2 respectively.

The Figures for comparing the treatment groups is attached as Figures⁷ 2.2.2 (Visit-wise) and 2.2.3 (Endpoint). The differences of the glimepiride groups with the placebo group are highly pronounced.

Fasting Plasma Glucose (FPG)

Same comments as with respect to HbA1c apply. The detailed analysis results are attached as Table 2.3.1 .

At endpoint, the median superiority of 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid glimepiride over placebo is 85.0, 92.5, 85.0, and 95.0 respectively.

The Figures for comparing the treatment groups, with respect to change from baseline, are attached as Figures 2.3.2 (Visit-wise) and 2.3.3 (Endpoint). The differences of the glimepiride groups with the placebo group are highly pronounced.

2-hour Postprandial Plasma Glucose (PPG)

In the subset of subjects who had 2-hour postprandial glucose data (collected at Weeks 0, 8, and 14), both "2-hour postprandial glucose" and "Fasting Plasma Glucose" were examined. However, we shall not discuss about the FPG here. FPG has been discussed above and this subset does not show anything of interest.

Same comments as with respect to HbA1c and FPG apply. The detailed analysis results are attached as Tables 2.4.1 .

At endpoint, the median superiority with respect to PPG of 8 mg qd, 4 mg bid, 16 mg qd, and 8 mg bid glimepiride over placebo is 119, 107, 103, and 113 respectively.

⁷ No separate numbering system has been followed for Figures. In the same numbering system, some are called Tables and some Figures as appropriate.

H. Reviewer's Comments and Conclusions on Study 8/USA/205/DM

This study has shown that all the four dose-regimen combinations of glimepiride studied are statistically significantly (even with multiple comparison adjustments) superior to placebo.

There is a weak (not statistically significant by multiple comparison adjustments) indication that 8 mg bid regimen may be negligibly superior (an observed difference of .3 with 16 mg qd) to the other three dose-regimen combinations: the p-values (in the attached Table 2.5.1) for the 8 mg bid vs 16 mg qd and 4 mg bid comparisons with respect to HbA_{1c} are .024 and .079 respectively.

The reviewer performed some statistical analyses (simple pairwise comparisons vs placebo) independently. Provided the data supplied by the sponsor on the diskette are reliable, no clues were found to raise any concern against the efficacy of glimepiride.

3. Study 8/USA/202/DM (Placebo-Controlled U.S. Study)

A. Objective

The study objective was to establish a suitable dosing range of glimepiride in the treatment of patients with Type II or noninsulin-dependent diabetes mellitus, whose plasma glucose concentration cannot be controlled by diet alone.

B. Design and Conduct of the Trial

This was a double-blind, 22-weeks double blind duration, 25-investigators, randomized, placebo controlled, parallel-groups (placebo and glimepiride) dose-titration study in patients with Type II or noninsulin-dependent diabetes mellitus (NIDDM).

Patients eligible for inclusion in this study were men and women with NIDDM, age 30 through 75, and weighing between 90% and 150% of ideal body weight as specified by Metropolitan Life Insurance tables.

During the 1-week screening period, subjects were treated by diet alone. At the end of this time, subjects who were dietary failures (fasting plasma glucose between 151 and 300 mg/dl on Days -7 and -1), qualified for randomization to either glimepiride or placebo. Initial daily dosage of study medication was 1 mg glimepiride or placebo. The dose was to be adjusted upward or downward at 2-week intervals until fasting plasma glucose was controlled at a level between approximately 90 and 150 mg/dl. Daily doses of glimepiride were 1, 2, 3, 4, 6, and 8 mg. Following the 10 weeks of dose adjustments, subjects were to be maintained at their optimal dose for the next 12 weeks of the study.

This reviewer was confused (10 weeks vs 12 weeks) with the statement on page 2 of the protocol regarding the titration period, "Those qualifying subjects ... will then be randomized and continue treatment with one of the study medications for 12 weeks of dose titration." The sponsor confirmed over the telephone that the report (10 weeks) is correct.

The schedule of observations is attached as Table 3.1.1⁸. Efficacy measures were taken at baseline and throughout the study. Primary efficacy variables were fasting plasma glucose and hemoglobin A1c (HbA1c). HbA1c, a secondary efficacy variable as stated in the protocol, was changed to a primary efficacy variable based on FDA input. Glucose response rate and 2-hour postprandial glucose were additional primary variables. Secondary efficacy variables were fasting and 2-hour postprandial C-peptide and insulin levels, lipid profiles, and FPG variability.

The number of patients in the centers varied from 1 to 24. The blind was not broken by any of the investigators during the conduct of this study for a medical emergency.

C. Study Completion Status

A total of 249 patients were randomized and 248 patients were treated; one subject randomized to glimepiride never took study drug.

The percentages of patients continuing at different weeks are provided in the attached Figure 3.1.2⁹ by treatment. The dropouts at different time-intervals can be seen from the attached Table 3.1.3 of Duration of Treatment. Percentages of dropouts due to different reasons are in the attached Table 3.1.4. In the glimepiride and placebo groups, respectively, 84% (83.87; the percentage given in the table, 84.6% is wrong) and 67% patients completed the study.

The percent of discontinuation due to the reason "Unreliable/Uncooperative" was 4.1% and 8.7%, respectively, in the glimepiride and the placebo groups.

D. Data Sets Analyzed

The sponsor stated, "Because of subject attrition, the primary analysis to determine the response to treatment was based on each subject's last treatment evaluation (Endpoint analysis)." A total 236 subjects (117 glimepiride, 119 placebo) were included in the efficacy analyses. Subjects with no baseline or postbaseline data (6 glimepiride, 7 placebo) were excluded from the efficacy analyses. One placebo subject had no baseline FPG data, but had both baseline and postbaseline data for some of the other efficacy variables.

In addition to the end-point analysis, visit-wise analysis of observed data for the intent-to-treat patients were done.

A set of day ranges or "windows" were defined for analysis purposes, which were different for

⁸ In the Table number i j k, i is the code for the study number and equals 1,2,3, and 4, respectively, for studies 8/USA/201/DM, 8/USA/205/DM, 8/USA/202/DM, and 8/USA/305/DM, j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

⁹ No separate numbering system has been followed for Figures. In the same numbering system, some are called Tables and some Figures as appropriate.

different efficacy variables (NDA Vol. 386, p.13). In the event that a patient had more than one measurement in any one window, the last measurement within that day range was analyzed.

E. Sponsor's Analysis Methods

Efficacy Data

The sponsor stated, "For evaluating efficacy and safety variables, nonparametric (Mantel-Haenszel) instead of parametric (linear models) analyses were used because the change from baseline data at Endpoint were not normally distributed". Both medians and means were used to describe the data.

The extended Mantel-Haenszel procedure was used to test for treatment group effects adjusted for investigator effects.

The data from those investigators who had fewer than 5 subjects in one of the treatment groups were combined into 4 investigator groups based on geographical area. For the linear models analyses, treatment and investigator effects were included in the model.

Demographic and Background Characteristics

Linear Model Analysis: Age and FPG at Admission and weight at baseline.

Mantel-Haenszel Test: Sex, race (white and nonwhite), and duration of diabetes (actual data used).

Demographic and background variables were summarized with descriptive statistics too.

F. Comparability of Treatment Groups

Demographic and Background Characteristics

Some demographic information follows:

	<u>Glimepiride</u>	<u>Placebo</u>
Mean Age (yr)	52.0	53.5
No. of Males	68(55%)	81(64%)
No. of Females	55(45%)	45(36%)
Mean Weight	191.1	191.9
White (Race)	86(70%)	85(68%)
Mean Dur.of Diab.(yr)	3.1	3.1

No statistically significant differences were found between the treatment groups.

Dose and Duration of Treatment

Percentages of subjects receiving study drug for at least 140 days were 70%, and 87%, respectively, for placebo and glimepiride.

For comparing treatments, placebo amounts are given as the equivalent dose of glimepiride, in the following statement. At endpoint, 34% of glimepiride patients and 64% of placebo patients were titrated to the highest dose (8 mg/day).

G. Efficacy Results (Sponsor's Analyses)

As mentioned under "Sponsor's analysis Methods," nonparametric instead of parametric analyses were used because the change from baseline data at Endpoint were not normally distributed. It was mentioned in the protocol, " ... will be compared using t test or nonparametric methods." However, no specific nonparametric method was mentioned in the protocol.

Hemoglobin A1c

According to the protocol, the change from baseline was to be considered. The detailed analysis results are attached as Tables 3.2.1 . The Figures for comparing glimepiride vs placebo are attached as Figures 3.2.2 (by visit) and 3.2.3 (Endpoint).

We see that at endpoint and at all (planned) timepoints (Weeks 12 and 24), glimepiride is statistically highly significantly superior to placebo. A subgroup question of interest is the following: Are the 25% or 20% patients with the highest baseline HbA1c really not as responsive to glimepiride as are the 75% or 80% remaining patients?

In the attached Table 3.2.4 (2nd part), we see that in patients with the top 20% baseline HbA1c, the p-value for the glimepiride vs placebo comparison is .576 (nonsignificant, median difference with placebo is -1.0); whereas, in the other group the p-value is <.001 (highly significant, median difference with placebo is -1.3). The sample size is smaller (25 patients in each of the treatment groups) than in the other group of patients with lower baseline HbA1c (81 in each of the treatment groups) but not too small.

At endpoint, the median superiority of glimepiride over placebo is 1.4.

Fasting Plasma Glucose (FPG)

Same comments as with respect to HbA1c apply. The detailed analysis results are attached as Tables 3.3.1 .

At endpoint, the median superiority of glimepiride over placebo is 46.

The Figures for comparing the treatment groups, with respect to change from baseline, are attached as Figures 3.3.2 (Visit-wise) and 3.3.3 (Endpoint). The difference of the glimepiride group with the placebo group is highly pronounced.

2-hour Postprandial Plasma Glucose (PPG)

In the subset of subjects who had 2-hour postprandial glucose data (collected at Weeks 0, 8, and 14), both "2-hour postprandial glucose" and "Fasting Plasma Glucose" were examined. In this subset the numerical superiority of glimepiride over placebo with respect to FPG varied slightly from that for the full set: 37 instead of 36 at Week 12, 34 instead of 38 at Week 24, and 43 instead of 46 at endpoint.

Comments for Postprandial Glucose are similar to those for HbA1c and FPG. The detailed analysis results are attached as Table 3.4.1.

At endpoint, the median superiority with respect to PPG of glimepiride over placebo is 72.

H. Reviewer's Comments and Conclusions on Study 8/USA/202/DM

This study has shown that glimepiride is statistically significantly superior to placebo.

The reviewer performed some statistical analyses (simple glimepiride vs placebo comparison) independently. Provided the data supplied by the sponsor on the diskette are reliable, no clues were found to raise any concern against the efficacy of glimepiride.

II.b) Reviewer's Comments and Conclusions on Indication I

The three studies (201, 205, and 202) considered above provide statistical evidence in favor of the efficacy of glimepiride. Study 8/USA/201/DM has shown that all the three (1, 4, and 8 mg) doses studied are statistically efficacious. Glimepiride 4 and 8 mg doses are comparable and better than 1 mg (statistically), with respect to efficacy.

The placebo patients in Study 202 showed improvement at endpoint contrary to the worsening of placebo patients in Studies 201 and 205.

The mean weight decreased from baseline in the placebo groups but generally increased slightly in the glimepiride groups (attached Table 0.2.1).

Subgroup Analyses

Age - With respect to HbA1c or FPG, there were no consistent trends across the three studies to say that the patients of age > 65 years respond any differently than patients <= 65 years. However, with respect to Median Postprandial Glucose, the patients of age > 65 years responded better (about the same or worse in Study 205) to glimepiride than the remaining patients.

Gender - Results for both the gender groups were about the same.

Race - No consistent trends across the studies with respect to race.

Baseline FPG - From the attached Table 1.6.1 (Study 201), we see that the superiority of glimepiride over placebo was larger in the stratum of patients with high baseline FPG, with respect to FPG and 2-hour Post-Prandial Glucose. This strata difference in superiority of glimepiride over placebo was more pronounced in the cases of 4 and 8 mg groups. For example, in the case of 4 mg and with respect to FPG, the median superiority over placebo was 89 (-75-14=-89) for the high baseline FPG stratum but was 58 for the low baseline FPG stratum.

The same trend can be seen in the attached Table 2.6.1 for the other Study 205, where stratified randomization was done.

III Indication II

4. Study 8/USA/305/DM (Placebo-Controlled U.S. Study)

A. Objective

The study objective (as stated in the protocol) was to compare combination therapy of glimepiride plus insulin with placebo plus insulin as measured by dose of injected insulin in subjects with type II diabetes (NIDDM) who do not respond to monotherapy with sulfonylureas. All patients will have their insulin dose titrated with the aim of achieving similar glucose target ranges.

B. Design and Conduct of the Trial

This 17-center study consisted of two parts:

- (1) an open-label 8-Week evaluation of the safety of glimepiride and
- (2) a double-blind, 24-weeks, randomized, placebo controlled, parallel-groups (placebo and insulin vs glimepiride and insulin) comparison of the efficacy and safety.

Patients eligible for inclusion in this study were men and women with NIDDM who were secondary failures to oral antidiabetic agents, age 45 through 70, and weighing between 130% and 170% of ideal body weight as specified by Metropolitan Life Insurance tables.

During the open-label period, each subject began with 8 mg of glimepiride daily before breakfast.

- If the FPG exceeded 150 mg/dl, the dose of glimepiride was to be increased at weekly intervals:

- (1) First, to 12 mg daily before breakfast;
- (2) Then, to 16 mg daily before breakfast;
- (3) Finally, to 8 mg bid (two 4-mg tablets before breakfast, and two 4-mg tablets before

dinner).

- If the FPG was $\geq$ 150 mg/dl on two consecutive weekly visits, the subject was disqualified from the study.

- If the FPG was $\leq$ 180 mg/dl or $>$ 300 mg/dl on the 8 mg bid dosage at Week -3 and on Day -3, the subject was disqualified from the study.

During the double-blind phase, the oral medication (glimepiride 8 mg bid or placebo bid) was to be held constant while the insulin qd dose was to be titrated to maintain FBG between 100 and 120 mg/dl. Details of the titration schedule is on page 4 of the NDA Report for this study.

The schedule of observations is attached as Table 4.1.1¹⁰. Primary efficacy variables were the 4-Week average insulin dose at Endpoint and the change in hemoglobin A1c (HbA1c) from Baseline to Endpoint. Secondary efficacy variables were the change in FPG from Baseline to Week 2 and the final daily insulin dose. Other efficacy variables were FPG variability, lipid profiles, blood pressure, weight, and fasting levels of insulin.

Some of these differ from what was stated in the original protocol:

Efficacy Variables: 1. Primary: Dose of injected insulin 2. Secondary: Fasting Plasma glucose at Week 2

Other Variables: 1. Fasting and post-prandial glucose 2. HbA1c 3. Fasting and post prandial C-peptide, glucagon, free insulin levels 4. Serum lipids 5. Glycemic variability

There was a Protocol Amendment (II) dated August 6, 1993, called Revised Statistical Plan. Important changes in efficacy variables were included in that amendment.

The number of patients enrolled in the centers varied from 6 to, generally, 17 (with one investigator enrolling 29). During the double blind phase, this number varied from 4 to 15.

C. Study Completion Status

Of the 208 patients treated during the open-label phase, 31 were discontinued, 32 were disqualified from entering the double-blind phase, and 145 were randomized to the double-blind phase (73 to the placebo plus insulin group and 72 to the glimepiride plus insulin group). Each site treated 4 to 15 patients.

The percentages of patients continuing at different weeks are provided in the attached Figure 4.1.2¹¹ by treatment. The dropouts at different time-intervals can be seen from the attached Table 4.1.3 of Duration of Treatment. Percentages of dropouts due to different reasons are in the attached Table 4.1.4. In each of the glimepiride plus insulin and placebo plus insulin groups, 97% and 85%, respectively, patients completed the study.

D. Data Sets Analyzed

The sponsor stated, "No protocol violation warranted the exclusion of a subject's data from any analysis. Since only 12 out of the 145 (8%) subjects evaluated for efficacy had major violations, a

¹⁰ In the Table number i j k, i is the code for the study number and equals 1,2,3, and 4, respectively, for studies 8/USA/201/DM, 8/USA/205/DM, 8/USA/202/DM, and 8/USA/305/DM, j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

¹¹ No separate numbering system has been followed for Figures. In the same numbering system, some are called Tables and some Figures as appropriate.

separate per protocol analysis was not done."

Visit-wise analysis of observed data for the intent-to-treat patients were done for some of the variables.

A set of day ranges or "windows" were defined for analysis purposes, which were different for different efficacy variables (NDA Vol. 1.533, p.23). In the event that a patient had more than one measurement in any one window, the last measurement within that day range was analyzed.

E. Sponsor's Analysis Methods

Efficacy Data

Comparisons of the treatment effect on insulin dose were made using the Proportional Hazards Model analysis with treatment group and titration procedure (aggressive or less aggressive) included in the model. Subjects with left (expected insulin dose smaller than observed) or undefined censored data were excluded from this analysis. The following supplemental analyses were performed to support the findings from the PH Model analysis:

- (1) Log rank test, which provided the p-value for the treatment effect without adjusting for titration procedure effect. Subjects with left or undefined censored data were excluded from this analysis.
- (2) Mantel-Haenszel procedure with adjustment for titration procedure effect. All subjects were included.

Comparisons of the treatment effect on change in HbA1c and Week 2 FPG were made using an analysis of variance model with treatment group and titration procedure as fixed effects. Two-sided 95% confidence intervals were calculated using observed means and the estimated variance derived from the above model.

Demographic and Background Characteristics

Demographic and background variables were summarized with descriptive statistics. Homogeneity in these variables was assessed using GLM analyses for age, height, weight, FPG, and HbA1c recorded at baseline and the Mantel-Haenszel test for the other variables.

F. Comparability of Treatment Groups

No statistically significant differences were detected among the treatment groups on any demographic or background characteristics.

Demographic and Background Characteristics

Some demographic information follows:

	<u>Placebo+Insulin</u>	<u>Glimepiride+Insulin</u>
Mean Age (yr)	57.9	57.9
No. of Males	40(55%)	45(63.5%)
No. of Females	33(45%)	27(38.5%)
Mean Weight	213.3	205.5
White (Race)	58(79%)	57(79%)
Mean Dur.of Diab.(yr)	3.7	3.7

Concomitant medication

The sponsor states that the use of concomitant medications that are known to affect blood glucose levels and that were started 30 days before study drug or during the double-blind phase were examined. The number of subjects who were treated with NSAIDS (Placebo+insulin group: 22, Glim.+Insulin group:18), diuretics, thyroid products, and estrogens was similar in each treatment group.

G. Efficacy Results (Sponsor's Analyses)

List of efficacy variables mentioned in the protocol and in the reports (described above under the Heading "Design and Conduct of the Study") are slightly different. However, insulin dose was mentioned as the primary efficacy variable in the protocol.

In Statistical Methods (Appendix IV), the sponsor stated, "At each visit and at the endpoint of the study, graphs of the insulin dose will be provided to facilitate a visual assessment of the relationship between glimepiride plus insulin and placebo plus insulin." Also, it was stated in the protocol. "Comparisons of insulin dose at each evaluation and at endpoint ... will be made..." This reviewer could not find any of these (except at endpoint).

Primary Efficacy Variables

Four-Week Average Insulin Dose at Endpoint

The 4-Week mean insulin dose was 77.9 for the placebo plus insulin group and 48.5 for the glimepiride plus insulin group. The difference was statistically highly significant (Attached Table 4.2.1).

Estimated Percent of Subjects Not in Control vs 4-week average insulin dose at endpoint is attached as Figure 4.2.2.

Change in HbA1c From Baseline to Endpoint

The mean change (reduction as indicated by a negative sign) in HbA1c from baseline to Endpoint was -2.0 for the placebo plus insulin group and -2.2 for the glimepiride plus insulin group (attached Table 4.3.1). The p-value for the difference is .26 (not significant) and the 95% confidence interval for the difference is: -.6 to .2 ("slightly more reduction for the glimepiride plus insulin group than the other group" is indicated but not statistically significant).

The Figures for comparing glimepiride vs placebo are attached as Figures 4.3.2 (by visit) and 4.3.3 (Endpoint).

Secondary Efficacy Variables

Change in FPG from baseline to Week 2

The mean change (reduction if indicated by a negative sign) in FPG from baseline to Week 2 was 6.7 mg/dl for the placebo plus insulin group and -45.5 mg/dl for the glimepiride plus insulin group (attached Table 4.3.1). The p-value for the difference is .001 (significant). The sponsor states, "The average insulin dose prior to the day on which the Week 2 FPG sample was collected was 11 U/day for both groups."

Box plots of the distributions of FPG for the two treatment groups by visits are in the attached Figure 4.3.4. Generally speaking, Glimepiride plus insulin patients were better than placebo plus insulin patients at Baseline. At Week 2, Placebo plus insulin group (Plac.+ Ins.) patients deteriorated and Glim.+Ins. patients improved making a large between treatment difference. At Week 4, both treatment patients improved (Glim.+Ins. more) and the large treatment difference was maintained or became even larger. At Week 8, placebo patients had drastic improvement. Both treatment group patients showed improvement up to Week 24, when the medians for both groups were similar (at Week 20 Glim.+Ins. median was higher).

Final Daily Insulin Dose at Endpoint

The mean final daily insulin dose was 78.4 for the placebo plus insulin group and 48.9 for the glimepiride plus insulin group. The difference was statistically highly significant (Attached Table 4.2.1).

Other Efficacy Variable

Weight

The results on weight changes are attached as Table 4.4.1. The weight gain in the glimepiride plus insulin group was statistically significantly more than in the placebo plus insulin group, up to Week 12. There was actually a median weight loss of 1 pound in the placebo plus insulin group up to Week 4. Statistically significantly more weight gain in the glimepiride plus insulin treatment group is of concern (goes against the efficacy of glimepiride, as this reviewer could understand by consultation

with the clinical reviewer).

From Week 16 to Week 24, weight gains in the two treatment groups were not statistically significantly different.

H. Reviewer's Comments and Conclusions on Study 8/USA/305/DM(Indication II)

In this study, significantly less exogenous insulin was required with glimepiride plus insulin therapy than with placebo plus insulin therapy. The reduction in HbA1c from baseline to endpoint was similar in the two treatment groups. This suggests that fewer patients will require multiple insulin injections with combination therapy than with insulin monotherapy.

Statistically significantly more weight gain in the glimepiride plus insulin treatment group than in the placebo plus insulin group, up to Week 12, is of concern (goes against the efficacy of glimepiride). However, out of so much efficacy results, this is the only result going against the efficacy of glimepiride combination therapy.

The reviewer performed some simple statistical analyses (glimepiride plus insulin vs placebo plus insulin comparison) independently. Provided the data supplied by the sponsor on the diskette are reliable, no clues were found to raise any concern against the efficacy of glimepiride in combination with insulin.

Subgroup Results

There was no detectable treatment by age, gender, or race interaction with respect to the primary efficacy variable "4-Week Average Insulin Dose". With respect to the Endpoint HbA1c, the F-test for interaction showed some indication of treatment by race interaction (p-value=.0861). Results by race are attached as Table 4.5.1. The mean superiority of Glim.+Ins. over Plac.+Ins. was .1 for Whites (n above 50 in each treatment group) and was .5 for Non-Whites (n=14 for each treatment group). The corresponding 4-Week Average Insulin dose (by Race) is attached as Table 4.5.2. Above interaction is explained by the fact that the Whites of the Plac.+Ins. group used a lot more insulin than the Non-Whites of the same treatment group.

IV. Reviewer's Overall Conclusions

For both indications, the results of the primary studies provide statistically highly significant evidence for the superiority of glimepiride (monotherapy or in combination with insulin) over placebo. [The sponsor states that the FDA agreed at a meeting on June 9, 1992, that, were it positive, the study under protocol 8/USA/305 alone would be sufficient to support labeling for Indication II.]

The dose response study 8/USA/201/DM showed that all three doses studied, 1, 4, and 8 mg of glimepiride were statistically efficacious. Glimepiride 4 and 8 mg doses were comparable and statistically superior to 1 mg glimepiride.

The mean weight decreased from baseline in the placebo groups (except in the placebo plus insulin group in Study 8/USA/305/DM) but generally increased slightly in the glimepiride groups (attached

Table 0.2.1).

Japobrata Choudhury 5-30-95
Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur:

Dr. Nevius *Jan 6-1-95*

Dr. Dubey *Smith
for SDD 6/1/95*

CC:

Arch NDA# 20-496

HFD-510

HFD-510/SSobel

HFD-510/AFleming

HFD-510/JGueriguian

HFD-510/JShort

HFD-344/ALisook

HFD-713/SDubey [File: DRU 1.3.2]

HFD-713/Group 2 File

HFD-713/JChoudhury

J.Choudhury:x45477:SERB:jc:11/28/94- 05/25/95

This review consists of 23 pages of text and 71 pages of tables.

Table 0.1.1.

Summary Information - US Trials

Protocol	Design	Doses	Treatment Duration	Total No. of Subjects				Study Totals
				Glim	Gly	Glip	Pbo	
8/USA/104	Fixed-dose	Pbo Glim: 1, 2, 4, 8 mg qd Gly: 10 mg qd	14 days	57	14	-	15	86
8/USA/105 ^a	Fixed-dose	Glim: 8, 16, 32 mg qd	14 days	20	-	-	-	20
8/USA/106	Fixed-dose	Glim: 16 mg bid; 32 mg qd Gly: 10 mg qd	13 days	13	5	-	-	18
8/USA/201	Fixed-dose	Pbo; Glim: 1, 4, 8 mg qd	14 weeks	230	-	-	74	304
8/USA/202	Dose titration	Pbo; Glim: 1, 2, 3, 4, 6, 8 mg qd	22 weeks	123	-	-	126	249
8/USA/205	Fixed-dose	Pbo Glim: 8 mg qd; 4 mg bid; 16 mg qd; 8 mg bid	14 weeks	337	-	-	79	416
8/USA/206	Fixed-dose Crossover	Glim: 3 mg bid; 6 mg qd	15 weeks	161	-	-	-	161
8/USA/301 (Interim)	Dose titration	Glim: 1, 2, 4, 8, 12, 16 mg qd; 8 mg bid Glip: 2.5, 5, 10 mg qd; 10 mg bid; 20 mg AM and 10 mg PM; 20 mg bid	12 months	86	-	44	-	130
8/USA/302	Dose titration	Glim: 1, 2, 4, 8 mg qd; 8 mg AM and 4 mg PM; 8 mg bid Gly: 1.25, 2.5, 5, 10 mg qd; 10 mg AM and 5 mg PM; 10 mg bid	12 months	289	288	-	-	577
8/USA/305OL	Dose titration	Glim: 8, 12, 16 mg qd; 8 mg bid	8 weeks	208	-	-	-	208
Treatment Totals				1524	307	44	294	2169

^aThese 20 subjects were previously enrolled in the 8/USA/104 study.
Glim = glimepiride, Gly = glyburide, Glip = Glipizide, Pbo = Placebo

Contd.

Amaryl™ (Glimepiride, HOE 490) NDA
 Item 8.B/10.B - Overview of the Clinical Program

Table 0.1.1 Contd.

Summary Information - European Trials

Protocol	Design	Doses	Treatment Duration	Total No. of Subjects			Study Totals
				Glim	Gly	Glic	
2/D/207	Dose titration	Glim: 1.5 - 6 mg qd	4-26 days	38	-	-	38
2/D/213	Dose titration	Glim: 2, 3, 4 mg qd Gly: 3.5, 7 mg qd; 7 mg AM/3.5 mg PM	21 days	11	14	-	25
2/D/221	Fixed-dose	Glim: 2 mg qd Gly: 7 mg AM/3.5 mg PM	28 days	36	38	-	74
2/D/223	Fixed-dose	Glim: 3 mg qd Gly: 7 mg AM/3.5 mg PM	28 days	12	12	-	24
8/GB/203 ^a	Dose titration Crossover	Glim: 1-4, 6, 8 mg qd Gly: 2.5, 5, 7.5, 10 mg qd; 10 mg AM/5 mg PM; 10 mg bid	28 days on Glim and 28 days on Gly	31	32	-	33
2/MN/201	Fixed-dose Crossover	Glim: 2 mg qd	28 days	202	-	-	202
2/MN/202	Fixed-dose	Glim: 3 mg qd; Gly: 10 mg qd	15-41 days	98	91	-	189
2/MN/301 (2/MN/312)	Dose titration	Glim: 1-4, 6, 8 mg qd Gly: 2.5, 5, 7.5, 10 mg qd; 10 mg AM/5 mg PM; 10 mg bid	1-2.8 years	522	519	-	1041
2/MN/311 (2/MN/312)	Dose titration	Glim: 1-4, 6, 8 mg qd Gly: 1.75, 3.5, 5.25, 7 mg qd; 7 mg AM/3.5 mg PM; 7 mg bid	1-2.8 years	425	426	-	851
8/F/301	Dose titration	Glim: 1-4 mg qd Glic: 80 mg qd; 80 mg bid; 160 mg AM/80 mg PM; 160 mg bid	14 weeks	114	-	115	229
Treatment Totals				1489	1132	115	2706

^aIn this crossover study, a total of 33 subjects were treated; 31 received glimepiride and 32 received glyburide.
 Glim = glimepiride, Gly = glyburide, Glic = Gliclazide

Summary Information - Japanese Trials

Protocol	Design	Daily Doses	Treatment Duration	Total No. of Subjects			Study Totals
				Glim	Glic	Pbo	
8/J/202	Dose-titration	Glim: 0.25, 0.5, 1, 1.5, 2 mg	12 weeks	53	-	-	53
8/J/203	Fixed-dose	Pbo; Glim: 0.25, 0.5 mg	2 weeks	63	-	32	95
8/J/204	Dose-titration	Glim: 0.5-6 mg	6 months	363	-	-	363
8/J/205 ^a	Dose-titration	Glim: 0.5-6 mg	6 months	65	-	-	65
8/J/201	Dose-titration	Glim: 0.5-7 mg; Glic: 40-200 mg	24 weeks	239	233	-	472

^aExtension of 8/J/204.

Glimepiride (HCE 490, Amaryl™) NDA
 Item 8.G - Integrated Summary of Efficacy

ISE TABLE 0.2.1

SUMMARY OF WEIGHT/BODY MASS INDEX(BMI) CHANGE FROM BASELINE TO ENDPOINT

VARIABLE: WEIGHT	PROTOCOL	TREATMENT	BASELINE		ENDPOINT		MEAN CHANGE
			N	MEAN	N	MEAN	
8/USA/201		Placebo	67	188.5	67	183.5	- 5.0
		Glim 1 mg qd	76	185.4	76	184.9	- 0.5
		Glim 4 mg qd	75	189.5	75	190.6	1.1
		Glim 8 mg qd	73	188.1	73	190.2	2.1
8/USA/202		Placebo	122	192.1	122	190.1	- 2.0
		Glimepiride	119	190.8	119	194.8	4.0
8/USA/205		Placebo	78	190.8	78	186.8	- 4.0
		Glim 8 mg qd	87	184.9	87	187.2	2.3
		Glim 4 mg bid	80	191.4	80	193.2	1.8
		Glim 16 mg qd	81	187.2	81	189.2	2.0
		Glim 8 mg bid	83	193.1	83	195.5	2.4
8/USA/302		Glimepiride	283	190.0	283	193.5	3.5
		Glyburide	286	190.0	286	193.9	3.9
8/USA/305		Placebo+Insulin	71	205.5	71	214.7	9.2
		Glim+Insulin	70	214.1	70	222.3	8.2
8/F/301		Glimepiride	112	76.9	82	78.3	0.5
		Glyburide	115	72.1	95	72.6	0.4

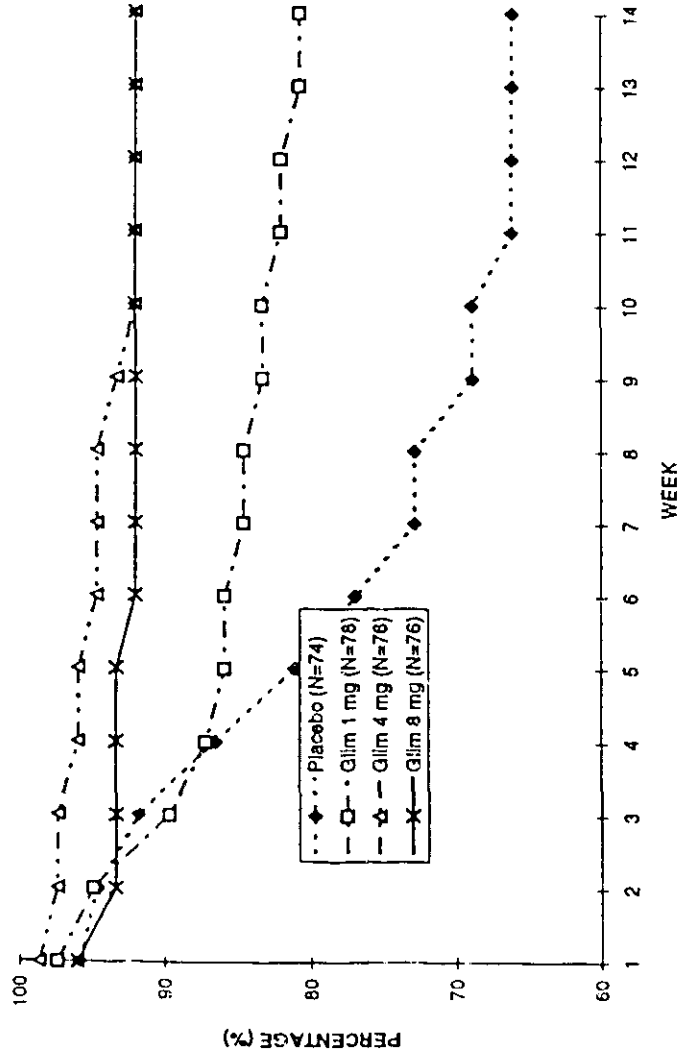
Table 1.1.1
SCHEDULE OF OBSERVATIONS

Day: Week	Prerandomization				Double-blind Forced Titration Randomization Phase									
	-21	-14	-7	-3	0	1	2	3	4	6	8	10	12	14
Medical history	X													
Physical examination	X				X						X			X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glucometer reading	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X				X						X			X
Hemoglobin A1c	X				X				X		X		X	X
2-hr PP glucose					X						X			X
Fasting and 2-hr PP C-peptide/insulin					X						X			X
Lipid profile					X						X			X
ECG					X									X
Final report														X

Week 0 = Baseline for the randomization phase

Figure 1.1.2

PERCENTAGE OF PATIENTS IN STUDY OVER TIME (IN WEEKS)
SUBJECTS DISCONTINUED FOR ANY REASON



H0E 490 8/USA/201/DM - Glimepiride

TABLE 1.1.3

DURATION OF TREATMENT

NO. DAYS TREATED	PLACEBO		GLIMEPIRIDE 1 mg		GLIMEPIRIDE 4 mg		GLIMEPIRIDE 8 mg	
	N	%	N	%	N	%	N	%
< 14	4	5.4	4	5.1	2	2.6	5	6.6
14-27	6	8.1	6	7.7	1	1.3	0	0.0
28-41	7	9.5	1	1.3	1	1.3	1	1.3
42-55	3	4.1	1	1.3	0	0.0	0	0.0
56-69	3	4.1	1	1.3	2	2.6	0	0.0
70-83	2	2.7	1	1.3	0	0.0	0	0.0
84-97	14	18.9	15	19.2	14	18.4	18	23.7
>97	35	47.3	49	62.8	56	73.7	52	68.4
TOTAL NO. OF SUBJ	74	100.0	78	100.0	76	100.0	76	100.0

TABLE 1.1.4
STUDY COMPLETION STATUS

	PLACEBO	GLIMEPIRIDE 1 mg	GLIMEPIRIDE 4 mg	GLIMEPIRIDE 8 mg
NO OF SUBJECTS RANDOMIZED	75	78	76	76
NO OF SUBJECTS TREATED	74 (100.0%)	78 (100.0%)	76 (100.0%)	76 (100.0%)
COMPLETED STUDY	49 (66.2%)	63 (80.8%)	70 (92.1%)	70 (92.1%)
DID NOT COMPLETE STUDY	25 (33.8%)	15 (19.2%)	6 (7.9%)	6 (7.9%)
P-VALUE FOR COMPARISON WITH PLACEBO	-	0.032	0.001	0.001
REASON FOR NOT COMPLETING				
Lack of Efficacy: Hypoglycemia	3 (4.1%)	1 (1.3%)	1 (1.3%)	0 (0.0%)
Safety/Lack of Eff: Hyperglycemia	12 (16.2%)	5 (6.4%)	1 (1.3%)	0 (0.0%)
Safety: Adverse Event	1 (1.4%)	2 (2.6%)	0 (0.0%)	1 (1.3%)
Safety: Other	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Safety: Intercurrent Medical Problem	1 (1.4%)	1 (1.3%)	0 (0.0%)	1 (1.3%)
Protocol Violation	2 (2.7%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
Unreliable/Uncooperative	0 (0.0%)	0 (0.0%)	2 (2.6%)	1 (1.3%)
Patient Dissatisfied With Treatment	4 (5.4%)	4 (5.1%)	1 (1.3%)	1 (1.3%)
Other	2 (2.7%)	0 (0.0%)	0 (0.0%)	1 (1.3%)

The Mantel-Haenszel Test (two-tailed) was used to compare proportions of subjects who did not complete the study.

TABLE 1.2.1
MEDIAN HEMOGLOBIN A1c (%)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM					
								1 mg	4 mg	8 mg	1 mg	4 mg	8 mg
Baseline	Placebo	59	7.80	5.5-11.2	-	---		0.00	0.00	0.00	0.737	0.832	0.534
	Glim 1 mg	65	7.80	6.0-11.2	-	---		-	0.00	0.10	-	0.933	0.566
	Glim 4 mg	65	7.70	5.6-10.2	-	---		-	-	0.10	-	-	0.491
	Glim 8 mg	62	7.80	5.9-11.2	-	---		-	-	-	-	-	-
Week 4	Placebo	56	8.65	6.0-12.0	0.70	-0.6-2.7	***	-0.40	-0.70	-0.80	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	60	7.95	5.6-10.5	0.30	-1.0-3.0	***	-	-0.30	-0.40	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	58	7.80	5.1-10.0	-0.10	-1.5-1.3	NS	-	-	-0.10	-	-	0.368
	Glim 8 mg	61	7.70	6.2-11.2	-0.10	-1.7-3.0	NS	-	-	-	-	-	-
Week 8	Placebo	50	9.30	6.1-12.3	1.20	-0.9-2.9	***	-0.90	-1.40	-1.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	63	7.90	5.4-10.8	0.30	-1.7-2.3	*	-	-0.50	-0.60	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	63	7.70	4.9-10.7	-0.30	-2.0-1.9	**	-	-	-0.10	-	-	0.551
	Glim 8 mg	64	7.50	5.5-11.0	-0.30	-3.0-2.6	***	-	-	-	-	-	-
Week 12	Placebo	37	9.60	5.7-12.5	1.40	-0.9-4.5	***	-1.10	-1.80	-1.90	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	50	7.85	5.5-11.0	0.40	-2.3-2.4	**	-	-0.70	-0.80	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	52	7.65	4.8-9.4	-0.40	-2.5-1.1	***	-	-	-0.10	-	-	0.541
	Glim 8 mg	54	7.55	5.2-11.3	-0.40	-1.7-3.0	***	-	-	-	-	-	-
Week 14	Placebo	41	9.40	5.8-13.8	1.40	-1.6-5.1	***	-1.20	-1.80	-1.80	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	57	8.00	5.6-11.2	0.40	-1.9-3.3	*	-	-0.60	-0.70	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	60	7.65	4.6-9.8	-0.40	-1.8-1.2	***	-	-	-0.10	-	-	0.751
	Glim 8 mg	63	7.40	5.5-12.0	-0.40	-4.0-3.1	**	-	-	-	-	-	-

N = no of subjects Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
*p < 0.050. **p < 0.010. ***p < 0.001. NS p > 0.050.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
***p < 0.001.

TABLE 1.2.1 Contd.

MEDIAN HEMOGLOBIN A1c (%)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM				COMPARISON WITH				
								1 mg	4 mg	8 mg	P-value	1 mg	4 mg	8 mg	P-value	
Endpoint	Placebo	59	9.50	7-13.8	1.40	-1.6-5.1	***	-1.20	-1.80	-1.90	< 0.001	***	< 0.001	***	< 0.001	***
	Glim 1 mg	65	8.00	5.6-11.2	0.40	-1.9-3.3	*	-	-0.60	-0.70	< 0.001	***	< 0.001	***	< 0.001	***
	Glim 4 mg	65	7.70	4.6-10.7	-0.40	-1.8-1.3	***	-	-	-0.10	< 0.001	***	< 0.001	***	< 0.001	***
	Glim 8 mg	68	7.50	5.5-12.0	-0.40	-4.0-3.1	**	-	-	-	< 0.001	***	< 0.001	***	0.705	

N = no. of subjects. Change = median change from baseline. - Not applicable.

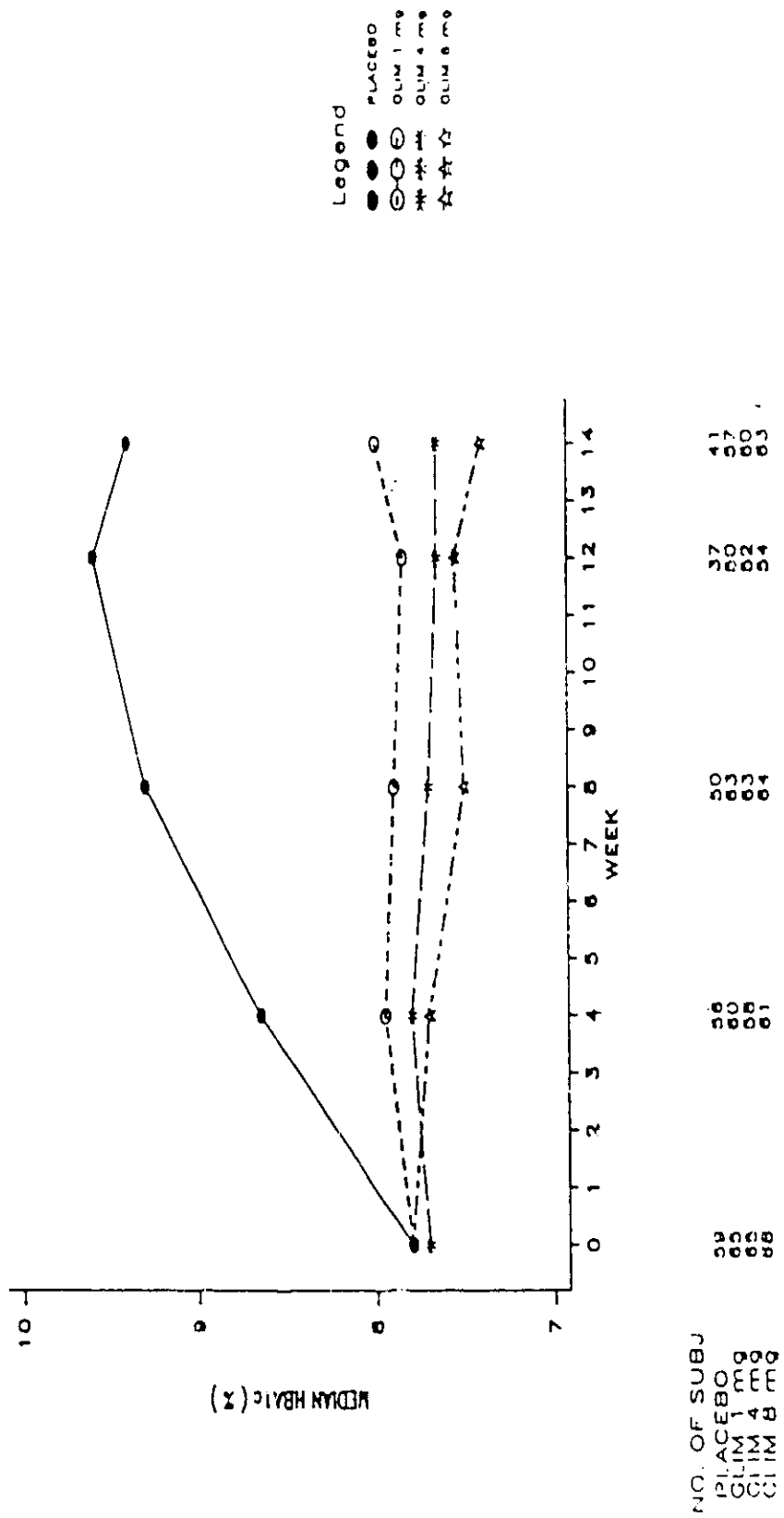
Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

*p < 0.050, **p < 0.010, ***p < 0.001.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 **p < 0.001.

Figure 1.2.2

MEDIAN HbA1c (%) LEVELS BY VISIT
VISIT-WISE DATA



All three treatment groups are significantly better (P<0.001) than placebo group at all visits.

Figure 1.2.3

MEAN HEMOGLOBIN A1c (%) LEVEL BY VISIT
CARRY-FORWARD DATA

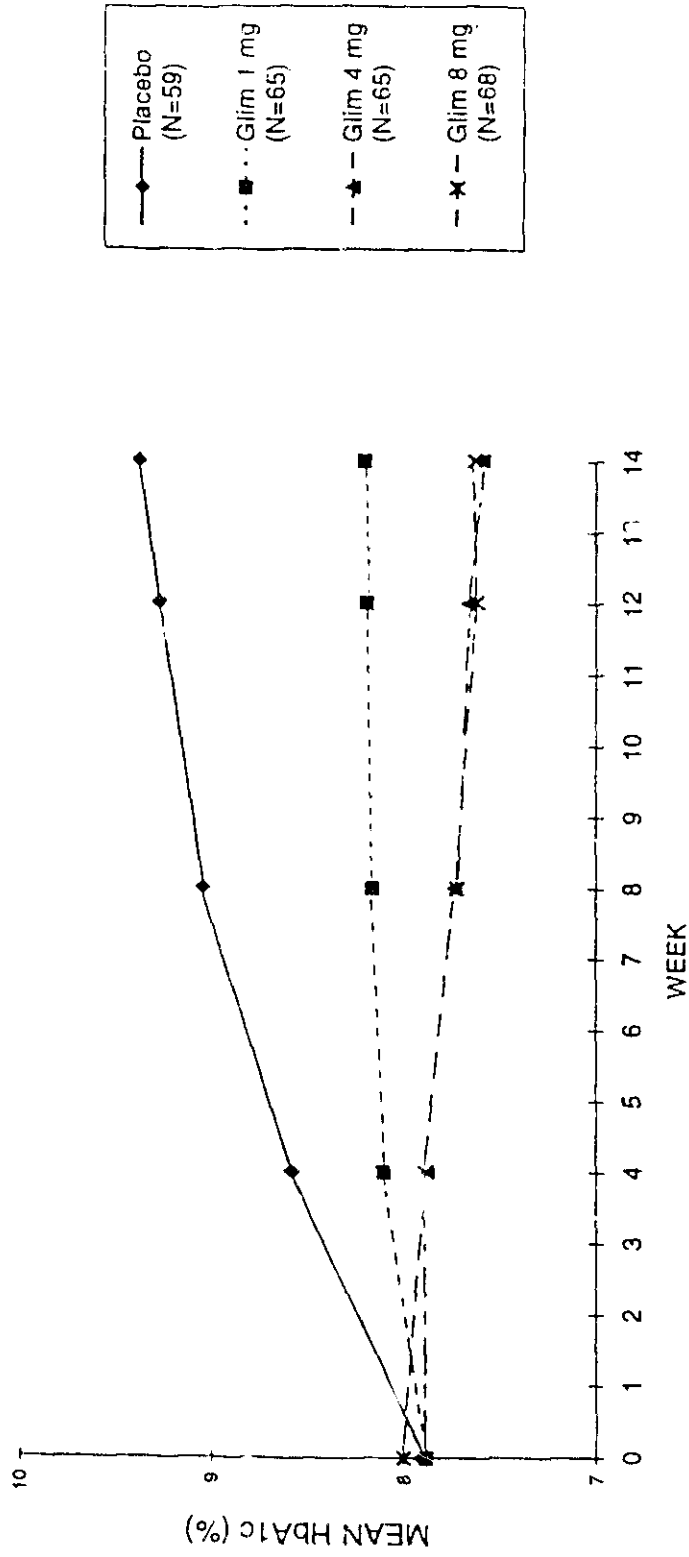


TABLE 1.3.1
 MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM						COMPARISON WITH	
								1 mg	4 mg	8 mg	1 mg	4 mg	8 mg	P-value	P-value
Baseline	Placebo	67	232.5	78-350	-	---	---	3.00	4.00	1.00	0.306	0.560	0.231		
	Glim 1 mg	76	231.8	157-344	-	---	---	-	1.00	-2.00	-	0.782	0.669		
	Glim 4 mg	75	236.5	152-345	-	---	---	-	-	-2.50	-	-	0.467		
Week 1	Placebo	66	216.5	125-366	3.3	-142-47	NS	-25.50	-28.00	-31.50	< 0.001 ***	< 0.001 ***	< 0.001 ***		
	Glim 1 mg	73	204.0	126-332	-23.5	-124-85	***	-	-3.50	-6.50	-	0.820	0.150		
	Glim 4 mg	73	205.5	114-325	-28.0	-98-41	***	-	-	-3.50	-	-	0.194		
Week 2	Placebo	62	236.8	111-351	8.8	-61-92	NS	-38.00	-58.00	-55.50	< 0.001 ***	< 0.001 ***	< 0.001 ***		
	Glim 1 mg	73	198.5	127-287	-34.0	-133-62	***	-	-20.50	-18.00	-	0.002 **	0.012 *		
	Glim 4 mg	72	180.8	91-310	-55.8	-160-64	***	-	-	2.50	-	-	0.929		
Week 3	Placebo	63	222.5	124-328	1.5	-66-116	NS	-36.00	-56.00	-62.50	< 0.001 ***	< 0.001 ***	< 0.001 ***		
	Glim 1 mg	69	194.5	115-305	-37.0	-152-78	***	-	-20.00	-27.00	-	0.002 **	0.001 ***		
	Glim 4 mg	72	174.3	92-306	-50.0	-137-61	***	-	-	-6.00	-	-	0.189		
Week 4	Placebo	70	166.5	93-317	-61.5	-209-97	***	-	-	-	-	-	-		
	Glim 1 mg	57	230.0	120-343	6.5	-73-75	*	-47.00	-69.50	-74.00	< 0.001 ***	< 0.001 ***	< 0.001 ***		
	Glim 4 mg	63	192.5	126-330	-35.0	-167-110	***	-	-22.00	-25.00	-	0.002 **	0.001 ***		
Week 4	Glim 8 mg	64	166.3	91-270	-65.0	-200-37	***	-	-	-3.00	-	-	0.265		

N = no of subjects. Change = median change from baseline. - Not applicable.
 Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 *p < 0.050, **p < 0.010, ***p < 0.001.

* Values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 p < 0.050, **p < 0.010, *p < 0.001.

TABLE 1.3.1 Contd.
 MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM			COMPARISON WITH		
								1 mg	4 mg	8 mg	1 mg	4 mg	8 mg
Week 6	Placebo	56	241.0	125-340	4.0	-87-108	NS	-45.00	-64.50	-71.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	67	188.0	125-299	-41.5	-145-71	***	-	-19.00	-26.00	< 0.003 **	< 0.001 ***	< 0.001 ***
	Glim 4 mg	71	173.0	96-304	-56.0	-209-59	***	-	-	-6.00	-	-	-
	Glim 8 mg	67	159.5	88-307	-65.5	-226-51	***	-	-	-	-	-	0.242
Week 8	Placebo	48	247.3	127-338	12.5	-81-127	**	-52.00	-80.00	-78.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	64	193.5	120-307	-36.0	-188-50	***	-	-27.00	-24.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	70	167.0	98-271	-60.3	-164-22	***	-	-	3.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 8 mg	69	167.0	101-280	-62.5	-208-31	***	-	-	-	-	-	0.837
Week 10	Placebo	47	233.0	122-349	8.0	-83-174	NS	-46.00	-68.00	-73.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	63	190.5	111-310	-35.5	-183-112	**	-	-23.00	-26.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	67	166.5	92-345	-58.5	-232-100	***	-	-	-3.50	< 0.006 **	< 0.001 ***	< 0.001 ***
	Glim 8 mg	67	162.0	90-284	-68.0	-166-28	***	-	-	-	-	-	0.417
Week 12	Placebo	46	233.0	131-343	11.0	-109-140	*	-53.50	-75.00	-76.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	64	188.0	100-315	-38.5	-201-105	***	-	-22.00	-23.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	69	161.0	104-310	-62.0	-167-94	***	-	-	-1.00	< 0.004 **	< 0.003 **	< 0.001 ***
	Glim 8 mg	65	162.5	92-329	-58.5	-188-128	***	-	-	-	-	-	0.613
Week 14	Placebo	43	235.5	129-456	13.5	-121-174	NS	-40.00	-66.00	-71.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	61	200.5	103-324	-33.5	-208-68	***	-	-25.00	-29.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	67	167.5	99-300	-59.5	-187-37	***	-	-	-4.50	< 0.001 **	< 0.001 **	< 0.001 ***
	Glim 8 mg	66	166.5	91-295	-65.0	-226-62	***	-	-	-	-	-	0.566

N = no of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 *p ≤ 0.050, **p ≤ 0.010, ***p ≤ 0.001, NS p > 0.050.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 *p ≤ 0.010, ***p ≤ 0.001.

TABLE I.3.1 Contd.
 MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE*	RANGE	SIG	DIFFERENCE FROM			COMPARISON WITH		
								1 mg	4 mg	8 mg	1 mg	4 mg	8 mg
Endpoint	Placebo	67	250.5	129-456	16.5	-121-174	**	-43.00	-70.50	-74.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	76	203.0	103-330	-26.0	-208-110	***	-	-26.50	-30.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	75	168.0	99-345	-57.0	-187-100	***	-	-	-3.50	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg	74	167.5	91-295	-56.5	-226-62	***	-	-	-	-	-	0.570

N = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test; (two-tailed).
 p ≤ 0.010, *p ≤ 0.001.

p-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 ***p ≤ 0.001.

FIGURE 1.3.2

MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE

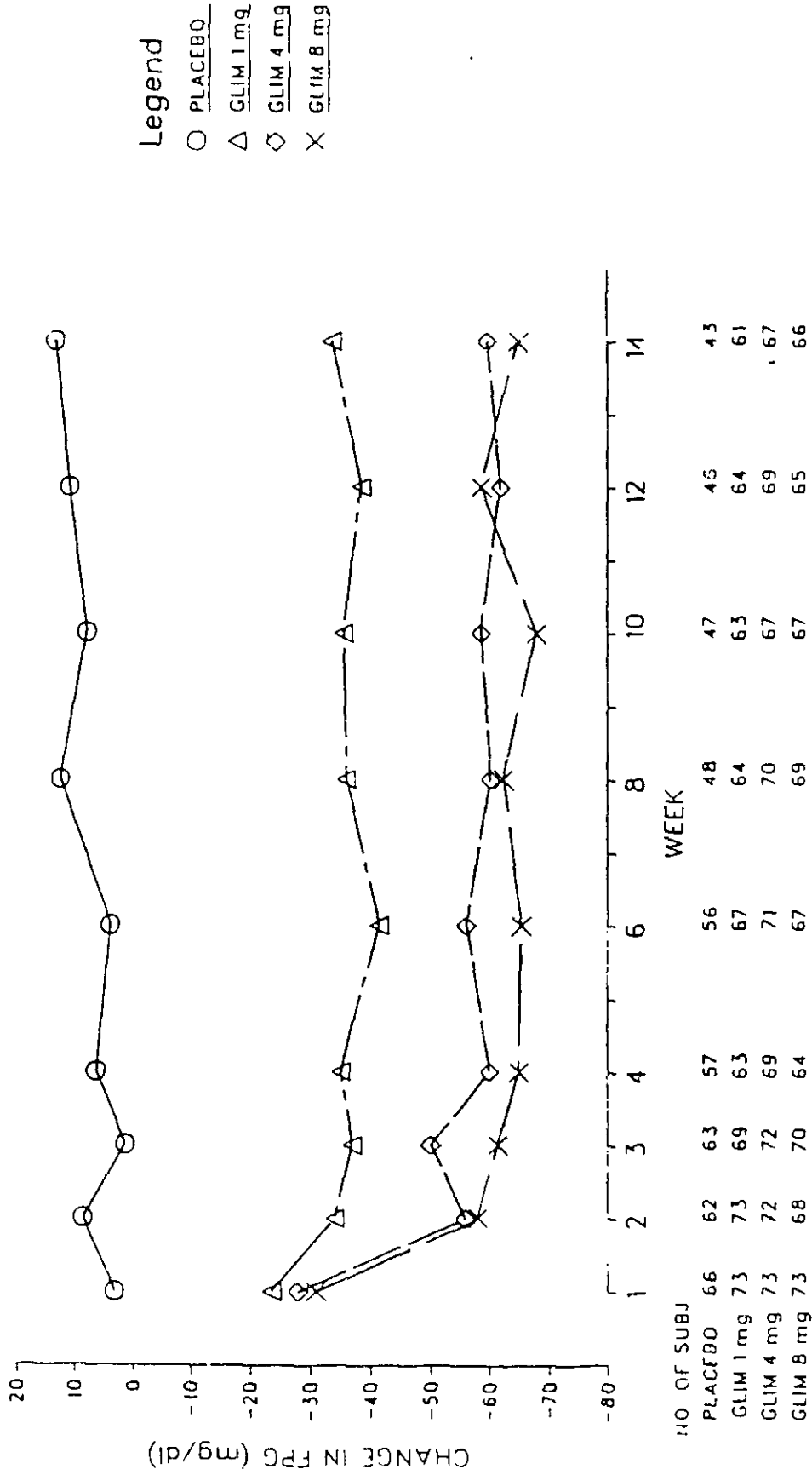


FIGURE 1.3.3

MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE AT ENDPOINT

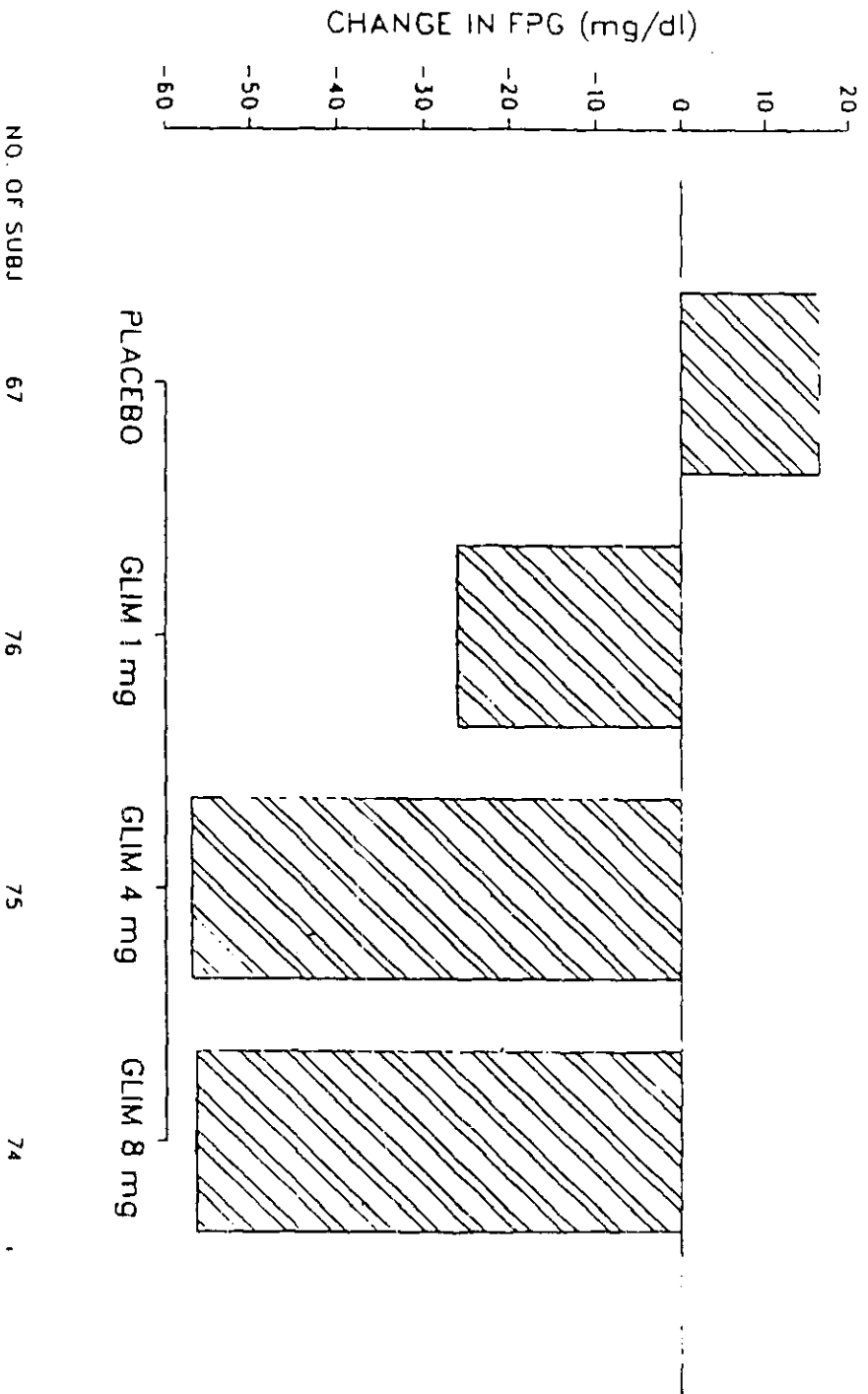


TABLE 1.4.1

MEDIAN FASTING AND POSTPRANDIAL GLUCOSE. (mg/dl) AT WEEK 8

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM			COMPARISON WITH		
								1 mg	4 mg	8 mg	1 mg	4 mg	8 mg
FPG	Placebo	53	250.0	125-338	13.0	-81-110	**	-49.50	-77.50	-78.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	65	196.0	120-307	-35.0	-188-71	***	-	-27.50	-28.50	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 4 mg	68	168.0	98-345	-60.0	-164-100	***	-	-	-1.00	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg	64	167.0	101-279	-64.3	-208-31	***	-	-	-	-	< 0.001 ***	0.762
2h PP Glyc	Placebo	54	325.0	146-474	14.5	-133-209	*	-74.00	-105.00	-108.00	< 0.001 ***	< 0.001 ***	< 0.001 ***
	Glim 1 mg	65	232.0	65-380	-56.0	-180-94	***	-	-30.00	-33.00	< 0.001 ***	< 0.001 **	< 0.001 **
	Glim 8 mg	64	210.5	96-370	-75.0	-262-15	***	-	-	-2.00	-	< 0.001 **	0.864

N = no of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
*p < 0.050, **p < 0.010, ***p < 0.001.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
*p < 0.010, **p < 0.001.

TABLE I.4.1 Contd.

MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dl) AT WEEK 14

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM				COMPARISON WITH			
								1 mg	4 mg	8 mg	P-value	1 mg	4 mg	8 mg	P-value
FPG	Placebo	42	235.0	131-456	14.8	-121-174	NS	-40.50	-67.00	-72.00	< 0.001 ***	< 0.001 ***	< 0.001 ***	< 0.001 ***	
	Gl1m 1 mg	60	199.3	123-324	-32.8	-208-105	***	-	-26.00	-30.00	0.001 **	0.001 **	0.001 **	0.001 **	
	Gl1m 8 mg	64	169.3	91-295	-62.0	-187-37	***	-	-	-4.00	-	-	-	0.791	
2h PP Gluc	Placebo	42	281.5	123-572	-0.5	-118-261	NS	-54.00	-79.00	-81.00	< 0.001 ***	< 0.001 ***	< 0.001 ***	< 0.001 ***	
	Gl1m 1 mg	60	215.5	104-420	-51.0	-197-135	***	-	-25.00	-26.00	0.025 *	0.025 *	0.065	0.817	
	Gl1m 8 mg	64	212.0	64-383	-80.0	-241-25	***	-	-	0.00	-	-	-	-	

N = no of subjects. Change = median change from baseline. - Not applicable.
 Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 ***p ≤ 0.001, NS p > 0.050.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 *p ≤ 0.050, **p ≤ 0.010, ***p ≤ 0.001.

TABLE 1.4.1 Contd.
 MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dl) AT ENDPOINT

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM				COMPARISON WITH			
								1 mg	4 mg	8 mg	P-value	1 mg	4 mg	8 mg	P-value
FPG	Placebo	54	243.8	131-456	17.0	-121-174	*	-43.50	-70.50	-77.50	< 0.001 ***	< 0.001 ***	< 0.001 ***	< 0.001 ***	
	Glim 1 mg	65	200.5	123-324	-26.0	-208-105	***	-	-26.00	-32.75	< 0.001 ***	< 0.001 ***	< 0.001 ***	< 0.001 ***	
	Glim 4 mg	69	168.0	101-345	-57.0	-187-100	***	-	-	-6.00	-	-	-	0.554	
2h PP Gluc	Placebo	55	313.0	123-572	13.0	-118-261	NS	-63.00	-91.00	-93.00	< 0.001 ***	< 0.001 ***	< 0.001 ***	< 0.001 ***	
	Glim 1 mg	65	216.0	104-420	-49.0	-197-135	***	-	-27.00	-29.00	< 0.001 ***	0.013 *	0.029 *	0.991	
	Glim 4 mg	69	204.0	77-433	-82.0	-241-52	***	-	-	-1.00	-	-	-	-	
Glim 8 mg	Glim 8 mg	64	212.0	64-383	-80.0	-294-53	***	-	-	-	-	-	-	-	

N = no of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 *p ≤ 0.050, ***p ≤ 0.001, NS p > 0.050.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 *p ≤ 0.050, ***p ≤ 0.001.

HOE 490 8/USA/201/DM - Glimepiride

TABLE 1.5.1
DOSE RESPONSE AT WEEK 8

VARIABLE	TREATMENT	N	MEDIAN	MIN	MAX	CHANGE	MIN	MAX	SHIRLEY'S t-STATISTIC
FPG	Placebo	48	247.3	127.0	338.0	12.50	-81.0	126.5	
	Glim 1 mg	64	193.5	119.5	306.5	-36.00	-187.5	50.0	6.45 **
	Glim 4 mg	70	167.0	97.5	270.5	-60.25	-163.5	22.0	8.81 **
	Glim 8 mg	69	167.0	101.0	280.0	-62.50	-208.0	30.5	8.36 **
2h PP Gluc	Placebo	54	325.0	146.0	474.0	14.50	-133.0	209.0	
	Glim 1 mg	65	232.0	65.0	380.0	-56.00	-180.0	84.0	6.41 **
	Glim 4 mg	68	202.0	78.0	433.0	-83.50	-212.0	52.0	8.55 **
	Glim 8 mg	64	210.5	86.0	370.0	-75.00	-262.0	15.0	8.42 **
HbA1c	Placebo	52	9.1	6.1	12.3	1.20	-0.9	2.9	
	Glim 1 mg	63	7.9	5.4	10.8	0.30	-1.7	2.3	5.38 **
	Glim 4 mg	63	7.7	4.9	10.7	-0.30	-2.0	1.8	7.78 **
	Glim 8 mg	64	7.5	5.5	11.0	-0.30	-3.0	2.6	8.02 **

N = no. of subjects, Change = median change from baseline, - Not applicable.
 Shirley's t-statistic from the Williams' modification of Shirley's nonparametric test (one-sided)
 on change from baseline.
 The respective one-sided critical values at the 1% level for comparing one, two, and three dose
 levels with a control are 2.326, 2.366, and 2.377.
 ** p ≤ 0.010.

TABLE 1.5.1 Contd.

DOSE RESPONSE AT WEEK 14

VARIABLE	TREATMENT	N	MEDIAN	MIN	MAX	CHANGE	MIN	MAX	SHIRLEY'S t-STATISTIC
FPG	Placebo	43	235.5	129.0	455.5	13.50	-120.5	173.5	-
	Glim 1 mg	61	200.5	103.0	324.0	-33.50	-208.0	67.5	4.21 **
	Glim 4 mg	67	167.5	98.5	300.0	-59.50	-186.5	36.5	6.48 **
	Glim 8 mg	66	166.5	91.0	295.0	-65.00	-226.0	61.5	6.54 **
2h PP Gluc	Placebo	42	281.5	123.0	572.0	-0.50	-118.0	261.0	-
	Glim 1 mg	60	215.5	104.0	420.0	-51.00	-197.0	135.0	4.31 **
	Glim 4 mg	66	201.5	77.0	395.0	-86.00	-241.0	25.0	6.20 **
	Glim 8 mg	64	212.0	64.0	383.0	-80.00	-294.0	53.0	5.95 **
HbA1c	Placebo	41	9.4	5.8	13.8	1.40	-1.6	5.1	-
	Glim 1 mg	57	8.0	5.6	11.2	0.40	-1.9	3.3	4.52 **
	Glim 4 mg	60	7.6	4.6	9.8	-0.40	-1.8	1.2	7.19 **
	Glim 8 mg	63	7.4	5.5	12.0	-0.40	-4.0	3.1	6.88 **

N = no. of subjects, Change = median change from baseline, - Not applicable.
 Shirley's t-statistic from the Williams' modification of Shirley's nonparametric test (one-sided)
 on Change from baseline.
 The respective one-sided critical values at the 1% level for comparing one, two, and three dose
 levels with a control are 2.326, 2.366, and 2.377
 ≤ 0.010.

Contd.

TABLE 1.5.1

DOSE RESPONSE AT ENDPOINT

VARIABLE	TREATMENT	N	MEDIAN	MIN	MAX	CHANGE	MIN	MAX	SHIRLEY'S 1-SIDED T-STATISTIC
FPG	Placebo	67	250.5	129.0	455.5	16.50	-120.5	173.5	-
	Glime 1 mg	76	203.0	103.0	330.0	-26.00	-208.0	110.0	5.42**
	Glime 4 mg	75	168.0	98.5	345.0	-57.00	-186.5	98.5	8.01**
	Glime 8 mg	74	167.5	91.0	295.0	-56.50	-226.0	61.5	8.04**
2h PP Gluc	Placebo	55	313.0	123.0	572.0	13.00	-118.0	261.0	-
	Glime 1 mg	65	216.0	104.0	420.0	-49.00	-197.0	135.0	5.42**
	Glime 4 mg	69	204.0	77.0	433.0	-82.00	-241.0	52.0	7.37**
	Glime 8 mg	64	212.0	64.0	383.0	-80.00	-294.0	53.0	7.06**
HbA1c	Placebo	61	9.4	5.7	13.8	1.40	-1.6	5.1	-
	Glime 1 mg	65	8.0	5.6	11.2	0.40	-1.9	3.3	5.20**
	Glime 4 mg	65	7.7	4.6	10.7	-0.40	-1.8	1.3	8.16**
	Glime 8 mg	68	7.5	5.5	12.0	-0.40	-4.0	3.1	8.03**

N = no. of subjects, Change = median change from baseline, - Not applicable.
 Shirley's t-statistic from the Williams' modification of Shirley's nonparametric test (one-sided)
 on change from baseline.
 The respective one-sided critical values at the 1% level for comparing one, two, and three dose
 levels with a control are 2.326, 2.366, and 2.377.
 p ≤ 0.010.

TABLE 1.6.1

FASTING AND POSTPRANDIAL PLASMA GLUCOSE (mg/dl), AND HEMOGLOBIN A1c (%)
AT ENDPOINT BY STRATUM

VARIABLE	TREATMENT	BASELINE FPG STRATUM	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	P-VALUE FOR STRATUM EFFECT
FPG	Placebo	Low	38	221.00	129.0-320.5	17.00	-85.0-145.5	*	< 0.001 ***
		High	29	271.00	161.0-455.5	14.00	-121-173.5	NS	
	Glim 1 mg	Low	43	180.50	122.5-330.0	-21.50	-93.0-110.0	**	
		High	33	236.50	103.0-324.0	-33.00	-208-67.5	***	
	Glim 4 mg	Low	40	153.00	98.5-252.5	-41.00	-111-36.5	***	
		High	35	185.50	132.5-345.0	-75.50	-187-99.5	***	
	Glim 8 mg	Low	45	157.00	91.0-287.0	-44.50	-132-61.5	***	
		High	29	184.00	99.5-295.0	-85.00	-226-27.0	***	
2h PP Gluc	Placebo	Low	33	280.00	123.0-474.0	22.00	-108-209.0	NS	< 0.001 ***
		High	22	331.50	169.0-572.0	-0.50	-118-261.0	NS	
	Glim 1 mg	Low	39	198.00	104.0-323.0	-49.00	-142-135.0	***	
		High	26	277.00	135.0-420.0	-51.50	-197-98.0	***	
	Glim 4 mg	Low	38	187.50	77.0-343.0	-71.00	-152-10.0	***	
		High	31	240.00	127.0-433.0	-104	-241-52.0	***	
	Glim 8 mg	Low	36	200.00	127.0-326.0	-59.00	-189-53.0	***	
		High	28	238.50	64.0-383.0	-110.5	-294-25.0	***	

Low = <= 240 mg/dl, High = > 240 mg/dl
 N = no. of subjects, Change = median change from baseline, - Not applicable.
 Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 *p < 0.050, **p < 0.010, ***p < 0.001, NS p > 0.050.
 P-values from Mantel-Haenszel test, adjusting for treatment groups effect, of change from baseline data (two-tailed).
 ***p < 0.001.

TABLE 1.6.1(CONT'D)

FASTING AND POSTPRANDIAL PLASMA GLUCOSE (mg/dl) AND HEMOGLOBIN A1c (%)
AT ENDPOINT BY STRATUM

VARIABLE	TREATMENT	BASELINE FPG STRATUM	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	P-VALUE FOR STRATUM EFFECT
HbA1c	Placebo	Low	33	9.00	5.7-13.2	1.40	-0.8-5.1	***	0.098
		High	26	10.05	5.8-13.8	1.75	-1.6-4.4	***	
	Glim 1 mg	Low	38	7.45	5.6-10.2	0.05	-1.9-3.0	NS	
		High	27	9.10	6.1-11.2	0.50	-0.9-3.3	***	
	Glim 4 mg	Low	36	7.10	4.6-8.7	-0.45	-1.8-1.0	***	
		High	29	8.20	6.7-10.7	-0.20	-1.5-1.3	NS	
	Glim 8 mg	Low	39	7.00	5.8-11.7	-0.30	-1.9-1.7	*	
		High	29	7.70	5.5-12.0	-0.70	-4.0-3.1	*	

Low = <= 240 mg/dl, High = > 240 mg/dl

N = no. of subjects, Change = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
*p < 0.050, ***p < 0.001, NS p > 0.050.

P-values from Mantel-Haenszel test, adjusting for treatment groups effect, of change from baseline data (two-tailed test).
No significant differences were found.

Table 2.1.1
SCHEDULE OF EVALUATIONS

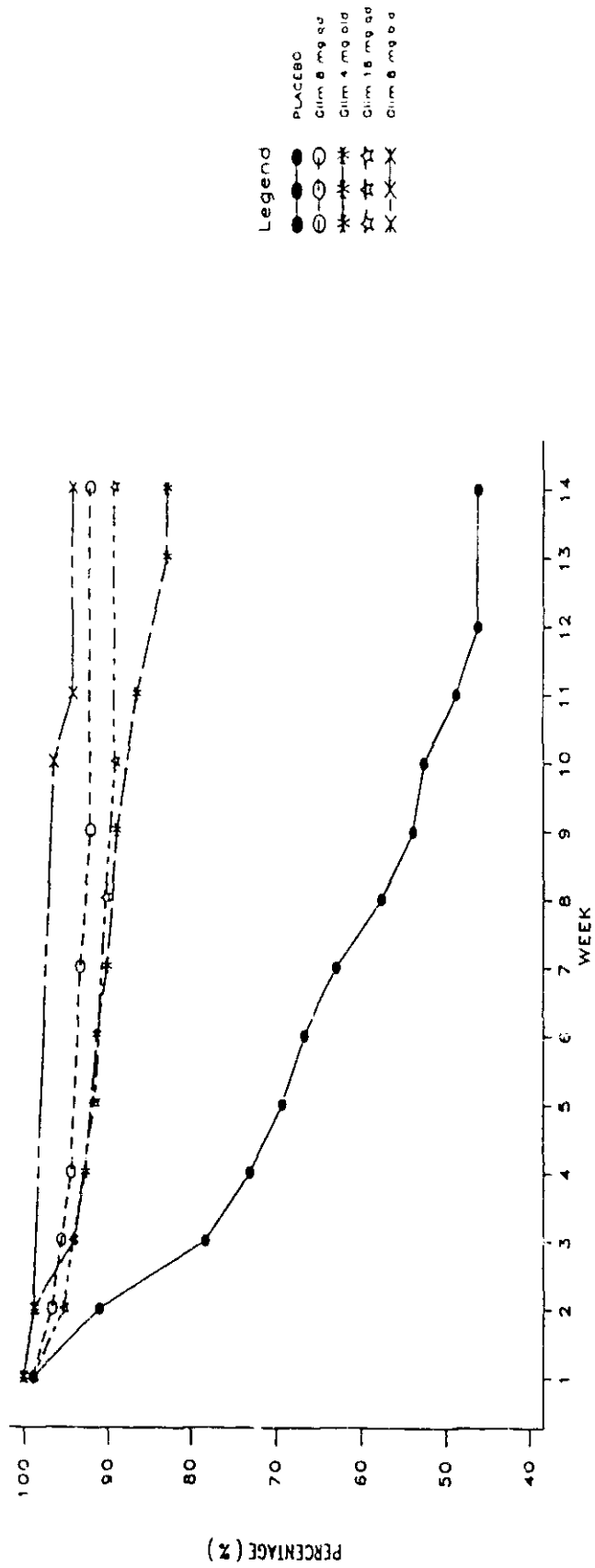
	Prerandomization				Double-blind Randomization Phase							
	Phase		B/R ^a		1	2	4	6	8	10	12	14
Day:	-21	-7	-3	1								
Week:				0	1	2	4	6	8	10	12	14
Medical history	X											
Physical examination	X			X					X			X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X
Glucometer reading	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X			X					X			X
Hemoglobin A1c	X			X			X		X		X	X
2-hr PPG				X		X			X			X
Fasting and 2-hr PP C-peptide/insulin				X		X			X			X
Lipid profile	X			X					X			X
ECG				X								X
Drug levels												
Fasting and 2-hr PP						X			X			X
Fasting					X		X	X		X	X	
Adverse events	As reported											
Concomitant Medications	As required											
Ad hoc visits	As required											
Final report												X

Week 0 = Baseline for the randomization phase

^aBaseline/Randomization

Figure 2.1.2

PERCENTAGE OF PATIENTS IN STUDY OVER TIME (IN WEEKS)
SUBJECTS DISCONTINUED FOR ANY REASON



HOE 490 8/USA/205/DM - Glimepiride

TABLE 2.1.3
DURATION OF TREATMENT

NO. DAYS TREATED	PLACEBO		Glim 8 mg qd		Glim 4 mg bid		Glim 16 mg qd		Glim 8 mg bid	
	N	%	N	%	N	%	N	%	N	%
< 14	8	10.1	3	3.4	1	1.2	4	4.8	2	2.4
14-27	14	17.7	2	2.3	5	6.2	1	1.2	0	0.0
28-41	5	6.3	0	0.0	1	1.2	2	2.4	0	0.0
42-55	7	8.9	1	1.1	1	1.2	1	1.2	0	0.0
56-69	4	5.1	1	1.1	1	1.2	1	1.2	2	2.4
70-83	5	6.3	0	0.0	2	2.5	1	1.2	2	2.4
84-97	11	13.9	26	28.5	16	19.8	15	18.1	19	22.4
> 97	25	31.6	55	62.5	54	66.7	58	69.9	60	70.6
TOTAL NO. OF SUBJ	79	100.0	88	100.0	81	100.0	83	100.0	85	100.0

TABLE 2.1.4
STUDY COMPLETION STATUS

	PLACEBO		Glim 8 mg qd		Glim 4 mg bld		Glim 16 mg qd		Glim 8 mg bld	
	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
NO. OF SUBJECTS RANDOMIZED	79		88		82		83		85	
NO. OF SUBJECTS TREATED	79 (100.0%)		88 (100.0%)		81 (100.0%)		83 (100.0%)		85 (100.0%)	
COMPLETED STUDY	36 (45.6%)		81 (92.0%)		67 (82.7%)		74 (89.2%)		79 (92.9%)	
DID NOT COMPLETE STUDY	43 (54.4%)		7 (8.0%)		14 (17.3%)		9 (10.8%)		6 (7.1%)	
P-VALUE FOR COMPARISON WITH PLACEBO	-		0.001		0.001		0.001		0.001	
REASON FOR NOT COMPLETING										
Safety/Lack of Eff: Hyperglycemia	32 (40.5%)		1 (1.1%)		4 (4.9%)		2 (2.4%)		0 (0.0%)	
Safety: Hypoglycemia	0 (0.0%)		0 (0.0%)		1 (1.2%)		2 (2.4%)		1 (1.2%)	
Safety: Adverse Event	1 (1.3%)		2 (2.3%)		3 (3.7%)		2 (2.4%)		0 (0.0%)	
Safety: Laboratory	1 (1.3%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)	
Safety: Intercurrent Medical Problem	1 (1.3%)		1 (1.1%)		0 (0.0%)		0 (0.0%)		1 (1.2%)	
Patient Unreliable/Uncooperative	2 (2.5%)		1 (1.1%)		1 (1.2%)		1 (1.2%)		0 (0.0%)	
Patient Dissatisfied With Treatment	4 (5.1%)		1 (1.1%)		0 (0.0%)		0 (0.0%)		0 (0.0%)	
Other	2 (2.5%)		1 (1.1%)		5 (6.2%)		2 (2.4%)		4 (4.7%)	

The Mantel-Haenszel Test (two-tailed) was used to compare proportions of subjects who did not complete the study.

TABLE 2.2.1
MEDIAN HEMOGLOBIN A1c (%)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
Baseline	PLACEBO	66	7.70	5-11	-	---		-	0.182	
	Glime 8 mg qd	76	7.90	6-10	-	---		0.10	-	0.881
	Glime 4 mg bid	74	8.00	6-11	-	---		0.20	-	0.369
	Glime 16 mg qd	75	8.00	6-11	-	---		0.10	-	0.561
	Glime 8 mg bid	80	8.05	6-11	-	---		0.30	-	0.046 *
Week 4	PLACEBO	60	8.70	6-13	0.9	-1-3	***	-	< 0.001 ***	< 0.001 ***
	Glime 8 mg qd	71	7.70	6-10	-0.2	-2-1	***	-1.10	-	< 0.001 ***
	Glime 4 mg bid	69	7.90	6-11	-0.1	-1-1	**	-1.10	-	< 0.001 ***
	Glime 16 mg qd	73	7.70	5-10	-0.2	-1-1	***	-1.10	-	< 0.001 ***
	Glime 8 mg bid	75	7.80	6-11	-0.2	-1-1	***	-1.20	-	< 0.001 ***
Week 8	PLACEBO	48	9.45	5-12	1.5	-2-3	***	-	< 0.001 ***	< 0.001 ***
	Glime 8 mg qd	73	7.50	5-10	-0.4	-4-1	***	-2.00	-	< 0.001 ***
	Glime 4 mg bid	69	7.70	6-12	-0.4	-2-3	***	-1.90	-	< 0.001 ***
	Glime 16 mg qd	71	7.60	5-10	-0.3	-2-1	***	-1.90	-	< 0.001 ***
	Glime 8 mg bid	78	7.60	5-11	-0.5	-2-1	***	-2.10	-	< 0.001 ***
Week 12	PLACEBO	31	9.50	6-13	1.3	-1-3	***	-	< 0.001 ***	< 0.001 ***
	Glime 8 mg qd	70	7.40	6-10	-0.5	-4-1	***	-1.90	-	< 0.001 ***
	Glime 4 mg bid	63	7.60	5-11	-0.6	-2-2	***	-1.90	-	< 0.001 ***
	Glime 16 mg qd	66	7.40	5-11	-0.5	-2-1	***	-1.80	-	< 0.001 ***
	Glime 8 mg bid	69	7.40	6-10	-0.6	-3-2	***	-2.00	-	< 0.001 ***

N = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
p ≤ 0.010, *p ≤ 0.001.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).
***p ≤ 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).
*p ≤ 0.050, **p ≤ 0.001.

TABLE 2.2.1 Contd.

MEDIAN HEMOGLOBIN A1c (%)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
Week 14	PLACEBO	34	9.15	6-13	1.4	-1-3	***	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	71	7.70	6-10	-0.5	-3-1	***	-2.10	-	< 0.001 ***
	Glim 4 mg bid	65	7.60	5-10	-0.6	-2-1	***	-1.90	-	< 0.001 ***
	Glim 16 mg qd	66	7.40	5-11	-0.5	-2-1	***	-2.30	-	< 0.001 ***
Endpoint	PLACEBO	66	9.65	6-13	1.4	-1-3	***	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	76	7.45	6-10	-0.5	-3-1	***	-2.00	-	< 0.001 ***
	Glim 4 mg bid	74	7.60	5-11	-0.5	-2-2	***	-2.00	-	< 0.001 ***
	Glim 16 mg qd	75	7.40	5-11	-0.5	-2-1	***	-1.90	-	< 0.001 ***
	Glim 8 mg bid	80	7.35	6-11	-0.7	-3-2	***	-2.20	-	< 0.001 ***

N = no. of subjects. Change = median change from baseline. - Not applicable.

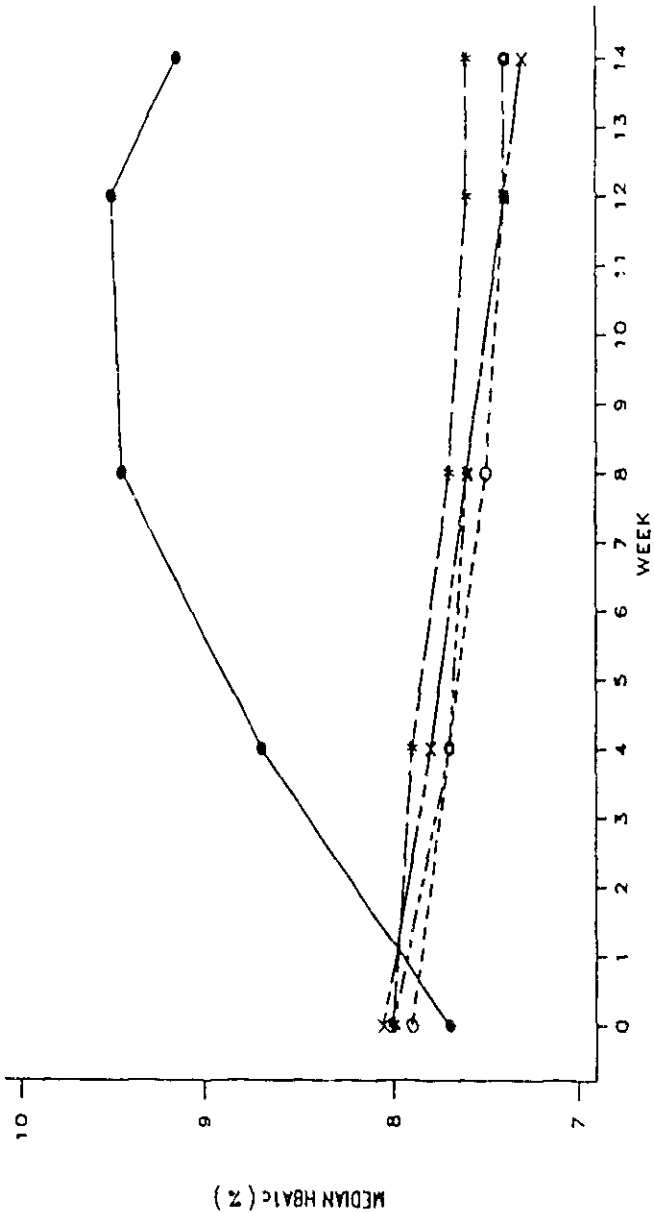
Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
***p < 0.001.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).
***p < 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).
***p < 0.001.

Figure 2.2.2

MEDIAN HbA1c (%) LEVELS BY VISIT



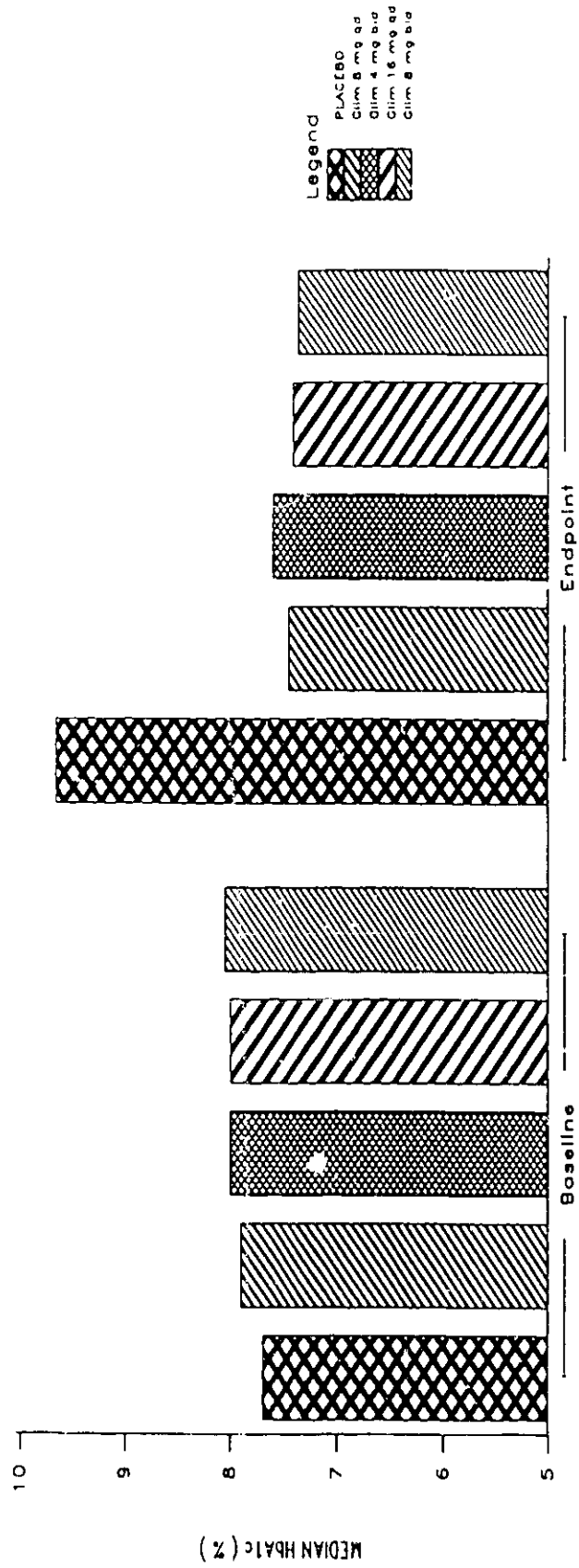
Legend
 ●—● PLACERO
 ○—○ Glim 8 mg qd
 — Glim 4 mg bid
 ☆—☆ Glim 16 mg qd
 X—X Glim 8 mg bid

NO. OF SUBJ	66	60	48	31	34
PLACERO	76	71	73	70	71
Glim 8 mg qd	74	69	69	63	65
Glim 4 mg bid	75	73	71	66	68
Glim 16 mg qd	80	75	79	69	73
Glim 8 mg bid					

At all post-saline visits, glimepiride lowered HbA1c more than placebo (p < 0.01).

Figure 2.2.3

HEMOGLOBIN A1c (%) - ENDPOINT DATA SET



WEEK

HOE 490 8/USA/205/DM - Glimepiride

TABLE 2.3.1
 MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
Baseline	PLACEBO	76	233.5	167-340	-	---		-	0.557	
	Glime 8 mg qd	87	231.0	183-324	-	---		4.0	-	0.895
	Glime 4 mg bid	80	229.0	140-306	-	---		0.0	-	0.448
	Glime 16 mg qd	82	222.5	144-342	-	---		-6.0	-	0.607
	Glime 8 mg bid	83	233.0	157-320	-	---		2.0	-	0.535
Week 1	PLACEBO	74	224.5	140-515	0.5	-69-230	NS	-	< 0.001	***
	Glime 8 mg qd	83	176.0	103-283	-56.0	-145-34	***	-57.0	-	< 0.001
	Glime 4 mg bid	80	179.5	79-280	-50.5	-162-8	***	-51.0	-	< 0.001
	Glime 16 mg qd	80	173.5	122-271	-40.5	-200-18	***	-44.0	-	< 0.001
	Glime 8 mg bid	82	178.0	70-268	-53.0	-150-9	***	-54.0	-	< 0.001
Week 2	PLACEBO	65	237.0	126-540	11.0	-103-281	NS	-	< 0.001	***
	Glime 8 mg qd	76	168.5	76-254	-66.0	-171-10	***	-71.0	-	< 0.001
	Glime 4 mg bid	75	160.0	100-234	-68.0	-152-26	***	-78.0	-	< 0.001
	Glime 16 mg qd	73	170.0	95-270	-55.0	-135-27	***	-68.0	-	< 0.001
	Glime 8 mg bid	73	166.0	86-260	-71.0	-170-35	***	-80.0	-	< 0.001
Week 4	PLACEBO	58	239.5	116-342	17.5	-111-98	**	-	< 0.001	***
	Glime 8 mg qd	80	168.0	93-307	-62.5	-194-10	***	-81.0	-	< 0.001
	Glime 4 mg bid	74	156.0	87-254	-65.5	-180-37	***	-84.0	-	< 0.001
	Glime 16 mg qd	75	163.0	106-283	-56.0	-158-50	***	-78.0	-	< 0.001
	Glime 8 mg bid	82	167.5	80-240	-65.0	-176-11	***	-82.0	-	< 0.001

N = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 p ≤ 0.010, *p ≤ 0.001, NS p > 0.050.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).
 ***p ≤ 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).
 ***p ≤ 0.001.

Contd.

TABLE 2.3.1 Contd.
 MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
Week 6	PLACEBO	49	249.0	108-368	4.0	-130-155	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	79	159.0	83-282	-72.0	-206-47	***	-83.0	-	< 0.001 ***
	Glim 4 mg bid	74	159.0	103-268	-69.5	-178-21	***	-80.0	-	< 0.001 ***
	Glim 16 mg qd	73	164.0	81-287	-59.0	-204-28	***	-71.0	-	< 0.001 ***
	Glim 8 mg bid	81	156.0	83-251	-72.0	-185-49	***	-83.0	-	< 0.001 ***
Week 8	PLACEBO	47	243.0	128-386	15.0	-124-138	*	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	82	161.5	83-353	-63.5	-168-56	***	-89.0	-	< 0.001 ***
	Glim 4 mg bid	68	157.0	62-277	-71.0	-174-30	***	-91.0	-	< 0.001 ***
	Glim 16 mg qd	76	164.5	104-309	-63.0	-141-72	***	-78.0	-	< 0.001 ***
	Glim 8 mg bid	82	156.5	78-262	-71.0	-196-18	***	-93.0	-	< 0.001 ***
Week 10	PLACEBO	41	252.0	161-341	8.0	-106-106	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	79	167.0	76-263	-63.0	-166-18	***	-77.0	-	< 0.001 ***
	Glim 4 mg bid	71	150.0	82-258	-74.0	-206-20	***	-83.0	-	< 0.001 ***
	Glim 16 mg qd	71	165.0	86-323	-56.0	-178-86	***	-64.0	-	< 0.001 ***
	Glim 8 mg bid	81	159.0	68-285	-73.0	-193-26	***	-82.0	-	< 0.001 ***
Week 12	PLACEBO	35	227.0	129-315	14.0	-120-97	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	79	161.0	79-408	-59.0	-152-111	***	-78.0	-	< 0.001 ***
	Glim 4 mg bid	69	154.0	79-279	-74.0	-156-26	***	-82.0	-	< 0.001 ***
	Glim 16 mg qd	70	166.5	103-353	-57.5	-141-120	***	-70.0	-	< 0.001 ***
	Glim 8 mg bid	77	161.0	64-275	-80.0	-240-73	***	-84.0	-	< 0.001 ***

H = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

*p ≤ 0.050. ***p ≤ 0.001. NS p > 0.050.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).

***p ≤ 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).

***p ≤ 0.001.

TABLE 2.3.1 Contd.
 MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
Week 14	PLACEBO	34	230.0	135-382	6.0	-149-179	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	76	175.0	105-255	-50.5	-154-27	***	-73.0	-	< 0.001 ***
	Glim 4 mg bid	66	151.5	79-292	-72.0	-166-70	***	-83.0	-	< 0.001 ***
	Glim 16 mg qd	70	159.0	78-358	-58.0	-150-121	***	-69.0	-	< 0.001 ***
Endpoint	Glim 8 mg bid	76	160.5	75-283	-73.0	-194-89	***	-81.0	-	< 0.001 ***
	PLACEBO	76	251.5	135-540	24.0	-149-291	***	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	87	177.0	103-408	-59.0	-154-111	***	-85.0	-	< 0.001 ***
	Glim 4 mg bid	80	154.5	78-292	-68.5	-166-70	***	-92.5	-	< 0.001 ***
	Glim 16 mg qd	82	158.0	78-358	-60.0	-200-121	***	-85.0	-	< 0.001 ***
	Glim 8 mg bid	83	160.0	75-293	-74.0	-194-99	***	-95.0	-	< 0.001 ***

N = no. of subjects. Change = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

***p < 0.001, NS p > 0.050.

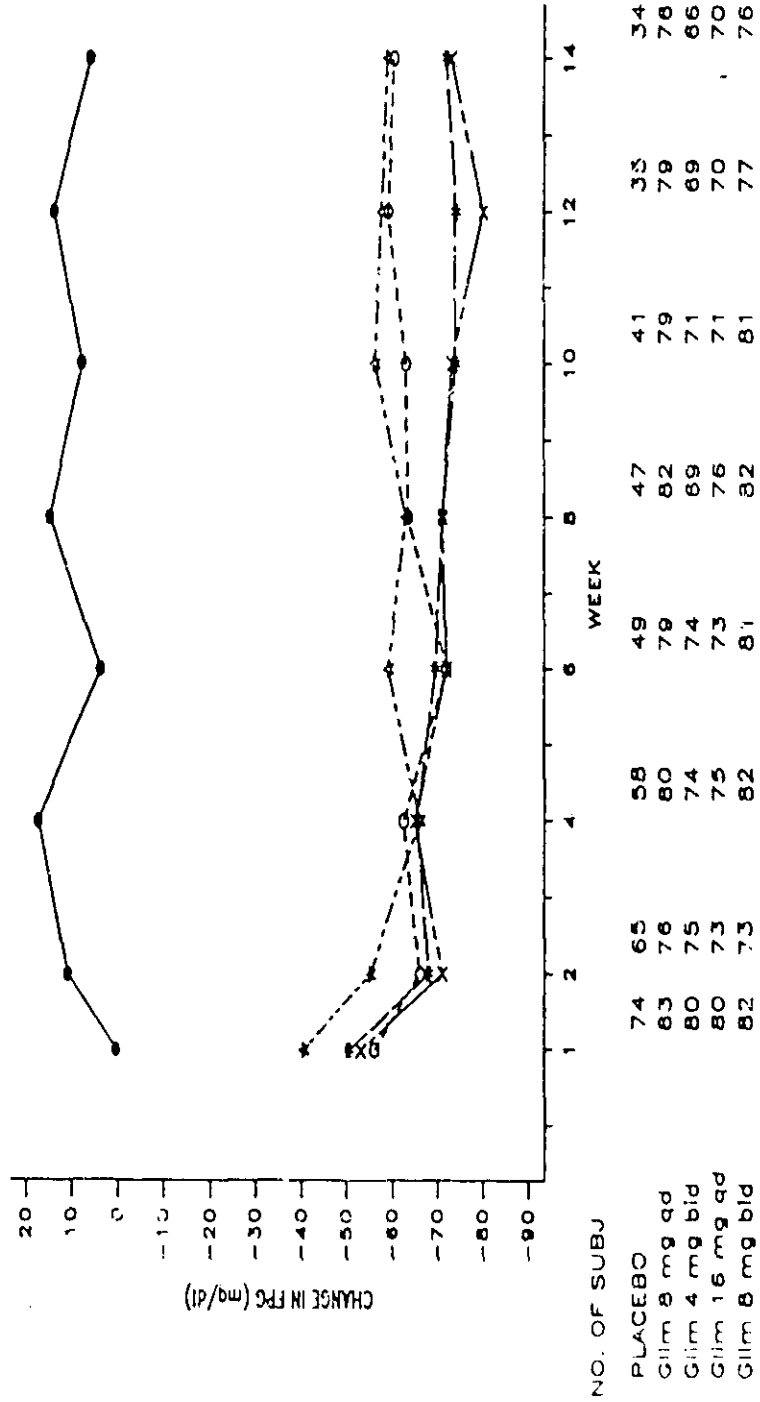
P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test)

***p < 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).

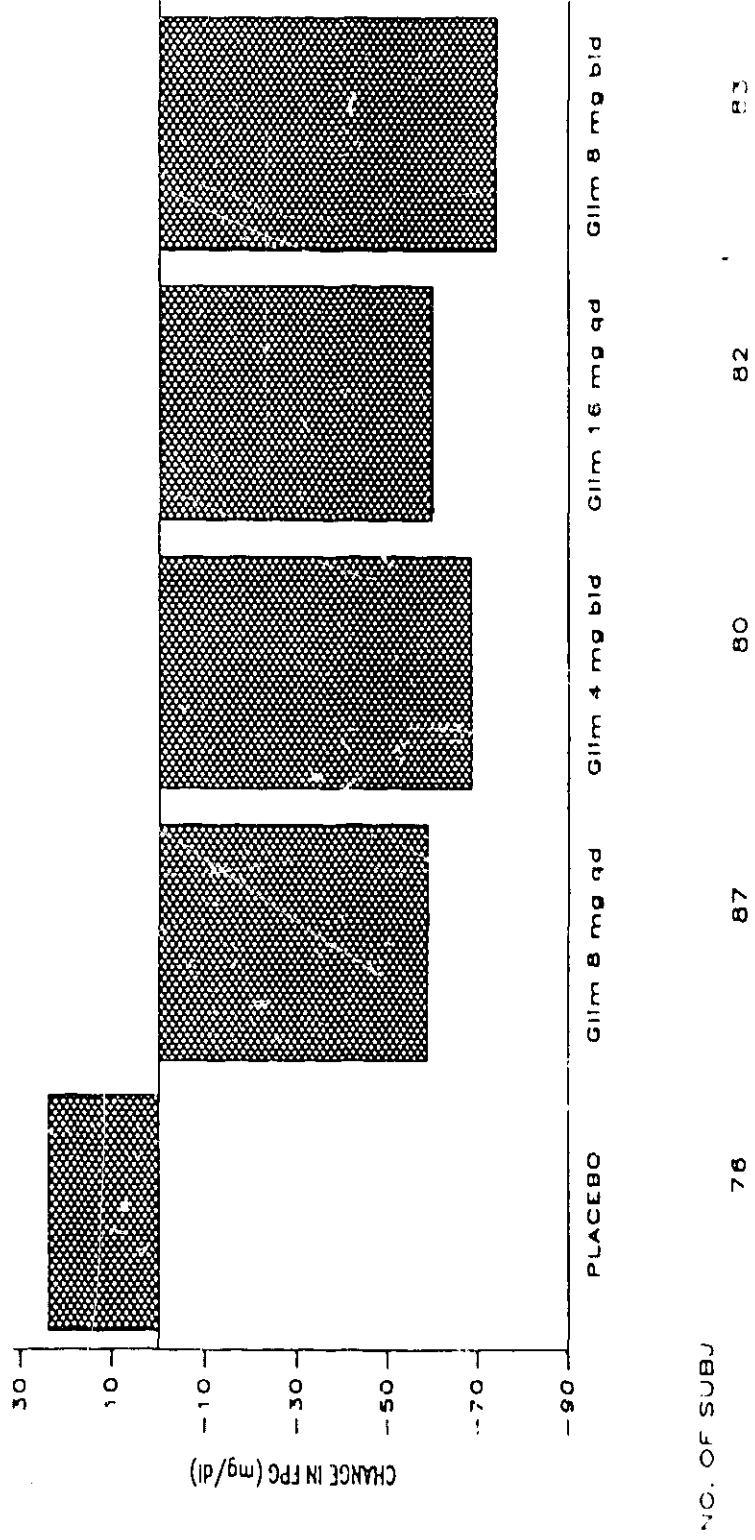
***p < 0.001.

FIGURE 2.3.2
 MEDIAN FASTING PLASMA GLUCOSE (FPG)
 CHANGE FROM BASELINE



Legend
 ● PLACEBO
 ○ Glim 8 mg qd
 * Glim 4 mg bid
 ☆ Glim 16 mg qd
 X Glim 8 mg bid

FIGURE 2.3.3
MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE AT ENDPOINT



HOE 490 8/USA/205/DM - Glimperide

TABLE 2.4.1
 MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dl) AT WEEK 2

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
FPG	PLACEBO	65	246.0	126-353	7.0	-103-108	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	81	170.0	76-254	-66.0	-171-10	***	-69.0	-	< 0.001 ***
	Glim 4 mg bid	74	158.0	100-234	-69.0	-152-26	***	-75.0	-	< 0.001 ***
	Glim 16 mg qd	77	170.0	95-270	-55.0	-135-27	***	-64.0	-	< 0.001 ***
	Glim 8 mg bid	78	167.5	86-260	-68.5	-153-35	***	-74.0	-	< 0.001 ***
2h PP Gluc	PLACEBO	65	309.0	170-512	15.0	-119-151	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	81	219.0	97-384	-85.0	-213-88	***	-91.0	-	< 0.001 ***
	Glim 4 mg bid	74	224.5	85-317	-67.5	-220-73	***	-78.0	-	< 0.001 ***
	Glim 16 mg qd	78	225.5	122-361	-73.0	-177-23	***	-80.0	-	< 0.001 ***
	Glim 8 mg bid	79	230.0	88-353	-76.0	-162-27	***	-69.0	-	< 0.001 ***

n = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

*** p < 0.001, NS p > 0.050.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test)

*** p < 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test)

*** p < 0.001.

Contd.

TABLE 2.4.1 Contd.

MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dL) AT WEEK 8

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
FPG	PLACEBO	46	243.5	129-386	17.5	-99-138	*	-	< 0.001	***
	Glim 8 mg qd	81	161.0	83-353	-65.0	-168-56	***	-90.0	-	< 0.001
	Glim 4 mg bid	69	157.0	62-277	-73.0	-174-30	***	-91.5	-	< 0.001
	Glim 16 mg qd	75	163.0	104-309	-61.0	-141-72	***	-77.5	-	< 0.001
	Glim 8 mg bid	81	157.0	79-262	-70.0	-196-8	***	-93.0	-	< 0.001
2h PP Gluc	PLACEBO	46	292.5	157-475	26.0	-157-139	*	-	< 0.001	***
	Glim 8 mg qd	81	202.0	87-386	-103.0	-221-46	***	-122.0	-	< 0.001
	Glim 4 mg bid	69	200.0	110-328	-74.0	-304-69	***	-101.0	-	< 0.001
	Glim 16 mg qd	75	218.0	98-412	-81.0	-206-79	***	-104.0	-	< 0.001
	Glim 8 mg bid	82	226.5	93-416	-81.5	-239-36	***	-110.0	-	< 0.001

N = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
*p ≤ 0.050, ***p ≤ 0.001.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).
***p ≤ 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).
***p ≤ 0.001.

TABLE 2.4.1 Contd.

MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dl) AT WEEK 14

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
FPG	PLACEBO	35	230.0	135-337	6.0	-149-121	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	77	175.0	105-255	-61.0	-154-27	***	-71.0	-	< 0.001 ***
	Glim 4 mg bid	64	151.5	79-292	-72.0	-166-70	***	-81.0	-	< 0.001 ***
	Glim 16 mg qd	73	164.0	78-358	-58.0	-150-121	***	-66.0	-	< 0.001 ***
2h PP Gluc	Glim 8 mg bid	76	161.5	75-293	-71.5	-194-99	***	-77.0	-	< 0.001 ***
	PLACEBO	35	298.0	174-448	9.0	-166-203	NS	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	77	214.0	72-329	-94.0	-267-44	***	-105.0	-	< 0.001 ***
	Glim 4 mg bid	64	202.5	77-364	-83.5	-201-72	***	-96.0	-	< 0.001 ***
	Glim 16 mg qd	73	220.0	117-419	-77.0	-218-108	***	-86.0	-	< 0.001 ***
	Glim 8 mg bid	77	222.0	89-412	-76.0	-259-109	***	-95.0	-	< 0.001 ***

N = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

***p < 0.001; NS p > 0.050.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).
***p < 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).
***p < 0.001.

TABLE 2.4.1 Contd.

MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dl) AT ENDPOINT

VARIABLE	TREATMENT	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	DIFFERENCE FROM PLACEBO	P-VALUE FOR OVERALL TREATMENT	P-VALUE FOR COMPARISON WITH PLACEBO
FPG	PLACEBO	65	260.0	135-386	18.0	-149-138	**	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	83	177.0	105-353	-59.0	-154-56	***	-83.0	-	< 0.001 ***
	Glim 4 mg bid	75	150.0	79-292	-71.0	-174-70	***	-93.0	-	< 0.001 ***
	Glim 16 mg qd	79	160.0	78-358	-83.0	-150-121	***	-83.0	-	< 0.001 ***
2h PP Gluc	Glim 8 mg bid	81	159.0	75-293	-72.0	-194-99	***	-92.0	-	< 0.001 ***
	PLACEBO	65	322.0	157-512	31.0	-166-203	***	-	< 0.001 ***	< 0.001 ***
	Glim 8 mg qd	83	214.0	72-386	-94.0	-267-88	***	-119.0	-	< 0.001 ***
	Glim 4 mg bid	75	204.0	77-364	-78.0	-304-72	***	-107.0	-	< 0.001 ***
	Glim 16 mg qd	79	220.0	117-419	-77.0	-218-108	***	-103.0	-	< 0.001 ***
	Glim 8 mg bid	82	221.5	89-412	-78.0	-259-109	***	-113.0	-	< 0.001 ***

N = no. of subjects. Change = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 p ≤ 0.010, *p ≤ 0.001.

P-value from Cochran-Mantel-Haenszel for overall treatment effect of baseline and change from baseline data (two-tailed test).
 ***p ≤ 0.001.

P-values from Mantel-Haenszel test for placebo comparisons of baseline and change from baseline data (two-tailed test).
 ***p ≤ 0.001.

HOE 490 8/USA/205/DM - Glimepiride

TABLE 2.5.1
INTERVAL ESTIMATIONS FOR BETWEEN TREATMENT DIFFERENCES
CHANGE FROM BASELINE AT ENDPOINT

VARIABLE	TREATMENT	DIFF	95 % CI	P-VALUE
HbA1c	8 mg qd vs 4 mg bid	0.1	-0.2 ; 0.3	0.694
	16 mg qd vs 8 mg bid	-0.3	-0.5 ; -0.0	0.024 *
	8 mg qd vs 16 mg qd	0.1	-0.1 ; 0.3	0.415
	4 mg bid vs 8 mg bid	-0.2	-0.5 ; 0.0	0.079

N = no. of subjects.

P-values from Wilcoxon rank sum test (two-tailed test).

Confidence interval (CI) based on Wilcoxon rank sum test.
*p ≤ 0.050.

HOE 490 8/USA/205/DM - Glimepiride

TABLE 2.6.1
FASTING AND POSTPRANDIAL PLASMA GLUCOSE (mg/dl), AND HEMOGLOBIN A1c (%)
AT ENDPOINT BY STRATUM

VARIABLE	TREATMENT	BASELINE FPG STRATUM	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	P-VALUE FOR STRATUM EFFECT
FPG	PLACE80	Low	44	227.0	135-382	37.0	-67-179	***	< 0.001 ***
		High	32	297.0	163-540	12.0	-149-291	NS	
	Glim 8 mg qd	Low	46	159.5	105-247	-45.0	-119-27	***	***
		High	41	185.0	119-408	-85.0	-154-111	***	
	Glim 4 mg bld	Low	44	145.5	79-288	-55.5	-109-70	***	***
		High	36	170.5	121-292	-103.0	-166-27	***	
	Glim 16 mg qd	Low	52	145.0	78-358	-55.0	-133-121	***	***
		High	30	189.0	130-294	-87.5	-200-33	***	
	Glim 8 mg bld	Low	48	156.0	75-293	-46.5	-137-99	***	***
		High	35	166.0	92-254	-106.0	-194--34	***	

Low = <= 240 mg/dl, High = > 240 mg/dl

N = no. of subjects, Change = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

***p ≤ 0.001, NS p > 0.050.

P-values from Mantel-Haenszel test, adjusting for treatment group effect, of change from baseline data (two-tailed test).
***p ≤ 0.001.

Contd.

TABLE 2.6.1 (CONTD)

FASTING AND POSTPRANDIAL PLASMA GLUCOSE (mg/dl), AND HEMOGLOBIN A1c (%)
AT ENDPOINT BY STRATUM

VARIABLE	TREATMENT	BASELINE FPG STRATUM	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	P-VALUE FOR STRATUM EFFECT
2h PP Gluc	PLACEBO	Low	38	280.5	157-478	42.5	-157-203	**	< 0.001 ***
		High	27	379.0	188-512	19.0	-166-139	NS	
	Glim 8 mg qd	Low	44	207.0	72-290	-72.0	-240-31	***	***
		High	39	231.0	131-386	-109.0	-267-88	***	
	Glim 4 mg bld	Low	42	176.0	77-321	-71.5	-207-72	***	***
		High	33	235.0	129-364	-105.0	-304-63	***	
	Glim 16 mg qd	Low	50	202.0	117-419	-56.5	-155-108	***	***
		High	29	266.0	120-349	-100.0	-218-50	***	
	Glim 8 mg bld	Low	48	218.5	89-412	-66.0	-139-109	***	***
		High	34	230.0	128-373	-113.0	-259--42	***	

Low = <= 240 mg/dl, High = > 240 mg/dl
 N = no. of subjects, Change = median change from baseline. - Not applicable.
 Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
 p < 0.010, *p < 0.001, NS p > 0.050.

p-values from Mantel-Haenszel test, adjusting for treatment group effect, of change from baseline data (two-tailed test).
 ***p < 0.001.

TABLE 2.6.1 (CONTD)

FASTING AND POSTPRANDIAL PLASMA GLUCOSE (mg/dl), AND HEMOGLOBIN A1c (%)
AT ENDPOINT BY STRATUM

VARIABLE	TREATMENT	BASELINE FPG STRATUM	N	MEDIAN	RANGE	CHANGE	RANGE	SIG	P-VALUE FOR STRATUM_EFFECT
HbA1c	PLACEBO	Low	37	8.7	6-12	1.4	-0-3	***	0.520
		High	29	10.4	6-13	1.5	-1-3	***	
	Glim 8 mg qd	Low	40	7.1	6-10	-0.6	-2-1	***	
		High	36	7.7	6-10	-0.5	-3-1	***	
	Glim 4 mg bid	Low	42	7.2	5-10	-0.6	-2-1	***	
		High	32	8.0	7-11	-0.5	-2-2	**	
	Glim 16 mg qd	Low	46	6.9	5-11	-0.5	-2-1	***	
		High	29	8.5	6-11	-0.4	-2-1	*	
	Glim 8 mg bid	Low	47	7.2	6-11	-0.5	-3-2	***	
		High	33	7.8	6-10	-1.0	-3-1	***	

Low = < 240 mg/dl, High = > 240 mg/dl

N = no. of subjects, Change = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

*p ≤ 0.050, **p ≤ 0.010, ***p ≤ 0.001.

P-values from Mantel-Haenszel test, adjusting for treatment group effect, of change from baseline data (two-tailed test).
No significant differences were found.

Table 3.1.1
SCHEDULE OF OBSERVATIONS

	Pretherapy Screen		Titration								Maintenance				
	Day: Week:	-7	-1	0	2	4	6	8	10	12	14	16	18	20	22
Medical history		X													
Physical examination		X		X						X					X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinic visit		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests		X		X						X					X
Fasting glucose		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin A1c				X						X					X
2-hr PP glucose				X						X					X
Fasting and 2-hr PP C-peptide/insulin				X						X					X
Lipid profile				X						X					X
ECG				X											X
Final report															X

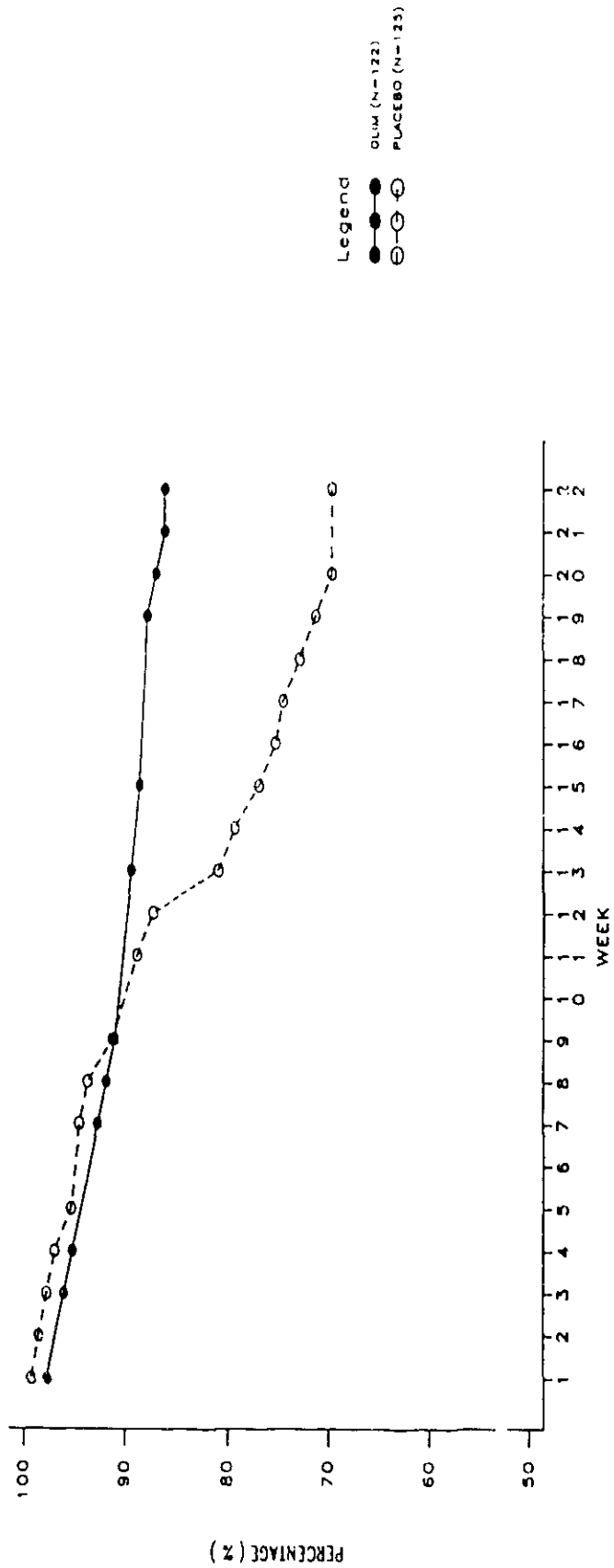
Week 0 = Baseline for the titration phase

Week 10 = Point of maximal titration dose and the beginning of the maintenance phase

Week 12 = Completion of the titration phase

Figure 3.1.2

PERCENTAGE OF PATIENTS IN STUDY OVER TIME (IN WEEKS)
SUBJECTS DISCONTINUED FOR ANY REASON



HOE 490 8/USA/202/DM - Glimepiride

TABLE 3.1.3
DURATION OF TREATMENT

NO. DAYS TREATED	GLIMEPIRIDE		PLACEBO	
	N	%	N	%
< 14	3	2.5	2	1.6
14-27	3	2.5	2	1.6
28-41	0	0.0	2	1.6
42-55	4	3.3	2	1.6
56-69	1	0.8	3	2.4
70-83	0	0.0	5	4.0
84-97	2	1.6	10	8.0
98-111	1	0.8	5	4.0
112-125	0	0.0	3	2.4
126-139	2	1.6	4	3.2
140-153	14	11.5	12	9.6
>153	92	75.4	75	60.0
TOTAL NO. OF SUBJ	122	100.0	125	100.0

HOE 490 8/USA/202/DM - Glimepiride

TABLE 3.1.4
STUDY COMPLETION STATUS

	<u>GLIMEPIRIDE</u>	<u>PLACEBO</u>	<u>BETWEEN TREATMENT P-VALUE</u>
NO. OF SUBJECTS RANDOMIZED	124	126	
NO. OF SUBJECTS TREATED	123 (100.0%)	126 (100.0%)	
COMPLETED STUDY	104 (84.6%)	84 (66.7%)	0.001 ***
DID NOT COMPLETE STUDY	19 (15.4%)	42 (33.3%)	
REASON FOR NOT COMPLETING			
Lack of Efficacy: Hyperglycemia	2 (1.6%)	7 (5.6%)	
Safety/Lack of Eff: Hyperglycemia	0 (0.0%)	6 (4.8%)	
Safety: Hypoglycemia	2 (1.6%)	0 (0.0%)	
Safety: Adverse Event	1 (0.8%)	2 (1.6%)	
Safety: Intercurrent Medical Problem	0 (0.0%)	2 (1.6%)	
Protocol Violation	1 (0.8%)	0 (0.0%)	
Unreliable/Uncooperative	5 (4.1%)	11 (8.7%)	
Lost to Follow-up	3 (2.4%)	3 (2.4%)	
Patient Dissatisfied With Treatment	1 (0.8%)	5 (4.0%)	
Other	4 (3.3%)	6 (4.8%)	

The Mantel-Haenszel Test (two-tailed) was used to compare proportions of subjects who did not complete the study
***p < 0.001

TABLE 3.2.1
 MEDIAN HEMOGLOBIN A1c (%)

VARIABLE	VISIT	GLIMEPIRIDE			PLACEBO			BETWEEN TREATMENT						
		N	MEDIAN	RANGE	CHG	RANGE	SIG	N	MEDIAN	RANGE	CHG	RANGE	SIG	DIFF
HbA1c	Base	106	9.1	6.0-14.3	-	-	-	97	8.9	5.6-13.3	-	-	0.3	0.282
	Wk 12	106	6.8	3.9-11.9	-2.0	-6.9-0.7	***	94	7.9	5.6-12.1	-0.6	-7.0-2.8	***	-1.4 < 0.001
	Wk 22	93	6.7	3.1-11.7	-2.0	-7.8-1.8	***	81	7.7	5.4-12.3	-1.0	-7.4-0.9	***	-1.1 < 0.001
	Endpt	106	6.7	3.1-11.7	-2.0	-7.8-1.8	***	97	7.9	5.4-12.3	-0.7	-7.4-2.8	***	-1.1 < 0.001

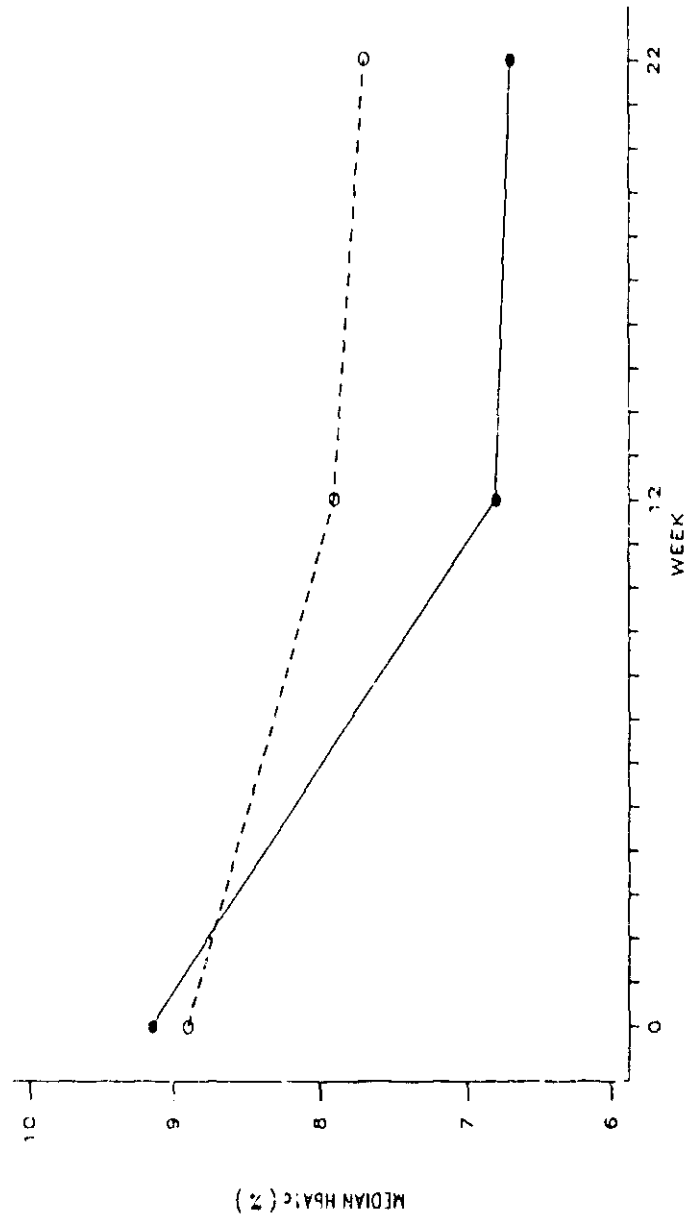
N = no of subjects. CHG = median change from baseline. - Not applicable

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed)
 *** ≤ 0.001

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test)
 *** ≤ 0.001

Figure 3.2.2

MEDIAN HbA1c (%) LEVELS BY VISIT



Legend
 ●—● G. MIPIRIDE
 ○—○ PLACEBO

N° OF SUBJ
 GLIMPIRIDE 106
 PLACEBO 97

93
81

At both baseline visits, glimpiride lowered HbA1c significantly more than placebo (p < 0.001).

Figure 3.2.3

HEMOGLOBIN A1c (%) - ENDPOINT DATA SET

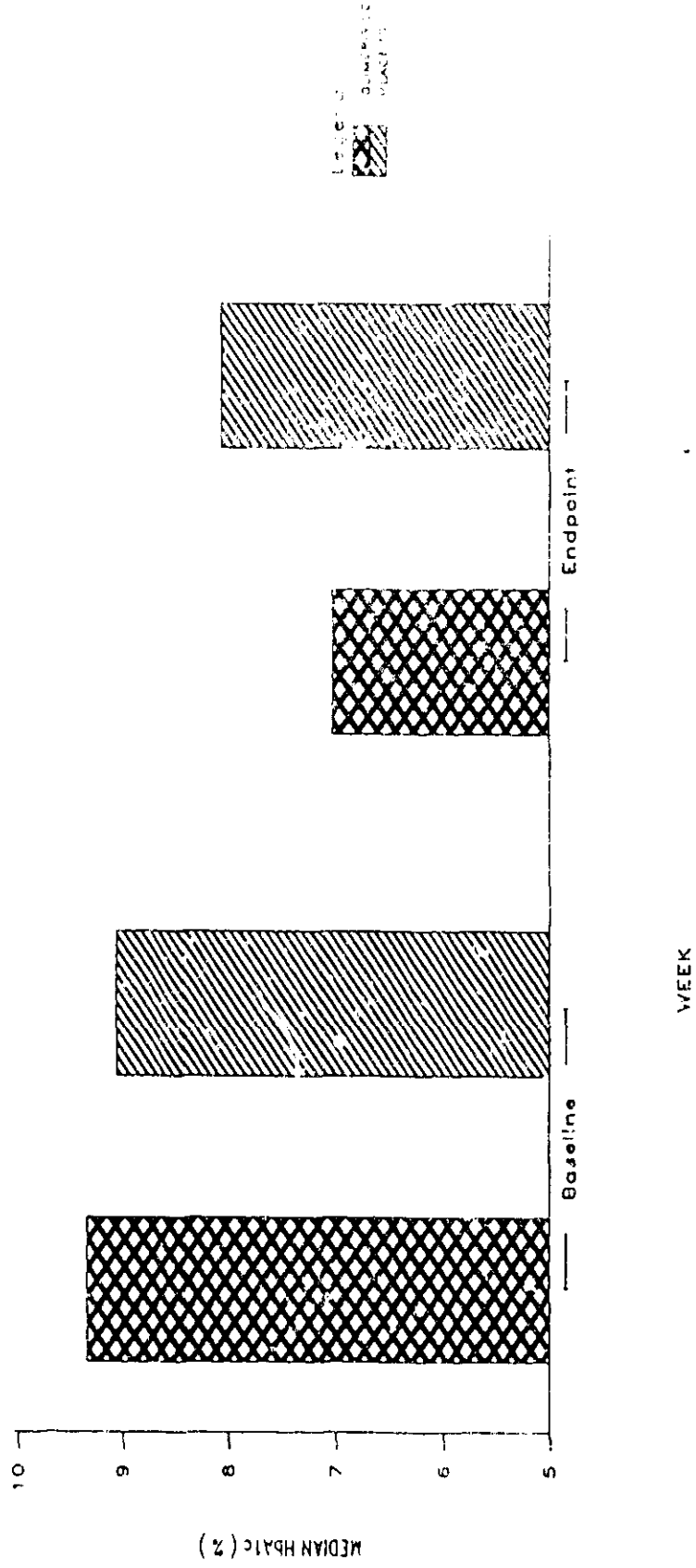


TABLE 3.2.4
 MEDIAN HbA1c AT BASELINE AND ENDPOINT
 SUBJECTS STRATIFIED BY BASELINE HbA1c VALUES

BASELINE HbA1c	VISIT	GLIMEPIRIDE			PLACEBO			BEFORE TREATMENT							
		N	MEDIAN	RANGE	CHG	RANGE	SIG	N	MEDIAN	RANGE	CHG	RANGE	SIG	DIFF	P-VALUE
< 75 PCNTL	Base	30	11.3	10.5-14.3	-	-	-	22	11.2	10.5-13.3	-	-	-	0.1	0.691
	Endpt	30	7.7	5.8-11.7	-3.7	-7.8	-1.6 ***	22	9.5	5.9-12.3	-1.3	-7.4	-0.7 ***	-1.6	0.033 *
75-90 PCNTL	Base	76	8.3	6.0-10.4	-	-	-	75	8.2	5.6-10.4	-	-	-	0.1	0.375
	Endpt	76	6.6	3.1-10.1	-1.6	-5.7	-1.8 ***	75	7.7	5.4-11.1	-0.6	-4.1	-2.8 ***	-1.2	0.001 ***
≥ 90 PCNTL	Base	106	9.1	6.0-14.3	-	-	-	97	8.9	5.6-13.3	-	-	-	0.3	0.282
	Endpt	106	6.7	3.1-11.7	-2.0	-7.8	-1.8 ***	97	7.9	5.4-12.3	-0.7	-7.4	-2.6 ***	-1.4	0.001 ***

* No. of subjects. CHG = median change from baseline. - Not applicable.

** significance of p-values from Wilcoxon signed-rank test (two-tailed). *** p < 0.001.

values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test). * p < 0.050, ** p < 0.001.

NIL = Percentile. Baseline HbA1c value for the 75th percentile is 10.5 %.

Contd.

TABLE 3.2.4 Contd.
 MEDIAN HbA1c AT BASELINE AND ENDPOINT
 SUBJECTS STRATIFIED BY BASELINE HbA1c VALUES

BASELINE HbA1c	VISIT	N	GLIMEPIRIDE			SIG	CHG	PLACEBO			SIG	BETWEEN TREATMENT		
			MEDIAN	RANGE	CHG			N	MEDIAN	RANGE		CHG	RANGE	DIFF
> 80 PCNTL	Base	25	11.4	10.9-14.3	-	---	-	11.4	10.9-13.3	---	---	0.1	0.259	
	Endpt	25	7.8	5.9-11.7	-3.6	-7.8--.6	***	17	8.6	5.9-12.3	-2.8	-7.4-0.7	***	-1.0
< 80 PCNTL	Base	81	8.5	6.0-10.3	-	---	-	8.3	5.6-10.7	---	---	0.1	0.373	
	Endpt	81	6.6	3.1-10.1	-1.6	-5.7-1.8	***	80	7.8	5.4-11.2	-0.6	-4.1-2.8	***	-1.3
Combined	Base	106	9.1	6.0-14.3	-	--	-	8.9	5.6-13.3	---	---	0.3	0.283	
	Endpt	106	6.7	3.1-11.7	-2.0	-7.8-1.8	***	97	7.9	5.4-12.3	-0.7	-7.4-2.8	***	-1.4

N = no. of subjects, CHG = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

***p < 0.001

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).

***p < 0.001

PCNTL = Percentile.

The baseline HbA1c value for the 80th percentile is 10.9 %

HCE 490 8/USA/202/DM - Glimepiride

TABLE 3.3.1

MEDIAN FASTING PLASMA GLUCOSE - FPG (mg/dl)

VISIT	GLIMEPIRIDE			PLACEBO			BETWEEN TREATMENT			
	N	MEDIAN	RANGE	CHG	N	MEDIAN	RANGE	SIG	DIFFERENCE	P-VALUE
Baseline	117	212.0	131-335	-	118	205.0	142-353	---	5.0	0.463
Week 2	117	176.0	92-347	-34.0	116	204.5	106-440	-9.5	-119-135	***
Week 4	112	163.5	84-366	-47.5	112	189.0	92-330	-13.0	-162-81	***
Week 6	110	157.0	95-376	-50.5	110	188.0	106-325	-10.5	-110-91	**
Week 8	108	149.0	87-349	-56.0	110	185.5	107-333	-12.5	-137-97	***
Week 10	105	149.0	86-312	-52.0	105	186.0	85-392	-9.0	-137-116	*
Week 12	96	151.0	95-299	-54.5	97	184.0	107-309	-21.0	-144-102	***
Week 14	102	149.5	92-292	-56.5	90	180.5	106-353	-26.5	-133-147	***
Week 16	100	151.5	93-315	-54.5	86	177.5	101-300	-20.0	-144-90	***
Week 18	99	152.0	103-356	-49.0	85	180.0	104-294	-24.0	-164-105	***
Week 20	98	149.5	95-384	-53.0	78	177.0	106-351	-21.0	-141-168	***
Week 22	100	150.5	95-307	-55.5	76	176.0	90-329	-25.0	-160-163	***
Endpoint	117	153.0	84-360	-52.0	118	192.0	90-354	-9.0	-164-163	*

N = no of subjects. CHG = median change from baseline. - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).
*p ≤ 0.050, **p ≤ 0.010, ***p ≤ 0.001.P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
***p ≤ 0.001.

HOE 490 8/USA/202/DM - Glimepiride

FIGURE 3.3.2

MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE

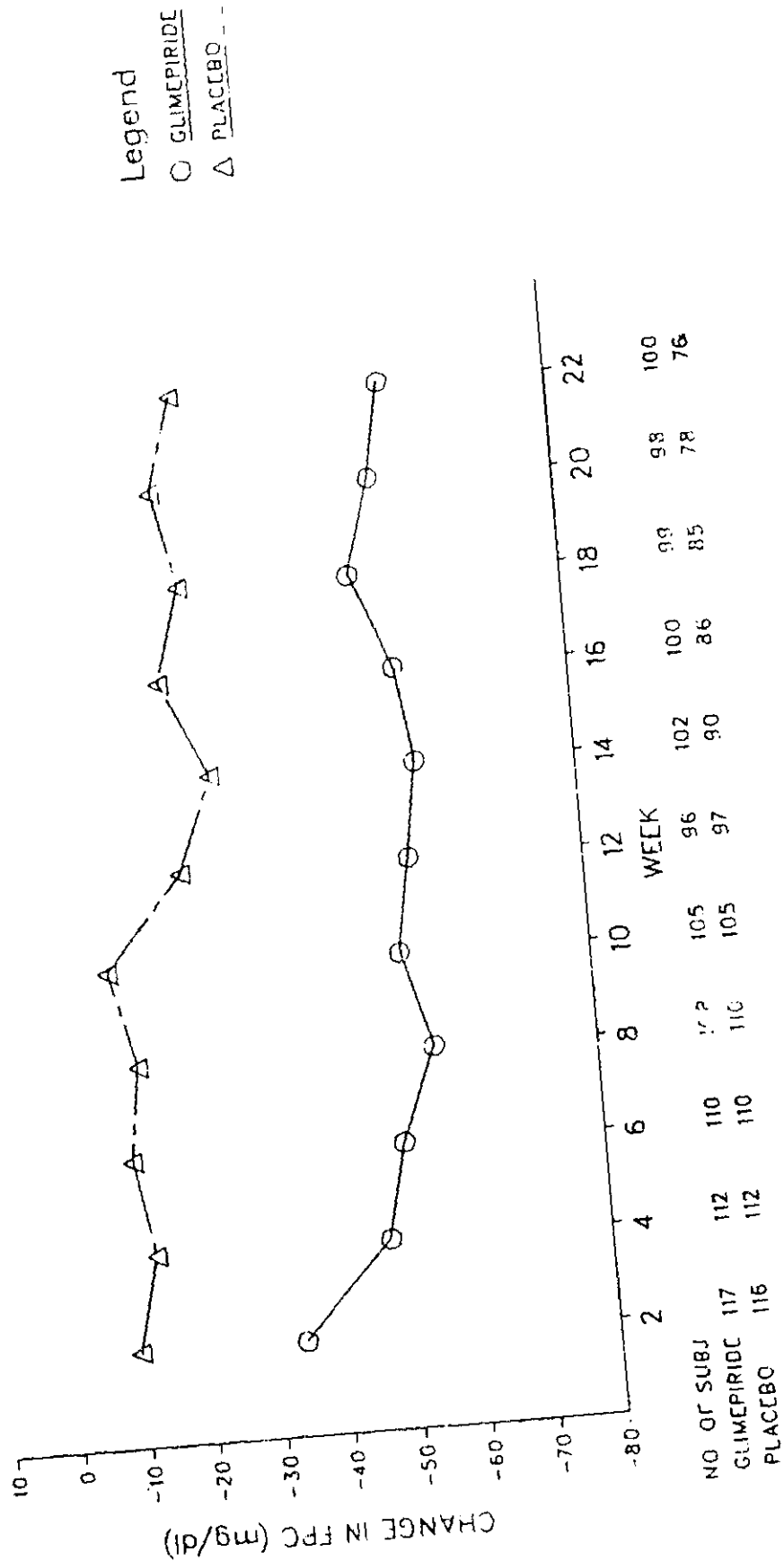
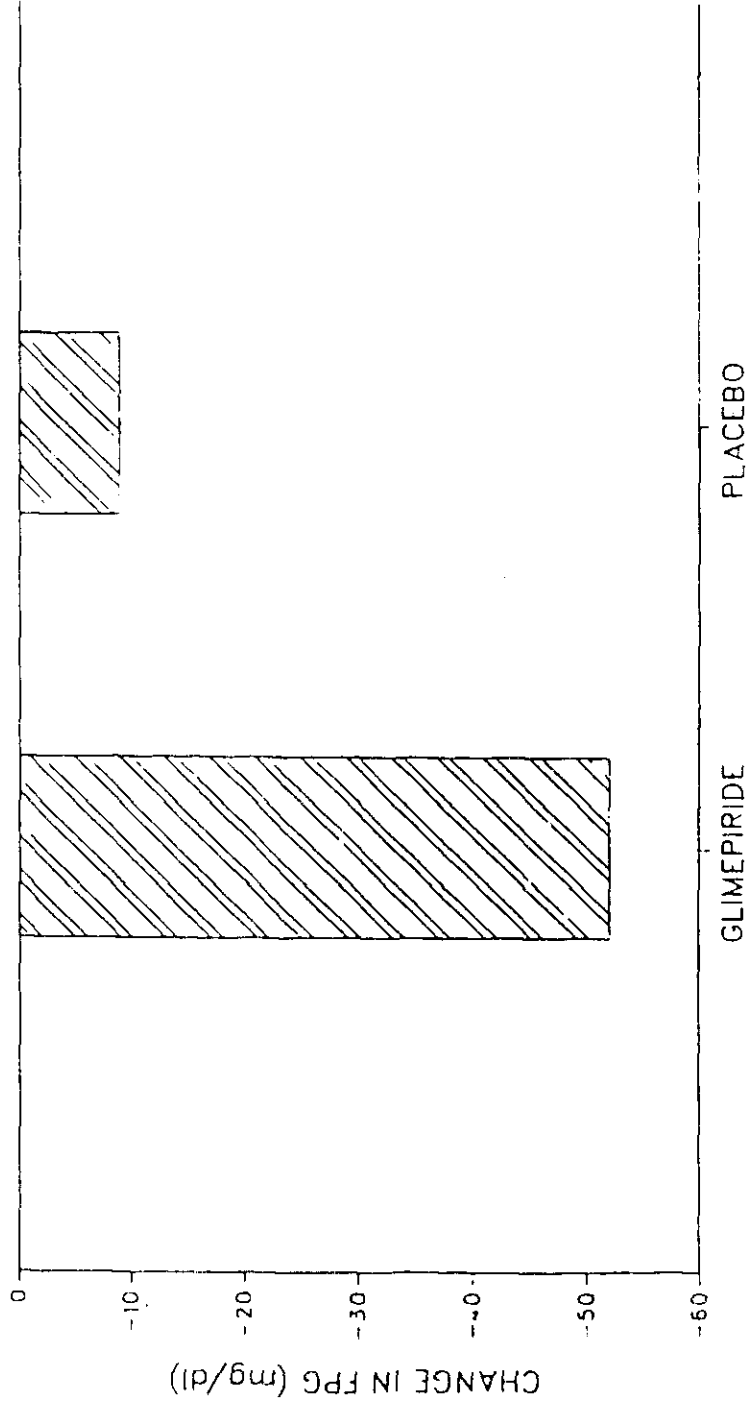


FIGURE 3.3.3

MEDIAN FASTING PLASMA GLUCOSE (FPG)
CHANGE FROM BASELINE AT ENDPOINT



NO. OF SUBJ

117

118

HOE 490 8/USA/202/DM - Glimepiride

TABLE 3.4.1

MEDIAN FASTING AND POSTPRANDIAL GLUCOSE (mg/dl)

VARIABLE	VISIT	GLIMEPIRIDE			PLACEBO			BETWEEN TREATMENT						
		N	MEDIAN	RANGE	CHG	RANGE	SIG	N	MEDIAN	RANGE	SIG	DIFF	P-VALUE	
FPG	Base	107	212	131-335	-	---	---	101	204	149-353	-	---	8	0.203
	Wk 12	104	153	95-298	-55	-159-90	---	100	187	107-362	-21	-144-116	-37	< 0.001 ***
	Wk 22	100	151	95-307	-53	-179-96	---	83	179	90-329	-28	-160-163	-34	< 0.001 ***
	Endpt	107	151	95-307	-54	-179-96	---	101	191	90-362	-13	-160-163	-43	< 0.001 ***
2h PP Gluc	Base	108	291	135-468	-	---	---	101	268	129-475	-	---	14	0.206
	Wk 12	108	171	55-395	-105	-297-76	---	100	236	90-705	-29	-238-466	-71	< 0.001 ***
	Wk 22	101	169	83-365	-98	-280-101	---	83	231	90-423	-27	-187-234	-61	< 0.001 ***
	Endpt	108	174	83-395	-98	-280-101	---	101	237	90-705	-17	-238-466	-72	< 0.001 ***

N = no of subjects, CHG = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon signed-rank test (two-tailed).

p ≤ 0.010, *p ≤ 0.001.

P-values from Mantel-Haenszel test of baseline and change from baseline data (two-tailed test).
 ***p ≤ 0.001.

Table 4.1.1
SCHEDULE OF OBSERVATIONS

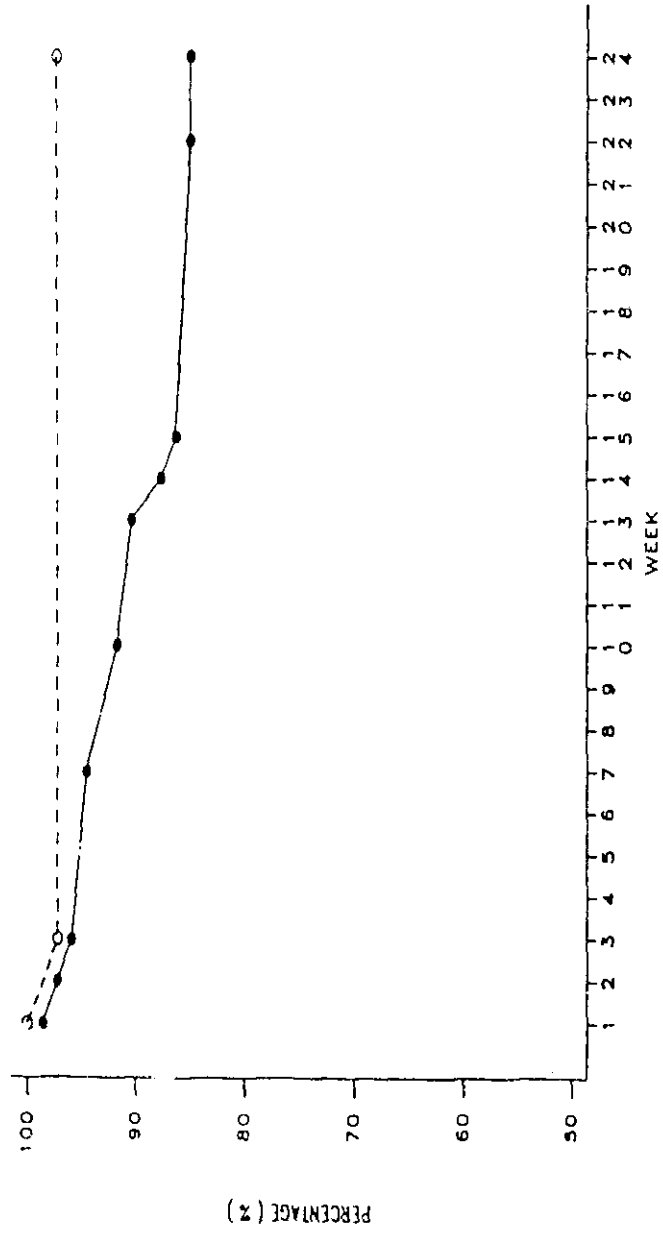
Week:	OPEN-LABEL PHASE						DOUBLE-BLIND PHASE								
	0	1	2	3	5	7	0	2	4	8	12	16	20	22	24
Medical history	X														
Physical examination	X						X								X
Clinical visit (weight, vital signs: blood pressure and heart rate, FPG, FBG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (blood chemistry including lipid profile, hematology, urinalysis)	X						X		X		X				X
HbA1c							X				X				X
Fasting level: C-peptide	X														
Fasting and postprandial (1, 2, 3, 4 hour) levels: glucose, free insulin, C-peptide, glucagon							X				X				X
ECG	X						X								X
Adverse events	Report as required														
Concomitant medications	As needed														
Home FBG monitoring	Twice daily, before breakfast and dinner														

The visit at Week 7 was scheduled for Day -3.
 The visit at Week 0 of the double-blind phase is the Baseline for the double-blind phase.
 FPG samples were analyzed by SKBL.
 FBG measurements were made with glucose meter.

HOE 490 8/USA/305/DM - Glimepiride

Figure 4.1.2

PERCENTAGE OF PATIENTS IN STUDY OVER TIME (IN WEEKS)
SUBJECTS DISCONTINUED FOR ANY REASON



Legend
● PBO + INS
○ Glim + INS

HOE 490 8/USA/305/DM - Glimepiride

TABLE 4.1.3

DURATION OF TREATMENT
DOUBLE BLIND PHASE

NO. DAYS TREATED	PLACEBO + INSULIN		GLIMEPIRIDE + INSULIN	
	N	%	N	%
< 14	2	2.7	0	0.0
14 - 27	1	1.4	2	2.8
28 - 41	0	0.0	0	0.0
42 - 55	1	1.4	0	0.0
56 - 69	2	2.7	0	0.0
70 - 83	0	0.0	0	0.0
84 - 97	3	4.1	0	0.0
98 - 111	1	1.4	0	0.0
112 - 125	0	0.0	0	0.0
126 - 139	0	0.0	0	0.0
140 - 153	1	1.4	0	0.0
154 - 167	7	9.6	7	9.7
TOTAL NO. OF SUBJ	55	75.3	69	87.5
	73	100.0	72	100.0

HOE 490 8/USA/305/DM - Glimepiride

TABLE 4.1.4
STUDY COMPLETION STATUS
DOUBLE BLIND PHASE

	PLACEBO + INSULIN	GLIMEPIRIDE + INSULIN	BETWEEN TREATMENT P-VALUE
NO. OF SUBJECTS RANDOMIZED	73	72	
NO. OF SUBJECTS TREATED	73 (100.0%)	72 (100.0%)	
COMPLETED STUDY	62 (84.9%)	70 (97.2%)	0.010 **
DID NOT COMPLETE STUDY	11 (15.1%)	2 (2.8%)	
REASON FOR NOT COMPLETING			
Lack of Eff: Hyperglycemia	1 (1.4%)	0 (0.0%)	
Safety/Lack of Eff: Hyperglycemia	2 (2.7%)	0 (0.0%)	
Safety: Adverse Event	2 (2.7%)	0 (0.0%)	
Safety: Other	1 (1.4%)	0 (0.0%)	
Patient Unreliable/Uncooperative	2 (2.7%)	0 (0.0%)	
Patient Decision	2 (2.7%)	0 (0.0%)	
Other	1 (1.4%)	1 (1.4%)	

The Mantel-Haenszel Test (two-tailed) was used to compare proportions of subjects who did not complete the study.
**p < 0.010.

HOE 490 8/USA/305/DM - Glimepiride

TABLE 4.2.1

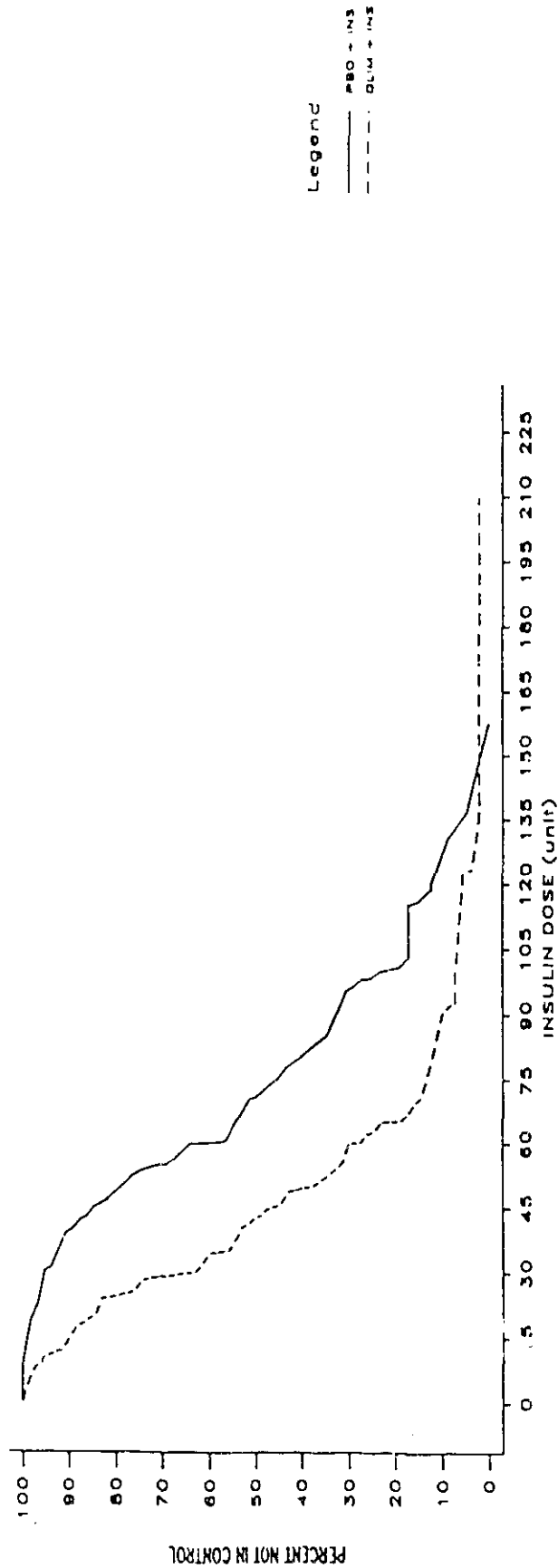
MEAN INSULIN DOSE - 4-WEEK AVERAGE AT ENDPOINT AND FINAL DAILY DOSE
SUBJECTS WITH NONCENSORED OR RIGHT CENSORED DATA

VARIABLE	PLACEBO + INSULIN		GLIMEPIRIDE + INSULIN		P-VALUE FOR BETWEEN TREATMENT COMPARISON
	N	MEAN SE	N	MEAN SE	
4-WEEK AVERAGE	69	77.9 4.41	72	48.5 3.70	< 0.001 ***
FINAL DOSE	69	78.4 4.61	72	48.9 3.80	< 0.001 ***

N = Number of Subjects. Mean and SE are the mean and standard error of the product-limit estimates.
P-value from Proportional Hazard Model Analysis (two-tailed test).
***p < 0.001.

FIGURE 4.2.2

ESTIMATED PERCENT OF SUBJECTS NOT IN CONTROL
VS 4-WEEK AVERAGE INSULIN DOSE AT ENDPOINT
(KAPLAN-MEIER PRODUCT-LIMIT ESTIMATES)



Number of evaluable subjects at baseline: PBO + INS: 69, GLIM + INS: 72

TABLE 4.3.1

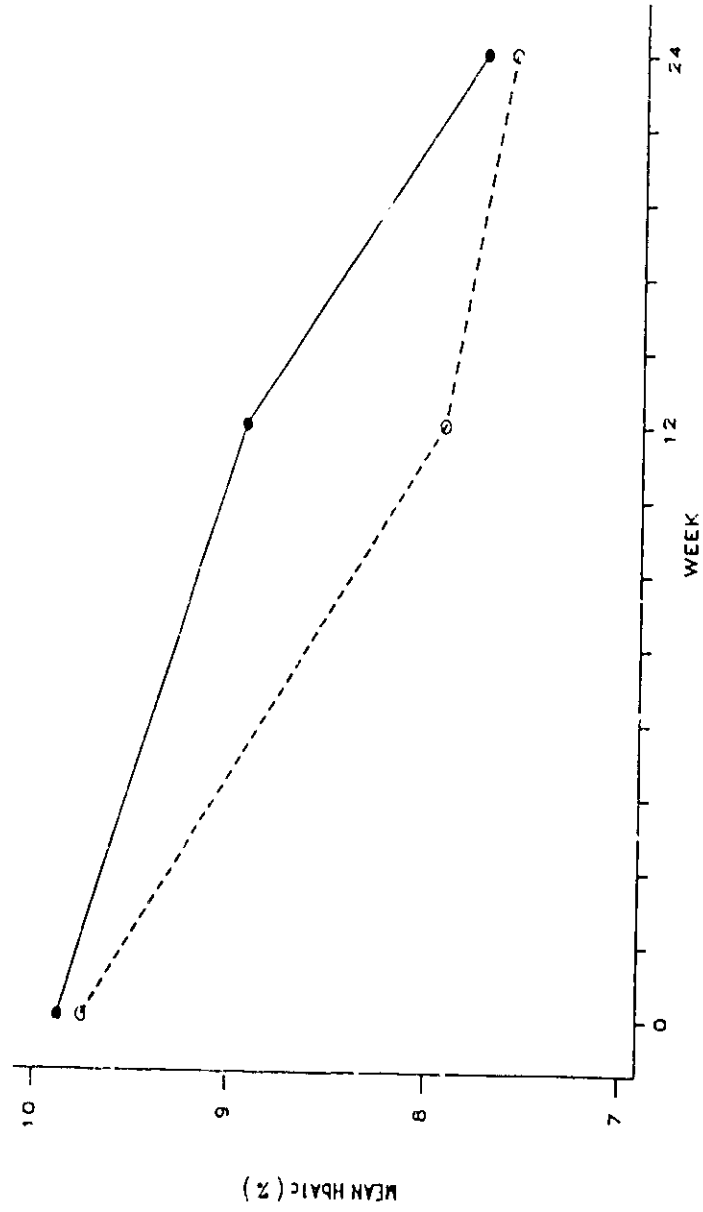
ENDPOINT HEMOGLOBIN A1c (%) AND WEEK 2 FASTING PLASMA GLUCOSE - FPG(mg/dl)
ALL SUBJECTS

VARIABLE	PLACEBO + INSULIN			GLIMEPIRIDE + INSULIN			BETWEEN TREATMENT		
	N	MEAN	SE	N	MEAN	SE	DIFF	95 % CI	P-VALUE
HbA1c	66	9.9	0.16	69	9.7	0.15	-0.2	(-0.6 , 0.2)	0.260
Week 2 FPG	67	259.3	5.00	69	204.7	5.47	-52.2	(-70.5 , -33.9)	< 0.001 ***

N = No. of Subjects, CHG = Mean change from baseline, SE = standard error.
P-value from Linear Models Analysis (two-tailed test) of change from baseline data.
***p < 0.001.

Figure 4.3.2

MEAN HbA1c (%) LEVELS BY VISIT



Legend
●—● PBO + INS
○—○ GLIM + INS

NO. OF SUBJ
PBO + INS 59
GLIM + INS 69

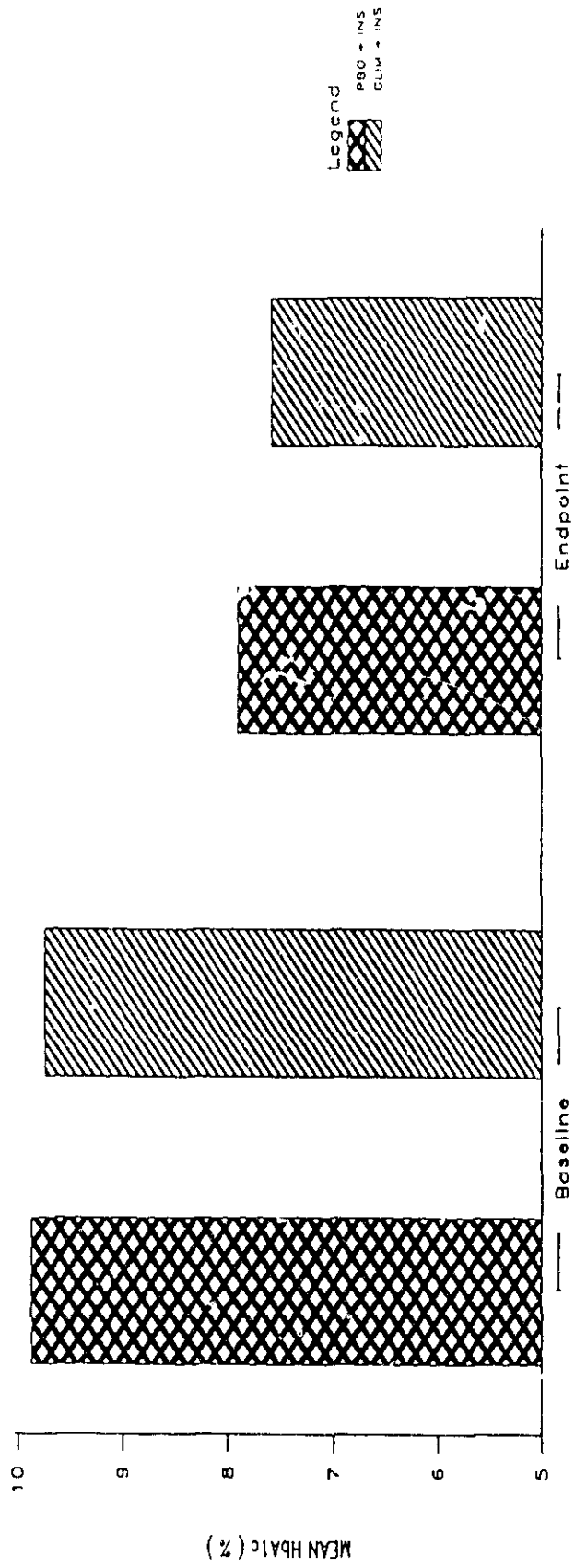
64 59
68 69

At week 12 glimepiride lowered HbA1c more than placebo ($p < 0.001$).

NDA 20496

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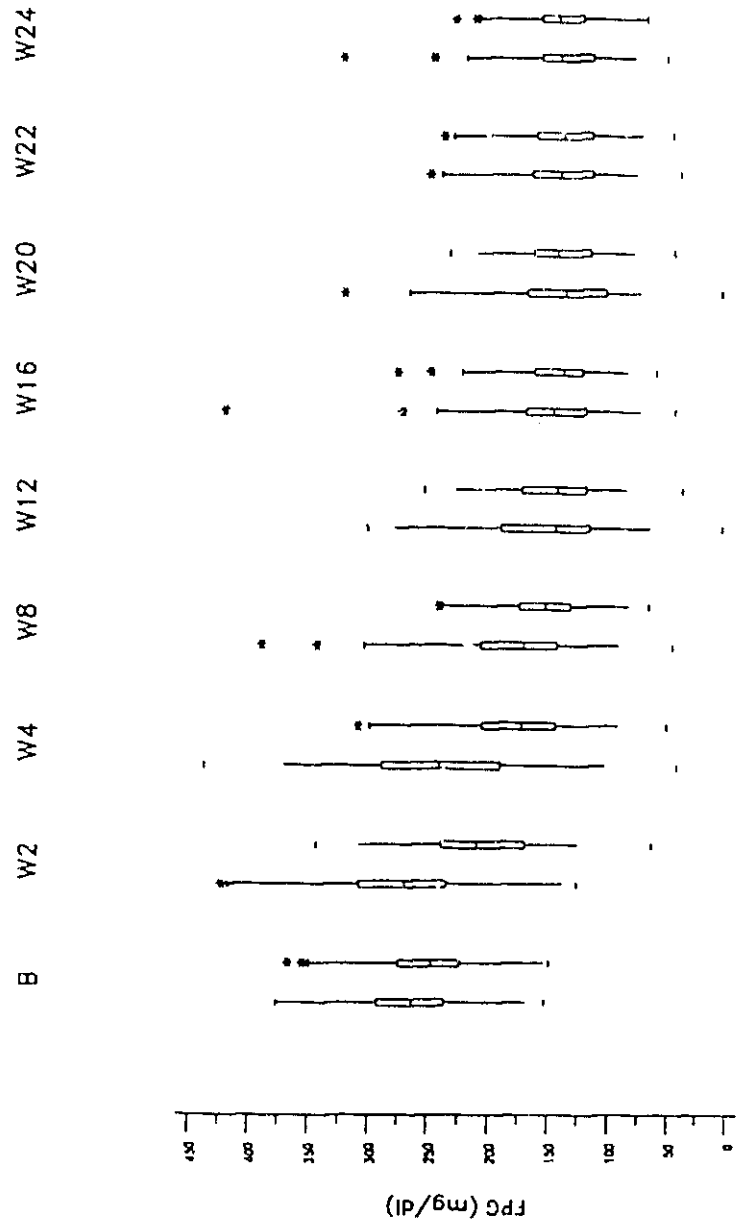
Figure 4.3.3
HEMOGLOBIN A1c (%) - ENDPOINT DATA SET



WEEK

FIGURE 4.3.4

BOX PLOT OF THE DISTRIBUTION OF FASTING PLASMA GLUCOSE (FPG)



N	P	G	P	G	P	G	P	G	P	G	P	G	P	G	P	G		
	70	71	67	69	65	65	68	70	68	67	60	68	49	61	55	64	61	68

WEF

TABLE 4.4.1

MEDIAN WEIGHT (1b)
DOUBLE BLIND PHASE

VISIT	PLACERO + INSULIN			GLIMEPIRIDE + INSULIN			P BETWEEN TREATMENT							
	N	MEDIAN	RANGE	CHG	RANGE	SIG	CHG	RANGE	SIG	DIFF	P-VALUE			
Baseline	70	206.0	132-335	-	---		71	208.0	122-297	-	---	-5.0	0.476	
Week 2	70	205.0	131-332	-1.0	-8-4	**	70	207.5	126-299	1.0	-6-9	**	2.0	< 0.001 ***
Week 4	65	210.0	128-332	-1.0	-8-5	**	66	210.0	125-281	2.0	-5-11	***	3.0	< 0.001 ***
Week 8	68	210.0	131-324	1.0	-11-14	*	69	213.0	125-300	4.0	-7-18	***	3.0	< 0.001 ***
Week 12	65	214.0	133-318	4.0	-17-19	***	66	213.5	129-301	6.0	-11-19	***	3.0	0.008 **
Week 16	61	218.0	135-318	7.0	-17-23	***	68	215.0	131-303	7.0	-13-21	***	2.0	0.161
Week 20	48	214.5	140-316	6.5	-19-18	***	61	216.0	146-308	8.0	-11-25	***	2.0	0.111
Week 22	54	225.5	141-317	8.5	-18-22	***	64	217.0	133-308	8.0	-13-25	***	1.0	0.522
Week 24	61	223.0	143-319	10.0	-16-27	***	58	218.5	130-301	9.0	-14-29	***	0.0	0.817
Endpoint	70	216.5	142-319	9.0	-16-27	***	71	216.0	130-301	9.0	-14-28	***	0.0	0.747

N = no. of subjects, CHG = median change from baseline, - Not applicable.

Sig = significance of p-values from Wilcoxon Signed-Rank Test (two-tailed).

*p < 0.050, **p < 0.010, ***p < 0.001.

P-values from Mantel-Haenszel Test of baseline and change from baseline data (two-tailed).

p < 0.010, *p < 0.001.

HOF 490 8/USA/305/DH - Glimepiride

TABLE 4.5.1
ENDPOINT HEMOGLOBIN A1c(%) BY RACE

RACE	PLACEBO + INSULIN			GLIMEPIRIDE + INSULIN			BETWEEN TREATMENT										
	N	MEAN	SE	N	MEAN	SE	DIFF	95% CI	P-VALUE								
White	52	9.9	0.17	7.9	0.16	-1.9	0.14	55	9.5	0.16	7.4	0.10	-2.1	0.13	-0.1	(-0.5 , 0.3)	0.551
Non-white	14	9.3	0.40	7.9	0.30	-2.0	0.37	14	10.7	0.28	8.1	0.20	-2.6	0.25	-0.5	(-1.5 , 0.4)	0.280

N = No. of Subjects, CHG = Mean change from baseline, SE = standard error.
P-value from Linear Models Analysis (two-tailed test) of change from baseline data.
No significant differences were found.

HOE 490 8/USA/305/DM - Glimepiride

TABLE 4.5.2
FOUR WEEK AVERAGE INSULIN DOSE BY RACE

RACE	PLACEBO + INSULIN			GLIMEPIRIDE + INSULIN			BETWEEN TREATMENT		
	N	MEAN	SE	N	MEAN	SE	DIFF	95 % CI	P-VALUE
White	58	72.1	4.25	57	49.6	4.59	-22.6	(-34.8 , -10.3)	< 0.001 ***
Non-white	15	52.4	6.72	15	42.0	8.52	-10.4	(-32.3 , 11.59)	0.518

* = No. of Subjects, SE = standard error.
P-value from Linear Models Analysis (two-tailed test) of mean.
***p ≤ 0.001.

Statistical Review and Evaluation
of Carcinogenicity Studies

NDA: 20-496

Date: September 6, 1995

Applicant: Hoechst-Roussel Pharmaceuticals INC.

Name of Drug: Amaryl (HOE 490, glimepride) Tablets.

Documents Reviewed: Original NDA volumes 1.37 to 1.58 with date referred April 7, 1995 and data on two floppy diskettes supplied by the sponsor.

I. Background: In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenic potential of HOE 490 in mice and rats when administered orally using some selected dose levels. Dr. Herman Rhee, HFD-510, who is the reviewing pharmacologist, requested the Division of Biometrics to perform the statistical review and evaluation of this study.

II. The mouse study

IIa. Design: Two separate experiments, one in male and one in female mice, were conducted over a period of 24 months. In each of these experiments there were three treated groups known as low, medium, and high, and two control groups. For each sex, two hundred fifty NMRI mice were randomly divided into equal groups of 50 animals each to form the treatment groups. The dose levels for the treated groups were 320, 1265, and 5000 ppm for the low, medium, and high dose groups, respectively. The control groups received untreated food.

The behavior and general health condition of each animal were assessed twice daily. The mice were checked twice daily for moribund and intercurrently dyings. Where no advanced autolysis had occurred, such animals were always dissected, the organ weights determined, and the organ submitted to histological examinations.

IIb. Sponsor's analysis

Survival analysis: Tables of intercurrent mortality for both male and female mice were constructed.

The sponsor claimed that mortality was similar in all study groups and statistical evaluation revealed no significant differences between control and HOE 490 treated animals.

Tumor data analysis: Summary tables for a number of neoplastic lesions by organ, lesion, and sex were generated. Then, the combined prevalence and death rate method proposed by Peto et al (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) was applied to conduct trend tests on tumor rates.

The sponsor concluded that feeding of 1265 and 5000 ppm HOE 490 resulted in an increased frequency of islet cell adenomas in the pancreas. This is considered as a result of the pharmacodynamic effect of HOE 490 on B cell when administered to mice over their lifetime. All other neoplastic organ findings are regarded incidental or species-specific and age-related spontaneous changes.

Iic. Reviewer's analysis

The reviewer independently performed analyses on the survival and tumor data. In the survival data analysis the methods described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965) were used. The tumor data analyses were done using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. The data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intersurrent mortality data of the mouse study are given in Table 1. The plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female mice are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of all five groups (Control1, Control2, Low, Medium, and High) was tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at 0.05 level) linear trend or pairwise difference in the mortality for both sexes.

The p-values of the linear trend and the pairwise tests are given in Tables 2A and 2B, respectively.

Tumor data analysis: The sponsor classified the tumor types as 'cause of death', 'not cause of death', and 'undetermined'. Following Peto et al.(1980), the reviewer applied the 'death rate method' to the first tumor type and the 'prevalence' method to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories

a combined test was performed. All tests were done using the method of exact permutation trend test, which is an extension of the Fisher exact test. The scores used in the reviewer's analyses were 0, 0, 320, 1265, and 5000 for the control1, control2, low, medium, and high dose groups, respectively. The time intervals used were 0 - 52, 53 - 78, 79-92, 93-104 weeks, and terminal sacrifice for both sexes.

Three sets of trend tests were performed. The first set called Cnt1 used the data of control1, low, medium, and high dose groups. The second set called Cnt2 used the data of control2, low, medium, and high dose groups. The third set called Cnt1 + Cnt2 used the data of control1 and control2 combined, low, medium, and high dose groups.

The incidence rates of tumor types with p-values less than .05 are listed below.

<u>Male mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>					<u>P-value using</u>		
	<u>C1</u>	<u>C2</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Cnt1</u>	<u>Cnt2</u>	<u>Cnt1+Cnt2</u>
	50	50	49	50	50			
Pancreas/Islet Cell Adenoma	0	0	1	3	7	.004*	.0013*	.0002*

<u>Female mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>					<u>P-value using</u>		
	<u>C1</u>	<u>C2</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Cnt1</u>	<u>Cnt2</u>	<u>Cnt1+Cnt2</u>
	50	50	49	50	50			
Lungs/Bronchiolo-Alve. Adenoma	0	4	3	2	7	.0041*	.057	.0108
Lungs/Alveolar Cell Adenocarcinoma	0	0	0	1	2	.0625	.0699	.0324

Multiple testing adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .025 level, otherwise the level should be set at .005.

On the basis of Division's p-value adjustment rule, the positive linear trends with P-values marked with asterisks are considered to be statistically significant.

The incidence rates of all tumor types tested for linear trend are given in table 3.

Pairwise comparisons of the controls with the high dose

The following are comparisons of the incidence rates of the control groups with that of the high dose group using the age adjusted Fisher exact test for tumor types whose linear trends were found to be statistically significant.

<u>Male mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>			Cnt1	<u>P-value using</u>	
	<u>Cnt1</u>	<u>Cnt2</u>	<u>H</u>		<u>Cnt2</u>	<u>Cnt1 + Cnt2</u>
Pancreas/Islet Cell Adenoma	0	0	7	.0034*	.004*	.0002*

<u>Female mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>			Cnt1	<u>P-value using</u>	
	<u>Cnt1</u>	<u>Cnt2</u>	<u>H</u>		<u>Cnt2</u>	<u>Cnt1 + Cnt2</u>
Lungs/Bronchiolo-Alve. Adenoma	0	4	7	.003*	.2306	.0206

P-values marked with asterisks are considered to be statistically significant after adjusting for the effect of multiple tests.

III. The rat study

The sponsor conducted two rat studies. Since the sponsor provided only data diskette for the second study, the statistical review is performed to evaluate the second one.

IIIa. Design: Two separate experiments, one in male and one in female rats, were conducted over a period of 30 months. In each of these experiments there were three treated groups known as low, medium, and high, and two control groups. For each sex, two hundred fifty Wistar rats were randomly divided into equal groups of 50 animals each to form the treatment groups. The dose levels for the treated groups were 320, 1265, and 5000 ppm for the low, medium, and high dose groups, respectively. The control groups received untreated food.

The behavior and general health condition of each animal were assessed twice daily. The rats were checked twice daily for moribund and intercurrently dyings. Where no advanced autolysis had occurred, such animals were always dissected, the organ weights determined, and the organ submitted to histological examinations.

IIIb. Sponsor's analysis

Survival analysis: Tables of intercurrent mortality for both male and female rats were

constructed.

The sponsor claimed that the intercurrent mortality occurring in this study was not considered to distinguish treated rats from controls.

Tumor data analysis: Summary tables for a number of neoplastic lesions by organ, lesion, and sex were generated. Then, the sponsor applied the combined prevalence and death rate method proposed by Peto et al in 1980 on tumor rates to conduct trend tests.

The sponsor concluded that no neoplastic lesions were diagnosed in rats treated with HOE 490 that were considered to represent an oncogenic effect of the test article.

IIIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and tumor data. In the survival data analysis the methods described in the papers of Cox (1972) and of Gehan (1965) were used. The tumor data analyses were done using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. The data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intercurrent mortality data of the rat study are given in Table 4. The plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female rats are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of all five groups (Control1, Control2, Low, Medium, and High) was tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at 0.05 level) linear trend or pairwise difference in the mortality for both sexes.

The p-values of the linear trend and the pairwise tests are given in Tables 5A and 5B, respectively.

Tumor data analysis: The sponsor classified the tumor types as 'cause of death', 'not cause of death', and 'undetermined'. Following Peto et al.(1980), the reviewer applied the 'death rate method' to the first tumor type and the 'prevalence' method to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories a combined test was performed. All tests were done using the method of exact permutation trend test, which is an extension of the Fisher exact test. The scores used in the reviewer's analyses were 0, 0, 320, 1265, and 5000 for the control1, control2, low, medium, and high dose groups, respectively. The time intervals used were 0 - 52, 53 - 78, 79-104, 105-117, 118-130 weeks, and terminal sacrifice for both sexes.

Three sets of trend tests were performed. The first set called Cnt1 used the data of control1, low, medium, and high dose groups. The second set called Cnt2 used the data of control2, low, medium, and high dose groups. The third set called Cnt1 + Cnt2 used the data of control1 and control2 combined, low, medium, and high dose groups.

The incidence rates of tumor types with p-values less than .05 are listed below.

<u>Male rats</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>					<u>P-value using</u>		
	<u>C1</u>	<u>C2</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Cnt1</u>	<u>Cnt2</u>	<u>Cnt1 + Cnt2</u>
	50	50	49	50	50			
Adrenal Medulla/ Pheochromocytoma (B)	5	1	2	3	7	.0881	.0033*	.024
Liver/Hepatocellular Adenoma, Solitary	0	4	2	0	4	.0436	.2429	.1223
Skin/Cutaneous Histiocytic Sarcoma	0	0	0	1	2	.0655	.0519	.0294

<u>Female rats</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>					<u>P-value using</u>		
	<u>C1</u>	<u>C2</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Cnt1</u>	<u>Cnt2</u>	<u>Cnt1 + Cnt2</u>
	50	50	49	50	50			
Hemolymphoret. Sys/ Malignant Lymphoma	6	3	2	5	7	.1756	.039	.1013
Lungs/Histiocytic Sarcoma (Infiltration)	0	0	0	0	2	.0687	.0631	.0415
Mammary Gland/Histiocytic Sarcoma (Infiltration)	0	0	0	0	2	.0714	.061	.0406
Uterus/Adenocarcinoma	3	3	1	1	7	.0099	.0092	.0136

Multiple testing adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .025 level, otherwise the level should be set at .005.

On the basis of Division's p-value adjustment rule, the positive linear trends with P-values marked with asterisks are considered to be statistically significant.

The incidence rates of all tumor types tested for linear trend are given in table 6.

Pairwise comparisons of the controls with the high dose

The following are comparisons of the incidence rates of the control groups with that of the high dose group using the age adjusted Fisher exact test for tumor types whose linear trends were found to be statistically significant.

<u>Male mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>			Cnt1	<u>P-value using</u>	
	<u>Cnt1</u>	<u>Cnt2</u>	<u>H</u>		<u>Cnt2</u>	<u>Cnt1 + Cnt2</u>
Adrenal Medulla/ Pheochromeytoma (B)	5	1	7	518	017	.1014

Since P values for the pairwise comparisons between two control groups versus high dose group using three sets of data are greater than 1 %, the tumor rate of high dose group is not significantly greater than those of two control groups.

IV. Evaluation of validity of the design of the rat study

The reviewer's analysis results show that only in male rat, there is one tumor was found to have a significant positive linear trend detected by the test using the second data set, Cnt2. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to look into the following two issues as having been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

In addition, Chu, Cueto, and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and Environmental Health, Vol. 8, pp 251-280, 1981), suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto, and Ward (1981), the following criteria are mentioned for dose adequacy.

i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10 % in a dosed group relative to the controls."

ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Amaryl rat carcinogenicity study, in the light of the above guidelines.

The following are summary survival data of rats in the high dose group.

	<u>End of 52 weeks</u>	<u>End of Study weeks (130)</u>
Male	100%	60%
Female	100%	50%

From the above summary data, and the survival criteria mentioned above, it can be concluded that there were enough rats exposed for sufficient amount of time to the drug.

The following are summary data of body weight gains of the rat study.

<u>Sex</u>	<u>Group</u>	<u>Mean body weight(gms)</u>			<u>Percentage of</u>	
		<u>Beginning of study</u>	<u>End of study</u>	<u>Weight gain</u>	<u>Control1</u>	<u>Control2</u>
Male	Control1	95.7	490.3	394.6		
	Control2	96.7	494.1	468.2		
	Low	95.0	468.2	373.2	94.6	93.91
	Medium	95.3	463.8	368.5	93.39	92.73
	High	95.2	466.1	370.9	93.99	93.33

<u>Sex</u>	<u>Group</u>	<u>Mean body weight(gms)</u>			<u>Percentage of</u>	
		<u>Beginning of study</u>	<u>End of study</u>	<u>Weight gain</u>	<u>Control1</u>	<u>Control2</u>
Female	Control1	89.4	313.2	223.8		
	Control2	90.4	321.6	231.2		
	Low	91.7	310.0	218.3	97.54	94.42
	Medium	91.9	306.3	214.4	95.8	92.73
	High	89.9	312.2	222.1	99.24	96.06

Therefore, relative to the control1 and control2, male and female rats had average decrement of weight gain in the high dose group equal to 6.34% and 2.35%, respectively.

The mortality rates at the end of the experiment are as follows:

	<u>Control1</u>	<u>Control2</u>	<u>High</u>
Male	50%	32%	40%
Female	58%	42%	50%

The mortality rate of the high dose group is approximately equal to the average of two controls for both sexes.

Thus, from the survival and body weight gain data it can be concluded that the high dose level may be close to MTD. However, before concluding that the high dose is close to MTD other clinical signs and histopathological effects must also be taken into consideration. Finally, since the rat study lasted for 10 weeks, this study duration may be too long such that the more spontaneous tumors were developed.

V. Summary

The mouse study: The tests showed that there are ~~not~~ significant linear trends ($p=0.7558$ in the Cox and $p=0.8083$ in the Generalized Wilcoxon tests for males; $p=0.9745$ in the Cox test and $p=0.9780$ in the Generalized Wilcoxon test for females) in the mortality for both sexes.

For tumor data analysis, the tests show that in male mice, tumor type Pancreas/Islet Cell was found to have a significant linear positive trend for all three sets of trend tests. Moreover, the pairwise comparison between the control and high dose groups for tumor type Pancreas/Islet Cell is also significant for all three sets of data. However, in female mice, the tests indicate that tumor type Lungs/Bronchiolo-Alve. Adenoma was found to have a significant linear positive trend only when the first set of data Cnt1 was used. The pairwise comparison between the control and high dose groups for tumor type Lungs/Bronchiolo-Alve. Adenoma is also significant when the first set of data was used. ✓

The rat study: The tests showed that there are ~~not~~ significant linear trends ($p=0.9241$ in the Cox and $p=0.985$ in the Generalized Wilcoxon tests for males; $p=0.8484$ in the Cox test and $p=0.7219$ in the Generalized Wilcoxon test for females) in the mortality for both sexes.

For tumor data analysis, the statistical results indicate that only in male rats, tumor type Adrenal Medulla /Pheochromeytoma (B) was found to have a significant linear positive trend detected by the test using the second data set, Cnt2. The corresponding pairwise comparisons between the control and high dose groups were not significant.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed

by experts in the field, it can be concluded that the high dose level may be close to MTD. However, before concluding that the high dose is lower than MTD other clinical signs and histopathological effects must also be taken into consideration. Finally, since the rat study lasted for 130 weeks, this study duration may be too long such that the more spontaneous tumors were developed.

Wen-Jen Chen

Wen-Jen Chen, Ph.D.
Mathematical Statistician

Concur:

Karl K. Lin 9/7/95

Karl K. Lin, Ph.D.
Group Leader

cc: Original NDA 20-496

HFD-510/Dr. Sobel

HFD-510/Dr. Rhee

HFD-710/Chron

HFD-715/Dr. K. Lin

HFD-715/Dr. Chen

HFD-715/DRU 2.1.1 NDA 20-496 Amaryl Mouse& Rat carcinogenicity study.

HFD-40/Dr. Contrera

HFD-502/Dr. Osterberg or Dr. Taylor or Dr. DeGeorge

PLAN & TOX

REVIEW

NDA#20-496

April 5, 1995

APR - 5 1995

Sponsor: Hoechst-Roussel Pharmaceuticals Inc.
Somerville, NJ. Tel: (908)231-2000/2107

Submission Date: 08/30/1994 Date Assigned: 09/01/1994

REVIEW AND EVALUATION OF PHARMACOLOGICAL AND TOXICOLOGY DATA
ORIGINAL NDA REVIEW

Drug: Glimepiride (Amaryl™, HOE 490, S 80 8490) Tablets
1, 2, and 4 mg

Chemical Name: 1-([p-(2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl)phenyl)sulfonyl]-3-(trans-4-methylcyclohexyl) urea, Mol. Wt. 490.62

Related to: IND (HOE 490)

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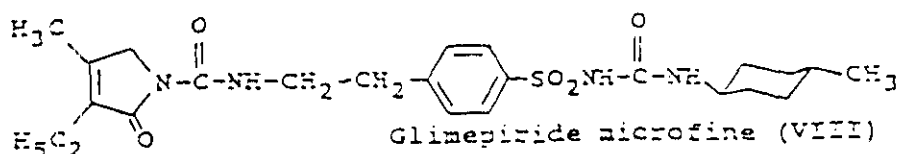
RECOMMENDATION: Approvable with labeling revision.

Herman M. Rhee
Herman M. Rhee, Ph. D.
Review Pharmacologist

cc: Original NDA20-496, HFD-510 NDA,
HFD-345, A. Jordan, H. Rhee

Letter
~~*[Signature]*~~
Issued
Reopen ok 5/17/95

Chemical Structure:



Category: Oral hypoglycemic agent (NIDDM patients not responding to diet and sulfonylurea therapy alone)

A. PHARMACOLOGY STUDIES

All NDA pharmacology data have been submitted in the original IND. Pharmacology for the NDA is briefly summarized.

Glimepiride is one of drugs that can be classified under the second generation of sulfonylurea for the treatment of Type II diabetes. It appears that glimepiride lowers blood glucose concentration through rapid release of insulin from the pancreatic beta cell. It is effective in doses as low as 10 $\mu\text{g}/\text{kg}$ in rabbits, 400 $\mu\text{g}/\text{kg}$ in rats, and 60 $\mu\text{g}/\text{kg}$ in dogs. It is completely absorbed by the animals and the serum protein binding is generally greater than 99% in all species tested. The major organ of localization in the rat was the liver, but the major sites of localization in rabbits was the kidneys. The primary route of excretion in the rat, mouse, and dog was through the feces, while in the rabbit it was eliminated by the kidneys. The plasma half life varied with species, being shortest in rats (about 2 hr), followed by rabbits (7 hr), dogs (13 hr), and human (approx. 8 hr).

Glimepiride was extensively metabolized to 2 major non-toxic metabolites. The hydroxymethyl derivative (M1) was common to all species while the carboxy metabolite (M2) was only detected in rats, mice, and rabbits. Glimepiride binds to 65 kDa pancreatic protein which is different from the usual sulfonylurea binding site (140 kDa). An additional intracellular site which is different from the ATP-dependent K^+ channel may contribute to the insulin release at high blood glucose concentration. Like other sulfonylureas, a persistent hypoglycemic effect may be responsible for the increased fetal death and skeletal anomalies observed in the reproductive studies. Glimepiride administration resulted in pancreatic adenomas in mice, but no increase in pancreatic adenomas or other tumors were observed in rats.

B. TOXICOLOGY STUDIES

In this NDA review toxicologic data that were not submitted previously by the sponsor are reviewed.

1. Toxicokinetics of Glimepiride in Mice after Repeated-Dose (2 weeks) Administration in the Diet (Project ID: 93.0720)

a. Objective: To validate the carcinogenicity study by estimation the exposure of drug using AUC.

b. Methods: 48 Crl:NMR1 Br mice/sex/group were administered glimepiride orally at doses of 320 ppm and 1265 ppm for 2 weeks.

c. Results: There was no intercurrent mortality. The two doses had no significant effects on body weight gain or on food consumption. The pharmacokinetic parameters are summarized below.

	320 ppm; male mice	320 ppm; female mice	1265 ppm; male mice	1265 ppm; female mice
C_{max} [$\mu\text{g/ml}$]	3.201	5.369	5.997	9.085
t_{max}	22:00	1:00	9:00	12:00
C_{min} [$\mu\text{g/ml}$]	0.396	1.376	1.544	2.541
t_{min}	15:00	13:00	4:00	5:00
C_{av} [$\mu\text{g/ml}$]	1.72	2.99	3.63	5.87
AUD ₂₄ [$\mu\text{g}\cdot\text{h/ml}$]	41.2	71.8	87.2	140.8

2. Study to Test the Possible Cocataractogenic Potential of Anti-diabetic Compound glimepiride in experimental cataract models in rats (Experiment No. 92-03; Document #013136)

a. This study was performed in

b. Introduction: Previous studies indicated that high dose (320 mg/kg/day for 12 months) of glimepiride produced posterior subcapsular cataracts in 2 out of 12 Beagle dogs. To elucidate a possible effect of the drug on lens transparency a study was performed testing the potential of the drug to act as a cocataractogenic risk under conditions where lenses already had an opacity. The opacity was produced by

streptozotocin-induced diabetes, naphthalene cataract, or cataract induced by irradiation.

c. Objective: 1) To evaluate the potential of glimepiride on lens transparency and 2) to examine the effects of this drug on eye lens protein metabolism.

d. Methods: 25 adults SD rats/sex/group were given either streptozotocin, naphthalene, or UV-irradiation. They were administered glimepiride orally at doses of 0, 1, 50, or 250 mg/kg/day for 6 weeks. General health, ocular opacity, and lens' protein and wet weight were monitored weekly and at the terminal stage.

e. Results:

1). Rats in the streptozotocin diabetic group showed depilation, increase the amount of urine and water consumption in the first week. There were two deaths in the second week, one death in the third week. In the 6th week two additional deaths were noted without a causal effect of glimepiride treatment. The classification of the lens opacities was based on Sasaki et al (Ophthalmic Res. 15:185-190, 1983). According to slit lamp microscopy, glimepiride did not have a cocataractogenic potential in streptozotocin-induced diabetic model. The intensity of the anterior capsular opacity was increased soon after induction of the diabetic condition, which was inhibited by glimepiride treatment.

2). Naphthalene group: Animals started to lose hair in the second week. Two rats died in the third week and 2 additional rats on the 4th week. One rat died in the 5th week and another rat on the terminal week. The light scattering intensity of the area anterior capsule and cortex of naphthalene and glimepiride treated animals showed from the early beginning of the drug administration, which may be due to the naphthalene typical zonular opacity.

3). UV Irradiated group: All rats in this group had slight corneal edema a week after the irradiation, but there was no impairment of body weight gain. one rat died on the 4th week and another rat died on the 5th week. On the 6th week two rats died and other rats were all in good conditions. Lens opacity-induced by UV irradiation was classified according to Hockwin et al. (Manual of Oculotoxicity Testing of Drugs, 1992). The anterior polar cataract showed a little earlier onset in the groups of 1 mg and 250 mg/kg, compared to the control, although it appeared that there was no relation to the glimepiride dosage.

4). Total lens wet weight: Lens growth is directly connected to the increase in the protein content, representing about 35% of the lens wet weight. Streptozotocin reduced the weight of lens, which was reversed by the treatment of glimepiride. However, in the case of naphthalene-treated rats glimepiride had no effect on lens weight.

f. Summary of Cocateract formation: It appears that the daily oral administration of 1 mg/kg glimepiride for 6 weeks prevented the usual formation of diabetic cataract in rats with streptozotocin-induced diabetes. No transparency changes of the lenses of the diabetic rats were observed in the 50 and 250 mg/kg groups. Slit lamp microscopy evaluation of the anterior eye segment did not show any cocataractogenic potential of glimepiride at doses of 1, 50, 250 mg/kg in both models of naphthalene - and irradiation-induced cataract. The separation of the lens proteins by thin layer isoelectrofocussing did not show any serious dose-dependent effects of glimepiride on eye lens protein profile.

C. REPRODUCTION TOXICITY

1. Oral Reproduction Toxicity Study of Glimepiride
(Investigation of the exposure of the F1 Offspring to the Test Compound via the Breast Milk: Document #011670)

a. Methods: A total 43 Wistar rats (strain: Wiskf, SPF 71) were used. The control group consisted of 18 untreated animals. A group of 15 female rats were administered the drug in the feed from the 6th day after mating until weaning on the 21st day after parturition. The dose group received 50,000 ppm glimepiride. In each litter, a third of the pups were killed on day 4 after birth, a third on day 10 after birth and a third on day 21 after birth. The dams were killed on day 21 of lactation.

In addition to standard tests, a toxicokinetic study was performed for the metabolites M1 and M2 in the breast milk. From all dams, milk was taken on days 4, 10 and 21 after birth.

b. Results: All dams treated with glimepiride gave birth and had live pups. Drug administration had no effect on the duration of pregnancy. The number of implants in the dose group did not differ from that in the control group. But, the number of live pups in the dose group was slightly reduced compared to that in the control. The live pups born in the dose group were normally developed and their weights at birth were comparable to those of the control pups. Body weight development in the pups in the dose group was not impaired in the first two weeks of the lactation period.

However, the weight of these animals was slightly lower than that of the control animals at the end of the third week, although the difference was not statistically significant.

Glimepiride serum concentration of the treated dams on the 21st day of lactation revealed a mean value of 2.14 ± 0.57 $\mu\text{g/ml}$. The value in the pups serum was 1.05 ± 0.42 , 1.21 ± 0.64 , and 4.19 ± 0.92 $\mu\text{g/ml}$ (N = 13) on the 4th, 10th, and 21st day after birth. Glimepiride concentration in the milk on the 4th day of lactation was 711 ng/ml, which rose to 1,377 and 3,025 ng/ml on the 10th and 21st day of lactation, respectively. The concentrations of M1 and M2 were below the detection limit of 100 ng/ml.

c. Conclusion: The data show that oral glimepiride is absorbed by the dams and is secreted during lactation in the milk.

2. Oral Reproduction Toxicity Study of Glimepiride in Wistar Rats (Investigation of the incidence of limb anomalies in the pups of the F₁ generation : Document #012029)

a. Objective: To determine the potential effect of glimepiride on the incidence and pathogenesis of limb formation in pups of the F₁ generation when the dams were exposed during pregnancy and during the lactation period. In addition, one of the objectives was to obtain indications of the etiology of the skeletal developments after glimepiride administration.

b. Methods: A total of 150 Wistar rats were divided into 7 groups as shown in the following table:

Group	Rat Number	Drug Dose	Vehicle
1	30	0 ppm	Feed-
2	20	20 ppm	Altromin
3	20	1,000 ppm	1311
4	30	50,000 ppm	
5	10	50,000 ppm	
6	10	0 mg/kg	Starch
7	10	2,500 mg/kg	mucilage (20 g/l)

On the day of birth the litters of 10 dams from group 1 were cross-exchanged with the litters of 10 dams from group 4 (Paired Feeding). The control dams with the exchanged pups

now formed group 8 and the corresponding dams in group 4 the new group 9.

c. Results:

1). Clinical: In control as well as drug treated groups, individual dams exhibited loss of hair. Body weight gain of the dams in the dose groups during pregnancy and also during the lactation period was unremarkable and corresponded to the control. All pregnant dams treated with glimepride via their feed or by stomach tube gave birth without complication. The drug had no effect on the duration of pregnancy. The cross-exchange of litters between the untreated dams and the treated dams of group 9 (pair d feeding) proved to be without complication except for one dam in group 9 which did not accept the strange litter.

The pups born live in the dose groups 2-4 and 7 were normally developed and their weights at birth were comparable to those of the control pups. No outwardly detectable anomalies were encountered either in the live pups in the dose groups or in the control pups. The body weight development of the pups in dose groups 2 - 4 and that of the pups in group 8 (drug exposed intrauterinely) did not differ from that of the control pups during the lactation period. After weaning, the body weight gain of the pups in groups 2 - 4 was impaired dose-dependently. In group 8, the female pups exhibited reduced body weight gain, compared to the control in the fifth week after birth.

2). Clinical Chemistry:

The parameters relevant to bone metabolism - alkaline phosphatase, calcium, glucose, and inorganic phosphorus - determined in the serum of the dams on the 22nd day of lactation revealed no findings related to the test compound. In the pups killed on the 4th day after birth, no deviations from the controls were found in the insulin values. Other parameters could not be determined due to a limited blood sample. Except for group 8, the glucose values were reduced in the 20 and the 1000 ppm dose groups but not in the 50,000 ppm dose group. A reduced somatostatin value in the 1,000 ppm dose group and an increased insulin value in the 2,500 mg/kg dose group were probably incidental.

3). Toxicokinetic studies:

Glimepride serum levels in the dams on the 22nd day of lactation increased from 0.62 to 6.53 $\mu\text{g/ml}$ in groups 2 - 4. On day 4 after parturition, the median for the blood level in the pups of the dams which had been treated with the 50,000 ppm dose via the feed was 0.59 $\mu\text{g/ml}$. The corresponding

values in the pups in groups 2 (20 ppm) and 3 (1000 ppm) of the medicated-feed study and in group 7 (2,500 mg/kg per stomach tube) were all below the detection limit. In the pups killed on day 22 after birth in groups 4, 5 and 9(4a), in which the dams had received an identical dose of glimepride via their feed, the median concentration of the test compound in the serum was 8.17, 6.52 and 8.50 μ g/ml, respectively.

4). Macroscopic findings in the pups:

The skeletal evaluation in the 4-day-old pups revealed no drug-induced deformations on the long tubular bones of the limbs and no compound-related malformations on the remaining skeleton. But, the growth of the diaphyseal endochondral ossification zone and the epiphyseal cartilage was evident in the long limb bones. On examination of the tubular bones in longitudinal axis, a bony substance stained with alizarin red S appeared in the entire cross section in almost all control animals. In the 2,500 mg/kg dose group, the light-colored zones were slightly larger but their incidence lower than those in the 1,000 ppm dose group. In one pup from the 1,000 ppm dose group, a circular zone of missing ossification was evident distally in the bone layer of the tibia and fibula. The distal end of the fibula was also bent.

The autopsy of the 22-day-old pups revealed no remarkable findings in the internal organs. The macroscopic examination of humeri and femora revealed no peculiarities in the 20 ppm and the 2,500 mg/kg dose groups. In the 1,000 ppm dose group, one pup exhibited shortening of the left humerus and bilateral shortening of the femora. In groups 4, 5, and 9, changes to the humeri and femora were encountered in practically all pups. The changes to the humeri consisted mostly of dysplasia of the humeral heads, resulting in shoulder joint dysplasia and instances of bending, shortening and, less frequently, thickening of the humeral shaft. Changes to the femora were less severe and consisted predominantly of shortening. Bending of the femur was only encountered in group 4(5 animals) and thickening of the femoral shaft was only observed in one animal from the same group.

The autopsy of the 70-day-old pups revealed no compound-related changes to the internal organs. As single findings, instances of dilatation of the renal pelvis and/or ureter were encountered in various study groups, including the control groups. In the 20 ppm dose group, one male exhibited light-brown and reddish-brown tessellation(forming into a mosaic pattern) on the surface areas and cut surfaces of the liver, and another animal exhibited reddish-white foci in the wall of the small intestine. In one male from the 50,000 ppm dose group, the urinary bladder was filled to tautness with

reddish fluid. The bladder wall was thickened in places and the mucosa exhibited red patches.

d. Summary of Teratologic Potential

In a reproduction toxicity study in rats, the incidence and pathogenesis of limb changes in adolescent pups of the F1 generation following exposure of the dams to the oral antidiabetic glimepiride during pregnancy and during the lactation period were examined macroscopically. On the day of birth, the litters of 10 dams from group 1 were cross-exchanged with the litters of 10 dams from group 4 ((paired feeding: groups 1a(8) and 4a(9))). The dams in group 1-4, including those in the later group 8 and 9, received the test compound continuously by way of their feed from the 6th day after mating until weaning on the 22nd day after parturition.

Glimepiride was not toxic for the dams. In the offspring, dosing of the dams during pregnancy with glimepiride lead dose-dependently in all groups treated to a slightly increased number of still births. Morphological examination of dissected humeri and femora of 22- and 70-day-old pups and of alizarin red S-stained skeletons of 4-, 21- and 70-day-old pups and histological examination revealed that the treatment of dams fed glimepiride in doses of 1,000 ppm and over resulted dose-dependently in irreversible limb deformations in adolescent pups. The deformations consisted primarily of shortening, bending and thickening of long tubular bones and joint dysplasia.

D. MUTAGENICITY TEST

1. Glimepiride- Study of the Mutagenic Potential in Strains of Salmonella Typhimurium and Escherichia coli (Document No. 012922).

a. Methods: Positive control agents were Na-azide (TA 100, TA 1535); 9-Aminoacridine (TA 1537); 2-Nitrofluorence (TA 98, TA 1538), N-Methyl-N-nitro-N-nitrosoguanidine (WP2uvrA) without metabolic activation. With metabolic activation positive control substances were Benzo(a)pyrene (TA 98, TA 100, TA 1535, TA 1537, TA 1538, WP2uvrA) and 2-Aminoanthracene (TA 98, TA 100, TA 1535, TA 1537, TA 1538, WP2uvrA). The doses of glimepiride in µg/plate were 0, 4, 20, 100, 500, 2,500 and 10,000 and glimepiride was dissolved in 100 µl DMSO. A reduced rate of spontaneously occurring colonies as well as visible thinning of the bacterial lawn were used as indicator for toxicity according to standard procedure.

b. Results and summary:

Glimepride was tested for mutagenicity with Salmonella typhimurium strains TA 98, TA 100, TA 1535,, TA 1537, TA 1538 and E. coli WP2urra in the absence or presence of a metabolic activation system. The test compound was used at doses of 4 to 10,000 µg/plate and proved to be not toxic to the bacterial strains. Visible precipitation of the test compound on the plates has been observed at 2,000 µg/plate. The test compound did not cause a significant increase in the number of revertant colonies with any of the tester strains either in the absence or in the presence of S-9 Mix.

2. Detection of Gene Mutations in Somatic Cells in Culture HGPRT-test with V79 Cells(Document No. 007265).

a. Objective: To examine the potential mutagenic activity of glimepride in V79 Chinese hamster cells. The induction of 6-thioguanine resistant mutants after in vitro treatment was investigated in the presence and absence of a fraction of liver homogenate for metabolic activation.

b. Methods: The study was performed according to the OECD guideline. Preparation of a liver homogenate fraction (S9) and cell culture were carried out according to standard operation procedures. To set appropriate dose levels for the mutation assay a preliminary cytotoxicity test was performed over a wide range of doses. Solvent control, negative and positive control were all included with or without S9-mix. Glimepride concentrations that were used for the study were 50, 100, 200, 300 or 400 µg/ml.

c. Results: According to preliminary cytotoxicity experiment glimepride was toxic to the V79 cells in the absence of metabolic activation at 400µg/ml. In the presence of metabolic activation a slight indication of toxicity was observed. A cytotoxic dose of glimepride with metabolic activation was 600 µg/ml. No relevant reproducible enhancement of the mutant colonies or mutant frequency over the range of the test dose was noted with or without metabolic activation.

3. Glimepiride-Urethane Chromosome Aberrations in vitro in V79 Chinese Hamster Cells(Document #012638)

a. Methods: Stocks of the V79 cell line stored in liquid nitrogen were seeded with about $8-10 \times 10^5$ cells per flask in 30 ml of medium containing approx. 10% fetal calf serum(FCS). Two-day old, exponentially growing stock

cultures which were over 50% confluent were trypsinized and a single-cell suspension was prepared. After 48 h, the medium was replaced with medium containing 10% FCS and the test substance without S9-mix. A preliminary cytotoxicity test was performed to set appropriate dose levels for the cytogenetic assay, which were 10, 25, 100, 250, and 500 $\mu\text{g/ml}$ without S9-mix. In the presence of S9-mix concentrations of glimepiride were 100, 500 and 1250 $\mu\text{g/ml}$. The test substance was classified as mutagenic if it induced a reproducible significant increased aberration rate, compared to control.

b. Results: The cytotoxicity experiment proved glimepiride-Urethane to be toxic to the V 79 cells in the presence of metabolic activation. In the absence of metabolic activation, the drug dose-dependent cytotoxicity was observed. Glimepiride treatment did not increase the number of polyploid cells as compared with the solvent controls, which indicates that the drug was not mutagenic in the chromosome aberration test system in vitro with cells of the V79 Chinese hamster cell line.

4. Glimepiride- Micronucleus test in Male and Female NMRI Mice After Oral Administration (Document #012264)

a. Introduction: This study was performed according to the Organization of Economic Cooperation and Development (OECD) guideline No. 474, 1983. Micronuclei are small secondary nuclear structures resulting from either chromosomal breakage or malfunction of the spindle apparatus of the cell which regulates the distribution of chromosomes during mitosis. It is a suitable in vivo method for investigating clastogenic substances and substances which affect the mitotic spindle mechanism as described by Schmid (The micronucleus test, Mutation Res. 31, 9, 1975).

b. Methods:

35 NMRI mice (Hoe: NMRKf, SPF71 strain)/sex were divided into 7 groups and treated as table below. The animals were killed and bone marrow from both femora were obtained. One thousand polychromatic erythrocytes were counted for each animal. As a control measure 1000 mature erythrocytes were counted and examined for micronuclei. The ratio of polychromatic to normochromatic erythrocytes was determined on slide reading based on double blinding. The results of the treatment groups in the micronucleus test at each dose and killing time were compared with control values. Endoxan was used as positive control.

ANIMAL GROUP AND CLASSIFICATION OF EXPERIMENTS

Group	Dose (mg/kg)	Animal# and Sex	Killing Time (hour)
1	0	5 males	24
		5 females	24
2	2500	5 males	24
		5 females	24
3	Endoxan + control	5 males	24
		5 females	24
4	0	5 males	48
		5 females	48
5	2500	5 males	48
		5 females	48
6	0	5 males	72
		5 females	72
7	2500	5 males	72
		5 females	72

c. Results: All animals survived without signs of toxicity. The bone marrow smears were examined for the occurrence of micronuclei in erythrocytes and the ratio of polychromatic erythrocytes to normal RBC was calculated. A significant increase of micronucleated polychromatic erythrocytes has been observed 24 and 72 hours after application. But the values were lower as compared to the controls of the 48 hr treatment groups. The number of normochromatic erythrocytes with micronuclei did not differ from the values of the simultaneous control animals for each of the three killing time. But endoxan, a positive control agent induced a marked increase of the number of polychromatic erythrocytes with micronuclei in both males and females indicating the validity of the test system.

d. Summary of genotoxicity study: Glimepride had no genotoxic effect in the Ames tests, induction of mutants at HGPRT, unscheduled DNA synthesis, and A549 human cell line studies.

E. Glimepride Oral Carcinogenicity Study in Rats for 30 Months (Report No. 91.0635/Document #08166)

a. Background: (The major portion of carcinogenicity studies was submitted by the sponsor under IND# which is enclosed in this NDA review.) This study was submitted to our Division on Nov. 18, 1991 and amended on June, 7, 1993 as Document #011894. Groups of 50 male and 50 female Wistar rats were given orally glimepride at doses of 32, 100 or 320 ppm in the feed over a period of 30 months. The doses correspond 1.73, 5.43, and 17.43 mg/kg/day for males and

2.26, 7.17, and 22.94 mg/kg/day for females. Evaluation of body weight development, food and water consumption, clinical observations and mortality, hematological examinations as well as organ weight determinations revealed no compound related changes of toxicological relevance. In the original report there was an increase in pancreatic adenomas in mice. Thus, Similar experiments were performed by the sponsor in rats as summarized below.

b.- Pathologist's Review of Pancreas(Document#013333)

Ten Wistar rats/sex/group were orally administered glimepiride at doses of 0, 320, 1265, and 5000 ppm/kg/day for 13 weeks. Microslides were prepared from the pancreas of the Wistar rats by the sponsor who selected at least 77 rats, which were identified as having either hyperplasia or benign adenomas for further pathological evaluation. The pathological evaluation was performed by

indicated that the quality of the histologic preparations was good. The results are listed below.

Pancreas: Islet Cell Adenomas

Dose (ppm/kg/day)	Male	Female
0	3	2
0	6	2
320	13	6
1,265	10	6
5,000	10	4

The pathologist concluded that glimepiride did not influence the incidence of benign tumors(adenomas) derived from pancreatic islet cells in female Wistar rats. In male rats there appeared to be an equivocal (but not statistical) increase in islet cell adenomas compared to controls. But, there was not a dose-response effect and the largest number of adenomas were in the mid-high dose groups of male rats. The pathologist further concluded that the numerically increased islet cell adenomas observed in the mid-high dose groups of male Wistar rats was most likely a chance event and not related to the administration of glimepiride.

F. LOCAL TOLERANCE TEST

Glimepiride- Testing for sensitizing Properties in the Pirbright-White guinea pig in the Maximization Study(Project ID 92.0008; Document#012923)

a. Objective: To test glimepride's potential for allergic reaction.

b. Methods: A total 29 Pirbright-White female guinea pig (strain DHPK, SPFLac) were divided into 5 groups:

Group 1: Control	5
Group 2: Placebo	6
Group 3: Escort	5
Group 4: Intradermal injection	3
Group 5: Treatment	10

The hair on the right and left flanks of the guinea pigs was removed and test substances were applied to a 2x2 cm² cellulose patch. Placebo was petrolatum and 1, 5 or 25% of the drug was applied. Intradermal injection was performed using 1% glimepiride- in semi-liquid paraffin. The procedure was performed according to the method of Magnusson and Klingman. The decisive criterion for evaluation of the drug was based on erythema and edema formation.

c. Results: No signs of irritation occurred after application of the different test concentrations of glimepride.

G. Labeling: See "Recommend Section" below.

H. Comments and Conclusion: (Parts of summaries from previous reviews included for completeness.)

Glimepiride is a sulfonylurea for the treatment of NIDDM. It is effective in doses as low as 10 µg/kg in different animals by release of insulin from the pancreatic cells. It binds to a 65 kDa pancreatic protein. It appears that glimepride has less effect on the cardiovascular system than other sulfonylureas.

The acute oral lethal toxicity of glimepride was greater than 10,000 mg/kg in both mice and rats. The maximum administered oral doses of 2,000 - 5,000 mg/kg were well tolerated with minor discomfort in rats. No signs of toxicity or death were noted in dogs following a dose of 2,000 mg/kg, which reduced blood glucose. There was no remarkable toxicity in 6- and/or 12-month toxicity studies in rats or dogs.

In a 24-month mouse oncogenicity study, increased incidences of islet cell hyperplasia and islet cell adenomas were noted in mice of the mid and high dose groups (210 - 830 mg/kg/day). In rats, glimepride (345 mg/kg/day) treatment for 30 months increased the incidence of pancreatic islet cell hyperplasia, but, did not increase the incidence of neoplastic pancreatic islet cells. One, 6 and 12-month dog studies were conducted

at dosages of 320 mg/kg/day (oral capsule). Glimepiride did not cause pancreatic adenomas in dogs. But, one female and one male dog developed bilateral posterior subcapsular cataracts 10 days after the drug treatment. At this time, the serum concentration of glimepiride was 35 µg/ml. But, cataracts were not present at the nine- and 12-month evaluation periods.

Glimepiride was extensively metabolized and the initial metabolic transformation in all species appeared to be the oxidation of the methyl group in the cyclohexyl ring to the hydroxymethyl derivative (M1) followed by formation of the carboxy derivative (M2). The major metabolites of glimepiride were not toxic because mice did not die after a single intraperitoneal injection of 2000 mg/kg of either of the two major metabolites of glimepiride. No evidence of toxicity was observed in rats after an intravenous infusion of either metabolite at the speed of 10 mg/kg/day for 2 weeks.

The fertility of male mice and rats was not affected by the drug treatment (up to 2500 mg/kg/day for 5 weeks). Fertility was also unaffected in rats at doses up to 50,000 ppm (approx. 4000 mg/kg/day), but some pups from the high dose (4000 mg/kg/day) exhibited postnatal shortening, thickening, and bending of the humerus. The shortening and bending might be related to drug-induced hypoglycemia, which impaired bone growth. No signs of toxicity were observed in either the dams or the surviving offspring. No embryotoxic or teratogenic effects were observed. In a segment III study, glimepiride (2,500 mg/kg/day) did not impair the general physical condition or parturition of the dams.

Glimepiride was negative in all the mutagenicity assays: Ames, HGPRT, unscheduled DNA synthesis, chromosome analysis in Chinese hamsters and mouse micronucleus tests.

I. RECOMMENDATION:

Pharmacology recommends approval of Amaryl for NIDDM. In the Pregnancy Section of the labeling, drug exposure comparisons between preclinical and clinical doses should be based on plasma concentration, rather than on mg/kg. If plasma concentrations of the drug are not known, exposure comparison should be based on surface area (mg/m²).

Commercialized to form in 9/17/95 letter. Revisions indicated in 6/20/95 submission. II. Meeting reconvened from on 6/22/95. Herman M. Rhee, Ph. D. Review Pharmacologist

Herman M. Rhee, Ph. D.
Review Pharmacologist

A. Jordan
4/7

JUN 14 1994 Free

IND

1/26/1994

Sponsor: Hoechst-Roussel Pharmaceuticals, Inc.
Somerville, NJ

Date of Submission: 6/7/1993

Document Name: Amendment #136

Drug: Glimepiride, HOE 490, or Amaryl

Class: Oral hypoglycemic agent

This amendment contains total 9 documents. Three of the documents [Dog#011845(8/26/92, Serial #94; Rat#008281(6/3/92) and #009623(8/12/92)] were reviewed already. The remaining 6 documents(009619, 011894, 009620, 012322, 011827 and 011739) are reviewed below. All of the studies were performed in West Germany.

I. HOE 490 repeated dose(24 months) oral carcinogenicity study in mice-document# 009619

(The sponsor performed this experiment based on Divisional communications originated from Dr. A. Jordan on Jan. 10, 1989)

A. METHODS:

Amaryl(HOE 490) was administered to groups of 50 mice/sex/group in concentrations of 0.0, 320, 1,265 or 5,000 ppm in the feed over a period of 24 months. Additionally one group of 50 mice/sex was served as control. The animals were 4-week old NMRI-mice(strain Hoe:NMRKf, spf71). The low dose(320 ppm) corresponds to about 200 times the therapeutic dose and the absorption seemed saturable at the high dose, since the blood level reached a plateau.

B. RESULTS:

1. Intake of Amaryl The daily intake of test substance in mg/kg body weight per day was as follows. The calculation was based on feed consumption and body weight for 24 months treatment period.

Group	Male	Female
320 ppm	46.69 mg/kg	54.31 mg/kg
1,265 ppm	178.93	209.50
5,000 ppm	713.63	813.87

2. Drug effects on body weight and food consumption

Amaryl did not affect body weight and food consumption including the consumption of drinking water.

3. Mortality There was no differences between control and drug treated animals in the number of animals died or had to be killed intercurrently in all groups(fig.1).

4. Hematology No indication of oncogenic changes of the hematopoietic system which would be related to Amaryl administration.

5. Post-mortem microscopic examinations

Autopsy of the mice revealed no changes which could be related to the drug treatment.

6. Post-mortem organ weights

The absolute organ weights revealed no significant differences between control and the drug treated mice except weight of the heart and the liver in the female mice(Tab. 1).

7. Histology It appeared that the drug caused a loss of granulation in β cells of the pancreatic islets, which resulted in an increased frequency of islet cell hyperplasia and islet cell adenomas in the pancreas.

8. Pathology report See table 3a, 3b and 3c.

II. HOE 490: Repeated-dose (30 months) Oral Carcinogenicity study in rats-Document No. 009620

(The sponsor performed this experiment based on divisional communications that was originated from Dr. A. Jordan on Jan. 10, 1989)

A. METHODS

Amaryl (Batch no. C011, C017 and C025) was given to 4-weeks old Wistar rats, 50 rats/sex/group (Strain HOE:WISKF, spf71) in the feed for 30 months. The rats were divided into 5 groups: two control, 320 ppm, 1,265 ppm and 5,000 ppm groups in accordance with the randomization plans 1145/89 and 1146/89. According to previous 90 day- and 12 month-feeding studies(87.1812 and 89.0984), Amaryl did not produce any notable adverse reaction at concentration level of 50,000 ppm, although serum drug levels reached a plateau at the 5,000 ppm. The lowest dose (320 ppm) represents about 100 times the therapeutic dose(0.1-0.2 mg/kg/day).

B. RESULTS

1. Mean drug intake The daily intake of Amaryl in mg/kg body weight per day was calculated on the basis of feed consumption and body weight development for 30 months.

<u>Group</u>	<u>Male</u>	<u>Female</u>
320 ppm	16.76 mg/kg	21.72 mg/kg
1,265 ppm	66.30	86.89
5,000 ppm	263.50	345.10

2. Body weight, feed and water consumption

The body weight development of male and female rats treated with Amaryl was normal, although slight differences between the control and drug treated groups. Absolute and relative feed consumption in male and female rats was not affected by the drug. No difference was noted in consumption of drinking water between treated animals and the control groups.

3. Mortality As shown in the table 2, mortality was not affected the drug.

4. Hematology Hematological examinations at study end (30 months) indicate that almost all parameters were similar for treated and control animals except reduced erythrocyte and hemoglobin values in 1,265 ppm male group. However, the difference might be incidental because all values are within the physiological range known for rats of this strain and age.

5. Pathological findings Autopsy of the rats revealed no changes which could be related to the feeding of Amaryl. No non-neoplastic changes were diagnosed in rats treated with Amaryl that were considered to represent toxic effects of the test article. The type and incidence of the non-neoplastic changes did not distinguish treated rats from controls. No neoplastic lesions were diagnosed in rats treated with Amaryl that were considered to represent an oncogenic effect of the drug. The most frequently diagnosed neoplasms occurred in the adrenals, hemolymphoreticular system, liver, mammary gland, mesenteric lymph node, pancreas, parathyroid glands, pituitary gland, testes, thyroid gland, and uterus (see table 4, pp18-43).

a. Pancreas: Primary neoplasms diagnosed in the pancreas were islet cell adenomas, and an acinar cell adenoma and carcinoma. The incidence of islet cell adenomas was 6.4%, 12.2%, 26%, 20.4%, and 20.8% in groups Control 1, Control 2, 320 ppm dose group, 1,265 ppm dose group, 5,000 ppm dose group, respectively. In females, the incidence of islet cell

adenomas was 4.2%, 4.1%, 12.2%, 12.0% and 8.2% for the five groups above.

b. Uterus: Primary neoplasms diagnosed in the uterus were adenocarcinomas, an adenoma, leiomyosarcomas, hemangiosarcomas, a hemangioma, a granular cell tumor, and stromal sarcomas. The incidence of uterine adenocarcinomas was 6%, 6%, 2%, 2%, and 14% for the 5 groups, respectively. The statistic test for a positive trend with respect to dose rates yielded a one-tailed p-value of 0.0064 for uterine adenocarcinomas.

c. Other organs/tissues: The incidence of the other neoplasms did not exceed 6% in any group. The incidence of neoplasms in the other protocol-designated organs/tissues did not distinguish treated rats from the controls.

d. Adenomas: A high number of islet cell adenomas was diagnosed in male rats of the drug treated groups. However, statistical evaluation with respect to dose rate revealed no evidence of a positive trend. The incidence of adenomas in the middle and the high dose groups did not show a significant increase, when compared with the controls. Only in males of the low dose group was a statistically significant increased incidence of adenomas calculated, when compared with the controls.

III. In Vitro Investigations of the effects of HOE490 on bovine lenses-Document no. 012322

To test preclinical oculotoxicity of Amaryl, Bovine lenses were removed immediately after death of the animals. The lenses were cleared from adhering iris and vitreous remnants. The lenses were incubated for 8 hours in a medium containing pyrrolidone (0.3 ml/ml) and the lenses were mechanically separated into an equatorial ring and a central lens cylinder which was subsequently separated into 5 2 mm sections. Glycolysis control enzyme, metabolic energy, protein conformation and content were determined.

The biochemistry of the lens substances and the quantity or quality of various metabolic processes is rather different within the lens. The drug is only slightly soluble in aqueous environment. The addition of the solubilizing agent Pyrrolidone enabled the incubation of bovine lenses as test objects. The results exclude a direct effect of Amaryl on the carbohydrate or energy metabolism of the lens. The redox potential of the single lens layers is hardly disturbed, the quantity and quality of the lens protein remain unchanged. The lens changes found in 2 of 123 beagle dogs subjected to high doses in a previous repeated-dose toxicity study (Document No. 008577).

IV. Study of HOE490 for formation of specific IgE antibodies in mice. Heterologous 4-hour passive cutaneous anaphylaxis test with rats-Document no. 011827

The abilities of Amaryl and its metabolite M1 to elicit IgE antibody formation in mice were examined by the rat 4-hr passive cutaneous anaphylaxis test. Nine weeks old mice were sensitized and 10 week-old male SD rats received 4-hr passive cutaneous anaphylaxis test. In the drug treated groups no IgE antibody formation was detected under the severe immunization conditions with Freund's complete adjuvant. In the group sensitized with ovalbumin, a positive control substance, plus Freund's complete adjuvant, IgE antibodies were detected in all mice. The data indicate that Amaryl might not cause antigenicity clinically.

V. Antigenicity study of HOE 490 in Guinea pigs-Active systemic anaphylaxis test and homologous 4-hour passive cutaneous anaphylaxis test-Document no. 011739

The objective of this study was to examine the antigenic potential of Amaryl in Guinea pigs by the active systemic anaphylaxis test and by the homologous 4-hr passive cutaneous anaphylaxis test. Sensitized male Hartley guinea pigs and the recipient animals were obtained from

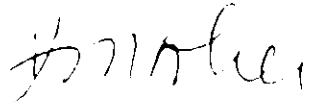
. When Amaryl or its metabolites was administered to guinea pigs orally, the animals showed no anaphylactic reactions. Their sera were all negative for passive cutaneous anaphylaxis reactions. In the positive control group, sensitized with ovalbumin plus adjuvants, the animals showed marked anaphylactic reactions.

VI. Summary and conclusions

According to sponsor's previous study (Serial no. 121 on Nov. 5, 1992), Amaryl produced drug-dose dependent increase in pancreatic islet cell adenomas when the drug was given to mice at a dose of 5,000 ppm for 24 months. However, in the present studies in rats which were treated with Amaryl at a top dose of 50,000 ppm for 30 months did not produce tumor. Additionally the drug was negative for anaphylaxis tests.

Vii. Recommendation:

The study may proceed.


Herman M. Rhee, Ph. D.

cc: IND, HFD-510/HFD-345
A Jordan/H. Rhee

Attachments: Tables 1, 2, 3, 4 and fig. 1.

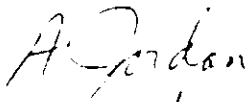

6/14

Table 1

SASPROGRAM: ORGA
 HOECHST AKTIENGESELLSCHAFT
 STUDY NO: DM0001
 COMPOUND: MOE 490
 TITLE: CARCINOGENICITY STUDY OF MOE 490 (S B0 B-90)
 SECTION: PHARMA DEVELOPMENT TOXICOLOGY
 SPECIES: MOUSE
 ROUTE: ORAL
 RUN DATE: 28/04/92

FINAL VALUE

ORGAN WEIGHTS (FEMALE)

		GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
		0	0	320	1265	5000
		PPM	PPM	PPM	PPM	PPM
BODY WEIGHT (g)	MEAN	33.3	32.1	30.9	30.3	30.8
	S.D.	3.9	5.0	4.4	5.6	5.0
	N	27	20	16	24	23
HEART (g)	MEAN	0.173	0.175	0.156	0.153	0.155
	S.D.	0.026	0.029	0.019	0.022	0.018
	N	27	20	16	24	23
LUNGS (g)	MEAN	0.232	0.230	0.216	0.227	0.232
	S.D.	0.026	0.054	0.031	0.038	0.041
	N	26	20	16	24	23
LIVER (g)	MEAN	1.642	1.690	1.331	1.386	1.356
	S.D.	0.451	0.433	0.248	0.294	0.180
	N	27	20	14	24	23
KIDNEYS (g)	MEAN	0.444	0.432	0.423	0.532	0.422
	S.D.	0.055	0.066	0.065	0.601	0.073
	N	27	20	16	24	23
SPLEEN (g)	MEAN	0.376	0.247	0.228	0.201	0.181
	S.D.	0.650	0.166	0.208	0.163	0.139
	N	27	20	16	24	23
OVARIES (g)	MEAN	0.4318	0.7330	0.2646	0.2798	0.1343
	S.D.	0.9777	1.5202	0.3740	0.2766	0.1316
	N	27	20	16	24	23

ONE-WAY ANALYSIS OF VARIANCE WITH SEQUENTIALLY REJECTIVE MULTIPLE COMPARISONS (P < 0.05)

* : SIGNIFICANTLY DIFFERENT FROM CONTROL

M : EVALUATION NOT POSSIBLE

ME : NO STATISTICAL EVALUATION

Table 2

1.5. Mortality

The following animals died or had to be killed intercurrently:

Week	Males					Females				
	control 1	control 2	320 ppm	1 265 ppm	5 000 ppm	control 1	control 2	320 ppm	1 265 ppm	5 000 ppm
1 - 26	0	0	0	0	0	0	0	0	0	0
27 - 52	2	0	0	1	0	0	0	1	1	0
53 - 78	1	0	0	1	2	2	1	2	1	2
79 - 104	4	0	4	7	3	8	4	5	6	7
105 - study end	18	16	14	16	15	19	16	17	22	16
Mortality	25	16	18	25	20	29	21	25	30	25
Mortality X	50	32	36	50	40	58	42	50	60	50

As shown in the table, mortality was not affected by feeding of HOE 490.

(Graphs, pages 41 - 42, Statistics, page 317, Individual deaths analysis, pages 453 - 477)

1.6. Behavior and general health condition

No difference was detected in behavior and general health condition in comparison with the control animals.

Tab. 3a

PATHOLOGY REPORT HOECHST AG
SUMMARY TABLES

PAGE : 20/1488
89.1312

TEST ARTICLE : HOE 490 (S 80.8490) PATHOL. NO.: 02503 DIR
TEST SYSTEM : MOUSE (NMRI), 24 months, feeding DATE : 15-DEC-92
SPONSOR : Drug Toxicology PATHDATA SYSTEM V3.5c

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +
M a l i g n a n t T u m o r s

	SEX :						MALE
		DOSE GROUP:	C1	C2	D1	D2	
		NO. ANIMALS:	50	50	50	50	50
LUNGS	NO. EXAM.:	50	50	50	49	50	
- Adenocarcinoma, al. c.		1		3	2	1	
- Hemangiosarcoma						1	
- Metastasis NOS		1					
STOMACH (forestom.)	NO. EXAM.:	48	48	48	47	45	
- Carcinoma, squam. c.		1					
LIVER	NO. EXAM.:	49	48	49	48	50	
- Hepatocell. carcinoma				2			
- Hemangiosarcoma		2	1	1	1	1	
URINARY BLADDER	NO. EXAM.:	47	50	48	49	47	
- Metas. malig. tum. NOS				2			
TESTES	NO. EXAM.:	49	50	50	49	50	
- Leydig cell tumor, m					1	1	
- Seminoma						1	
PROSTATE	NO. EXAM.:	47	46	47	44	47	
- Tumor, malignant NOS			1				
HEMOLYMPHORET. SYS.	NO. EXAM.:	50	50	50	49	50	
- Histiocytic sarcoma		1		1	1		
- Mal. fib. histiocyto		1					
- Malignant lymphoma		10	14	13	10	7	
- Plasma cell tumor				1			
MESENT. LYMPH NODE	NO. EXAM.:	39	41	40	42	45	
- Lymphosarcoma				2			
HARDERIAN GLAND	NO. EXAM.:	1		5		3	
- Adenocarcinoma		1					
SKIN	NO. EXAM.:	49	48	50	48	49	
- Hemangiosarcoma					1	1	
- Sarcoma NOS						1	

Tab. 3b

PATHOLOGY REPORT HOECHST AG
SUMMARY TABLES

PAGE : 21/1488
89.1312

TEST ARTICLE : HOE 490 (S 80.8490) PATHOL. NO.: 02503 DUR
TEST SYSTEM : MOUSE (NMRI) 24 months, feeding DATE : 15-DEC-92
SPONSOR : Drug Toxicology PATHDATA SYSTEM V3.5c

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +
M a l i g n a n t T u m o r s

	SEX	MALE				
	DOSE GROUP:	C1	C2	D1	D2	D3
	NO. ANIMALS:	50	50	50	50	50
STERNUM	NO. EXAM.:	46	50	48	49	48
- Spindle cell sarcoma					1	
- Granular c.t. malig.				1		
- Sarcoma NOS			1			
TAIL	NO. EXAM.:		1			2
- Hemangiosarcoma						1
- Fibrosarcoma						1
UNSPECIFIED TISSUE	NO. EXAM.:				1	
- Sarcoma NOS					1	

Tab. 30

PATHOLOGY REPORT HOECHST AG PAGE : 22/1488
 SUMMARY TABLES 89.1312

TEST ARTICLE : HOE 490 (S 80.8490) PATHOL. NO.: 02503 DUR
 TEST SYSTEM : MOUSE (NMRI), 24 months, feeding DATE : 15-DEC-92
 SPONSOR : Drug Toxicology PATHDATA SYSTEM V3.5c

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: KO, INCL. +
 M a l i g n a n t T u m o r s

	SEX :						FEMALE
	DOSE GROUP:	C1	C2	D1	D2	D3	
	NO. ANIMALS:	50	50	50	50	50	
LUNGS	NO. EXAM.:	50	50	50	50	49	
- Adenocarcinoma, a.l.c.					1	2	
DUODENUM	NO. EXAM.:	39	33	34	43	33	
- Adenocarcinoma					2		
LIVER	NO. EXAM.:	50	49	49	49	49	
- Hepatocell. carcinoma				1			
- Kupffer's cell sarc.			1				
OVARIES	NO. EXAM.:	50	50	49	50	49	
- Tubulostr. carcinoma		1					
- Granulosa c.t., mal.		2	4	3	1	1	
- Thecoma, malignant					1		
- Hemangiosarcoma			1				
UTERUS	NO. EXAM.:	50	49	45	44	45	
- Hemangiosarcoma						1	
- Leiomyosarcoma		1			1	1	
- Endom.strom. sarcoma		2	1	1	1	1	
- Schwannoma, malig.				2			
- Sarcoma NOS		3					
- Granular c.t. malig.			1				
- Adenocarcinoma				1	2		
- Yolk sac carcinoma					1		
- Carcinoma NOS				1			
VAGINA	NO. EXAM.:	49	50	45	45	46	
- Adenocarcinoma						1	
- Stromal sarcoma			1				
- Schwannoma, malig				1			
ADRENAL GLANDS	NO. EXAM.:	49	50	49	50	49	
- Pheochromocytoma, m.						1	

Tab. 3d

PATHOLOGY REPORT HOECHST AG
SUMMARY TABLES

PAGE : 23/1488
89.1312

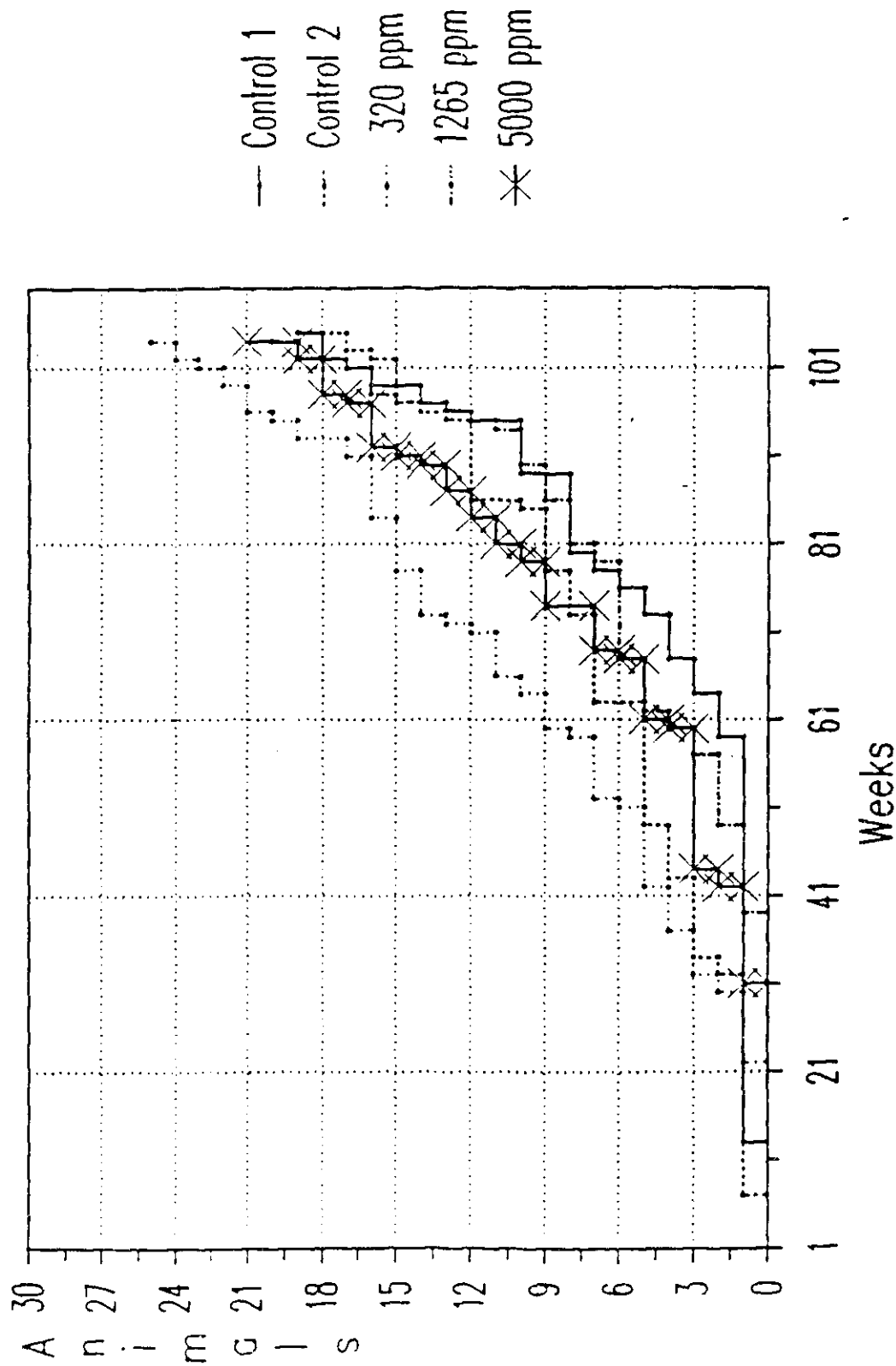
TEST ARTICLE : HOE 490 (S 80.8490) PATHOL. NO.: 02503 DUR
TEST SYSTEM : MOUSE (NMRI), 24 months, feeding DATE : 15-DEC-92
SPONSOR : Drug Toxicology PATHDATA SYSTEM V3.5c

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +
M a l i g n a n t T u m o r s

	SEX :						FEMALE
	DOSE GROUP:	C1	C2	D1	D2	D3	
	NO. ANIMALS:	50	50	50	50	50	
HEMOLYMPHORET. SYS.	NO. EXAM.:	50	50	50	50	49	
- Histiocytic sarcoma		2	1	5			
- Mal.fib.histiocytoma					2	1	
- Malignant lymphoma		24	16	10	13	15	
- Myeloid leukemia		1				1	
- Erythroleukemia				1			
- System. mast cell t.					1	1	
HARDERIAN GLAND	NO. EXAM.:		1	2	1	1	
- Adenocarcinoma					1		
MAMMARY GLAND	NO. EXAM.:	43	36	39	39	43	
- Adenocarcinoma			1	1	1	1	
SKIN	NO. EXAM.:	50	49	50	50	49	
- Fibrosarcoma			1				
- Hemangiosarcoma			2	2	1		
SKELETAL MUSCLE	NO. EXAM.:	50	50	49	50	49	
- Rhabdomyosarcoma					1		
FEMUR/TIBIA	NO. EXAM.:	50	48	48	49	48	
- Sarcoma NOS				1			
TAIL	NO. EXAM.:			1			
- Schwannoma, malig.				1			

CARCINOGENICITY STUDY (24 MONTHS) OF HOE 490

FIGURE 1 Mortality of male mice



CLEM

REVIEW

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS HFD-510

Review of Chemistry, Manufacturing and Controls

NDA N° 20-496 CHEMISTRY REVIEW # 3 DATE REVIEWED: 04-OCT-1995

SUBMISSION	ORIGINAL	Doc. 31-AUG-1994	Rec. 01-SEP-1994
	Amendmen (s):	Doc. 13-SEP-1995	Rec. 15-SEP-1995

APPLICANT: Hoechst-Roussel Pharmaceuticals Inc.
Route 202-449
P.O. Box 2500
Somerville, NJ 08876-1258 (908) 231-2107

DRUG PRODUCT NAME	Proprietary:	Amaryl® Tablets
	Nonproprietary/Established/USAN:	Glimepiride Tablets
	Code Name / #:	HOE 490, S 80 8490
	Chem. Type / Ther. Class:	1 P

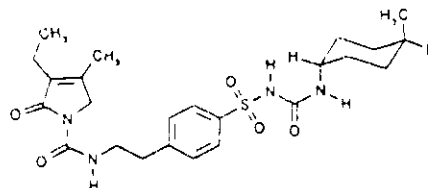
PHARMACOLOGICAL CATEGORY/INDICATION: Antihyperglycemic Agent. Adjunct to diet in NIDDM patients whose hyperglycemia cannot be controlled by diet alone. In combination with insulin in NIDDM patients not responding to diet and sulfonylurea therapy alone.

DOSAGE FORM:	Tablet
STRENGTHS:	1, 2, and 4 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	Rx

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

C₂₄H₃₄N₄O₅S 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*-

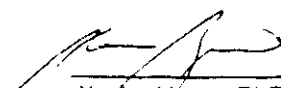


REMARKS: This amendment provides a response to the Agency letters dated August 30 (environmental assessment) and September 13 (starting materials), 1995.

CONCLUSIONS & RECOMMENDATIONS: All the pending issues regarding Chemistry and Manufacturing Controls have been satisfactorily answered by the firm. The application is **approvable** from the Chemistry viewpoint.

Orig. NDA 20-496
cc: HFD-510/Division File
HFD-510/Gueriguian/Hertig/Moore/Short/Ysern
R/D Initialed:

J. Moore
10/4/95


Xavier Ysern, PhD
Review Chemist

filename: 20496_3.NDA

AUG 30 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-496 CHEMISTRY REVIEW # 2 DATE REVIEWED: 30-AUG-1995

SUBMISSION ORIGINAL Amendments	Doc 31-AUG-1994	Rec 01-SEP-1994
	Doc 10-MAY-1995	Rec 17-MAY-1995
	Doc 20-JUN-1995	Rec 21-JUN-1995
	Doc 22-JUN-1995	Rec 03-JUL-1995
	Doc 26-JUN-1995	Rec 29-JUN-1995
	Doc 10-JUL-1995	Rec 17-JUL-1995
	Doc 12-JUL-1995	Rec 14-JUL-1995
	Doc 17-JUL-1995	Rec 19-JUL-1995

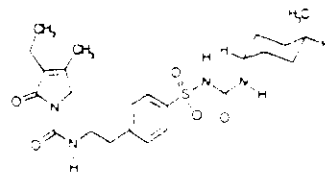
APPLICANT: Hoechst-Roussel Pharmaceuticals Inc
Route 202-449
P.O. Box 2500
Somerville, NJ 08876-1258 (908) 231-2107

DRUG PRODUCT NAME	Proprietary: Nonproprietary/Established/USAN Code Name / # Chem. Type / Ther. Class	Amaryl® Tablets Glimepiride Tablets HOE 490, S 80 8490 1 P

PHARMACOLOGICAL CATEGORY/INDICATION: Antihyperglycemic Agent. Adjunct to diet in NIDDM patients whose hyperglycemia cannot be controlled by diet alone. In combination with insulin in NIDDM patients not responding to diet and sulfonylurea therapy alone.

DOSAGE FORM:	Tablet
STRENGTHS:	1, 2, and 4 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	<u>X</u> Rx

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



C₂₄H₃₄N₄O₅S MW = 490.62
CAS 93479-97-1

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

CONCLUSIONS & RECOMMENDATIONS: The application is **approvable** from the Chemistry viewpoint pending a favorable **Environmental Impact Assessment** evaluation, favorable evaluation of the inspections of the **manufacturing facilities** and the sponsor's acceptance of the Agency's designation of glimepiride as an **intermediate compound**. See Draft Deficiency Letter.

Orig NDA 20-496
cc: HFD-510/Division File
HFD-510/Gueriguian/Hertig/Short/Ysern
R/D Initialed:

FR accepted as of 8/30/95

Xavier Ysern, PhD
Review Chemist

Ysern 8/30/95

filename: 20496_2.NDA

DRAFT DEFICIENCY LETTER

We have completed our review of your amendment June 26, 1995, in response to our letter of May 17, 1995. Your submission addresses the question of whether glimepiride is the starting material for the drug substance, glimepiride. For the following reasons we do not believe that glimepiride- can be considered a starting material

(1) We did not require additional information during the IND process because CMC comments from the Agency at that time are, in general, more flexible due to the changing nature of an experimental drug where synthesis and controls of the active drug, drug product composition and proper specifications are not only being modified but in most of the cases experience is being gained at this stage.

(2) Glimepiride- can not be considered a widely commercially available compound. Apparently only two manufacturers seem to produce glimepiride- One of the suppliers is Hoechst Aktiengesellschaft, Frankfurt am Main, Germany (HAG), the manufacturer of the drug substance and the holder of the patent for the synthesis of The other is the contract manufacturer

(3) Starting materials are in general very pure materials. The controls/specifications established by you, for the assay and for the sum of all by-products are only adequate for an intermediate compound

(4) Glimepiride- which is also the main degradation product is not a simple compound. The synthesis of glimepiride- can be accomplished by

After careful consideration of your viewpoints, we reiterate (as previously expressed in our May 31, 1995 letter) the designation of glimepiride as a synthesis intermediate, not a starting material.

B) Labeling

The second sentence of the Description section refers to the active drug substance and should read "Glimepiride is a white to yellowish-white ^{Amaryl}" instead of "It is a white to yellowish-white ^{Amaryl} mentioned in the first and previous sentence, is the trade name of the drug product, glimepiride tablets (established name)"

This is your have it which would refer to the drug product and is not correct

*XY
7/13/95*

MAY 3 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA N° 20-496 CHEMISTRY REVIEW # 1 DATE REVIEWED: 2-MAY-1994

SUBMISSION ORIGINAL Doc. 31-AUG 1994 Rec. 01-SEP-1994

APPLICANT: Hoechst-Roussel Pharmaceutical Inc.
Route 202-449
P.O. Box 2500
Somerville, NJ 08876-1258 (908) 231-2107

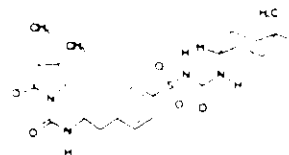
*Letter issued
~~5/17/95~~
5/17/95*

DRUG PRODUCT NAME
Proprietary: Amarin® Tablets
No. proprietary/Established/USAN: Glimperide Tablets
Code Name/#: HOE 490, S 80 8490
Chem. Type/Ther. Class: 1 P

PHARMACOLOGICAL CATEGORY/INDICATION: Antihyperglycemic Agent. Adjunct to diet in NIDDM patients whose hyperglycemia cannot be controlled by diet alone. In combination with insulin in NIDDM patients not responding to diet and sulfonylurea therapy alone

DOSAGE FORM: Tablet
STRENGTHS: 1, 2, and 4 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

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



C₂₃H₃₄N₄O₄S
MW = 490.62
CAS 93479-97-1
trans-3-Ethyl-2,5-dihydro-4-methyl-N-[2-[[[[(4-methylcyclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-1H-pyrrole-1-carboxamide

CONCLUSIONS & RECOMMENDATIONS: The application is **approvable** from the Chemistry viewpoint pending a favorable Environmental Impact Assessment evaluation (Consulted) and the sponsor response to the [minor] deficiencies delineated in draft letter. See Draft Deficiency Letter.

Orig. NDA 20-496
cc: HFD-510/Division File
HFD-510/Gueriguian/Hertig/Short/Ysem
HFD-102/CKumkumian
R/D Initialed:

Xavier Ysem
Xavier Ysem, PhD
Review Chemist

see draft letter 5/17/95

filename: 20496_1.NDA

H. DRAFT DEFICIENCY LETTER

*Letter (company) and
5/10/95 (Dissolution spec) and
6/26/95 (starting material)
J. West
7/5/95*

Glimepiride is not a widely commercially available compound and consequently it is not considered a starting material. For Regulatory purposes, the synthesis of glimepiride route is considered part of the synthesis of the active drug. Glimepiride is an intermediate compound and its specifications according to volume 1.3, pages 66 and 67.

Labelling: *+ description of dissolution specification*

1) The dosage form should immediately follow the established name in all the labels, glimepiride Tablets instead of only glimepiride

*is the company the option of whether to
include within its name ()*

NDA 20496 CMC Review # 1

*Letter issued 5/17/95
Company not responded
as of 7/5/95
J. West
7/5/95*

E A + F O W S I

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

Amaryl™

(glimepiride tablets)

1, 2 and 4 mg

NDA 20-496

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-496

Amaryl

(glimepiride tablets)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Amaryl, Hoechst-Roussel Pharmaceuticals Incorporated** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Glimepiride is a synthetic drug which is administered as an oral tablet in the treatment of Type II Non-Insulin Dependent Diabetes Mellitus. The drug substance will be manufactured by Hoechst Aktiengesellschaft, Germany. The drug product will be manufactured by Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey. Packaging of the drug product will occur at Hoechst Roussel Pharmaceuticals, Inc. or a contract facility identified in the environmental assessment. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Glimepiride may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Chemical and physical test results indicate that the drug may exist in the aquatic environment or terrestrial environment. No rapid environmental depletion mechanism has been identified, although the compound is expected to bind tightly to soils and sediments thus removing a significant portion of the drug from the aquatic environment and limiting its bioavailability to environmental organisms. As glimepiride is expected to persist

in the environment for some time, the toxicity of the material to organisms was characterized. Studies including: 1) acute toxicity to water fleas (*Daphnia magna*), 2) acute toxicity to bluegill sunfish (*Lepomis macrochirus*), 3) acute toxicity to an amphipod (*Hyalella azteca*), 4) 14-day toxicity green algae (*S. capricornutum*), 5) 14-day toxicity blue-green algae (*Microcystis aeruginosa*) and 6) microbial growth inhibition indicate that the substance is not expected to affect the environment at the expected environmental concentrations

Disposal of the drug may result from out of specification lots, process related waste, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be disposed of by the manufacturer at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the drug substance and drug product are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects.

9/28/95 Nancy B. Sager
DATE PREPARED BY/

Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

10/10/95 Robert A. Jerussi
DATE CONCURRED

Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

APPENDIX I
FREEDOM OF INFORMATION (FOI)
ENVIRONMENTAL ASSESSMENT
INFORMATION

(Non-Confidential)

AMARYL® (glimepiride; HOE 490) Tablets
1 mg, 2 mg, 4 mg

New Drug Application

NDA 20-496

FREEDOM OF INFORMATION (FOI)
ENVIRONMENTAL ASSESSMENT
INFORMATION

(Non-Confidential)

AMARYL® (glimepiride; HOE 490) Tablets
1 mg, 2 mg, 4 mg

New Drug Application

NDA 20-496

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FREEDOM OF INFORMATION (FOI)
ENVIRONMENTAL ASSESSMENT
INFORMATION

(Non-Confidential)

AMARYL® (glimepiride; HOE 490) Tablets
1 mg, 2 mg, 4 mg

New Drug Application

NDA 20-496

1. DATE

September 11, 1995

2. NAME OF APPLICANT/PETITIONER

Hoechst-Roussel Pharmaceuticals Incorporated (HRPI)

3. ADDRESS

Route 202-206 North
PO Box 2500
Somerville (Bridgewater Township)
New Jersey 08876-1258

4. DESCRIPTION OF THE PROPOSED ACTION

(a) Briefly describe the requested approval:

The purpose of this NDA application is to request approval from FDA to market AMARYL Tablets, a new drug for use in the treatment of Type II Non-Insulin Dependent Diabetes Mellitus (NIDDM).

(b) Need for the action:

Glimepiride is a new hypoglycemic agent of the sulfonylurea class for the treatment of patients with Type II Non-Insulin Dependent Diabetes Mellitus. Approximately 4,030,000 people are currently afflicted with this disease (1992 Crossley Tracking Survey). Glimepiride lowers the plasma glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent on functioning beta cells in the pancreatic islets. There is evidence that this drug may have enhanced potency with respect to plasma glucose lowering on a mg-for-mg basis relative to currently available sulfonylureas.

4. (c) *The locations where the products will be produced:*

Glimepiride

Manufacturing, packaging, and distribution of glimepiride are performed at the following facility. Certain chemicals used in the synthesis of glimepiride (eg, starting materials, solvents, reagents, auxiliary materials) are purchased from various commercial suppliers located elsewhere in Europe or the USA. These materials are not specifically listed in this EA because the information relates to the synthesis of glimepiride which is confidential and proprietary to Hoechst AG.

Hoechst Aktiengesellschaft (HAG)
D-65926 Frankfurt am Main
Germany

AMARYL (glimepiride) Tablets

The bulk drug substance is distributed from the Hoechst AG facility to HRPI for manufacturing and packaging of the drug product. The facility is located at:

Hoechst-Roussel Pharmaceuticals Inc. (HRPI)
Route 202-206 North
PO Box 2500
Somerville (Bridgewater Township)
New Jersey 08876-1258
FDA Drug Establishment (Registration) No.: 2222017; re-registered yearly

Packaging and labeling of the drug product into blister packages may be performed for HRPI by the following contract facility:

The drug product is distributed by HRPI from the Somerville (NJ) facility, or from the following HRPI distribution facilities:

3140 Route 22
Branchburg, NJ 08876

5225 West 81st Street
Indianapolis, IN 46268

734 West North Carrier Parkway
Grand Prairie, TX 75050

4. (d) *To the extent possible, the locations where the products will be used and disposed of:*

Glimepiride

National and State (federated), and local environmental and occupational regulations in Germany determine the appropriate system for disposal of and exposure to waste. Standard operating procedures at Hoechst AG assure compliance with relevant regulations and Company practices.

Certain non-recyclable solid waste resulting from synthesis, packaging, and distribution of glimepiride (spillage, discarded, or rejected materials, damaged containers, filters/dust collectors) is disposed by incineration or contained in disposal sites (under- or aboveground). In addition, certain non-recyclable organic liquid waste from synthesis is incinerated. Sludge recovered from Hoechst AG's own wastewater treatment plant, which contains strongly-adsorbed residual amounts of glimepiride, is incinerated or contained in disposal sites (landfills). Ashes from incinerators are typically contained in above- or underground disposal sites.

Certain waste produced during manufacturing and packaging of glimepiride may be recycled. Such recyclable waste consists of paper, cardboard, aluminum, plastic, or glass, and certain solvents recovered during the synthesis process.

The under- or aboveground disposal sites and recycling facilities used by Hoechst AG are located in Germany. Hoechst AG may also recycle certain solvents at their own facility. Hoechst AG may use their own facility or the following contract facility for incineration of waste:

- Permit Nos./Expiration Dates: Although all recycling, incineration, and disposal sites/facilities are officially approved by the German Government, with stringent emission requirements, there are no available permit numbers for these facilities.

4. (d) *Continued*

AMARYL (glimepiride) Tablets

The consumption (use and excretion) of Amaryl Tablets is limited to patients being treated for Type II Non-Insulin Dependent Diabetes Mellitus. However, treatment will occur in patients located throughout the USA. The drug product will be available only by prescription.

Federal (USA), State, and local environmental and occupational-exposure regulations determine the appropriate system for disposal of and exposure to waste. Standard operating procedures at HRPI assure compliance with relevant regulations and Company practices.

Certain non-recyclable solid waste resulting from manufacturing, packaging, and distribution of AMARYL Tablets (spillage, discarded, or rejected materials, damaged containers, and filters/dust collectors) is incinerated at a Government-approved facility. Waste from the contract packaging facility and from the HRPI distribution facilities (New Jersey; Indiana; Texas) is shipped to HRPI for transfer to the incineration facility. The incinerator used by HRPI is:

Permit No./Expiration Date: NY0000352658: The permit number is assigned by the Federal and/or State Environmental Protection Agency (EPA), and is not subject to expiration.

Liquid waste is discharged by HRPI and into publicly-owned (wastewater)treatment works (POTWs) or wastewater treatment plants (WWTPs) during manufacturing, packaging, and cleaning of equipment and exposed surfaces. is registered in New Jersey only to package and *not manufacture* finished dosage forms; accordingly, air and liquid discharge permits are not available for this facility. The following treatment facilities are used:

Hoechst-Roussel Pharmaceuticals Incorporated (HRPI)

Somerset Raritan Valley Sewerage Authority (SRVSA)
PO Box 6400
Bridgewater, NJ 08876
Permit No./Expiration Date: 10A; October 1995

South Hackensack Sewerage Authority (SHSA)
New Jersey

4. (d) *Continued*

The majority of sludges recovered from POTW/WWTPs are incinerated. Ashes from incinerators are disposed in monofill landfills. All incineration facilities and disposal sites used by treatment plants are Government-approved. The incinerator used by SRVSA is the same as that used by HRPI. SRVSA owns and operates their own monofill landfill for disposal of incinerator ashes.

Some of the recovered sludges from POTW/WWTPs throughout the United States may be amended into farmland. The participating treatment facilities who recover sludge, the facilities involved in processing, testing, or distributing sludge, as well as the land owners who apply sludge on farmland, are issued permits by the Office of Environmental Protection of the governing State.

Certain waste produced during manufacturing and packaging of AMARYL Tablets at HRPI or at [redacted] is collected at HRPI and transported to a recycling facility. Such recyclable waste consists of paper, cardboard, aluminum, plastic, or glass. The facility used by HRPI is located at:

Permit No./Exp. Date: There is no available permit number for this facility.

The common practice by customers in controlled settings, such as, pharmacies, Health Management Organizations (HMOs), and hospitals, is to return any outdated, rejected, or defective drug product to HRPI for appropriate disposal (incineration). However, if such waste drug product is not returned to HRPI for disposal, the waste is disposed by the customers. Customers may dispose the waste by incineration or by microwaving the waste prior to transport to a disposal site (landfill). All incineration facilities and disposal sites used by customers in controlled settings are Government-approved.

(e) The types of environments present at and adjacent to those locations:

Glimepiride

The Hoechst AG manufacturing facility is a major complex of buildings covering about 4 km², situated on both sides of the Main River, in the western periphery of the city of Frankfurt (Federated State of Hesse, Germany). The Main River is a major stream of about 500 km (310 miles), flowing through Central Germany into the Rhine River. The surrounding topography is mostly flat, rising in elevation away from the major urban centers. The climate in this region is temperate.

All Government-approved incineration facilities, recycling facilities, and above- and underground disposal sites in Germany used by Hoechst AG are located in environments of similar topography and climate.

AMARYL (glimepiride) Tablets

The HRPI manufacturing facility is situated on a parcel of 110 acres, in the Township of Bridgewater, about 1/2 mile south of the Town of Pluckemin, and about 4 miles northwest of the City of Somerville. The HRPI facility is bordered on the East by Route 202-206 and the First Watchung Mountain Ridge, Route 287 on the West, and residential properties to the North and South. The facility is 1/4 mile south of the South Branch Chambers Brook, one of three branches which are fed from the First Watchung Mountain Ridge, including Sunset Lake, and flow into the North Branch Raritan River. The facility is also 3/4 mile northeast of branches of Peters Brook, which are fed by the First Watchung Mountain Ridge, and flow into the Raritan River. The Raritan River is a major stream in central New Jersey which flows into the Atlantic Ocean. The facility is situated at 180 feet above mean sea level; the surrounding terrain rises from 100 to 500 feet. The climate in this area is temperate.

The other outside facilities used for packaging, distribution, recycling, and disposal of AMARYL Tablets will occur throughout the USA, in urban to rural locations of varying environments. Consumption (use and excretion) of the drug product will occur in urban to rural locations of varying environments.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

This information is required to be adequate to allow accurate location of data about chemicals in the scientific literature and to allow identification of closely related chemicals:

(a) Provide complete nomenclature, CAS Reg. No. (if available):

The name of the new drug substance is Glimepiride. This is the recognized international nonproprietary name (INN) listed in the compendium, United States Adopted Names (USAN) and USP Dictionary of Drug Names. The Trademark of the Drug Product is AMARYL®. The drug substance, glimepiride, is formulated into AMARYL Tablets for distribution to the market.

The Chemical Abstracts Service (CAS) name for Glimepiride is:

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

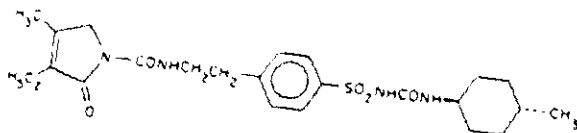
Alternatively, the following chemical names are used throughout the chemical, pharmaceutical, and medical literature:

- 1-[[*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]-sulfonyl]-3-(*trans*-4-methylcyclohexyl) urea

The following codes for Glimepiride are also used:

- Internal Company Codes: HOE 490 and S 80 8490
- CAS Registry Number (Glimepiride): 93479-97-1
- WHO Number: 5718

(b) Structural formulae, molecular weight:



Empirical Formula: $C_{18}H_{24}N_4O_3S$

Molecular Weight: 490.62

5. (c) *Physical description, additives, and impurities:*

Information on the physicochemical properties, additives, and impurities in glimepiride drug substance and AMARYL Tablets is provided in this section. Certain specific information on glimepiride that would normally be available in the chemical, pharmaceutical, or patent literature is included; whereas, certain other information that is proprietary or confidential has been omitted.

Glimepiride

The physicochemical properties of glimepiride were determined in accordance with the Environmental Assessment Technical Assistance Handbook (FDA and Dept. of Commerce, National Technical Information Service [PB87-175345]; March 1987). Refer to *Non-Confidential Attachments 5-1 and 5-1a*.

AMARYL (glimepiride) Tablets

The additives (including CAS numbers), impurities, and stability profile of the tablet formulation are described in this section. The impurity and stability profiles of the tablets are identical with those of glimepiride drug substance. The impurities and degradates detected in the product are the same as those detected in the substance. Refer to *Non-Confidential Attachment 5-2*.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

- (a) *For the site(s) of production, list the substances [and quantities] expected to be emitted:*
- (b) *State the controls exercised:*

Information on the substances expected to be emitted, quantitative/qualitative estimates, and controls exercised during manufacturing, packaging, distribution, and disposal of waste from glimepiride and AMARYL Tablets is provided in this section. Certain specific information on glimepiride is included; whereas, certain other information (eg, synthesis raw materials) is considered proprietary and confidential. Accordingly, certain specific information has been omitted, but is described in general terms. MSDS Sheets for all synthesis starting materials, solvents, reagents, auxiliary materials, formulation components, and final products are available on file at Hoechst AG, HRPI, and other manufacturing, packaging, distribution, and disposal facilities as necessary.

Glimepiride is eliminated from patients as the unchanged drug substance and--to a lesser extent--as two hydroxylated metabolites that are structurally-similar to the parent compound (glimepiride). Releases from manufacturing of the drug substance and drug product may contain--in addition to the drug substance--trace amounts of two impurities that are structurally-similar to glimepiride. The structural similarity of the metabolites and impurities to the structure of glimepiride will ensure their removal from the environment by the same processes that remove glimepiride. Therefore, it is not necessary to discuss their environmental fate in this EA Report.

Glimepiride

Air Emissions

The emission controls at Hoechst AG assure that there are practically no airborne emissions from the synthesis, packaging, and distribution of glimepiride. Substances and waste resulting from air-emission controls are limited to disposal of used filters and dust collectors that are part of the _____ system. The _____ system of the manufacturing plant is inspected regularly; calibration and repairs are performed as necessary. To limit materials from becoming airborne, there is quantitative and controlled transfer of raw materials and intermediates in compartmentalized and ventilated areas of the manufacturing plant. Materials are kept in closed containers until use. Reactions occur in sealed vessels. Dusts from non-volatile components are trapped by dust collectors and filters. Vapors from certain volatile components, which exhaust from reaction vessels, are recovered and recycled during the synthesis process using scrubbers. Other air-emission control devices may be used to achieve a high level of compliance with emission requirements. Operators wear particle masks or respirators as required.

6. (a)(b) Continued

A variety of solid waste may be accepted for incineration, including, certain packaging components that are not recycled. The types of materials that may be destroyed by incineration is strictly limited and controlled by EPA (21 CFR, Part 60) and similar German regulations to assure that there are no harmful levels of emissions from the destruction process. For example, certain components containing heavy metals or halogenated compounds (eg, vinyl chloride) are either prohibited or extremely limited to incineration. Emissions from incineration are predominately water vapor, carbon dioxide, carbon monoxide, nitrogen oxides, and sulfur oxides. Specific limitations for these combustion products are set by EPA and German regulations.

Incineration facilities, including Hoechst AG's own facility and contract facilities, (no available permit), must meet very stringent standards of qualification, operation, and emissions to be licensed by EPA and German regulations. Incinerators typically maintain a Destruction Removal Efficiency (DRE) rating of 99.95% with average operating temperatures of 2200-2500 °F. Continuous emission monitoring (CEM) devices are installed to assure that airborne-emitted constituents (ie, carbon monoxide, nitrogen oxides, sulfur oxides) are held within the specifications set by the facility operating permit. The CEM system provides operators with the assurance that there are no unrecognizable air-emission releases into the environment. Acid and gas scrubbers and baghouse particle filters are the final controls on the incinerator which prevent any undesirable airborne releases.

Liquid Emissions

Liquid waste from the synthesis of glimepiride and cleaning operations is treated, recycled, disposed by incineration, or contained in above- or underground disposal sites. There is essentially no emission of glimepiride in the effluent water that is discharged from Hoechst AG's wastewater treatment plant. Liquid waste from the synthesis of glimepiride is separated into organic and aqueous waste streams. The organic stream may be recycled by distillation or other separation techniques at the Hoechst AG manufacturing site; whereas, the aqueous waste stream is chemically and biologically treated at Hoechst AG's own facility before filtration and discharge into the Main River. Any organic liquid waste that cannot be recycled is incinerated.

There are practically no emissions of glimepiride into water streams that receive effluent water from Hoechst AG's wastewater treatment plant during manufacturing. The total amount of water required for manufacturing glimepiride to meet the USA market demand in the year 2000 (fifth year maximum production) is

6. (a)(b) Continued

Since Hoechst AG's waste-processing capacity is similar to that of a typical bulk chemical wastewater treatment plant (5.7×10^9 L waste/day or 2.08×10^{10} L waste/year), then the yearly water requirement for the production of glimepiride would represent only 0.002-0.0034% of the total waste-processing capacity of the Hoechst AG wastewater treatment plant. Accordingly, this waste stream is considered inconsequential to the total capacity of the Hoechst AG plant.

Based on maximum production (fifth year) in the year 2000, the amount of released glimepiride from the Hoechst AG wastewater treatment plant can be estimated. Based on synthesis yields of intermediates and glimepiride, several kilograms of these substances could be emitted in the wastewater treated in the plant. Based on the yearly treatment capacity of the plant, this results in a concentration of 0.43 µg/L. As wastewater is treated at the plant, glimepiride becomes strongly adsorbed to the sludge culture. Soil sorption and desorption studies (Item 5) show that glimepiride is strongly adsorbed to sludge cultures, and moderately adsorbed to soils/sediments. Results show 98.4% adsorption of glimepiride on sludge, with only $\leq 9\%$ desorption. Accordingly, *regardless of the initial concentration of glimepiride discharged into the treatment plant*, the concentration of glimepiride (at the treatment plant) would be about 2.9 µg/L. The effluent from the treatment plant is discharged into the Main River (Frankfurt, Germany). Presuming that the water flow in the Main River is similar to other major rivers (eg, Raritan River, NJ), then the mean annual flow rate of the river would be 1,213 cf or 784 million gal/day (USGS, 1992). Therefore, the dilution factor from the treatment plant (13 million gal/day) (SRVSA, 1992) to the river is 1.6×10^{-2} , and the concentration of glimepiride in the river due to synthesis and cleaning operations would be 46 ng/L. Adsorption to river sediment would reduce the concentration in the effluent by a factor of 3.2×10^{-3} (Item 7). Thus, the actual concentration in the effluent would be 9.3 ng/L. In the Main River, the concentration would be diminished to essentially zero downstream from the effluent by adsorption to fresh river sediment.

Solid Emissions

There are no emissions of glimepiride into terrestrial ecosystems from Hoechst AG from synthesis, packaging, and distribution of the drug substance. Certain non-recyclable solid waste (spillage, discarded, rejected, outdated, returned, or damaged materials, filters/dust collectors, sludge from Hoechst AG's wastewater treatment plant) is disposed by incineration or contained in disposal sites (under- or aboveground). Leaching of glimepiride from disposal sites would not be expected because it is strongly adsorbed to sludge, soils, and sediments. Ashes from incinerators is typically contained in above- or underground disposal sites. Other waste produced during manufacturing and packaging of glimepiride may be recycled (paper, cardboard, aluminum, plastic, or glass).

6. (a)(b) Continued

AMARYL (glimepiride) Tablets

Air Emissions

The controls at HRPI and _____ (contract packaging facility) assure that there are no airborne emissions from manufacturing, packaging, and distribution of AMARYL Tablets. Substances and waste resulting from air-emission controls are limited to disposal of used filters and dust collectors that are part of the _____ systems at HRPI and _____. The _____ systems of the manufacturing and packaging plants are inspected regularly; calibration and repairs are performed as necessary. To limit materials from becoming airborne, there is quantitative and controlled transfer of raw materials and finished products in compartmentalized and ventilated areas of the manufacturing and packaging plants. Materials are kept in closed containers until use. Dusts from non-volatile components are trapped by dust collectors and filters. There are no volatile components used in the manufacturing process. Operators wear particle masks or respirators as required.

The HRPI facility is registered with the State of New Jersey to produce finished pharmaceutical dosage forms. The FDA Drug Establishment Number is 2222017 (re-registered yearly). The facility has been granted a variety of air-emission permits by EPA. A listing of all the approved emission permits for the manufacturing plant (Building J) is provided in *Non-Confidential Attachment 6(a)-1*. Not all listed rooms are used for production of AMARYL Tablets; however, they are retained on the list to demonstrate the degree of control in the entire plant. _____ is registered in New Jersey only to package and not manufacture finished dosage forms; accordingly, air-emission permits are not available.

The total amount of airborne glimepiride trapped by dust collectors/filters during manufacturing at HRPI was determined on full-scale production batches; results are reported in *Non-Confidential Attachment 6(a)-2*. Dusts produced during packaging at _____ are anticipated to be far less than the amount recovered at HRPI during manufacturing; accordingly, calculations for such waste were not performed. Waste produced at the other HRPI distribution facilities (New Jersey, Indiana, Texas) is limited to solid waste from damaged, returned, rejected, or outdated drug product; thus, there are no air emissions at these facilities because dusts practically do not occur, and the materials are contained. Information on potential emissions from incinerators and controls exercised to limit emissions, during incineration of solid waste, is identical with that submitted previously for incineration of waste at Hoechst AG.

6. (a)(b) Continued

Liquid Emissions

There are practically no emissions of glimepiride (or related compounds) into water streams that receive effluent water from the public local wastewater treatment plants as a result of manufacturing, packaging, and cleaning of equipment for AMARYL Tablets. Liquid waste from manufacturing, packaging, and cleaning operations at HRPI and _____ is chemically and biologically treated at the wastewater treatment plants before filtration and discharge. HRPI has been granted a permit (No. 10A; expiration October 1995) for discharge into the sewerage system controlled by the Somerset Raritan Valley Sewerage Authority (SRVSA). _____ is registered in New Jersey only to package and not manufacture finished dosage forms; accordingly, a discharge permit is not available for this facility.

The total amount of glimepiride contained in the aqueous wastestream discharged by HRPI into the sewerage system during manufacturing and cleaning operations for AMARYL Tablets was determined on full-scale production batches; results are reported in *Non-Confidential Attachment 6(a)-3*. Liquid waste from cleaning of equipment during packaging at _____ is anticipated to be far less than the amount recovered at HRPI during manufacturing; accordingly, calculations for such waste were not performed.

The amount of water required at HRPI for manufacturing and cleaning operations for AMARYL Tablets to meet the USA market demand in the year 2000 (fifth year max. production) is _____. Since the processing capacity of the local wastewater treatment plant is about 13.0×10^6 gal waste/day (4.745×10^9 gal waste/year), then the yearly water requirement for manufacturing and cleaning would represent about 0.001% of the total processing capacity of the treatment plant, and less than 10% of HRPI's yearly potential aqueous liquid wastestream. Accordingly, this waste stream is considered inconsequential.

The effect of tableting releases in the year 2000 (fifth year maximum production) from the HRPI (Somerville, Bridgewater) site on the concentration of glimepiride in the Raritan River--the surface water that receives effluent from the Somerset Raritan Valley Sewerage Authority (SRVSA)--can be estimated.

As the wastewater is treated in the facility, glimepiride will become strongly adsorbed to the sludge culture. Soil sorption and desorption studies (Item 5) show that glimepiride is strongly adsorbed to sludge cultures, and moderately adsorbed to soils and sediments. Results show that 98.4% adsorption of glimepiride occurs on sludge, with only $\leq 2.9\%$ desorption. Accordingly, *regardless of the initial concentration of glimepiride discharged into the sewerage system*, the concentration of glimepiride (at SRVSA) would be about $2.9 \mu\text{g/L}$.

6. (a)(b) Continued

The effluent from this wastewater facility is discharged to Cuckels Brook which flows into the Raritan River. (The brook is 90 percent effluent.) Below this juncture, the Raritan River has a mean annual flow rate of 1,213 cubic feet or 784 million gal/day (USGS, 1992). Therefore, the dilution factor from the SRVSA facility (13 million gal/day) (SRVSA, 1992) to the river is 1.6×10^{-2} , and the concentration of glimepiride in the river would be 46 ng/L. Adsorption to river sediment would reduce the concentration in the effluent by a factor of 3.2×10^{-3} (Item 7). Thus, the actual concentration in the effluent would be 9.3 ng/L. In the Raritan River, below its juncture with Cuckels Creek, the concentration would be 150 pg/L. This concentration would be diminished to essentially zero downstream from the effluent by adsorption to fresh river sediment.

The effect of the releases from consumption (use and excretion) by patients in the year 2000 (fifth year maximum consumption) on the concentration of glimepiride in waterstreams can be estimated. The maximum expected emitted concentration (MEEC) of glimepiride in the wastewater treated in a typical public treatment plant, from consumption of AMARYL Tablets drug product, is 2.5×10^{-5} ppm (equivalent to 25 ppt or 25 ng/L).

As wastewater is treated in the facility, glimepiride will become strongly adsorbed to the sludge. Soil sorption/desorption studies (Item 5) show that glimepiride is strongly adsorbed to sludge, and moderately adsorbed to soils and sediments. Results show that 98.4% adsorption of glimepiride occurs on sludge, with only $\leq 2.9\%$ desorption. Adsorption to sludge will reduce the concentration in released effluent by a factor of 3.2×10^{-3} [Item 7(b)(5)]. Thus, the actual concentration in the released effluent would be about 80 pg/L. Dilution in the river in the vicinity of the outfall would further decrease the concentration to 0.08 pg/L. Because of variations in plant capacity and in rates of surface water flow, dilution factors for effluent can vary (depending on geographic location) from about 10^{-7} to essentially no dilution (ie, settling ponds or intermittently dry drainage channels) (Linsley et al 1975). A typical dilution factor for many rivers of the USA is 10^{-3} . Downstream from the outfall the expected concentration in surface water would be almost zero.

Solid Emissions

Certain non-recyclable solid waste from manufacturing, packaging, and distribution of AMARYL Tablets (spillage, discarded, or rejected materials, Jamaged containers, and filters/dust collectors) is incinerated at a Government-approved facility. Waste from the contract packager and from the HRPI distribution facilities (NJ; IN; TX) is shipped to HRPI for transfer to the incinerator: Permit NY0000352658 (no expiry date).

Based on accountability of packaged tablets vs starting amount, up to 3% of the batch size may result as waste from discarded tablets during packaging and sampling. Refer to *Non-Confidential Attachment 6(a)-4*

6. (a)(b) *Continued*

Certain waste produced during manufacturing and packaging of AMARYL Tablets at HRPI or at . is collected at HRPI and transported to a recycling facility. Such recyclable waste consists of paper, cardboard, aluminum, plastic, or glass. The facility used by HRPI is:
no available permit.

The common practice by customers in controlled settings, such as, pharmacies, Health Management Organizations (HMOs), and hospitals, is to return any outdated, rejected, or defective drug product to HRPI for appropriate disposal (incineration). However, if such waste drug product is not returned to HRPI for disposal, the waste is disposed by the customers. Customers may dispose the waste by incineration or by microwaving the waste prior to transport to a disposal site (landfill). All incineration facilities and disposal sites used by customers in controlled settings are Government-approved.

Sludges recovered from public wastewater treatment plants, which contain strongly-adsorbed residual amounts of glimepiride, are incinerated. Ashes from incinerators are disposed in monofill landfills. All incineration facilities and disposal sites used by public wastewater treatment plants are Government-approved. Leaching of glimepiride from disposal sites would not be expected because the drug substance is strongly adsorbed to sludge, soils, and sediments.

Some of the POTWs (Publicly-Owned Treatment Works) and WWTPs (Wastewater Treatment Plants) throughout the United States participate in sludge-recovery for land application (farmland). About 13.5 % of the total amount of sludge recovered throughout the United States is land applied; the remainder is either landfilled or incinerated. The participating treatment facilities who recover sludge, the facilities involved in processing, testing, or distributing sludge, as well as the land owners who apply sludge on farmland, are issued permits by the Office of Environmental Protection of the governing State.

- The procedures and limitations used to control the quality of the sludge for land application must be in compliance with USEPA (United States Environmental Protection Agency) Regulations in Title 40 CFR §503. Recovered sludge is tested for the following parameters before it can be used in land application: pH (after lime-treatment), heavy metals, pathogens, pesticides, PCBs (polychlorinated biphenyls), phenols, oils, greases, and other pollutants. Results are reviewed and approved on a regular basis by the Office of Environmental Protection of the governing State.

6. (a)(b) *Continued*

Through the use of guidelines provided by NJDEP (New Jersey Department of Environmental Protection), the residual amount of glimepiride that could become available in farmland from a single, maximum allowable, daily application of liquid sludge has been calculated. A typical farming season is 9 months; and, typically, fertilizers are applied not more than once or twice during the active growing season(s). Therefore, the results from this calculation provide a crude, but realistic estimate of the potential exposure of farmland to residual glimepiride from POTW/WWTP-recovered sludge. The results from this calculation are based on the MEEC (maximum expected emitted concentration) of 25 ppt in wastewater from human consumption (use and excretion) of the drug during the fifth year of marketing the drug. This amount is essentially adsorbed in its entirety onto sludge. The calculation uses a maximum, daily application of 15,000 gallons of liquid sludge (consisting of 9% solids): 31 ng/m² (1.03 ng/cm² or 1.03 ppb).

(c) *Include a citation of, and statement of compliance with, applicable emissions requirements (including occupational) at the Federal, State, and local level.*

Glimepiride

The State of Hesse and the City of Frankfurt employ responsible agents to assure compliance with regulations for emission control (air, water, soil) and occupational exposure. The operations involved in manufacturing, packaging, distribution, and disposal of glimepiride are in compliance with these regulations and any applicable/available emission requirements contained therein. A summary of the current emission-control and occupational-exposure regulations, along with signed statements of compliance, are provided in *Non-Confidential Attachment 6(c)-1*. An MSDS Sheet for glimepiride is provided in *Non-Confidential Attachment 6(c)-2*.

AMARYL (glimepiride) Tablets

The applicable emission- (air, water, soil) and occupational-control regulations of the New Jersey Department of Environmental Protection (NJDEP) are listed in *Non-Confidential Attachment 6(c)-3*. The Federal EPA recognizes NJDEP as the agent in administering these regulations. The local (Somerville, Bridgewater,) Government depends on the State for emission- and occupational-control regulations. A statement from HRPI certifying compliance with emission- and occupational-control regulations is included in *Non-Confidential Attachment 6(c)-3*. MSDS Sheets for AMARYL Tablets 1 mg, 2 mg, and 4 mg are provided in *Non-Confidential Attachment 6(c)-4*.

6. (c) *Continued*

is registered in New Jersey to package, not manufacture, pharmaceutical dosage forms. Therefore, the facility does not hold water- or air-emission permits. Accordingly, inspection of the facility by NJDEP is limited. Nevertheless, the local Government (S. Hackensack, NJ) depends on the State for emission- and occupational-control. certifies that they are in compliance with relevant emission- and occupational-controls. A statement of compliance from is submitted in *Non-Confidential Attachment 6(c)-5*.

(d) *Discuss the effect the approval of the proposed action will have upon compliance with current emissions requirements at the production site(s):*

Glimepiride

Approval of Hoechst AG as a manufacturer of the bulk drug substance, glimepiride, will have no adverse effect on the Company's ability to comply with the applicable environmental- and occupational-control regulations, and any applicable/available emission requirements of Germany. Because of the controls exercised at Hoechst AG, substances emitted from manufacturing, packaging, distribution, and disposal of waste from glimepiride will remain within the limits (if any) of applicable/available discharge permits.

The environmental-control, occupational exposure, and emission-control practices at the Hoechst AG manufacturing site (Frankfurt, Germany), including facilities used for disposal of waste, are approved by the German Government upon submission of a comprehensive application for the construction and operation of manufacturing plants. A summary of the application process is provided in the Hoechst AG report entitled, *Environmental Assessment [EA]*, (English translation dated April 13, 1992; German original dated March 27, 1992) [*Non-Confidential Attachment 6(c)-1*].

The Hoechst AG EA Report describes the environmental-control and occupational- exposure regulations and operating conditions that Hoechst AG must satisfy to be an approved manufacturing facility in Germany. As described in the report, approval of the manufacturing facility is conferred by the Regierungspräsidium of Darmstadt (translation: Directorate of the Administrative District), State of Hesse, Germany, after acceptance of the application and satisfactory inspection of the facility to assure compliance.

6. (d) *Continued*

In addition to the Government-certified Hoechst AG EA Report, evidence that the Hoechst AG (Frankfurt, Germany) facility is specifically approved to manufacture glimepiride is provided in a Certificate issued by the Regierungspräsidium on June 11, 1993. This Certificate is issued by the German Government to foreign countries (eg, USA) in accordance with PhRMA/FDA Guideline Option 2 (referenced below) to show that the manufacturing of glimepiride is in full compliance with pertinent regulations of Germany. The name of the compound (glimepiride) appears on the Certificate.

Reference: Interim Guidance to the Pharmaceutical Industry for EA Compliance Requirements for the FDA. Pharmaceutical Research Manufacturers Assoc. (PhRMA)/FDA. July 1991, Vers. 7, Item 6, p. 14: "OPTION 2: Provide a letter from the appropriate government authority certifying that the site is in compliance with that country's environmental laws, with inclusion of some specificity as to the specific drug substance that is subject of the FDA action."

AMARYL (glimepiride) Tablets

Approval of the HRPI facility to manufacture and package AMARYL Tablets will have no adverse effect on the Company's ability to comply with the applicable environmental- and occupational-control regulations, and any applicable/available emission requirements of the Federal (US), State (New Jersey), and local (Somerville, Bridgewater) Governments. The HRPI facility is inspected periodically by the New Jersey Department of Environmental Protection (NJDEP) for compliance with existing emission permits. As a result of the emission controls exercised at HRPI, substances from manufacturing, packaging, and disposal of waste from AMARYL Tablets will be emitted within the established limits of existing discharge permits. As discussed previously, these emissions are inconsequential because they are either contained or at extremely low levels.

is registered in New Jersey as a facility to package, not manufacture, pharmaceutical products. Accordingly, does not hold air- or water-emission permits from EPA. Although is inspected periodically by NJDEP, the inspections are limited in scope. However, approval of to package AMARYL Tablets will have no adverse effect on their ability to comply with environmental- and occupational-control regulations, and any applicable emission requirements of the Federal, State (NJ), and local (So. Hackensack) Governments because of controls exercised -- solid waste is transported to HRPI for disposal; and, waste from cleaning operations is inconsequential.

6. (e) *Through use of calculations and/or direct measures, estimate to the extent possible, the quantities and concentrations of substances expected to enter the environment as a result of use and/or disposal of products affected by the action:*

Glimepiride: Disposal

AMARYL (glimepiride) Tablets: Use and Disposal

Refer to Items 6(a) and 6(b) of this EA Report for information on potential emissions from disposal of the drug substance, and use and disposal of the drug product.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT:

Predict environmental concentrations of and exposures to substances entering the environment as a consequence (direct or indirect) of the use and/or disposal of the products affected by the action for the following environmental compartments, including consideration of the major environmental transport and transformation processes involved:

- a) AIR--taking into account, to the extent possible, factors such as volatilization, photochemical and chemical degradation, rainout, and dispersion:*
- b) FRESHWATER, ESTUARINE, AND MARINE ECOSYSTEMS--taking into account, to the extent possible, factors such as chemical and biological degradation, exchange between the water column and sediments via sorption/desorption and biological processes, accumulation in animals, plants, and other organisms, introductions due to rainfall and losses due to volatilization:*
- c) TERRESTRIAL ECOSYSTEMS--taking into account, to the extent possible, factors such as chemical and biological degradation, sorption/desorption and leaching in soils, accumulation in animals and plants, introductions due to rainfall, losses due to volatilization, and entry into groundwater:*

Items 7 and 8 were prepared for Hoechst-Roussel Pharmaceuticals Inc. by

In Item 7, information is presented that is relevant to the environmental transport and fate of glimepiride. Assessment of its transport and fate is accomplished by an evaluation of processes affecting the distribution of glimepiride between air, water, and soil and processes affecting its structural degradation. The methodology involved in this evaluation and its application to specific chemicals is discussed in *Water-Related Environmental Fate of 129 Priority Pollutants* (USEPA, 1979).

Glimepiride is eliminated from patients as the unchanged drug substance and--to a lesser extent--as two hydroxylated metabolites that are structurally-similar to the parent compound (glimepiride). Releases from manufacturing of the product may contain--in addition to the drug substance--trace amounts of two impurities that are structurally-similar to glimepiride. The structural similarity of the metabolites and impurities to the structure of glimepiride will ensure their removal from the environment by the same processes that remove glimepiride. Therefore, it is not necessary to discuss their environmental fate in this EA Report.

7. (a) *AIR—taking into account, to the extent possible, factors such as volatilization, photochemical and chemical degradation, rainout, and dispersion:*

No emission of glimepiride to the atmosphere occurs during preparation of the product or its use by patients. Glimepiride is a solid (or solute in solution) at ambient temperatures. Its volatility from water will be impeded by its adsorption to soil, sludge, and sediment [Subsection 7(b)(4)]. Particulates from the manufacturing facility will be trapped by vent filters that are collected for incineration. If any drug substance should escape the particulate filtration system, it will precipitate with rain and become adsorbed to soil or sediment.

(b) *FRESHWATER, ESTUARINE, AND MARINE ECOSYSTEMS—taking into account, to the extent possible, factors such as chemical and biological degradation, exchange between the water column and sediments via sorption/desorption and biological processes, accumulation in animals, plants, and other organisms, introductions due to rainfall and losses due to volatilization:*

Glimepiride will be introduced to the aqueous environment via elimination by patients and via releases from manufacturing. Adsorption to sewage sludge is expected to effectively remove it from the sewage effluent before the effluent is released to the surface water [Subsection 7(b)(5)]. However, worst-case concentrations of the drug in surface water can be calculated, if it is assumed that processes leading to abatement are not operative.

From Items 6(a) and 6 (b), the maximum expected emitted concentration (MEEC) of glimepiride at a typical wastewater treatment plant during the year 2000 (the fifth year following approval) is 25 ppt (or 25 ng/L). Because of variations in plant capacity and in rates of surface water flow, dilution factors for effluent can vary (depending on geographic location) from about 10^7 to essentially no dilution (ie, settling ponds or intermittently dry drainage channels) (Linsley et al. 1975). A typical dilution factor for many rivers of the United States is 10^3 and, thus, the concentration of glimepiride in surface waters that receive sewage plant effluent would be about 0.025 ppt (or 25 pg/L). The concentration would be much less downstream from the effluent outfall.

The effect of tableting releases from the Bridgewater site on the concentration of glimepiride in the Raritan River--the surface water that receives effluent from the Somerset Raritan Valley Sewerage Authority (SRVSA)--can be estimated with a similar calculation. From EA Item 6(a), the concentration of glimepiride at SRVSA that would be due to tableting releases during the year 2000 would be about 2.9 µg/L.

7. (b) *Continued*

The effluent from this wastewater facility is discharged to Cuckels Brook which flows into the Raritan River. (The brook is 90 percent effluent.) Below this juncture, the Raritan River has a mean annual flow rate of 1,213 cfs or 784 million gal/day (USGS, 1992). Therefore, the dilution factor from the SRVSA facility (13 million gal/day) (SRVSA, 1992) to the river is 1.6×10^{-2} , and the concentration of glimepiride in the river would be 46 ng/L.

In the water of a sewage treatment facility, or in the surface water that dilutes the effluent, glimepiride could potentially be affected by environmental processes that include photolysis, oxidation, hydrolysis, volatilization, adsorption, bioaccumulation, and biodegradation. These processes are evaluated individually (in this subsection) before a concluding statement is made on the probable fate and concentration of released drug substance in the aqueous environment.

7(b)(1) Photolysis

The electromagnetic absorption spectrum of glimepiride exhibits no absorption within the wavelength range of terrestrial sunlight (Item 5, *Non-Confidential Attachment 5-1*). Therefore, its photodegradation, after being released to the environment, is not expected.

7(b)(2) Oxidation

Photochemically produced hydroxy radicals in water have been observed to oxidize many organic chemicals, including amides and nitrogen-containing heterocyclics (Dorfman and Adams, 1973). Hydroxyl radicals (and alkylperoxy radicals) are generated in surface water from the photolysis of naturally occurring substances that absorb terrestrial sunlight (Mill et al, 1980). These oxidants may be significant for the degradation of glimepiride and its metabolites. Oxidation by this pathway would be limited, however, by the low concentration of the radical species, estimated to be present at levels of 10^{-9} M (Mill et al, 1980). The half-life for similar chemicals (eg, substituted amides) would be more than 80 days.

7(b)(3) Hydrolysis

The stability of glimepiride in aqueous solution was determined at pH 5, 7 and 9 (Item 5, *Non-Confidential Attachment 5-1*). After a 5-day period at 50 °C, the percentages of glimepiride remaining in solution at pH 5 and 7 were 88 and 95, respectively. No degradation was observed at pH 9. Glimepiride is considered, therefore, to be hydrolytically stable in environmental surface waters, with an estimated half-life of $\geq$ one year at 25 °C.

7. (b) *Continued*

7(b)(4) Volatilization

The vapor pressure of glimepiride (Item 5, *Non-Confidential Attachment 5-1*) and the corresponding Henry's constant were determined. The measured vapor pressure ($\leq 1.29 \times 10^{-7}$ torr at 24°C) indicates that there is very little tendency for glimepiride to volatilize from the solid state during preparation of the product. The volatility of glimepiride from aquatic systems, such as sewage or surface water, will be impeded by its adsorption to sludge or sediment. From Item 5 (*Non-Confidential Attachment 5-1a*), it is evident that glimepiride is strongly adsorbed to these natural materials. In fact, after it is adsorbed to sludge, it does not appear to be capable of desorption. Although the Henry's constant of an organic chemical is often used to calculate the rate of its volatility from water, these estimations are invalid, if the chemical becomes adsorbed (Mackay and Wolkoff, 1973; Lyman et al, 1982). Thus, volatilization is not expected to be an important transport process.

7(b)(5) Sorption/Desorption

The procedures outlined in USFDA (1978) were followed to obtain the distribution adsorption coefficient, K_d , for glimepiride, after equilibration between 0.01 M CaCl₂ and each of four natural adsorbents: two silty loams, one sandy loam, and a municipal sewage sludge. The use of 0.01 M CaCl₂ instead of distilled water is regarded as a close approximation of natural conditions. The K_d values reported in Item 5 (*Non-Confidential Attachment 5-1a*) were calculated:

$$K_d = \frac{\text{chemical sorbed (ug/gram)}}{\text{chemical in solution (ug/mL)}}$$

Attempted extraction of glimepiride from the adsorbents with 0.01M CaCl₂ demonstrated that the drug became desorbed from sludge only to the extent of 2.9% or less. The two silty loams and the sandy loam retained about 83, 90, and 64 percent of the adsorbed drug, respectively, after being leached.

Sorption/desorption, as studied under the test conditions, measures the result of a closed-system process that has reached equilibrium, ie, the measurements are conducted on batches of material at the end of a prescribed time period. These test conditions are similar to the conditions for adsorption of glimepiride to sludge during sewage treatment. In a natural setting, however, sorption/desorption is a dynamic, open-system process that does not reach a comparable equilibrium, ie, leaching-and re-adsorption from the leachate--continuously involve fresh unaffected adsorbent. The drug substance that is leached from a specific portion of sediment could concertedly become adsorbed to the adjacent mass of sediment that has not yet been exposed to it. Thus, the state of adsorption for the drug substance could continue.

7. (b) *Continued*

Based on the values of K_d reported in Item 5 (*Non-Confidential Attachment 5-1a*), the concentration of glimepiride in the effluent of a sewage treatment facility would be reduced by a factor of about 1/313 (or 3.2×10^{-3}) as the drug substance becomes adsorbed to the sludge. After the effluent is released, the remaining glimepiride would be removed from the surface water by adsorption to sediment.

7(b)(6) Bioaccumulation/Bioconcentration

Bioaccumulation of chemicals generally refers to their introduction into animals by ingestion, while the bioconcentration of chemicals refers to their absorption from water by aquatic organisms. A surface water bioconcentration factor (BCF) can be calculated from the following equation (Lyman et al, 1982):

$$\log BCF = 0.76 \log K_{ow} - 0.23 \quad (r^2 = 0.823; n = 84)$$

where:

- K_{ow} = octanol-water partition coefficient
- r^2 = coefficient of determination (proportional reduction in error)
- n = number of chemicals from which the regression was developed

Using the log octanol-water partition coefficient (2.14) derived from the value for K_{ow} at pH 7 (Item 5, *Non-Confidential Attachment 5-1*), the BCF calculated by this method is 25. This value indicates little tendency for bioconcentration.

If terrestrial organisms come into contact with sediments, surface water, or landfilled sludge in which glimepiride is present, bioaccumulation (via ingestion) is also not expected. Trabalka and Garten (1982) have reported that chemicals with log K_{ow} values of less than 3.5 do not accumulate in mammals or birds. This cutoff value for log K_{ow} is based on a frequency analysis of 123 paired observations for 68 chemicals. The log K_{ow} of glimepiride is 2.14, precluding bioaccumulation of the drug in these animal receptors.

7(b)(7) Biodegradation

The aerobic biodegradation of glimepiride in water was studied in accordance with the guidelines in USFDA (1987). As measured by the production of carbon dioxide and other volatiles, the drug substance degraded to the extent of only 0.3% during the 28-day testing period. Based on these data, it can be concluded that glimepiride is resistant to biodegradation under the conditions of the test. The negative test results, however, do not exclude the possibility that the drug substance could be (1) biodegradable at a rate slower than the test protocol is designed to measure or (2) biodegradable under some other environmental conditions that the test does not mimic.

7. (b) *Continued*

Within the mass of a sludge or sediment, the degradation of xenobiotic chemicals is often facilitated by cometabolism and the release of extracellular enzymes from the extant microorganisms (Bumpus and Aust, 1987; USEPA, 1987). Cometabolism is the process whereby the presence of another organic substance--other than the one under consideration--induces the formation of enzymes that then catalyze the degradation of both substances. Extracellular enzymes are released by microorganisms to degrade macromolecules to smaller more easily absorbed fragments. These enzymes include hydrolases, oxidases, and peroxidases (Bumpus and Aust, 1987; USEPA, 1987; Janssen, 1979; Koenigs, 1972). Biodegradation of many synthetic organic chemicals proceeds via these pathways in the natural environment (Bumpus and Aust, 1987). Glimepiride may be similarly degraded.

7(b)(8) Probable Fate and Concentration of Glimepiride in Aquatic Systems

The processes that affect the environmental fate of glimepiride are summarized in *Non-Confidential Attachment 7-1*. As glimepiride enters a sewage treatment facility, it will become adsorbed to the sludge culture. The small amount ($\leq 2.9\%$) that will be released in effluent will be diluted in the receiving body of surface water and will eventually become adsorbed to the sediment. Based on the behavior of other synthetic chemicals, slow biodegradation is expected after the drug's adsorption.

The concentrations of glimepiride that were discussed at the beginning of Subsection 7(b) did not consider the effect of adsorption on the amount of drug substance that would be present in effluent or surface water. The maximum expected emitted concentration of the drug (in the year 2000) was calculated to be 25 ng/L. Adsorption to sludge will reduce the concentration in released effluent by a factor of 3.2×10^3 [Subsection 7(b)(5)]. Thus, the actual concentration in the released effluent should be about 80 pg/L. Dilution in the river in the vicinity of the outfall would further decrease the concentration to 0.08 pg/L. Downstream from the outfall the expected emitted concentration of glimepiride in the surface water would be essentially zero.

The concentration of glimepiride in the effluent released from the Somerset Raritan Valley Sewerage Authority--2.9 ug/L [Subsection 7(b)]--will be similarly reduced by a factor of 3.2×10^3 to 9.3 ng/L. In the Raritan River, below its juncture with Cuckels Creek, the concentration would be 150 pg/L. This concentration would also be diminished by adsorption to the sediment to essentially zero.

7. (c) *TERRESTRIAL ECOSYSTEMS—taking into account, to the extent possible, factors such as chemical and biological degradation, sorption/desorption and leaching in soils, accumulation in animals and plants, introductions due to rainfall, losses due to volatilization, and entry into groundwater:*

Glimepiride may be released into the soil during landfilling or land farming from sludge to which it is adsorbed. If this situation should occur, the glimepiride could undergo slow biodegradation. Leaching of glimepiride from the landfill is not expected, because the drug substance is strongly adsorbed to sludge and soil.

No formal studies were conducted to determine aerobic soil biodegradation of glimepiride because the data obtained under aerobic aquatic conditions [Subsection 7(b)(7)] showed slow biodegradation (0.3% in 28 days). Although actual soil biodegradation data have not been determined, the possibility for glimepiride to undergo slow degradation in terrestrial environments is indicated in the literature [Subsection 7(b)(7)]. The literature discusses the possibility for similar molecules to undergo biodegradation via this pathway.

Ultimately, although soil biodegradation could yield meaningful results, the study seems unnecessary because the emission of glimepiride into terrestrial ecosystems will be limited. The drug substance becomes strongly sorbed to sludge in wastewater treatment plants, the majority of which is disposed by incineration or contained in approved disposal sites; some may be amended into farmland. Leaching from contained disposal sites would not be expected.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Given the information developed on the introduction (Item 6) and the fate (Item 7) of the substances which would be released as a consequence of the use and/or disposal of the products affected by the action, use any relevant toxicological data or other appropriate measures to predict, to the extent possible, effects on animals, plants, humans, or other organisms and effects at the ecosystem level in each of the compartments listed in Item 7:

Six environmental effects studies have been conducted with glimepiride: (1) 14-day algal toxicity (green algae), (2) 14-day algal toxicity (blue-green algae), (3) microbial growth inhibition, (4) *Daphnia* acute toxicity, (5) amphipod acute toxicity, and (6) freshwater fish acute toxicity. These studies were conducted in accordance with the accordance with the Environmental Assessment Technical Assistance Handbook (FDA and Department of Commerce, National Technical Information Service [PB87-175345]; March 1987). The results are presented in *Non-Confidential Attachment 8-1*.

The lowest no-observed-effect concentration (NOEC) is 0.06 mg/L for freshwater green algae. The next higher NOEC is 0.07 mg/L for the blue-green algae. These tests were conducted in a medium of aqueous mineral salts. However, inasmuch as glimepiride is strongly adsorbed by sludge and sediment, it is unlikely that algae could become exposed to the drug when it is released to the environment.

In Subsection 7(b), the worst-case (no abatement) concentration of glimepiride in a typical river that would receive effluent from a municipal sewerage treatment facility is 25 pg/L. This is six orders of magnitude lower than the lowest concentration at which toxic effects were observed. Moreover, because glimepiride is strongly adsorbed to sewerage sludge, the actual expected concentration at the outfall of released effluent is 0.08 pg/L [Subsection 7(b)(8)]. Thus, it is obvious that the concentration of glimepiride in a typical river that could potentially result from approval of the proposed action will not have an adverse effect on living organisms.

Similarly, the worst-case (no abatement) concentration of the glimepiride at the Somerset Raritan Valley Sewerage Authority could be as much as 2.9 µg/L, and the corresponding worst-case concentration in the Raritan River would be 46 ng/L [Subsection 7(b)]. These concentrations are about one to four orders of magnitude lower than the lowest toxic effect concentration of glimepiride. Moreover, these worst-case concentrations were calculated as if adsorption to sediment were not continually diminishing the concentration of released glimepiride. In fact, the maximum expected emitted (MEEC) concentration of glimepiride in the surface waters of the United States is essentially zero [Subsection 7(b)(8)].

8. Continued

The ultimate fate of the small amounts of drug substance potentially released to surface water from the effluent outfall of wastewater treatment facilities is adsorption to river sediment. *Hyaella azteca* is considered to be representative of organisms potentially exposed by this route. It is a benthic amphipod which often rests among vegetation and debris or occasionally burrows slightly within soft substrate. It is an omnivore-detrivore.

The potential drug concentration in the vicinity of the outfall is predicted to be 0.08 pg/L. The No Observed Effects Concentration (NOEC) for *Hyaella azteca* was determined to be 3.8 mg/L. Thus, the predicted drug concentration is eleven orders of magnitude lower than the NOEC of *Hyaella*. Even the worst-case (no abatement) concentration of glimepiride would provide at least eight orders of magnitude safety factor relative to *Hyaella* toxicity. Although biodegradation of adsorbed glimepiride is expected to be slow, it is obvious from the extremely large safety factors that the concentration of glimepiride in a typical river that could potentially result from approval of the proposed action will not have an adverse effect on benthic organisms.

As discussed in Items 6 and 7, glimepiride may be released into the soil during landfilling or land farming from sludge to which it is adsorbed. Leaching of glimepiride from the landfill is not expected, because the drug substance is strongly adsorbed to sludge and soil. Through the use of guidelines provided by NJDEP (New Jersey Department of Environmental Protection), the residual amount of glimepiride that could become available in farmland from a single, maximum allowable, daily application of liquid sludge has been calculated. A typical farming season is 9 months; and, typically, fertilizers are applied not more than once or twice during the active growing season(s). Therefore, the results from this calculation provide a crude, but realistic estimate of the potential exposure of farmland to residual glimepiride from POTW/WWTP-recovered sludge. The results from this calculation are based on the MEEC (maximum expected emitted concentration) of 25 ppt in wastewater from human consumption (use and excretion) of the drug during the fifth year of marketing the drug [Subsection 7(b)]. This amount is essentially adsorbed in its entirety onto sludge. The calculation uses a maximum, daily application of 15,000 gallons of liquid sludge (consisting of 9% solids): 31 ng/m² (1.03 ng/cm², or 1.03 ppb, or 0.00103 mg/L).

Thus, the predicted drug concentration is seven orders of magnitude lower than the NOEC of *Hyaella*. Although biodegradation of adsorbed glimepiride is expected to be slow, it is obvious from the extremely large safety factors that the concentration of glimepiride in farmland that could potentially result from approval of the proposed action will not have an adverse effect on benthic organisms.

9. USE OF RESOURCES AND ENERGY

(a) Specify the natural resources, including land use, minerals, and energy required to produce, transport, use, and/or dispose of a given amount of any product which is the subject of the action, including resources and energy required to dispose of wastes generated from production, use, and/or disposal:

Glimepiride

Hoechst AG is a producer of multiple products, including bulk Glimepiride drug substance for the world market. The natural resources (land, minerals, energy) necessary for the production, transportation (distribution), and disposal of Glimepiride represents a negligible portion of the facility's total capacity.

AMARYL (glimepiride) Tablets

The natural resources necessary for the manufacturing, packaging, transportation, and disposal of the drug product are listed below. An estimate of the yearly natural resources required at the anticipated maximum production level (2000), as a percentage of the HRPI total capacity, is included.

HRPI Resources -

The required amount of natural resources represents about 10% of HRPI's total capacity. Accordingly, the natural resources required for the production of the drug product are viewed as insignificant.

Water:

Electricity:

Natural gas, diesel fuel,
heating oil (incinerators; generators): decatherms

Resources -

packages and labels multiple products, including AMARYL Tablets. The natural resources (land, minerals, energy) necessary for packaging, labeling, and transportation (distribution) represents a negligible portion of the facility's total capacity, and very much less than that required to manufacture the product at HRPI.

9. (b) *Effects, if any, upon endangered or threatened species and upon property listed in the National Register of Historic Places must be discussed:*

Hoechst AG (Frankfurt, Germany) and Hoechst-Roussel Pharmaceuticals (HRPI) (Somerville, Bridgewater, New Jersey) will produce glimepiride drug substance and AMARYL (glimepiride) Tablets drug product within the existing facilities. There will be no new construction of facilities required for production.

As applicable only to the manufacture of the drug product in New Jersey (USA), there will be no adverse effect on surrounding properties listed in the National Register of Historic Places. A letter of acknowledgment from the Historic Preservation Office of New Jersey concurring with the proposed action is on file at HRPI.

Based on the available information from Fate (Item 7) and Effect (Item 8) studies of glimepiride, there will be no effect on endangered or threatened species of plants and animals.

10. MITIGATION MEASURES

Describe measures taken to avoid or mitigate potential adverse environmental impacts associated with the proposed action:

The design and use of facilities, buildings, equipment, and procedures for manufacturing, packaging, distribution, and disposal of glimepiride drug substance and AMARYL (glimepiride) drug product meet current standards of operation (building and energy codes), pharmaceutical production (Good Manufacturing Practices), environmental protection, and occupational exposure (OSHA). The controls exercised to mitigate potential adverse environmental impacts associated with operations have been described comprehensively in Item 6. Internal and external inspections help assure that mitigation practices are maintained. There is no potential adverse environmental impact from disposal of the drug product by consumers, which would require special disposal instructions in the package circular.

11. ALTERNATIVES TO THE PROPOSED ACTION

If potential adverse environmental impacts have been identified for the proposed action, describe in detail the environmental impact of all the reasonable alternatives to the proposed action (including no action, and including measures that FDA or another Government Agency could undertake as well as those the applicant/petitioner would undertake). Describe particularly those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental impacts of the proposed action. Discuss the environmental benefits and risks of the proposed action. Discuss the environmental benefits and risks of each alternative.

Adverse Environmental Impacts

There have been no adverse environmental impacts identified with the proposed action to manufacture glimepiride and market AMARYL (glimepiride) Tablets. Manufacturing, packaging, distribution, disposal, and use of the drug have not been associated with any known environmental impacts. Because of strict environmental controls and mitigation practices exercised, there is low risk for adverse environmental impact.

Reasonable Alternatives

There are no known reasonable alternatives for the proposed action. The only alternative would be not effecting the proposed action, which would deprive persons with Type II Diabetes of a safe and effective drug treatment, which has been shown to be directly associated with improvement in the quality of life and reduction of the economic burden of the disease. The benefit of FDA approval of the NDA for AMARYL Tablets far outweighs the slight risk to the environment.

12. LIST OF PREPARERS

Those persons preparing the assessment together with their qualifications (expertise, experience, professional disciplines) shall be listed. Persons and agencies consulted shall also be listed:

John S. Pandolfino

Hoechst-Roussel Pharmaceuticals Incorporated
Assistant Director, Drug Regulatory Affairs
Chemistry, Manufacturing, Controls

Over 18 years experience in the pharmaceutical industry: non-clinical pharmacology, toxicology, metabolism; aquatic, soil, microbiological, and analytical environmental fate/effect testing; analytical research; quality assurance; drug regulatory affairs.

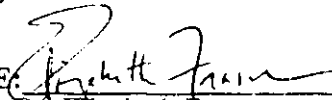
Rutgers University
New Brunswick, New Jersey
Bachelor of Arts in Biological Psychology (cum laude)

Additional credits (25) towards an advanced degree: Inorganic Chemistry (Qualitative/Quantitative Analysis), Organic and Biochemistry, Experimental Organic (Analytical) Chemistry, Biological Science, Pharmacology, Neurophysiology, and Statistics.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best interest of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

SIGNATURE: _____



Dr. Elizabeth Fraser
Vice President,

Department of Environmental Health and Safety Affairs

DATE: 9/11/95

14. REFERENCES

List complete citations for all referenced material. Copies of referenced articles not generally available should be attached:

Complete references are provided within the narrative section of this Non-Confidential version of the Environmental Assessment Report.

15. APPENDICES

- a) *Data summary charts (eg, structural formula, vapor pressure, water solubility, n-octanol/water partition coefficient, biodegradation half-life, LC₅₀ for each species tested, etc.:*

Complete information is contained in the *Confidential Version of the Environmental Assessment Report*. However, certain information required to support the present *Non-Confidential Version of the Environmental Assessment Report*, is submitted in the attachments.

- b) *Test reports for each experiment: research objective, experimental design and procedure, all data relevant to interpretation of the test result given in Item 15(a), sample calculations and statistical analyses:*

This information is not required except to the extent needed to support the information in the present *Non-Confidential Version of the Environmental Assessment Report*.

AMARYL® (glimepiride) Tablets

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Freedom of Information (FOI) (Non-Confidential) Environmental Assessment

Attachment 5-1 Physicochemical Properties and Impurities of Glimepiride Drug Substance

<i>Description</i>	Microfine, white powder
<i>Vapor Pressure</i>	$\leq 1.29 \times 10^{-7}$ torr
<i>Melting Temperature</i>	194.7-197.6°C
<i>UV/Visible Absorption</i>	No absorption (290-800 nm)
<i>Hydrolysis</i>	None
<i>Density and Relative Density</i>	1.225 g/mL (density) 1.228 g/mL (relative density)
<i>Dissociation Constant</i>	Not applicable (solubility $\leq 10^{-7}$)
<i>Photodegradation in Water</i>	Not applicable (no absorption)
<i>Aerobic Biodegradation in Water</i>	0.3% in 28 days
<i>Water Solubility</i>	
pH 5.0	≤ 0.060 mg/mL
pH 7.0	0.407 mg/mL
pH 9.0	4.046 mg/mL
<i>n-Octanol/Water Partition Coefficient (K_{ow})</i>	
pH 5.0	706
pH 7.0	148
pH 9.0	6.36
<i>Soil Sorption and Desorption</i>	Attached
<i>Impurities</i>	Refer to following summary

The synthesis of glimepiride yields material containing a very low level of impurities, consisting of residues of synthesis reagents, solvents, starting materials, intermediates, by-products, and isomeric forms of glimepiride. Degradates identified during storage of the drug substance are the same as those detected during initial manufacture of the material.

AMARYL® (glimepiride) Tablets

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Freedom of Information (FOI) (Non-Confidential)
Environmental
Assessment

Attachment 5-1a
Physicochemical Properties and Impurities of
Glimepiride Drug Substance
Soil Sorption and Desorption

	Silty Loam (Arkansas)	Sandy Loam (Wisconsin)	Silty Loam (Kansas)	Sludge/Sand (Milwaukee)
pH	6.3	7.1	5.8	4.2
Organic Matter (%)	1.3	4.5	2.9	68.7
Cation Exchange (meq/100g)	9.7	16.9	22.1	19.6
Average Adsorption (%)	77.8	64.9	91.3	98.4
Average Desorption (%)	16.5	35.5	10.3	≤2.9
K_d (soil-solution coefficient)	19.5	9.26	52.4	313.0
K_{oc} (organic-carbon coefficient)	2540.0	350.0	3070.0	774.0

Adsorption of glimepiride from solutions in 0.01M CaCl₂ and desorption of glimepiride into solutions of 0.01M CaCl₂. Glimepiride is immobile in the Arkansas and Kansas soils, it is moderately mobile in the Wisconsin soil, and it is moderately bound to Milorganite.

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**Freedom of Information (FOI) (Non-Confidential)
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*Attachment 5-2
Additives and Impurities in
AMARYL (glimepiride) Tablets Drug Product*

The additives (including CAS numbers) of the tablet formulation is as follows. The impurity and stability profiles of the tablets are identical with those of glimepiride drug substance. The impurities and degradates detected in the product are the same as those detected in the substance.

<i>Additive</i>	<i>CAS Number</i>
FD&C Blue #2, Aluminum Lake	16521-38-3
Ferric Oxide NF (yellow)	1309-37-1
Ferric Oxide NF (red)	1309-37-1
Lactose NF (hydrous)	64044-51-5
Magnesium Stearate NF	557-04-0
Microcrystalline Cellulose NF (PH 101)	9004-34-6
Povidone USP (26-28)	9003-39-8
Purified Water USP	7732-18-5
Sodium Starch Glycolate NF	9063-38-1

AMARYL® (glimepiride) Tablets

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*Attachment 6(a)-1
Hoechst-Roussel Pharmaceuticals Incorporated
Building J Air-Emission Permits*

CERTIFICATE NO.	STACK NO.	DESCRIPTION OF AIR-EMISSION CONTROL	PERMIT EXPIRATION
2810	1	J-RM 122 dust collector (center)	04/24/97
2811	2	J-RM 1028 dust collector (center)	04/24/97
2812	3	J-RM 122 dust collector (south)	04/24/97
2813	4	J-RM 1028 dust collector (east)	04/24/97
2814	5	J-RM 1053 dust collector (east)	04/24/97
2815	6	J-RM 1053 dust collector (west)	04/24/97
2816	7	J-RM 1028 dust collector (west)	04/24/97
94631	8	J-RM 1052 central house vacuum	02/15/97
5155	10	J-RM 1064 Glat fluid dryer	01/25/97
39327	23	J-RM 122 central house vacuum	11/21/98
72594	25	J-RM 1036 PRTE-1 roto-clone	08/24/96
71305	26	J-RM 1036 PRTE-2 roto-clone	08/24/96
71678	31	J-RM 1036 PRTE-3 roto-clone	08/24/96
71679	32	J-RM 1036 PRTE-4 roto-clone	08/24/96
71680	33	J-RM 1036 PRTE-5 roto-clone	08/24/96
71915	34	J-RM 1036 PRTE-6 roto-clone	08/24/96
92857	35	J-RM 1096 Azo pneumatic conveyor	08/24/96
97516	36	J-RM 1064 Michigan Oven #2	03/27/97
97517	37	J-RM 1064 Michigan Oven #1	03/27/97
105116	46	J-RM 122 Central house vacuum	05/14/98
105478	47	J-RM 1043 Aeromatic dryer	06/07/98

AMARYL® (glimepiride) Tablets

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**Freedom of Information (FOI) (Non-Confidential)
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*Attachment 6(a)-2
Hoechst-Roussel Pharmaceuticals Incorporated
Airborne Glimepiride Captured by Air-Emission Controls
Building J*

AMARYL TABLET (MG)	GLIMEPIRIDE WASTE/BATCH (KG)	GLIMEPIRIDE WASTE (% OF BATCH)
1	0.0338	1.35
2	0.0573	1.15
4	0.1200	1.20

AMARYL® (glimepiride) Tablets

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Freedom of Information (FOI) (Non-Confidential)
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*Attachment 6(a)-3
Hoechst-Roussel Pharmaceuticals Incorporated
Amount of Glimepiride Discharged into Sewerage System
Building J*

AMARYL TABLET (MG)	GLIMEPIRIDE WASTE/BATCH (KG)	GLIMEPIRIDE WASTE (% OF BATCH)
1	0.0282	1.10
2	0.0409	0.82
4	0.0902	0.90

AMARYL® (glimepiride) Tablets

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Environmental
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*Attachment 6(a)-4
Hoechst-Roussel Pharmaceuticals Incorporated
Amount of AMARYL (glimepiride) Tablets Solid Waste
Packaging and Sampling*

AMARYL TABLET (MG)	GLIMEPIRIDE WASTE/ BATCH (KG)	GLIMEPIRIDE WASTE (% OF BATCH)
1	0.075	3
2	0.150	3
4	0.300	3

AMARYL® (glimepiride) Tablets

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Freedom of Information (FOI) (Non-Confidential)
Environmental
Assessment

Attachment 6(c)-1

*Summary of Environmental and Occupational Control at Hoechst AG
(Frankfurt, Germany)
Manufacture of Glimepiride Drug Substance*

*Current Environmental and Occupational Control Regulations of Germany
Signed Statements of Compliance*

*Report Titles, Numbers, Dates,
and References*

Hoechst AG Environmental Assessment Report
German-Language Original Certified by Darmstadt, Germany
March 27, 1992

NOV 1992
Hoechst AG Environmental Assessment Report
German Language Original

Hoechst AG Environmental Assessment Report
English Translation of Certified German Language Original
April 13, 1992

NOV 1992
Hoechst AG Environmental Assessment Report
English Translation of Certified German Language Original

Hoechst AG Self-Certification of Compliance with Environmental-Control and
Occupational-Exposure Regulations of Germany (regulations included)
April 20, 1993

Certificate from the Regierungspräsidium (Directorate of the Administrative District) of
Darmstadt, Federated State of Hesse, Germany, for Manufacture of Glimepiride at Hoechst
AG, Frankfurt, Germany
June 11, 1993

NDA 20496

5 OF 6

Attachment 1

Hoechst 

Hoechst AG Postfach 80 03 20 D-6230 Frankfurt am Main 80

Hoechst Aktiengesellschaft
Pharmatechnik
Qualitätssicherung/GMP, D 610

Postfach 80 03 20 Brünningstraße 50
5230 Frankfurt am Main 80
Telefon (0 69) 3 05 0 Telex 41 234 0 hnd d
Telegramm Hoechstag Frankfurt/Main
Telex (0 69) 31 36 63/66

Dresdner Bank AG Frankfurt am Main 80
(BLZ 500 800 00) Kto. Nr. 7 355 535 00
Commerzbank AG Frankfurt am Main 80
(BLZ 500 400 00) Kto. Nr. 2570729
Deutsche Bank AG Frankfurt am Main 1
(BLZ 500 700 10) Kto. Nr. 925006
Hessische Landesbank - Girozentrale -
Frankfurt am Main 1
(BLZ 500 500 00) Kto. Nr. 24100 000
Landeszentralbank in Hessen Frankfurt am Main 1
(BLZ 500 500 00) Kto. Nr. 500 08190
Postprogramm Frankfurt am Main 1
(BLZ 500 100 60) Kto. Nr. 1442 605

TO WHOM IT MAY CONCERN

Ihre Zeichen

Ihre Nachricht vom

Unsere Zeichen

Dr. Bdt./C1

Telefon Durchwahl

(0 69) 3 05- 6831

Frankfurt am Main

April 20, 1993

Environmental Assessment

HOECHST AKTIENGESELLSCHAFT, as the producer of drug substances and finished drug products at its factory:

HOECHST AKTIENGESELLSCHAFT
Hoechst Works
Brünningstrasse 50
Postfach 80 03 20
D-6230 Frankfurt/M.-Höchst 80
Federal Republic of Germany

herewith certifies that the above mentioned plant is run in compliance with the existing environmental control laws and regulations of the Federal Republic of Germany.

Environmental protection in the Federal Republic of Germany is subject to a number of laws and regulations which are strictly enforced.

The most important ones are listed below:

Empfänger: ^{Unsere Zeichen} TO WHOM IT MAY CONCERN ^{Datum} Dr. Bdt./CT April 20, 1993

Blatt
2

- Immissions (Air etc.):

"Gesetz zum Schutz vor schädlichen Umwelteinwirkungen durch Luftverunreinigungen, Geräusche, Erschütterungen und ähnliche Vorgänge ("Bundesimmissionsschutzgesetz"),

(Federal Law for Protection of the Environment against the Adverse Influences Caused by Contamination of the Air, by Noise, Vibration, and Similar Events).

March 15, 1974,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 721, corrected 1193,

amended May 14, 1990/Federal Law Gazette ("Bundesgesetzblatt") I, 880.

- Water protection:

"Gesetz zum Schutze des Wasserhaushaltes"

("Wasserhaushaltsgesetz"),

(Federal Law for Protection of Water Resources).

October 16, 1976,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 3017,

amended March 28, 1980/Federal Law Gazette ("Bundesgesetzblatt") I, 373.

- Solid Waste:

"Gesetz zur Vermeidung und Entsorgung von Abfällen" ("Abfallgesetz"), (Federal Law for Avoidance and Disposal of Waste).

August 27, 1986,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 1718.

Erbringer TO WHOM IT MAY CONCERN
Antragsteller Dr. Bdt./CT
Datum April 20, 1993

Blatt
3

- Technical Directions for Handling of Waste

"Technische Anleitung zur Lagerung, chemisch-physikalischen und biologischen Behandlung und Verbrennung von besonders überwachungsbedürftigen Abfällen"

(Technical Directions for Storage, Treatment and Burning of Waste).

April 10, 1990,

published in Joint Ministerial Gazette ("Gemeinsames Ministerialblatt") no. 11, 170.

- Technical Directions for Maintaining Clean Air:

"Technische Anleitung zur Reinhaltung der Luft" ("TA Luft"),

(Technical Directions for Maintaining Clean Air).

published in Joint Ministerial Gazette ("Gemeinsames Ministerialblatt") 95; February 27, 1986,

amended in Joint Ministerial Gazette ("Gemeinsames Ministerialblatt"), 202; April 4, 1986.

- Technical Directions for Noise Protection:

"Technische Anleitung zum Schutz gegen Lärm" ("TA Lärm"),

(Technical Directions for Protection Against Noise).

July 16, 1968,

published in Enclosure to Federal Register ("Beilage zum Bundesanzeiger") no. 137,

July 26, 1968.

- Chemicals:

"Gesetz zum Schutz vor gefährlichen Stoffen"

("Chemikaliengesetz"),

(Federal Law for Protection Against Dangerous Chemicals).

March 14, 1990,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 521

Empfänger
TO WHOM IT MAY CONCERN

unsere Zeichen
Dr. Bdt./CT

Datum
April 20, 1993

Seit
4

- Regulations for Dangerous Goods:
"Gefahrstoffverordnung",
(Regulations for Dangerous Goods).
April 23, 1990,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 790.

- Regulations for Pressurized Systems
"Druckbehälterverordnung",
(Regulations for pressurized systems, e.g. pressurized
containers etc.).
April 21, 1989,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 830.

- Regulations for Notifications of Immissions:
"Zwölfte Verordnung zur Durchführung des Bundesimmissions-
schutzgesetzes" ("Störfallverordnung"),
(12th Regulation for the Implementation of the Federal Law for
Protection of the Environment Against the Adverse Influences
Caused by Contamination of the Air, by Noise, Vibration, and
Similar Events).
May 19, 1988,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 626.

- Regulations for Storage of Inflammable Liquids:
"Verordnung über Anlagen zur Lagerung, Abfüllung und
Beförderung brennbarer Flüssigkeiten zu Lande",
(Regulations for Facilities for Storage, Filling, and
Transportation of Inflammable Liquids on Land).
February 27, 1980,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 229,
amended May 3, 1982 in Federal Law Gazette ("Bundes-
gesetzblatt") I, 569.

Empfänger: TO WHOM IT MAY CONCERN Unsere Zeichen: Dr. Bdt./CT Datum: April 20, 1993

Seite: 5

- Regulations for Transportation of Dangerous Goods
(road, rail, sea, river, air):

-- For Transportation on the Road:

"Gefahrgutverordnung Straße",

(Regulations for Transportation of Dangerous Goods on the Road).

July 22, 1985,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 1550,

amended December 21, 1987,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 2858.

-- For Transportation by Rail:

"Gefahrgutverordnung Eisenbahn",

(Regulations for Transportation of Dangerous Goods by Rail).

July 22, 1985,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 1560,

amended December 21, 1987,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 2862.

-- For Transportation by Sea:

"Gefahrgutverordnung See",

(Regulations for Transportation of Dangerous Goods by Sea).

July 5, 1978,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 1917,

amended December 21, 1987,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 2863.

Empfänger
TO WHOM IT MAY CONCERN

Unsere Zeichen

Dr. Bdt./CT

Datum

April 20, 1993

Seit
6

- For Transportation on Waterways within Germany:
"Gefahrgutverordnung Binnenschifffahrt",
(Regulations for Transportation of Dangerous Goods on
Waterways within the Federal Republic of Germany).
March 24, 1983,
published in Federal Law Gazette ("Bundesgesetzblatt") I,
1977,
amended March 16, 1989,
published in Federal Law Gazette ("Bundesgesetzblatt") I,
489.

- Dangerous Products Regulations of the IATA (International
Air Transport Association):
"IATA - DGR" (Dangerous Goods Regulations),
28th edition.

- Regulations for Drinking Water:
"Verordnung über Trinkwasser und über Wasser für Lebensmittel-
betriebe",
(Regulations for Drinking Water and for Water to be Used in
Food Industries).
May 22, 1986,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 760.

- Feedstuffs (Animal Nutrition):
"Futtermittelgesetz",
(Federal Law on Feedstuffs).
July 2, 1975,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 1745,
and:
"Futtermittelverordnung",
(Regulations on Feedstuffs).
April 8, 1981,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 352.

Empfänger

TO WHOM IT MAY CONCERN

unsere Zeichen

Dr. Bdt./CT

Datum

April 20, 1993

Blatt

7

- Regulations for Work Places:

"Verordnung über Arbeitsstätten" ("Arbeitsstättenverordnung"),
(Regulations for Work Places).

May 20, 1975,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 729.

- Drug Law:

"Gesetz über den Verkehr mit Arzneimitteln" ("Arzneimittelge-
setz"), (Federal Law for Handling of Drugs).

August 24, 1976,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 2445,
2448,

last amendment April 11, 1990,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 717;

and:

"Betriebsverordnung für pharmazeutische Unternehmer",
(Operations Ordinance for Pharmaceutical Entrepreneurs).

March 8, 1985,

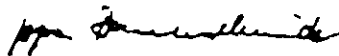
published in Federal Law Gazette ("Bundesgesetzblatt") I, 546,
(and amendments).

Yours faithfully

HOECHST ARTIENGESELLSCHAFT



(Dr. Schütte)



(ppa. Dr. Bauerschmidt)



Regierungspräsidium
Darmstadt

II 16 e - 18 1 02/03 (8) - FA 49

1. Confirmation

In the Federal Republic of Germany the supreme Health Authority of each individual federal state is responsible for issuing and confirming documents, for signature confirming for the production and the sales of medicines, pharmaceutical raw materials, food stuffs and cosmetics.

For the

Hoechst Aktiengesellschaft
Brüningstr. 50
D-6230 Frankfurt/Main 80

my office is the responsible authority. A second confirmation of a certificate issued or certified by my office by a superior federal authority is not necessary and will not be regarded incidentally for principle reasons.

Recipient of this document:

To whom it may concern.

For registration and all official purposes in

United States of America.

Attachment 2

Luisenplatz 2 - Postfach 11 12 53
D-6100 Darmstadt, den 11. 06. 93

Telephon: (06151) 12 62 42
12 53 13
Telefax: (06151) 12 60 05

1. Bestätigung

Für die Ausstellung und Bestätigung von Urkunden und Unterschriften über die Herstellung und den Vertrieb von Arzneimitteln, pharmazeutischen Rohstoffen, Lebensmitteln und Kosmetika sind in der Bundesrepublik Deutschland die Bundesländer zuständig.

Für die Firma

Hoechst Aktiengesellschaft
Brüningstr. 50
D-6230 Frankfurt/Main 80

ist mein Haus die zuständige Behörde. Eine Überbeglaubigung eines von mir ausgestellten oder beglaubigten Zertifikates scheidet im übrigen aus grundsätzlichen Erwägungen aus.

Zu Registrierungs- und allen amtlichen Zwecken in:

Vereinigte Staaten von Amerika

2. Statement of Manufacturing/Processing
Sales Activities

The Hoechst AG ist in the Federal Republic of Germany an acknowledged pharmaceutical and chemical factory. They have the permission to produce pharmaceutical products (§ 13 Drug Law).

They are producing chemical and pharmaceutical raw materials for the manufacturing of finished pharmaceutical products, cosmetics and food-additives.

They are marketing and selling these products at home and abroad.

3. Certificate

This is to certify to the Hoechst AG, that they hold as a pharmaceutical manufacturer an manufacturing licence according to § 13 of the Medicines Law from August 24 th in 1976 (BGB1. I, page 2445).

It is certified, that

- a) the manufacturing plant, in which the product is produced is subject to inspections at suitable intervals,

2. Herstell-/Verkaufsbescheinigung
Verkaufstätigkeit

Die Firma Hoechst AG ist in der Bundesrepublik Deutschland eine anerkannte pharmazeutische und chemische Fabrik. Sie hat die Erlaubnis zur Herstellung von Arzneimitteln (§ 13 Arzneimittelgesetz).

Sie stellt chemisch-pharmazeutische Rohmaterialien zur Fabrikation von Arzneimitteln und Kosmetika sowie Lebensmittelzusatzstoffe her.

Sie verkauft und vertreibt diese Produkte im Inland und im Ausland.

3. Bescheinigung

Hiermit wird der Firma Hoechst AG bestätigt, daß sie als pharmazeutischer Herstellerbetrieb im Besitz einer Herstellungserlaubnis gemäß § 13 des Gesetzes über den Verkehr mit Arzneimitteln vom 24.08.1976 (BGB1. I, S. 2445) ist.

Es wird bestätigt, daß

- a) der Herstellerbetrieb, in dem das Produkt hergestellt wird, in angemessenen Abständen überwacht wird.

b) the manufacturer conforms to requirements for good practices in the manufacturing and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

4. Productlist

This certificate refers to the following product:

Glimepirid.

b) der Hersteller hinsichtlich der Produkte, die im Herkunftsland verkauft und vertrieben werden oder für die Ausfuhr vorgesehen sind, den von der Weltgesundheitsorganisation empfohlenen Grundregeln für die Herstellung von Arzneimitteln und die Sicherung ihrer Qualität entspricht.

4. Aufzählung der Produkte

Diese Bescheinigung gilt für folgende Produkte:

Glimepirid.

Im Auftrage



Völlw

Tillmann
Tillmann

12.06.93

AMARYL® (glimepiride) Tablets

NDA 20-496

**Freedom of Information (FOI) (Non-Confidential)
Environmental
Assessment**

Attachment 6(c)-2

*Glimepiride Drug Substance
MSDS Sheet*

Product Name: Glimepiride
MSDS Version Date: 10/11/93

Section 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Imported By:
Hoechst-Roussel Pharmaceuticals Inc.
Route 202-206
P.O. Box 2500
Somerville, N.J. 08876-1258

Emergency Telephone Numbers:
24 Hours - (908) 231-4126
CHEMTREC - (800) 424-9300 (Transportation emergencies ONLY)

Product Name: Glimepiride

Product Class: Hypoglycemic, antidiabetic

Chemical Name: 1-[[p-{2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)-ethyl}phenyl]-sulfonyl]-3-trans-(4-methylcyclohexyl)urea

Synonyms: HOE490; S 80 8490; Amaryl

Section 2. COMPOSITION/INFORMATION ON INGREDIENTS

Components	Cas Number	Workplace Exposure Limit
Active Ingredient Glimepiride	93479-97-1	None Established

Section 3. HAZARDS IDENTIFICATION

Emergency Overview

Overexposure to this product can cause severe hypoglycemia (low blood sugar). Avoid dermal contact and avoid inhalation. This material is a powder. Take precautions to prevent the possibility of dust explosions. Ground equipment. Use non-sparking tools.

Product Name: Glimpiride
MSDS Version Date: 10/11/93

Potential Health Effects

Routes of Exposure - Inhalation, skin, ingestion

Signs and Symptoms of Overexposure - Profound and sometimes prolonged hypoglycemia. Hypoglycemia symptoms include rapid heart beat, tremors, sweating, weakness, anxiety, nervousness and hunger. Severe hypoglycemia can cause coma.

Immediate effects

- Skin - None known.
- Eyes - Glimpiride is not expected to irritate the eyes more than any powder or particle in the eye.
- Inhalation - Hypoglycemia.
- Ingestion - Hypoglycemia.

Target Organs - Appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas.

Medical Conditions Aggravated by Exposure - Hypoglycemia and existing hypersensitivity to glimepiride.

Section 4. FIRST AID MEASURES

Skin: Wash contacted skin with soap and water. Launder work clothes after every wearing.
Eyes: Flush eyes with water for 15 minutes. Get immediate medical help.

Inhalation: Remove to fresh air and get immediate medical help. If person is not breathing, give artificial respiration.

Ingestion: If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Immediately get medical attention.

Note to Physicians: If hypoglycemic signs and symptoms develop do not delay treatment. If the patient is conscious, administer glucose (sugar). If the patient is unconscious, administer intravenous glucose.

Product Name: Glimepiride
MSDS Version Date: 10/11/93

Section 5. FIRE FIGHTING MEASURES

Hazardous Properties of Combustion: Compounds of carbon, hydrogen and oxygen, including carbon monoxide, nitrogen and sulfur oxides. The exact composition will depend on the conditions of combustion.

Extinguishing Media: Alcohol foam, carbon dioxide, dry chemicals or water fog (fire extinguisher types A,B or C).

Fire Fighting: Wear full bunker gear, including SCBA, for fighting fires involving this material.

Other: Electrical grounding of equipment is required when handling powder to prevent possibility of dust explosion.

Section 6. ACCIDENTAL RELEASE MEASURES

Utilize engineering controls and/or wear appropriate respiratory protection to prevent signs and symptoms in Section 3 when responding to release or during cleanup activities. Use a wet mop or filtered vacuum to pick up spilled product. Do not dry sweep as this will cause dust to become airborne.

Section 7. HANDLING AND STORAGE

Keep containers tightly closed. Protect containers from damage.

All handling equipment should be grounded and bonded when material is being transferred to and from containers. Use non-sparking tools.

Section 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Utilize engineering controls and/or filtered or supplied air respiratory protection to minimize inhalation exposure. Utilize gloves and arm covers to minimize dermal exposure.

Product Name: Glimepiride
MSDS Version Date: 10/11/93

Explosion-proof equipment (for example fans, switches, grounded ducts) should be used in mechanical ventilation systems.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Chemical Formula: $C_{14}H_{14}N_4O_5S$
Molecular Weight: 490.62
Appearance: White to yellowish-white crystalline powder
Odor: None
Melting Point: 207° C

Section 10. STABILITY AND REACTIVITY

Chemical Stability: Chemically stable
Conditions to Avoid: None
Hazardous Decomposition Products: None
Hazardous Polymerization: None

Section 11. TOXICOLOGICAL INFORMATION

Acute Effects

Oral LD₅₀ (rat) > 10,000 mg/kg
Oral LD₅₀ (mouse) > 10,000 mg/kg
Intraperitoneal LD₅₀ (rat) > 3,950 mg/kg
Intraperitoneal LD₅₀ (mouse) > 4,000 mg/kg

Chronic Effects

Two glimepiride feeding studies in mice (3 months) and rats (12 months) with doses up to 50,000 ppm resulted in decreased serum glucose, a pharmacologic effect of the compound, and degranulation of pancreas beta cells. Some organ weight changes were observed in rats at doses of 25,000 and 50,000 ppm. Intravenous glimepiride studies in rats, for up to one month, at dose levels up to 10 mg/kg resulted in reduced serum glucose, a pharmacologic effect of the compound. After 9 months of a 12-month glimepiride feeding study at 320 mg/kg (500 times the highest dose used in human clinical trials), 2 of 12 dogs developed cataracts. Decreased serum glucose and degranulation of pancreas beta cells was also a consistent finding in the dog study.

Product Name: Glimpiride
MSDS Version Date: 10/11/93

Mutagenicity

Ames test: Negative
HGPRT in V79 Chinese Hamster cells: Negative
Unscheduled DNA synthesis: Negative
Mouse micronucleus test (*in vivo*): Negative

Carcinogenicity

No toxicologic or carcinogenic effects were found in a 30-month glimepiride feeding study in rats at dose levels up to 320 ppm.

This product is not listed by NTP, IARC or OSHA as a carcinogen.

Teratogenicity

A consistent result of a Segment II reproduction study in Wistar rats and Himalayan rabbits was fetal death, due to marked persistent hypoglycemia (a pharmacologic effect of glimepiride) in the dams. A fertility study conducted in male mice, according to Japanese guidelines, showed that glimepiride had no effect on the fertility of male mice. A fertility and general reproductive performance (Segment I) study in rats at dose levels of 1,000 and 5,000 ppm glimepiride in food resulted in marked persistent hypoglycemia in dams, a pharmacologic effect of the compound. A shortening, bending and thickening of the humerus was seen postnatally in the one rat at the low dose level and eleven rats at the high dose level. This effect was also seen in a peri/postnatal toxicity reproductive (Segment III) study in rats at 2500 mg/kg by gavage. The lowest dose level at which this effect was seen was 234 times the highest anticipated human dose. This developmental abnormality appeared postnatally and was interpreted as a pharmacodynamically induced impairment.

Section 12. ECOLOGICAL INFORMATION

None available.

Section 13. DISPOSAL CONSIDERATION

Waste glimepiride should be incinerated.

Product Name: Glimepiride
MSDS Version Date: 10/11/93

Section 14. TRANSPORT INFORMATION

Glimepiride is not subject to DOT transportation regulations.

Section 15. REGULATORY INFORMATION

Glimepiride is regulated under the Food, Drug and Cosmetic Act. Employees processing glimepiride should have access to this MSDS per the OSHA Hazard Communication Standard.

Section 16. OTHER INFORMATION

Right-To-Know labeling for inclusion on drums of bulk Glimepiride:

WARNING!

Pharmacologically Active Compound

Overexposure to this product can cause severe hypoglycemia (low blood sugar). Avoid dermal contact and avoid inhalation. Wash thoroughly after handling. Electrical grounding of equipment is required when handling powder to prevent possibility of dust explosion.

FIRST AID:

Skin: Wash contacted skin with soap and water. Launder work clothes after every wearing.

Eyes: Flush with plenty of water for 15 minutes. If irritation develops, get medical attention.

Inhalation: Remove to fresh air and get medical attention. If person is not breathing, give artificial respiration.

Ingestion: If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Immediately get medical attention.

Note to Physicians: If hypoglycemic signs and symptoms develop do not delay treatment. If the patient is conscious, administer glucose (sugar). If the patient is unconscious, administer intravenous glucose.

BEFORE USING, READ MATERIAL SAFETY DATA SHEET (MSDS) FOR THIS PRODUCT.

AMARYL® (glimepiride) Tablets

NDA 20-496

**Freedom of Information (FOI) (Non-Confidential)
Environmental
Assessment**

Attachment 6(c)-3

*Hoechst-Roussel Pharmaceuticals Incorporated (HRPI)
Manufacturer of AMARYL Tablets*

*Current US Federal and State (New Jersey)
Air-Emission, Water-Emission, and Solid-Emission Control Regulations
OSHA (Occupational, Safety, and Health Act) Standards*

Signed Statement of Compliance

Direct dial number

Environmental Compliance Summary

Hoechst Celanese Corporation
Hoechst-Roussel Pharmaceuticals, Inc.
(HRPI)

Somerville (Bridgewater), NJ

Air Emissions

The Hoechst Celanese Corporation Bridgewater Site is required to comply with the air emission regulations administered by the New Jersey Department of Environmental Protection and Energy Subchapters 3, 4, 5, 6, 8, 13, 16, and 18, et seq. (NJAC 7:27-et seq.)

The Bridgewater Site is also subject to Federal air emission regulations, which are codified at 40 CFR Parts 60, 61, 70, and 82, as well as the new Clean Air Act Amendments of 1990.

Currently, the Bridgewater Site has 33 active air permits, issued by the NJDEPE, which regulate active sources. Annual inspections are performed by the Regional Enforcement Bureau of the NJDEPE. (See attached list of Permits.)

Wastewater

Wastewater discharges from the Bridgewater Site are subject to both State and Federal regulations. State regulations are found at NJAC 7: 1E, 8, 9, 14, and 14A, Federal Regulations are found at 40 CFR Parts 112, 116, 117, and 122. Additional requirements are enforced by the Somerset Raritan Valley Sewerage Authority (SRVSA).

The Bridgewater Site discharges process and sanitary wastewater to the SRVSA under a permit issued by the SRVSA. Semi-annual sampling and analysis is conducted and reported. Annual inspections are conducted by the SRVSA.

Non-hazardous aqueous wastes from reactor washes and rinses, and non-hazardous aqueous chemical wastes are collected and transported to _____ in _____ for biological treatment.

Stormwater from the site discharges into Peters Brook. The site has obtained a permit under the NJDEPE General Stormwater Permit program.

Solid Waste Disposal

The site is required to comply with the United States Environmental Protection Agency (USEPA) Resources Conservation and Recovery Act (RCRA) regulations, codified at 40 CFR Parts 259, 260, 261, 262, and 268. Additional requirements are set forth by NJDEPE at NJAC 7:26-3, 3A, 4A, 7, 8, and 9, as well as 7:26B.

Currently, the site is designated as a "90-day generator"; that is, hazardous waste that is generated on the site must be removed and transported off site to a licensed Treatment, Storage or Disposal Facility (TSDF), within 90 days of the date the waste was generated.

Disposal of medical wastes are regulated by the NJDEPE at NJAC 7:26-3A. All medical wastes generated at the site are collected and transported routinely to a licensed TSDF for incineration.

It is the policy of Hoechst Celanese Corporation, that all wastes be destroyed to the extent that technology exists for the destruction of particular materials. Under no circumstances are any of these wastes placed into a landfill. (See attached list of TSDF's).

Superfund Amendments and Reauthorization Act (SARA)/CERCLA

Sections 312 and 313 of SARA Title III, are complied with. Each year, a SARA 312/NJ Right-To-Know survey (Chemical substances inventory) is completed and submitted to NJDEPE and various local agencies and authorities. In addition, each year the site submits a "negative declaration of non-applicability" pursuant to the requirements for annual reporting of releases under Section 313.

In addition, any accidental release of a hazardous substance is subject to the requirements of the USEPA Comprehensive Environmental Response, Compensation and Liability Act (CERCLA).

The above requirements are codified at NJAC 7:1G and 40 CFR Parts 302, 355, 370, and 372.

Safety

In addition to the environmental regulations cited above, the Bridgewater Site also complies with the requirements for worker safety, set forth in the various areas of the Occupation Safety and Health Act. Most of the applicable regulations are set forth in 29 CFR Part 1910 et seq. Federal OSHA regulates worker safety in the state of New Jersey. Federal OSHA does not issue an occupational safety permit. A separate state agency for occupational safety does not exist in New Jersey.

Hoechst-Roussel Pharmaceuticals Inc.



Route 202-206 • PO Box 2500 • Somerville, NJ 08876-1258
Telephone (908) 231-2000 • FAX (908) 231-3225

Direct dial number

Hoechst Celanese Corporation
Hoechst-Roussel Pharmaceuticals, Inc.
(HRPI)
Somerville (Bridgewater), NJ

Compliance Certification

Hoechst Celanese Corporation, HRPI certifies that it is in compliance with applicable Environmental, Health and Occupational Safety regulations. Hoechst Celanese Corporation, HRPI certifies that the information contained herein is true, accurate and complete to the best of knowledge. (See attached list of Regulations.)

A handwritten signature in black ink, appearing to read "S. F. Olp", written over a horizontal line.

Steven F. Olp
Manager, EH&S
Bridgewater Site

A handwritten date "9/21/94" written in black ink over a horizontal line.

Date

Environmental Regulations

Air

- New Jersey Administrative Code (NJAC) Title 7 Chapter 27 - Air Pollution Control
 - Subchapter 3 - Control and Prohibition of Smoke from Combustion of Fuel (NJAC 7:27-3)
 - Subchapter 4 - Control and Prohibition of Particles from Combustion of Fuel (NJAC 7:27-4)
 - Subchapter 5 - Prohibition of Air Pollution (NJAC 7:27-5)
 - Subchapter 6 - Control and Prohibition of Particles from Manufacturing Processes (NJAC 7:27-6) -
 - Subchapter 8 - Permits and Certificates (NJAC 7:27-8)
 - Subchapter 13 - Ambient Air Quality Standards (NJAC 7:27-13)
 - Subchapter 16 - Control and Prohibition of Air Pollution by Volatile Organic Compounds (NJAC 7:27-16)
 - Subchapter 18 - Control and Prohibition of Air Pollution from New or Altered Sources Affecting Ambient Air Quality (Emission Offset Rules) (NJAC 7:27-18)
- Code of Federal Regulations (CFR)
 - 40 CFR Part 60 - Standards of Performance for New Stationary Sources
 - 40 CFR Part 61 - National Emission Standards for Hazardous Air Pollutants
 - 40 CFR Part 70 - State Operating Permit Programs
 - 40 CFR Part 82 - Protection of the Stratospheric Ozone
 - Clean Air Act Amendments - November 1990

Water

- NJAC Title 7 Chapter 1E - Discharges of Petroleum and Other Hazardous Substances (NJAC 7:1E)
- NJAC Title 7 Chapter 8 - Stormwater Management (NJAC 7:8)
- NJAC Title 7 Chapter 9 - Water Pollution Control (NJAC 7:9)
- NJAC Title 7 Chapter 14 - Water Pollution Control Act (NJAC 7:14)
- NJAC Title 7 Chapter 14A - The New Jersey Pollutant Discharge Elimination System (NJAC 7:14A)
- Code of Federal Regulations (CFR)
 - 40 CFR Part 112 - Oil Pollution Prevention
 - 40 CFR Part 116 - Designation of Hazardous Substances
 - 40 CFR Part 117 - Determination of Reportable Quantities of Hazardous Substances
 - 40 CFR Part 122 - National Pollutant Discharge Elimination System

Solid And Hazardous Waste

- NJAC Title 7 Chapter 26 - Division of Waste Management (NJAC 7:26)
 - Subchapter 3 - Transportation (NJAC 7:26-3)
 - Subchapter 3A - Regulated Medical Waste (NJAC 7:26-3A)
 - Subchapter 4A - Hazardous Waste Fees (NJAC 7:26-4A)
 - Subchapter 7 - Labeling, Records and Transportation Requirements (NJAC 7:26-7)
 - Subchapter 8 - Hazardous Waste Criteria, Identification and Listing (NJAC 7:26-8)
 - Subchapter 9 - Requirements for Hazardous Waste Facilities (NJAC 7:26-9)
- NJAC Title 7 Chapter 26B - Environmental Cleanup Responsibility Act Rules (NJAC 7:26B)
- Code Of Federal Regulations (CFR)
 - 40 CFR Part 259 - Standards for the Tracking and Management of Medical Waste
 - 40 CFR Part 260 - Hazardous Waste Management System - General
 - 40 CFR Part 261 - Identification and Listing of Hazardous Waste
 - 40 CFR Part 262 - Standards Applicable to Generators of Hazardous Waste
 - 40 CFR Part 268 - Land Disposal Restrictions

SARA Title III/CFRCLA

- NJAC Title 7 Chapter 1G - Worker and Community Right to Know Regulations (NJAC 7:1G)
- Code of Federal Regulations (CFR)
 - 40 CFR Part 302 - Designation, Reportable Quantities and Notification
 - 40 CFR Part 355 - Emergency Planning and Notification
 - 40 CFR Part 370 - Hazardous Chemical Reporting: Community Right-To-Know
 - 40 CFR Part 372 - Toxic Chemical Release Reporting: Community Right-To-Know

Safety

- Code of Federal Regulations (CFR)
 - 29 CFR 1910 - Occupational Safety and Health Standards

AMARYL® (glimepiride) Tablets

NDA 20-496

**Freedom of Information (FOI) (Non-Confidential)
Environmental
Assessment**

Attachment 6(c)-4

*AMARYL Tablets Drug Product
MSDS Sheets*

Product Name: Amaryl (Glimepiride) Tablets 1mg

MSDS Version Date: 1/6/94

Section 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Manufactured and Distributed By:
Hoechst-Roussel Pharmaceuticals Inc.
Route 202-206
PO Box 2500
Somerville, NJ 08876-1258

Emergency Telephone Number:
24 Hours - (908) 231-4126

Product Information Number:
1-800-451-4455

Product Name:
Amaryl (Glimepiride) Tablets 1mg
(synonyms = HOE 490; S 80 8490)

Product Class:
Antidiabetic

Section 2. COMPOSITION/INFORMATION ON INGREDIENTS

Amaryl (Glimepiride) Tablets 1mg are not hazardous per the OSHA Hazard Communication Standard.

Components of Tablets	Cas Number
Active ingredient - Glimepiride	93479-97-1
Pharmaceutical excipients:	
Ferric Oxide NF, Red	1309-37-1
Lactose NF, Hydrous	64044-51-5
Magnesium Stearate	557-04-0
Microcrystalline Cellulose NF, PH101	9004-34-6
Povidone USP, 26-28	9003-39-8
Sodium Starch Glycolate NF	9063-38-1

Product Name: Amaryl (Glimepiride) Tablets 1mg

MSDS Version Date: 1/6/94

Section 3. HAZARDS IDENTIFICATION

Emergency Overview

In the healthcare environment, dispensing Amaryl (Glimepiride) Tablets 1mg presents no occupational exposure hazards.

Potential Health Effects

Routes of Exposure - Ingestion, Inhalation

Signs and Symptoms of Overexposure (Glimepiride) - Profound and sometimes prolonged hypoglycemia. Hypoglycemic symptoms include rapid heart beat, tremors, sweating, weakness, anxiety, nervousness and hunger. Severe hypoglycemia can cause coma.

Immediate effects of contact with glimepiride

Skin - None

Eyes - None

Ingestion - hypoglycemia

Inhalation - None

Delayed effects of occupational contact with tablets - None

Target Organ Effect - Pancreas

Medical Conditions Aggravated by Exposure - Hypoglycemia and existing hypersensitivity to glimepiride.

Section 4. FIRST AID MEASURES

Skin: Wash contacted skin with soap and water. Launder work clothes after every wearing.

Eyes: Flush eyes with water for fifteen minutes. Get immediate medical attention.

Inhalation: Remove to fresh air and get immediate medical help. If person is not breathing, give artificial respiration.

Ingestion: If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Immediately get medical attention.

Note to physicians: If hypoglycemic signs and symptoms develop, do not delay treatment. If the patient is conscious, administer glucose (sugar). If the patient is unconscious, administer intravenous glucose.

Product Name: Amaryl (Glimepiride) Tablets 1mg

MSDS Version Date 1/6/94

Section 5. FIRE FIGHTING MEASURES

Wear full bunker gear, including SCBA, when responding to fires involving facilities where pharmaceutical products are stored. Water, foam or CO₂ may be used to fight fires involving this product.

Section 6. ACCIDENTAL RELEASE MEASURES

Spilled tablets should be cleaned up in the proper manner and disposed of as pharmaceutical waste.

Section 7. HANDLING AND STORAGE

Store at controlled room temperature (59-86° F) in well-closed containers with safety closures.

Section 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

The dispensing of Amaryl (Glimepiride) Tablets 1mg requires no specialized exposure controls or personal protective equipment.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Amaryl (Glimepiride) Tablets 1mg are supplied as pink, flat-faced, beveled edge, double bisected, oblong tablets with "AMARYL" embossed on one side and on the other side the Hoechst AG logo embossed on both parts of the bisect.

Product Name: Amaryl (Glimepiride) Tablets 1mg

MSDS Version Date: 1/6/94

Section 10. STABILITY AND REACTIVITY

Chemical Stability: Chemically stable

Conditions to Avoid: None

Hazardous Decomposition Products: None

Hazardous Polymerization: None

Section 11. TOXICOLOGICAL INFORMATION

Acute Effects

Oral LD₅₀ (rat) > 10,000 mg/kg

Oral LD₅₀ (mouse) > 10,000 mg/kg

Chronic Effects

Two glimepiride feeding studies in mice (three months) and rats (twelve months) with doses up to 50,000 ppm resulted in decreased serum glucose, a pharmacologic effect of the compound, and degranulation of pancreas beta cells. Some organ weight changes were observed in rats at doses of 25,000 and 50,000 ppm. Intravenous glimepiride studies in rats, for up to one month, at dose levels up to 10 mg/kg resulted in reduced serum glucose, a pharmacologic effect of the compound. After nine months of a twelve month glimepiride feeding study at 320 mg/kg (500 times the highest dose used in human clinical trials), two of twelve dogs developed cataracts. Decreased serum glucose and degranulation of pancreas beta cells was also a consistent finding in the dog study.

Mutagenicity: Ames test: Negative
HGPRT in V79 Chinese hamster cells: Negative
Unscheduled DNA synthesis: Negative
Mouse micronucleus test (*in vivo*): Negative

Carcinogenicity: No toxicologic or carcinogenic effects were found in a thirty month glimepiride feeding study in rats.

None of the components of this product are listed by NTP, IARC or OSHA as a carcinogen.

Teratogenicity: A consistent result of a Segment II reproduction study in Wistar rats and Himalayan rabbits was fetal death, due to marked persistent hypoglycemia (a pharmacologic effect of glimepiride) in the dams. A fertility study conducted in male mice, according to Japanese guidelines, showed that glimepiride had no effect on the fertility of male mice. A fertility and general reproductive performance (Segment I) study in rats at dose levels of 1,000 and 5,000 ppm glimepiride in food resulted in marked persistent hypoglycemia in dams, a pharmacologic effect of the compound. A shortening, bending and thickening of the humerus was seen postnatally in the one rat at the low dose level and eleven rats at the high dose level. This effect was also seen in a peri/postnatal toxicity reproductive (Segment III) study in rats at 2500 mg/kg by gavage. The lowest dose level at which this effect was seen was 23.4 times the highest anticipated human dose. This developmental abnormality appeared postnatally and was interpreted as a pharmacodynamically induced impairment.

Product Name: Amaryl (Glimepiride) Tablets 1mg

MSDS Version Date: 1/6/94

Section 12. ECOLOGICAL INFORMATION

Amaryl (Glimepiride) Tablets 1mg administered to patients presents negligible impact on the environment.

Section 13. DISPOSAL CONSIDERATION

This product should be disposed of by incineration, in accordance with local, state and federal regulations.

Section 14. TRANSPORT INFORMATION

Amaryl (Glimepiride) Tablets 1mg are not subject to transportation regulations.

Section 15. REGULATORY INFORMATION

Amaryl (Glimepiride) Tablets 1mg are regulated under the Food, Drug and Cosmetic Act.

Section 16. OTHER INFORMATION

None

Product Name: Amaryl (Glimperide) Tablets 2mg

MSDS Version Date: 1/6/94

Section 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Manufactured and Distributed By:
Hoechst-Roussel Pharmaceuticals Inc.
Route 202-206
PO Box 2500
Somerville, NJ 08876-1258

Emergency Telephone Number:
24 Hours - (908) 231-4126

Product Information Number:
1-800-451-4455

Product Name:
Amaryl (Glimperide) Tablets 2mg
(synonyms = HOE 490; S 80 8490)

Product Class:
Antidiabetic

Section 2. COMPOSITION/INFORMATION ON INGREDIENTS

Amaryl (Glimperide) Tablets 2mg are not hazardous per the OSHA Hazard Communication Standard.

Components of Tablets	Cas Number
Active ingredient - Glimperide	93479-97-1
Pharmaceutical excipients:	
FD&C Blue #2 Aluminum Lake	16521-38-3
Ferric Oxide NF, Yellow	1309-37-1
Lactose NF, Hydrous	64044-51-5
Magnesium Stearate	557-04-0
Microcrystalline Cellulose NF, PH101	9004-34-6
Povidone USP, 26-28	9003-39-8
Sodium Starch Glycolate NF	9063-38-1

Product Name: Amaryl (Glimperide) Tablets 2mg

MSDS Version Date: 1/6/94

Section 3. HAZARDS IDENTIFICATION

Emergency Overview

In the healthcare environment, dispensing Amaryl (Glimperide) Tablets 2mg presents no occupational exposure hazards.

Potential Health Effects

Routes of Exposure - Ingestion, Inhalation

Signs and Symptoms of Overexposure (Glimperide) - Profound and sometimes prolonged hypoglycemia. Hypoglycemic symptoms include rapid heart beat, tremors, sweating, weakness, anxiety, nervousness and hunger. Severe hypoglycemia can cause coma.

Immediate effects of contact with glimepiride

Skin - None

Eyes - None

Ingestion - hypoglycemia

Inhalation - None

Delayed effects of occupational contact with tablets - None

Target Organ Effect - Pancreas

Medical Conditions Aggravated by Exposure - Hypoglycemia and existing hypersensitivity to glimepiride.

Section 4. FIRST AID MEASURES

Skin: Wash contacted skin with soap and water. Launder work clothes after every wearing.

Eyes: Flush eyes with water for fifteen minutes. Get immediate medical attention.

Inhalation: Remove to fresh air and get immediate medical help. If person is not breathing, give artificial respiration.

Ingestion: If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Immediately get medical attention.

Note to physicians: If hypoglycemic signs and symptoms develop, do not delay treatment. If the patient is conscious, administer glucose (sugar). If the patient is unconscious, administer intravenous glucose.

Product Name: Amaryl (Glimepiride) Tablets 2mg

MSDS Version Date: 1/6/94

Section 5. FIRE FIGHTING MEASURES

Wear full bunker gear, including SCBA, when responding to fires involving facilities where pharmaceutical products are stored. Water, foam or CO₂ may be used to fight fires involving this product.

Section 6. ACCIDENTAL RELEASE MEASURES

Spilled tablets should be cleaned up in the proper manner and disposed of as pharmaceutical waste.

Section 7. HANDLING AND STORAGE

Store at controlled room temperature (59-86° F) in well-closed containers with safety closures.

Section 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

The dispensing of Amaryl (Glimepiride) Tablets 2mg requires no specialized exposure controls or personal protective equipment.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Amaryl (Glimepiride) Tablets 2mg are supplied as green, flat-faced, beveled edge, double bisected, oblong tablets with "AMARYL" embossed on one side and on the other side the Hoechst AG logo embossed on both parts of the bisect.

Product Name: Amaryl (Glimepiride) Tablets 2mg

MSDS Version Date: 1/6/94

Section 10. STABILITY AND REACTIVITY

Chemical Stability: Chemically stable

Conditions to Avoid: None

Hazardous Decomposition Products: None

Hazardous Polymerization: None

Section 11. TOXICOLOGICAL INFORMATION

Acute Effects

Oral LD₅₀ (rat) > 10,000 mg/kg

Oral LD₅₀ (mouse) > 10,000 mg/kg

Chronic Effects

Two glimepiride feeding studies in mice (three months) and rats (twelve months) with doses up to 50,000 ppm resulted in decreased serum glucose, a pharmacologic effect of the compound, and degranulation of pancreas beta cells. Some organ weight changes were observed in rats at doses of 25,000 and 50,000 ppm. Intravenous glimepiride studies in rats, for up to one month, at dose levels up to 10 mg/kg resulted in reduced serum glucose, a pharmacologic effect of the compound. After nine months of a twelve month glimepiride feeding study at 320 mg/kg (500 times the highest dose used in human clinical trials), two of twelve dogs developed cataracts. Decreased serum glucose and degranulation of pancreas beta cells was also a consistent finding in the dog study.

Mutagenicity: Ames test: Negative
HGPRT in V79 Chinese hamster cells: Negative
Unscheduled DNA synthesis: Negative
Mouse micronucleus test (*in vivo*): Negative

Carcinogenicity: No toxicologic or carcinogenic effects were found in a thirty month glimepiride feeding study in rats.

None of the components of this product are listed by NTP, IARC or OSHA as a carcinogen.

Teratogenicity: A consistent result of a Segment II reproduction study in Wistar rats and Himalayan rabbits was fetal death, due to marked persistent hypoglycemia (a pharmacologic effect of glimepiride) in the dams. A fertility study conducted in male mice, according to Japanese guidelines, showed that glimepiride had no effect on the fertility of male mice. A fertility and general reproductive performance (Segment I) study in rats at dose levels of 1,000 and 5,000 ppm glimepiride in food resulted in marked persistent hypoglycemia in dams, a pharmacologic effect of the compound. A shortening, bending and thickening of the humerus was seen postnatally in the one rat at the low dose level and eleven rats at the high dose level. This effect was also seen in a peri/postnatal toxicity reproductive (Segment III) study in rats at 2500 mg/kg by gavage. The lowest dose level at which this effect was seen was 234 times the highest anticipated human dose. This developmental abnormality appeared postnatally and was interpreted as a pharmacodynamically induced impairment.

Product Name: Amaryl (Glimepiride) Tablets 2mg

MSDS Version Date: 1/6/94

Section 12. ECOLOGICAL INFORMATION

Amaryl (Glimepiride) Tablets 2mg administered to patients presents negligible impact on the environment.

Section 13. DISPOSAL CONSIDERATION

This product should be disposed of by incineration, in accordance with local, state and federal regulations.

Section 14. TRANSPORT INFORMATION

Amaryl (Glimepiride) Tablets 2mg are not subject to transportation regulations.

Section 15. REGULATORY INFORMATION

Amaryl (Glimepiride) Tablets 2mg are regulated under the Food, Drug and Cosmetic Act.

Section 16. OTHER INFORMATION

None

Product Name: Amaryl (Glimpiride) Tablets 4mg

MSDS Version Date: 1/6/94

Section 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Manufactured and Distributed By:
Hoechst-Roussel Pharmaceuticals Inc.
Route 202-206
PO Box 2500
Somerville, NJ 08876-1258

Emergency Telephone Number:
24 Hours - (908) 231-4126

Product Information Number:
1-800-451-4455

Product Name:
Amaryl (Glimpiride) Tablets 4mg
(synonyms = HOE 490; S 80 8490)

Product Class:
Antidiabetic

Section 2. COMPOSITION/INFORMATION ON INGREDIENTS

Amaryl (Glimpiride) Tablets 4mg are not hazardous per the OSHA Hazard Communication Standard.

Components of Tablets	Cas Number
Active ingredient - Glimpiride	93479-97-1
Pharmaceutical excipients:	
FD&C Blue #2 Aluminum Lake	16521-38-3
Lactose NF, Hydrous	64044-51-5
Magnesium Stearate	557-04-0
Microcrystalline Cellulose NF, PH101	9004-34-6
Povidone USP, 26-28	9003-39-8
Sodium Starch Glycolate NF	9063-38-1

Product Name: Amaryl (Glimperide) Tablets 4mg

MSDS Version Date: 1/6/94

Section 3. HAZARDS IDENTIFICATION

Emergency Overview

In the healthcare environment, dispensing Amaryl (Glimperide) Tablets 4mg presents no occupational exposure hazards.

Potential Health Effects

Routes of Exposure - Ingestion, Inhalation

Signs and Symptoms of Overexposure (Glimperide) - Profound and sometimes prolonged hypoglycemia. Hypoglycemic symptoms include rapid heart beat, tremors, sweating, weakness, anxiety, nervousness and hunger. Severe hypoglycemia can cause coma.

Immediate effects of contact with glimepiride

Skin - None

Eyes - None

Ingestion - hypoglycemia

Inhalation - None

Delayed effects of occupational contact with tablets - None

Target Organ Effect - Pancreas

Medical Conditions Aggravated by Exposure - Hypoglycemia and existing hypersensitivity to glimepiride.

Section 4. FIRST AID MEASURES

Skin: Wash contacted skin with soap and water. Launder work clothes after every wearing.

Eyes: Flush eyes with water for fifteen minutes. Get immediate medical attention.

Inhalation: Remove to fresh air and get immediate medical help. If person is not breathing, give artificial respiration.

Ingestion: If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Immediately get medical attention.

Note to physicians: If hypoglycemic signs and symptoms develop, do not delay treatment. If the patient is conscious, administer glucose (sugar). If the patient is unconscious, administer intravenous glucose.

Product Name: Amaryl (Glimepiride) Tablets 4mg

MSDS Version Date: 1/6/94

Section 5. FIRE FIGHTING MEASURES

Wear full bunker gear, including SCBA, when responding to fires involving facilities where pharmaceutical products are stored. Water, foam or CO₂ may be used to fight fires involving this product.

Section 6. ACCIDENTAL RELEASE MEASURES

Spilled tablets should be cleaned up in the proper manner and disposed of as pharmaceutical waste.

Section 7. HANDLING AND STORAGE

Store at controlled room temperature (59-86° F) in well-closed containers with safety closures.

Section 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

The dispensing of Amaryl (Glimepiride) Tablets 4mg requires no specialized exposure controls or personal protective equipment.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Amaryl (Glimepiride) Tablets 4mg are supplied as blue, flat-faced, beveled edge, double bisected, oblong tablets with "AMARYL" embossed on one side and on the other side the Hoechst AG logo embossed on both parts of the bisect.

Product Name: Amaryl (Glimepiride) Tablets 4mg

MSDS Version Date: 1/6/94

Section 10. STABILITY AND REACTIVITY

Chemical Stability: Chemically stable

Conditions to Avoid: None

Hazardous Decomposition Products: None

Hazardous Polymerization: None

Section 11. TOXICOLOGICAL INFORMATION

Acute Effects

Oral LD₅₀ (rat) > 10,000 mg/kg

Oral LD₅₀ (mouse) > 10,000 mg/kg

Chronic Effects

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Product Name: Amaryl (Glimepiride) Tablets 4mg

MSDS Version Date: 1/6/94

Section 12. ECOLOGICAL INFORMATION

Amaryl (Glimepiride) Tablets 4mg administered to patients presents negligible impact on the environment.

Section 13. DISPOSAL CONSIDERATION

This product should be disposed of by incineration, in accordance with local, state and federal regulations.

Section 14. TRANSPORT INFORMATION

Amaryl (Glimepiride) Tablets 4mg are not subject to transportation regulations.

Section 15. REGULATORY INFORMATION

Amaryl (Glimepiride) Tablets 4mg are regulated under the Food, Drug and Cosmetic Act.

Section 16. OTHER INFORMATION

None

SENSITIVE

REVIEW
OF
ENVIRONMENTAL ASSESSMENT
FOR

NDA 20-496

Amaryl®

(glimepiride)

Tablets

1, 2 or 4 mg

DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: September 28, 1995

ENVIRONMENTAL ASSESSMENT

1. Date:

Review #1:	05/04/1995 (Mitre)
Letter:	05/31/1995
Amendment:	07/10/1995
EA dated:	07/09/1995
Amendment:	09/13/1995*
EA dated:	09/11/1995*

*Information reviewed

CSO: John Short

2. Name of applicant/petitioner:

Hoechst-Roussel Pharmaceuticals Inc.

3. Address:

Route 202-206 North
P.O. Box 2500
Somerville (Bridgewater Township)
New Jersey 08876-1258

RESPONSE TO DEFICIENCIES LISTED IN N/A LETTER DATED 08/30/1995:

1. In discussions regarding disposal of sludge (sections 4.d., 6, 7) you have stated that sludge from wastewater treatment facilities are either incinerated or disposed of in a landfills. Although you may be able to state this assuredly for the WWTP/POTW associated with the manufacturing sites, we do not believe that this general statement would be appropriate for all POTW's throughout the United States. Although the majority of sludge may be disposed of in that manner, some may be amended to farm land. Please discuss and revise those statements regarding general sludge disposal procedures as appropriate. Replacement pages for the non-confidential EA should be provided.

RESPONSE: The company has submitted a comprehensive discussion of the potential use of sludge on land. They estimate the concentration to be 1 ppb. **ADEQUATE.** Section 8 (page

36) was not updated to reflect the discussion that some material may be introduced into the terrestrial environment and now contradicts sections 4, 6 and 7. An updated page should be provided. **DEFICIENT**

2. The following should be included as attachments to the non-confidential EA:

- a. the MSDS for glimepiride; and
- b. the statements of compliance with emission and occupational requirements.

RESPONSE: The documents have been included in the non-confidential document. **ADEQUATE**

TELECON:

On September 25, I contacted Dr. DeMartino ((908) 231-2385) to discuss the following deficiency. John xxx who revised the EA also participated. The company is planning to FAX in the revised page and send a hard copy to the division.

Section 8 (page 36) was not updated to reflect the discussion that some material may be introduced into the terrestrial environment. An updated page should be provided.

RESPONSE:

The company submitted a revised page on September 25 that is acceptable. **ADEQUATE**

SUMMARY:

A FONSI MAY BE WRITTEN:

The company has estimated the concentrations of material as follows:

Germany @wwtp	2.9 ppb
Germany @river	0.046 ppb*
U.S. @potw	2.9 ppb
U.S. @river	0.046 ppb*
Use:	0.025 ppb*
Sludge/farm:	1 ppb*

*Point of entry

The lowest aquatic toxicity value reported was for green algae @120 ppb. There is greater than 1000 times difference between

this value and the maximum expected concentration in the environment (river or use).

Although there was no terrestrial toxicity testing *per se*, *Hyalella azetca* an amphipod that lives in river sediment was tested as was *Daphnia magna* which is often used as a surrogate test organism for the terrestrial environment. The EC_{50} for these two organisms are > 1 ppm which is more than 1000 times greater than the concentration entering the terrestrial environment.

Endorsements:

HFD-004/NBSager

AS 9/28/95

HFD-004/RAJerussi

Ru Jerussi 7/29/95

CC: Original NDA 20-496/JShort copy to NDA/HFD-510
EA File 20486.REV

File: 20496E02.nbs

AUG - 9 1995

SENSITIVE

REVIEW

*IL Letter
received 8/30/95*

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-496

Amaryl®

(glimepiride)

Tablets

1, 2 or 4 mg

DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: August 9, 1995

ENVIRONMENTAL ASSESSMENT

1. **Date:**

Review #1: 05/04/1995 (Mitre)
Letter: 05/31/1995
Amendment: 07/10/1995*
EA dated: 07/09/1995*
Consult to HFD-004: 07/26/1995

*Information reviewed

CSO: John Short

2. **Name of applicant/petitioner:**

Hoechst-Roussel Pharmaceuticals Inc.

3. **Address:**

Route 202-206 North
P.O. Box 2500
Somerville (Bridgewater Township)
New Jersey 08876-1258

RESPONSE TO DEFICIENCIES LISTED IN N/A LETTER DATED 05/31/1995:

1. The company has supplied a non-confidential EA. The FOI'able EA is acceptable except for (1) deficiency noted below, (2) inclusion of the MSDS and (3) inclusion of the statements of compliance with emission and occupational regulations. **DEFICIENT**
- 2a. The company has identified the facilities used for waste disposal in Germany and the United States and have provided the permitting information when applicable. **ADEQUATE**
- 2b. The information regarding methods of disposal for rejected, expired, returned or waste drug substance or product was originally submitted in the application but has been updated in this submission. **ADEQUATE**

- 2c. The company is disposing of these items at licensed facilities which must meet the EPA requirements (similar ones in Germany) for recycling or destroying a particular kind of packaging. The information that is provided in the EA is sufficient. **ADEQUATE**
- 2d. None are proprietary and the emitted substances have been identified. **ADEQUATE**
3. The CAS numbers have been included as requested. **ADEQUATE**
- 4a. The CAS numbers for the input chemicals have been provided. **ADEQUATE**. The specific information regarding batch size and processing time have been provided as requested, although its relevance to an EA is not understood by this reviewer. **ADEQUATE**
- 4bi. The controls used in production have been discussed. The information provided is judged to be sufficient. **ADEQUATE**
- 4bii. The company has not provided the requested qualitative and quantitative emission requirements as they believe that emissions are controlled to practically nil. They have provided additional supportive information regarding the strict controls used to manufacture the bulk drug and product. As per current thinking this information is not necessary in the EA and therefore the EA is acceptable regarding this point as is. **ADEQUATE**
- 4b3. The estimates of glimepiride entering the environment are provided (maximum).
- | | |
|----------------|-----------|
| Germany @wwtp | 2.9 ppb |
| Germany @river | 0.046 ppb |
| U.S. @potw | 2.9 ppb |
| U.S. @river | 0.046 ppb |
| Use: | 0.025 ppb |
- The lowest toxicity value reported was for green algae @120 ppb. There is greater than 1000 times difference between this value and the maximum expected concentration in the environment (river or use). **ADEQUATE**
- 4biv. The company does not expect to have any problems meeting either quantitative or qualitative emission requirements based on the quantities emitted (above). **ADEQUATE**
- Due to the adsorptive properties of glimepiride to sludge, aerobic biodegradation is not a pathway that has to be considered as the majority of the material will be removed from the aquatic environment. **ADEQUATE**.

The company states that sludge from wastewater treatment facilities are either incinerated or disposed of in a landfill (sections 4.d., 6, 7). Although they may be able to say this assuredly for the wwtp/potw associated with the manufacturing sites, this general statement may not be true for all POTW's. Although the majority of sludge is expected to be handled in the is way, some may be applied to farmland. The company should revise the statements to indicate that the majority of sludge is expected to be disposed of in this manner. **DEFICIENT**

- 4c. The requested concentrations have been included in response to 4.b.iii. **ADEQUATE**

The company has change the language used about emissions from incinerators to indicate the control of the emissions. **ADEQUATE**

Information has been included regarding disposal practices in hospitals. **ADEQUATE**

5. The company has not performed a soil biodegradation test based on (1) the compound showed little biodegradation under aerobic test conditions, (2) the majority of the sludge is expected to go into landfills (controlled environment), and (3) the material is strongly bound to sludge. The possibility of biodegradation exists but it may be at a rate slower then the rate the test is designed to measure or is dependent on actual environmental conditions. **ADEQUATE**
6. The company used *Hyaella azteca* because they believe that exposure to organisms in river sediment, where this amphipod resides, is more relevant than to worms as the majority the material entering the terrestrial environment will be landfilled. In the past CDER has used *Daphnia* and other aquatic organisms as surrogates for actual terrestrial testing. Due to the route of exposure, they are probably a worse case. Material tightly bound to sludge/soil would be expected to be limited in its bioavailability to terrestrial organisms. There is sufficient "safety margin" between the expected concentrations and the reported toxicity values to provide assurance that this material will not impact the environment. **ADEQUATE**

DRAFT DEFICIENCY LETTER

1. In discussions regarding disposal of sludge (sections 4.d., 6, 7) you have stated that sludge from wastewater treatment facilities are either incinerated or disposed of in a landfills. Although you may be able to state this assuredly for the WWTP/POTW associated with the manufacturing sites, we do not believe that this general statement would be appropriate for all POTW's throughout the United States. Although the majority of sludge may be disposed of in that manner, some may be amended to farm land. Please discuss and revise those statements regarding general sludge disposal procedures as appropriate. Replacement pages for the non-confidential EA should be provided.
2. The following should be included as attachments to the non-confidential EA:
 - a. the MSDS for glimepiride; and
 - b. the statements of compliance with emission and occupational requirements.

Endorsements:

HFD-004/NBSager *[Handwritten signature]*

CC: Original NDA 20-496/JShort copy to NDA/HFD-510
EA File 20486.REV

File: 20496E01.nbs

F/T by NBS/08/09/1995

DIVISION COPY

SENSITIVE

*Included
in letter
dated 5/31/95*

REVIEW
OF

ENVIRONMENTAL ASSESSMENT
FOR

NDA 20-496

AMARYL[™] (Glimepiride) Tablets

REVIEW DIVISION: HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-004

DATE COMPLETED: May 04, 1995

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: March 17, 1994
NDA submitted: August 31, 1994

Consult #1
to HFD-102: September 27, 1994

Assigned: February 10, 1995

CSO: John Short
Review May 04, 1995

2. Name of Applicant/Petitioner:

Hoechst-Roussel Pharmaceuticals Incorporated (HRPI)

Adequate.

3. Address:

Route 202-206
P. O. Box 2500
Somerville (Bridgewater Township), NJ 08876-1258

Adequate.

4. Description of the proposed action:

a. Requested Approval:

- Adequate.

b. Need for Action:

The product is a hypoglycemic agent for the treatment of patients with Type II non-insulin dependent diabetes mellitus.

Adequate.

c. Production Locations:

i. Proprietary Intermediate(s):

Proprietary starting materials and intermediates are not discussed. The company should confirm that any intermediates used in the manufacture of the drug substance are commercially available in the open marketplace. If proprietary intermediates are used, the manufacturing facility and information relating to that facility must be provided.

DEFICIENT.

ii. Drug Substance:

The address of the location of manufacture of the drug substance and the types of environments present at and adjacent to the location are given. The bulk drug substance will be manufactured at:

Hoechst Aktiengesellschaft (HAG)
Werk Hoechst
D-65926 Frankfurt am Main
Federal Republic of Germany

Adequate.

iii. Finished Dosage Form:

The address of the location of production of drug product is given. A description of the environments at and adjacent to the production facilities is given. The address of the location of the packaging and labeling of the product into blister packages is given, but no description is provided of the environments at and adjacent to the packing facility is given.

DEFICIENT.

The drug product will be manufactured at:

Hoechst-Roussel Pharmaceuticals Inc. (HRPI)
Route 202-206

P. O. Box 2500
Somerville (Bridgewater Township), NJ 08876-1258

The drug product will be packaged into blister packages at:

Adequate.

d. **Expected Locations of Use (Drug Product):**

Adequate.

e. **Disposal Locations:**

The identity and location of all facilities used for recycling and disposal of wastes from manufacturing, formulation, and packaging activities must be provided, along with applicable permit numbers and expiration dates, if any.

The document should describe the method(s) of disposal by the manufacturers of rejected, expired, returned, or waste drug substance and product, including the license or permit number, the EPA or other issuing authority's identification number, if any, the license or permit expiration dates, and the identity of the issuing agency. A reference to EPA format item 6, "Introduction of Substances into the Environment," may be provided if the disposal operations are described there. Specific information regarding contract disposal facilities may be included in a confidential appendix.

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals or clinics, empty or partially empty packages will be disposed of according to hospital/clinic regulations and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, while minimal quantities of unused drug may be disposed of in the sewer system.

The EA should specifically describe the emission controls and their effectiveness with respect to the destruction of the packaging components.

DEFICIENT.

5. Identification of chemical substances that are the subject of the proposed action:

Drug Substance: Glimepiride
Chemical Name: Trans-3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[(4-methyl cyclohexyl) amino] carbonyl] amino] sulfonyl] phenyl] ethyl]-2-oxo-1H-pyrrole-1-carboxamide
CAS #: 93479-97-1
Molecular Weight: 490.62
Molecular Formula: $C_{24}H_{34}N_4O_5$
Structural Formula: Given on P. 13 of EA
Physical Descrip.: White powder
Additives: Given
Impurities: Given

The CAS numbers for the additives are given in the MSDS for the finished drug product. The CAS numbers should be included in the body of the EA.

DEFICIENT.

6. Introduction of substances into the environment: For the site(s) of production:

a. Potential Emitted Substances:

Lists of materials used in the manufacture of the drug substance and drug product are provided on pages 22-23 and 20, respectively. No information is provided concerning potentially emitted substances from the contract packaging plant.

DEFICIENT.

The waste streams from manufacture of the drug substance and drug product and from packaging are identified.

Adequate.

CAS numbers should be provided for all input chemicals when known. For the German facility, the production batch size of the drug substance and its intermediates should be included in a confidential attachment. Estimated information for the production of the drug substance on a both kg per kg of final product basis and on a per year basis (for a five year period) should be provided.

DEFICIENT.

b. Controls (Air, Liquid Effluent, Solid):

For air, liquids, and solids emissions from the production operations for this drug substance, the following should be provided:

- i. Identification of the emission control;
- ii. Applicable emission requirements (both qualitative and quantitative);
- iii. An estimate, through the use of calculations and/or direct measure, of the possible quantities and concentrations of substances expected to enter the environment (fifth year production levels);
- iv. Effect of the quantities/concentrations (from 6.a.iii) on meeting both the qualitative and quantitative emission requirements.

The controls mentioned for wastewater for production of both drug substance and drug product include chemical and biological treatment prior to discharge into public waterways. However, testing showed no biodegradation of the drug substance. In addition, the drug substance showed a high affinity for most soils. No information is given that adequately addresses appropriate controls for water discharges, including sludges and sediments.

DEFICIENT.

c. Compliance with Federal, State and Local Emission Requirements:

A list of applicable regulations and laws as well as a statement of compliance is included.

Adequate.

d. **Effect of Approval on Compliance with Current Emissions Requirements:**

See Attachments 1, 2, and 3.

A statement that approval will not cause the plants to violate permit requirements is included.

Adequate.

e. **Estimated Expected Emitted Concentration/Quantities:**

The maximum expected emitted concentration (MEEC) of glimepiride is calculated to be 2.5×10^{-4} parts per million. The calculation was done correctly.

No information is given for estimated expected emitted concentrations or quantities for the German drug substance plant.

Insufficient information is given to justify the statement that "no substances are expected to enter the environment because solid waste from [various activities] is incinerated." Information on standard disposal practices for unused and expired goods in controlled setting such as hospitals must be included.

DEFICIENT.

7. **Fate of emitted substances in the environment:**

Parent Compound: Glimepiride

In vivo: Glimepiride

Metabolites: Two metabolites of the drug substance are identified. Both are more polar than the parent compound.

Tier 0 attributes are presented and are summarized in Attachment 4.

Adequate.

Since the drug substance is strongly sorbed by sludge and moderately sorbed by soils representing river sediment, the primary environmental process affecting the transport and fate of glimepiride is sorption. Test data included in the EA demonstrated that aerobic degradation only eliminated 0.3% of the drug substance in 28 days. The EA briefly discusses the possibility of biodegradation occurring in sludges, but does not include any data demonstrating the validity of this possibility. The EA should include test data from soil biodegradation testing.

DEFICIENT.

The toxicity data given in the EA on page 44 demonstrates that for all test organisms, the MEEC is several orders of magnitude less than 1% of the concentration needed for any inhibitory effects in the aqueous compartment.

Adequate.

8. Environmental effects of released substances:

Toxicity information is provided for test organisms for the aquatic compartment. For the terrestrial component, acute toxicity data are given for *Hyalella azteca*. However, since glimepiride undergoes extremely slow aerobic biodegradation, the appropriate test organisms for subacute toxicity in the terrestrial compartment (e.g., *Lumbricus terrestris*, *Lirubellus*, *E.foetida*, or other earthworms) should be tested. Ecotoxicology data indicate this class of chemicals to have apparent high toxicity.

DEFICIENT.

9. Use of resources and energy:

a. Production:

The production of drug substance and drug product and the packaging processes will require approximately 10% of the facility's resources.

Adequate.

b. **Effect on Endangered/Threatened Species and National Register of Historic Places:**

No adverse effects are anticipated on any endangered or threatened species based on the fate and effect studies. Certification is enclosed from the New Jersey Historic Preservation Office documenting no adverse effects on surrounding properties listed in the National Register of Historic Places.

Adequate.

10. **Mitigation measures:**

The description of mitigating measures refers to controls described in Item 6. If the deficiencies in Item 6 in describing these controls are corrected, Item 11 will also be adequate. One mitigation might be to incinerate waste from production and disposal.

DEFICIENT.

11. **Alternatives to the proposed action:**

The information provided adequately addresses this issue, including identifying no action as an alternative.

Adequate.

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

A list of preparers and consultants with resumes is included.

Adequate.

13. **Certification:**

Provided.

Adequate.

14. **References:**

Provided.

Adequate.

15. Appendices:

Test study reports, MSDS, resumes, and reference articles not generally available are included.

Adequate.

General Issues:

As defined by CEQ in 40 CFR 1508.9, the EA is a public document. Please submit a non-confidential version of the EA.

DRAFT DEFICIENCY LETTER

1. General Issues:

As defined by CEQ in 40 CFR 1508.9, the EA is a public document. Please submit a non-confidential version of the EA.

2. The following comments address Section 4:

- The identity and location of all facilities used for recycling and disposal of wastes must be provided, along with applicable permit numbers and expiration dates, if any.
- The EA should describe the method(s) of disposal of rejected, expired, returned, or waste drug substance and product along with applicable permit information.
- The EA should specifically describe the emission controls and their effectiveness with respect to the destruction of the packaging component.
- The EA should identify any proprietary starting materials and intermediates, and supply all required information for the production location of the proprietary compounds.

3. The following comment addresses Section 5:

- The CAS numbers for the additives should be included in the body of the EA.

4. The following comments address Section 6:

- CAS numbers should be provided for all input chemicals when known. The production batch size of the drug substance and its intermediates and the process time required to manufacture a batch should be included in a confidential attachment.

- For air, liquids, and solids emissions from the production operations for this drug substance, the following should be provided:
 - i. Identification of the emission control;
 - ii. Applicable emission requirements (both qualitative and quantitative);
 - iii. An estimate, through the use of calculations and/or direct measure, of the possible quantities and concentrations of substances expected to enter the environment (fifth year production levels);
 - iv. Effect of the quantities/concentrations (from 6.a.iii) on meeting both the qualitative and quantitative emission requirements.

The controls mentioned for wastewater for production of both drug substance and drug product include chemical and biological treatment prior to discharge into public waterways. However, testing showed no biodegradation of the drug substance. In addition, the drug substance showed a high affinity for most soils. No information is given that adequately addresses appropriate controls for water discharges, including sludges and sediments.

- No information is given for estimated expected emitted concentrations or quantities for the German drug substance plant.

Insufficient information is given to justify the statement that "no substances are expected to enter the environment because solid waste from [various activities] is incinerated." Information on standard disposal practices for unused and expired goods in controlled setting such as hospitals must be included.

5. The following comment applies to Section 7:

Since the drug substance is strongly sorbed by sludge and moderately sorbed by soils representing river sediment, the primary environmental process affecting the transport and fate of glimepiride is sorption. Test data included in the EA demonstrated that aerobic degradation only eliminated 0.3% of the drug substance in 28 days. The EA briefly discusses the possibility of biodegradation occurring in

sludges, but does not include any data demonstrating the validity of this possibility. The EA should include test data from soil biodegradation testing.

6. The following comment applies to Section 8:

Toxicity information is provided for test organisms for the aquatic compartment. For the terrestrial component, acute toxicity data are given for *Hyalella azteca*. However, since glimepiride undergoes extremely slow aerobic biodegradation, justify a rationale why the appropriate test organisms for subacute toxicity in the terrestrial compartment (e.g., *Lumbricus terrestris*, *Lirubellus*, *E.foetida*, or other earthworms) should not be tested.

ATTACHMENT 1

SITE: Hoechst AG, Frankfurt, Germany FUNCTION: Manufacture of Drug Substance BASIS FOR EMISSIONS EST.: Not given					
Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements.	Effect of Action on Current Emission Requirements	
Air emission permits	Not given	Not given	Laws listed in Appendix 15(E) (xx)	Statement of compliance with all applicable laws and regulations is included	
Municipal sewer system, aqueous waste streams	Not given	Not given	Laws listed in Appendix 15(B) (xx)	Statement of compliance with all applicable laws and regulations is included	

Note: The facility is under the jurisdiction of the Regierungspraesidium Darmstadt of the Federal Republic of Germany.

ATTACHMENT 2

SITE: HRFI, Scottsville, NJ FUNCTION: Preparation of Drug Product BASIS FOR EMISSIONS EST.: Not given					
Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements	Effect of Action on Current Emission Requirements	
Air emission permits	Listed in Appendix 15(b)(1)(x) (1)	Given in Appendix 15(b)(1)(x) (1)	Regulations are listed in Appendix 15(b)(1)(x)(1)	A statement is included that 5 year production will not cause an exceedance of permit levels	
Municipal sewer system, aqueous waste streams	Listed in Appendix 15(b)(1)(x) (1)	Given in Appendix 15(b)(1)(x) (1)	Regulations are listed in Appendix 15(b)(1)(x)(1)	A statement is included that 5 year production will not cause an exceedance of permit levels	
Stormwater	Listed in Appendix 15(b)(1)(x) (1)	Given in Appendix 15(b)(1)(x) (1)	Regulations are listed in Appendix 15(b)(1)(x)(1)	A statement is included that 5 year production will not cause an exceedance of permit levels	
Hazardous waste	Listed in Appendix 15(b)(1)(x) (1)	Given in Appendix 15(b)(1)(x) (1)	Regulations are listed in Appendix 15(b)(1)(x)(1)	A statement is included that 5 year production will not cause an exceedance of permit levels	

Note: Severe, off-site disposal companies and intermediates (activities are indicated) for appropriate permits/license numbers are included

ATTACHMENT 3				
SITE:		Packaging of Drug Product		
FUNCTION:		Not given		
BASIS FOR EMISSIONS EST.:		Not given		
Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements.	Effect of Action on Current Emission Requirements
Air emission permits	None	None	Not given	A statement of compliance is included (Appendix 15(b)(xxiii))
Municipal sewer system, aqueous waste streams	None	None	Not given	A statement of compliance is included (Appendix 15(b)(xxiii))

Note: All solid wastes will be returned to HPI for processing.

ATTACHMENT 4					
TIER 0					
Attribute	Compound	Test Method	Compliance w/Method (Y/N)	Result	Comments
Water Solubility	glimepiride	EATAD 3.01	Y	41.22 x 10 ⁻⁶ M pH 5.0 8.296 x 10 ⁻⁶ M pH 7.0 8.247 x 10 ⁻⁶ M pH 9.0	The document states the result obtained for pH 5.0 was less than the limit of quantitation for the assay.
Hydrolytic Stability (K ₁₂) 4.21ppm	glimepiride	EATAD 3.09	Y	<10% hydrolysis after 5 days at 50°C for pH 5, 7, and 9	Glimepiride is considered hydrolytically stable with a half-life equal to or greater than one year at 25°C.
Dissociation Constant	glimepiride	EATAD 3.04	Y	Not determined	Method 3.04, Section IV states that chemicals with water solubility below 10 ⁻⁶ M need not be tested for dissociation constants.
Octanol:Water (K _{ow})	glimepiride	EATAD 3.02	Y	1M 5.245 1M 7.215 1M 9.0804	The EA explains the partition behavior by citing the changing chemical moieties of glimepiride.
Vapor Pressure or Henry's Law Constant	glimepiride	EATAD 3.03	Y	4.109 x 10 ⁻¹¹ Torr	The vapor pressure was calculated from triplicate measurements determined by the gas saturation procedure at a flow rate of 30.0 ml/min and 24°C.
UV Visible Spectrophotometry	glimepiride	EATAD 3.05	Y	No absorption between 290-400 nm in solutions at pH 7.0 and 9.0. The compound is insoluble at pH 5.0.	The compound was dissolved in 1% dimethyl-formamide (DMF), not water/methanol or water/acetonitrile as specified in the method. 1% DMF was used as the reference blank.
Melting Temperature	glimepiride	EATAD 3.06	Y	194.7-197.6°C (capillary method)	
Density and Relative Density	glimepiride	EATAD 3.07	Y	Density 1.263 g/ml Relative density 1.229 (DMF determined at 25°C)	DMF was used since glimepiride is slightly soluble in water.

ATTACHMENT 4

TIER 0

Attribute	Compound	Test Method	Compliance w/Method (Y/N)	Result	Comments
Soxhlet and Description	glimepiride	EATAD 3.06	Y	Table of results found on page 16. Compound is considered immobile in Arkansas and Kansas soils in both 0.01M CaCl ₂ and reagent water. Moderately mobile in the Wisconsin soil at both 0.01 M CaCl ₂ and reagent water.	All tests were performed with ¹⁴ C-labeled glimepiride. The mass balance was performed by combustion of the aliquots, collection of ¹⁴ CO ₂ , and analysis by liquid scintillation counting.
Photodegradation	glimepiride	EATAD 3.10		Not tested at 10 ⁻⁵ M glimepiride at 290-600 nm.	
Aerobic Biodegradation in Water	glimepiride	EATAD 3.11	Y	Compound did not degrade. Half-life > 28 days.	Radio-labeled compound was used.
REVIEW					

Review Guidance:

- H₂O solubility > 10⁻⁵ M, Log P < 2, VP < 10⁻⁶ Torr - Tier 1
- H₂O solubility > 10⁻⁵ M, Log P ~2-3, VP < 10⁻⁶ Torr - Tiers 1 & 2
- H₂O solubility > 10⁻⁵ M, Log P < 2, VP > 10⁻⁶ Torr - Tiers 1 & 3
- H₂O solubility < 10⁻⁵ M, Log P > 3, VP > 10⁻⁶ Torr - Tiers 2 & 3
- H₂O solubility > 10⁻⁵ M, Log P ~> 3, VP < 10⁻⁶ Torr - Tier 2
- H₂O solubility > 10⁻⁵ M, Log P ~> 3, VP > 10⁻⁶ Torr - Tier 3

Endorsements:

MITRE:RDMavis

HFD-102/PGVincent

CG Vincent 5/4/95

CC: Original NDA 20-496 copy to NDA/HFD-510
EA File 20496
CGood/HFD-102

*R.A. Janni
5/17/95*

File: 20496E00.RKE

MICROBIOLOGY REVIEW

**Not Applicable Because This Is
A Tablet Formulation**

CORRESPONDENCE

NDA 20-496

OCT 31 1995

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

Dear Dr. Reit:

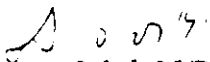
We refer to your new drug application for Amaryl (glimepiride tablets), 1, 2, and 4 mg.

Our letter dated July 19, 1995, extended the user fee clock for this NDA, based on a major amendment received within 3 months of the original user fee due date, to November 28, 1995. This new date was incorrectly calculated; it should be November 30, 1995.

If you have any questions regarding this communication, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,


Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-004/NSager
HFD-005/MJones
HFD-244/AReb
HFD-427/TChen/HAhn
HFD-713/JChoudhury, ENevius
HFD-510/CSO/J.R.Short
HFD-510/JGueriguian, AFleming, XYsern, YYChiu, HRhee, AJordan,

drafted: JShort/10/25/95/N20496RV.2JS

r/d Initials: EGalliers 10/25/95

final: JShort 10/26/95

REVIEW EXTENSION (correction)

J. Short
10/26/95

1) & 2) *signature*
to on 10/2/95.

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

SEP 29 1995

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We also refer to your amendment dated August 28, 1995, in response to one of our letters dated July 12, 1995, addressing biopharmaceutics issues.

We have completed our review of this communication and have the following comment:

Our letter of July 12, 1995, requested that you modify the dissolution method and specification used for Amaryl tablets as follows:

900 ml of simulated intestinal fluid without enzymes (pH 7.50) at 37° C.
USP Apparatus II (paddle) at 50 rpm

Your August 28 communication provides information why the dissolution method and specifications should not be changed from that in the original application. We agree with your reasoning and conclude that they should stay the same as provided for in the original application as follows:

900 ml of phosphate buffer pH 7.8 at 37° C.
USP Apparatus II (paddle) at 75 rpm

We also offer the following additional comments:

- 1) You indicate that Study No. HOE490/1/YU/201/LI entitled "Safety, Pharmacokinetic and Feasibility Efficacy Study of Multiple Doses of Glimepiride (HOE490) in Type II-Diabetic Patients with Liver Impairment" was initiated on May 27, 1993 in Europe, but the study report is not available at this time. It is recommended that when it becomes available, the study report be submitted to the NDA for review. If it is not available by the time the NDA is approved (assuming it will be approved), the results may be submitted following approval.

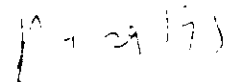
- 2) It is recommended that *in vitro* inhibition studies be carried out with various concentrations of phenytoin, diclofenac, ibuprofen, naproxen, mefenamic acid, and S-warfarin (i.e., sources of potential interaction due to metabolism by CYP2C9 reported in the insert). We acknowledge that if microsomes are utilized in these studies, the presence of an interaction *in vitro* may not translate to a clinically significant interaction due to factors such as cellular transportation of the compounds in question. However, the absence of observed *in vitro* interaction would offer additional evidence that an *in vivo* interaction is unlikely, and the package insert could be revised accordingly. If further assistance is necessary concerning these studies, please contact the Division of Biopharmaceutics. These studies will not be conditions of approval (assuming it will be approved) for this NDA.

Please respond to items 1) and 2) so that we know what you intend to do.

If you have any questions, please contact:

John R. Short, R.Ph.
 Consumer Safety Officer
 (301) 443-3510

Sincerely yours,



Solomon Sobel, M.D.
 Director
 Division of Metabolism and
 Endocrine Drug Products (HFD-510)
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research

cc:

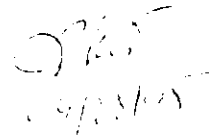
- Original NDA 20-496
- HFD-510/Div. Files
- DISTRICT OFFICE
- HFD-427/TChen, GBarnette, JHunt
- HFD-510/CSO/J.R.Short
- HFD-510/JGuerguian, AFleming, XYsern, YYChiu

drafted: JShort/9/26/95/N20496IR.7JS

r/d Initials: TChen, GBarnette 9/26, JHunt, XYsern, SMoore for YYChiu, Jguerguian, AFleming 4/27/95

final: JShort 9/28/95

INFORMATION REQUEST (IR)



NDA 20-496

*Responded to
9/13/95 (same
day as this letter),
Items 1-4.*

SEP 13 1995

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

*HESI responded on 9/13/95
(same day as this letter received)
giving in to our wishes*

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We have completed our review of your amendment dated June 26, 1995, in response to our letter of May 17, 1995. Your submission addresses the question of whether glimepiride- is the starting material for the drug substance, glimepiride. For the following reasons we do not believe that glimepiride- can be considered a starting material:

- 1) We did not require additional information during the IND process because CMC comments from the Agency at that time are, in general, more flexible due to the changing nature of an experimental drug where synthesis and controls of the active drug, drug product composition, and proper specifications are not only being modified but in most of the cases experience is being gained at this stage.
- 2) Glimepiride- cannot be considered a widely commercially available compound. Apparently only two manufacturers seem to produce glimepiride- . One of the suppliers is Hoechst Aktiengesellschaft, Frankfurt am Main, Germany (HAG), the manufacturer of the drug substance and the holder of the patent for the synthesis of heterocyclic-substituted sulfonyl ureas. The other is a contract manufacturer.
- 3) Starting materials are, in general, very pure materials. The controls/specifications established by Hoechst-Roussel, for the assay and for the sum of all by-products, are only adequate for an intermediate compound.
- 4) Glimepiride- which is also the main degradation product, is not a simple compound. The synthesis of glimepiride- can be accomplished by three whereas the formation of glimepiride from glimepiride-

After careful consideration of your viewpoints, we reiterate (as expressed in our May 17, 1995 letter) that glimepiride- is a synthesis intermediate, not a starting material.

With regard to package insert (PI) included in your June 20, 1995 submission, we offer the following comment:

The second sentence of the DESCRIPTION Section refers to the active drug substance and should read "Glimepiride is a white to yellowish-white . . .", instead of "It is a white to yellowish-white . . ." (which would refer to the drug product and is not correct).

Please do NOT submit a revised PI with these corrections until you receive our comments on the entire PI submitted June 20.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

9/13/95
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-510/CSO/JShort
HFD-510/XYsern/YChiu

drafted: JShort/9/7/95/N20496IR.6JS
revised as per Dr. Chiu's comments & Dr. Ysern's revised text -- 9/11/95
revised as per Dr. Chiu and Dr. Ysern's revised text -- 9/13/95
final: JShort 9/13/95
Concurrences: XYsern, YYChiu 9/13/95

INFORMATION REQUEST (IR)

JShort
9/13/95

NDA 20-496

AUG 30 1995

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

*Responded
to 9/13/95*

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

Our letter dated May 31, 1995, commented on the deficiencies in the environmental assessment portion of your application. You responded on July 10, 1995, with responses to these deficiencies. We have completed our review of this amendment and have the following comments:

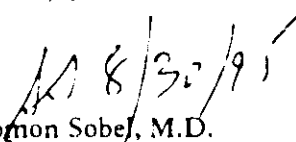
- 1) In discussions regarding disposal of sludge (sections 4.d., 6, 7) you stated that sludge from wastewater treatment facilities are either incinerated or disposed of in a landfill. Although you may be able to state this assuredly for the WWTP/POTW associated with the manufacturing sites, we do not believe that this general statement would be appropriate for all POTW's throughout the United States. Although the majority of sludge may be disposed of in that manner, some may be amended to farm land. Please discuss and revise those statements regarding general sludge disposal procedures as appropriate. Replacement pages for the non-confidential EA should be provided.
- 2) The following should be included as attachments to the non-confidential EA:
 - a) the MSDS for glimepiride; and
 - b) the statements of compliance with emission and occupational requirements.

Please respond to these environmental assessment deficiencies as soon as possible.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

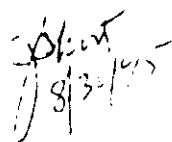
Sincerely yours,


Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-004/RJerussi
HFD-005/MJones
HFD-102/PVincent
HFD-510/CSO/J.R.Short
HFD-510/XYsern, YYChiu

drafted: JShort/8/24/95/N20496IR.5JS
r/d Initials: XYsern/8/24/95, YYChiu/8/25/95
final: henryt/8/29/95

INFORMATION REQUEST (IR)



NDA 20-496

JUL 19 1995

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

Dear Dr. Reit:

We acknowledge receipt on July 17, 1995 of your July 10, 1995 amendment to your new drug application for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is November 28, 1995.

In addition, we would like to obtain your agreement to conduct a Phase 4 study. We believe a Phase 4 study should be conducted to define better the safety of glimepiride therapy in the treatment of Type II Diabetes Mellitus under the conditions of medical care that are generally prevalent in the United States. Such a study would consist of a randomized, comparative, parallel, open-label, long-term (1 year) surveillance of serious adverse events. Eligible patients should be randomized to either glimepiride (or glimepiride + metformin) or usual care (insulin and/or metformin). The feasibility of such a study has been demonstrated in a publication by Lesko, SM et al., "An Assessment of the Safety of Pediatric Ibuprofen," JAMA (1995) 273:929-33.

We prefer that such a study be carried out under IND and that the study design be submitted to this Division for review and comments prior to implementation.

Please respond to this recommendation as soon as possible.

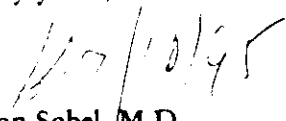
Also, please submit a new safety update to supplement the information included in your last safety update submitted on December 29, 1994.

*Correction letter
dated ~ 10/25/95.
changed date to
11/20/95*

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,



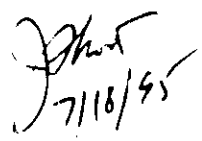
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-004/RJerussi
HFD-005/MJones
HFD-102/PVincent
HFD-244/AReb
HFD-427/TChen/JHunt
HFD-713/JChoudhury, ENevius
HFD-510/CSO/J.R.Short
HFD-510/JGueriguian, AFleming, XYsern, YYChiu, HRhee, AJordan,

drafted: JShort/7/11/95/N20496RV.4JS
r/d Initials: EGalliers 7/12, JGueriguian, AFleming 7/14/95
final: js/7/18/95

REVIEW EXTENSION/ADVICE/INFORMATION REQUEST Ltr



NDA 20-496

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

JUL 12 1995

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We also refer to your amendment dated June 20, 1995, providing for revisions in the package insert.

The June 20 version of the package insert was discussed at a meeting between HRPI representatives and FDA staff on June 23, 1995. We are in the process of reviewing your revisions and will communicate with you soon regarding our conclusions.

At this time we are commenting on the additional indication you included in the June 20 version of the package insert. In that submission you revised the fifth paragraph of the INDICATIONS AND USAGE Section to include Amaryl-metformin combination therapy (*italicized* portion) as follows:

During maintenance programs, AMARYL monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations. AMARYL may be used concomitantly with metformin in suitable patients when diet and AMARYL alone do not result in adequate glycemic control (see metformin Package Insert). Secondary failures to AMARYL monotherapy can be treated with AMARYL-insulin combination therapy.

From a regulatory perspective, adding the "metformin" combination therapy constitutes the addition of a new indication. FDA's policy is that an additional indication cannot be added to a pending NDA. If one chooses to add another indication for use of the drug while an NDA is pending, a separate NDA may be filed, or one may submit a supplement following approval of the NDA.

This policy was discussed at the June 23, 1995 meeting, and you agreed to delete this indication from the INDICATIONS AND USAGE Section of the package insert. We also discussed the possibility of the Division establishing a position whereby all sulfonylurea preparations could include a sulfonylurea/metformin combination indication, and if this should happen prior to

NDA 20-496

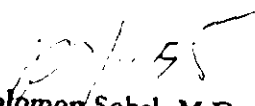
Page 2

an action on this NDA, the package insert could be revised accordingly. If not, a supplemental application could be submitted if/when the NDA is approved.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,


Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-510/CSO/J.R.Short
HFD-510/JGueriguian, AFleming, EGalliers

drafted: JShort/7/6/95/N20496AD.2JS
r/d Initials: JGueriguian 7/6, AFleming 7/10/95
final: js/7/11/95

ADVICE LETTER (AD)


7/11/95

NDA 20-496

JUL 12 1995

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We have completed our review of the biopharmaceutics section of your submission and have identified the following deficiencies:

1. The following comments/suggestions relate to the entire biopharmaceutics data submitted to date (with the exception of the May 19, 1995 submission which is addressed below):
 - a. We recommend that the following dissolution method and specification be used for Amaryl tablets:

900 ml of simulated intestinal fluid without enzymes (pH 7.50) at 37° C.
USP Apparatus II (paddle) at 50 rpm
 - b. No information on the use of glimepiride in patients with hepatic impairment was provided. Therefore, it is recommended that you:
 - (1) determine if any patients enrolled in any of the completed clinical safety and efficacy trials had liver function tests that were outside normal ranges, and
 - (2) determine whether these patients had any unexpected efficacy or adverse effect findings.

The package insert should be revised accordingly based on the results of the above data analyses. In addition, such data/information should be monitored if/when the product is approved and marketed.

*Not responded as of 8/3/95
Submission dated 8/2/95*

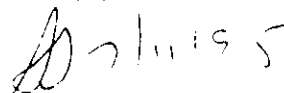
2. The following comments relate to your May 19, 1995 submission in which you provided results of the study entitled "Investigations on the Enzymes Responsible for the Main Metabolic Routes of Biodegradation of Glimepiride (HOE 490) in Man":
- a. Although a thorough study of the *in vitro* metabolism of glimepiride is included in this submission, ideally such studies should be included in the original NDA submission because they are essential to understand the pharmacokinetics and safety of a given xenobiotic and/or formulation.
 - b. In addition to the drugs listed in the penultimate paragraph on page 17 of this submission (phenytoin, diclofenac, ibuprofen, naproxen, mefenamic acid and S-warfarin), an interaction between glimepiride and ethinylestradiol (also metabolized by CYP2C9) should be tested.
 - c. It is apparent that 20-25% of the dose is unaccounted for by the formation of M I and M II. Metabolism of glimepiride by other CYP450 isozymes is the probable fate of this fraction of the dose. To completely characterize the metabolic pathways of this glimepiride, ideally these metabolites should be identified and quantitated.

Please respond to these biopharmaceutics concerns as soon as possible.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,



Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-427/TChen, GBarnette, JHunt
HFD-510/CSO/J.R.Short
HFD-510/JGueriguian, AFleming, XYsern, YYChiu

drafted: JShort/7/6/95/N20496IR.4JS

revised as per Biopharm comments - JShort 7/11/95

r/d Initials: GBarnette, JHunt for TChen, JHunt 7/7/95, XYsern, YYChiu 7/11/95

final: js/7/11/95

INFORMATION REQUEST (IR)

A handwritten signature in black ink, appearing to be 'J. Short', with the date '7/11/95' written below it.

MAY 31 1995

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

Responded 7/10/95

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We have completed our review of the environmental assessment section of your submission and have identified the following deficiencies:

1. General Issues:

As defined by CEQ in 40 CFR 1508.9, the EA is a public document. Please submit a nonconfidential version of the EA.

2. The following comments address Section 4:

- a. The identity and location of all facilities used for recycling and disposal of wastes must be provided, along with applicable permit numbers and expiration dates, if any.
- b. The EA should describe the method(s) of disposal of rejected, expired, returned, or waste drug substance and product along with applicable permit information.
- c. The EA should specifically describe the emission controls and their effectiveness with respect to the destruction of the packaging component.
- d. The EA should identify any proprietary starting materials and intermediates, and supply all required information for the production location of the proprietary compounds.

3. The following comment addresses Section 5:

The CAS numbers for the additives should be included in the body of the EA .

4. The following comments address Section 6:

- a. CAS numbers should be provided for all input chemicals when known. The production batch size of the drug substance and its intermediates and the process time required to manufacture a batch should be included in a confidential attachment.
- b. For air, liquids, and solids emissions from the production operations for this drug substance, the following should be provided:
 - i. Identification of the emission control;
 - ii. Applicable emission requirements (both qualitative and quantitative);
 - iii. An estimate, through the use of calculations and/or direct measure, of the possible quantities and concentrations of substances expected to enter the environment (fifth year production levels); and
 - iv. Effect of the quantities/concentrations (from 6.a.iii) on meeting both the qualitative and quantitative emission requirements.

The controls mentioned for wastewater for production of both drug substance and drug product include chemical and biological treatment prior to discharge into public waterways. However, testing showed no biodegradation of the drug substance. In addition, the drug substance showed a high affinity for most soils. No information is given that adequately addresses appropriate controls for water discharges, including sludges and sediments.

- c. No information is given for estimated expected emitted concentrations or quantities for the German drug substance plant.

Insufficient information is given to justify the statement that "no substances are expected to enter the environment because solid waste from [various activities] is incinerated." Information on standard disposal practices for unused and expired goods in controlled settings, such as hospitals, must be included.

5. The following comment applies to Section 7:

Because the drug substance is strongly sorbed by sludge and moderately sorbed by soils representing river sediment, the primary environmental process affecting the transport and fate of glimepiride is sorption. Test data included in the EA demonstrated that aerobic degradation only eliminated 0.3% of the drug substance in 28 days. The EA briefly discusses the possibility of biodegradation occurring in

NDA 20-496

sludges, but does not include any data demonstrating the validity of this possibility. The EA should include test data from soil biodegradation testing.

6. The following comment applies to Section 8:

Toxicity information is provided for test organisms for the aquatic compartment. For the terrestrial component, acute toxicity data are given for *Hyalella azteca*. However, since glimepiride undergoes extremely slow aerobic biodegradation, please justify a rationale why the appropriate test organisms for subacute toxicity in the terrestrial compartment (e.g., *Lumbricus terrestris*, *Lirubellus*, *E. foetida*, or other earthworms) should not be tested.

Please respond to these EA concerns as soon as possible.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

JS
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-004/RJerussi
HFD-005/MJones
HFD-102/PVincent
HFD-510/CSO/J.R.Short
HFD-510/XYsern/YChiu

drafted: JShort/5.29.95/N20496IR.3JS
r/d Initials: XYsern, HDavies for YYChiu 5/31/95
final: js/5/31/95

INFORMATION REQUEST (IR)

JS
5/31/95

NDA 20-496

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
SOMERVILLE NJ 08876-1258

MAY 17 1995

Dear Dr. Reit:

Please refer to your pending August 31, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets.

We have completed our review of the pharmacology and chemistry sections of your submission and have the following comment and requested revisions:

Chemistry

Drug Substance Synthesis

We found your designation of glimepiride as the "starting material" unacceptable because it is not a widely commercially-available compound. Glimepiride- is an intermediate compound with specifications listed in Volume 1.3, pages 66 and 67 of the application. The starting materials are:

considered part of the synthesis of the active drug.

Drug Product

Please provide the corrected version of the description of the dissolution specification.

Labeling

The dosage form should immediately follow the established name in all labeling, i.e., glimepiride tablets, instead of only glimepiride.

Pharmacology

Although package insert (PI) comments will be communicated to you in their entirety following our internal labeling meeting scheduled for June 6, 1995, we offer the following comment regarding the "Pregnancy" subsection of the PRECAUTIONS Section to give you advanced notice regarding the revision:

*Included in PI submission
6/20/95*

Responded 6/26/95

*Submitted 5/10/95 but
also addressed in 6/20/95 amendment*

Responded 7/12/95

Drug exposure comparisons between preclinical and clinical doses should be based on plasma concentration rather than on mg/kg. If plasma concentrations of the drug are not known, exposure comparison should be based on surface area (mg/m².)

Please do NOT submit a revised PI with these corrections until you receive our comments on the entire PI.

But, a revised label for each strength tablet and package size, according to the above chemistry comment, should be submitted prior to June 30, 1995.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

J. Tremblay 5-16-95
for

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-496
HFD-510/Div. Files
DISTRICT OFFICE
HFD-510/CSO/JShort
HFD-510/HRhee/AJordan/XYsern/YChiu

drafted: JShort/5.10.95/N20496IR.2JS
final: LStockbridge/5.15.95/N20496IR.2JS

Concurrences: XYsern 5.10/YChiu/HRhee/AJordan 5.11.95

INFORMATION REQUEST (IR)

NDA 20-496

OCT -6 1994

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
Somerville, NJ 08876-1258

Dear Dr. Reit:

Reference is made to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) Tablets.

We have completed our initial screening of the Human Pharmacokinetics and Bioavailability section (Item 6) of your application and have the following comment (which was already conveyed to Dr. Jim DeMartino of your staff by Dr. Albert Chen of our Biopharmaceutics staff):

Please submit in vitro dissolution profiles for the three tablet strengths (each strength should employ 12 tablet units and should cover the proposed bulk drug surface area of 5 to 8 m²/g) in simulated gastric fluid and simulated intestinal fluid, as well as in the proposed dissolution media, using 75 rpm and 50 rpm.

This information should be submitted as soon as possible so that the Biopharmaceutics review will not be delayed.

Should you have any questions in regard to these requests, please contact Mr. John Short at 301-443-3510.

Sincerely yours,

S. Trussell 10-4-94
for

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch.
HFD-510
HFD-426/ACHen, JHunt
HFD-511/JShort 9/27/94/ft/lp/9/30/94/N2049cIR.JRS
Concurrence: AChen, JHunt 8/27/94

INFORMATION REQUEST

J. Short
10/5/94

NDA 20-496

SEP - 1 1994

Hoechst-Roussel Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Director, Drug Regulatory Affairs
Route 202-206 North
Somerville, NJ 08876-1258

Dear Dr. Reit:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Amaryl (glimepiride) 1, 2, and 4 mg Tablets
Therapeutic Classification: S
Date of Application: August 31, 1994
Date of Receipt: August 30, 1994
Reference Number: NDA 20-496

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on **October 29, 1994**, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an *informal conference* with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Mr. John R. Short
Consumer Safety Officer
(301) 443-3510

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

LLP

F03

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

9/1/94

cc: Orig. NDA
HFD-510
DISTRICT OFFICE
HFD-510/JShort 9/1/94 \N20496AC.JRS

ACKNOWLEDGEMENT - AC

JShort
9/1/94

August 29, 1995

NDA 20-496
Amaryl (glimepiride) Tablets
Hoechst-Roussel Pharmaceuticals Inc. (HRPI)

MEMORANDUM OF TELECONFERENCE

HRPI Representatives:

Carla Canabarro, M.D., Assistant Director, Safety, Surveillance, and Epidemiology
Philip Chaikin, M.D., Pharm.D., Vice President, Clinical Development
Charlene Danca-Eastwood, Brand Team Manager for Amaryl, Metabolism
James DeMartino, Ph.D., Assistant Director, Drug Regulatory Affairs
Won-Chin Huang, Ph.D., Assistant Director, Biostatistics
Barry Reit, Ph.D., Senior Director, Drug Regulatory Affairs
Jill Schneider, M.D., Director, Metabolism
Hillary Stanbrook, Ph.D., Associate Director, Clinical Development
Joyce Zimmerman, Ed.D., Associate Director, Biostatistics

FDA Staff:

Dr. Sobel
Dr. Fleming
Dr. Gueriguian
Dr. Stadel
Mr. Short (CSO)
Dr. Nevius (HFD-713)

Purpose: The meeting was requested by HRPI to discuss the protocol design and other aspects of the Phase 4 study requested in our letter dated July 19, 1995.

Discussion and Conclusions: Dr. Stadel was requested to provide the FDA objectives of this Phase 4 study. Dr. Stadel noted that the idea originated from the E&M Advisory Committee meeting on metformin. He said we would just like to take this opportunity with a new sulfonylurea to obtain basic data from a large-scale (~10,000 patients), simple-outcome (mortality, major morbidity, cancer incidence, etc.) trial of about 2 years duration.

Dr. Chaikin asked if there was any specific signal which triggered this request, e.g., was there a safety problem with Amaryl. Drs. Stadel and Gueriguian both indicated that there was nothing other than a general intent which triggered the request for this Phase 4 study. Dr. Gueriguian further indicated that this would be standard operating procedure for the approval of each new oral anti-diabetic compound approval in the future. He said this would be the best opportunity to test in the real clinical setting the advantages and disadvantages of the drug. Dr. Gueriguian suggested that the

NDA 20496

6 OF 6

study only be about 1 year in length; Dr. Fleming said that he favored a study longer than 1 year.

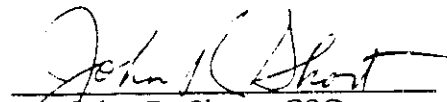
Dr. Schneider asked if HRPI was being required to do this type of study. FDA staff indicated that these were only suggestions, but we really would like the study performed. Dr. Fleming noted that HRPI should look at the potential outcome advantages of this study, indicating that this would be the perfect opportunity to demonstrate in a real clinical practice setting the beneficial effects of the drug, other than its effect on a surrogate endpoint (HbA_{1c}).

HRPI representatives noted that they had planned a short Phase 4 study, but would consider our proposal and try to come up a revised protocol. Dr. Gueriguian requested that this protocol be submitted (to the IND, as per our July 19, 1995 letter) for our consideration as soon as possible. HRPI representatives said they would first communicate informally with the FDA reviewers and then submit a protocol to the IND. Dr. Stadel stated that the Division would arrange for peer review of the protocol, and would provide the reviewer's comments to HRPI.

ACTION ITEMS:

HRPI to submit a draft Phase 4 protocol to their IND as soon as possible.

submitted 10/20/95



John R. Short, CSO

cc: NDA Arch

HFD-510

attendees

HFD-510/GTroendle, EGalliers, YJohnson

HFD-713/JChoudhury

HFD-511/JShort 8/31/95/ft/js/9/11/95 \N20496MT.JRS

Concurrence: BStadel 8/31, JGueriguian 9/4, AFleming 9/5, SSobel 9/7/95

June 23, 1995

NDA 20-496
Amaryl (glimepiride) Tablets
Hoechst-Roussel Pharmaceuticals Inc. (HRPI)

MEMORANDUM OF MEETING

HRPI Representatives:

Philip Chaikin, M.D., Pharm.D., Vice President, Clinical Development
Paul Delisle, Business Director, Metabolism
Eberhard Draeger, Ph.D., Director, Clinical Research/Metabolism -- HAG
James DeMartino, Ph.D., Assistant Director, Drug Regulatory Affairs
Tim Gau, M.D., Vice President, Clinical Research & New Drug Development
Won-Chin Huang, Ph.D., Senior Biostatistician
Barry Reit, Ph.D., Senior Director, Drug Regulatory Affairs
Jill Schneider, M.D., Director, Metabolism
Umesh Shukla, Ph.D., Associate Director, Clinical Pharmacology
Joyce Zimmerman, Ed.D., Associate Director, Biostatistics

FDA Staff:

Dr. Troendle
Dr. Fleming
Dr. HRhee
Mr. Short (CSO)
Ms. Reb (HFD-244)
Dr. TChen (HFD-427)
Dr. Choudhury (HFD-713)

Purpose: The meeting was requested by FDA to go over revisions in the package insert, which was FAX'd to HRPI on June 8, 1995, and resulted in a subsequent amendment to the NDA by HRPI dated June 20, 1995. The latter document is the one reviewed during the meeting.

Discussion and Conclusions: Dr. Reit began the meeting by describing the agenda and indicating that Drs. Chaikin and Schneider would give a 30-minute presentation to set the stage for discussion of the primary package insert (PI) agenda items.

Mr. Short said that the inclusion of the indication for the combination therapy of glimepiride and metformin could not be allowed because no additional indications can be added to an NDA original submission while it is pending. Dr. Fleming clarified this somewhat by stating that some reference to the combined use of glimepiride and metformin may be allowed in the CLINICAL PHARMACOLOGY Section but not in the INDICATIONS AND USAGE Section of the package insert. Mr. Short also

mentioned that the Division is generating a position whereby all sulfonylureas may be able to include a sulfonylurea/metformin combination indication, and if this happens prior to an action on this application, the PI could be revised accordingly.

Extraprocreatic Effects and Comparative Glycemic Control

Dr. Chaikin presented information about the extrapancreatic effects of glimepiride and comparative hypoglycemic episodes in support of changes made in the CLINICAL PHARMACOLOGY Section of the PI. (See attachments for details.)

Regarding the extrapancreatic effects (CLINICAL PHARMACOLOGY Section, Mechanism of Action subsection, p. A.1, lines 21-22 and p. A.2, lines 1-8), Dr. Fleming noted that he is still not convinced that there is a clear extrapancreatic effect. He believes that the evidence for a significant extrapancreatic effect is unconvincing and that providing the proposed information in the PI may give clinicians a false hope that the drug will have more beneficial effect than would appear to be the case. Dr. Fleming said that he and Dr. Gueriguian would look at the proposed revision in the coming weeks and reach a consensus opinion.

Regarding the proposed changes of comparative clinical data (vs. glyburide and glipizide) in effects on glycemic control (CLINICAL PHARMACOLOGY Section, Pharmacodynamics subsection, p. A.3, lines 12-21), Dr. Fleming said that based on the data presented, he would react favorably. But, he said he and Dr. Gueriguian would need to review the data in detail to come to a final decision.

Combination Therapy of Glimepiride w/Insulin

Dr. Schneider presented information supporting HRPI's proposed indication (INDICATIONS AND USAGE Section, p. A.10, lines 9-11) for the use of glimepiride in combination with insulin. It primarily consisted of data generated from Study 8/USA/305. (See attachments for details.)

Dr. Fleming noted that he was personally persuaded by the additional data presented that the combination therapy does not result in a significant increase in hypoglycemic events, but that the data will need further evaluation by him and Dr. Gueriguian.

General Comments

Only these major areas of concern were discussed even though HRPI considerably revised the PI that was FAX'd to them on June 8, 1995. HRPI was informed that we would review the June 20 submission of the PI in detail and get back to them with our comments.

ACTION ITEMS:

FDA staff to review the PI as submitted June 20, 1995, and get back to HRPI with comments.

9/29/95
js



John R. Short, CSO

Attachments

Overheads Used During the Presentation

[POST-MEETING NOTE: HRPI representatives talked to Dr. Chen immediately following the meeting and agreed that the third sentence of the "General" subsection of the PRECAUTIONS Section (p. A.13, lines 4-6) would be revised as follows: "Renal insufficiency may cause elevated blood levels of glimepiride metabolites."]

cc: NDA Arch

HFD-510

attendees

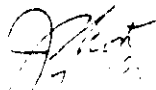
HFD-427/JHunt

HFD-510/SSobel, JGueriguian, YYChiu, XYserr, AJordan, EGalliers, YJohnson

HFD-713/ENevius

HFD-511/JShort 6/27/95/ft/js/7/11/95 \N20496MM.3JS

Concurrence: HRhee 6/28, AReb, GTroendle 7/6, AFleming 7/10/95



NDA 20-496
Amaryl (glimepiride) Tablets 1, 2, and 4 mg
Hoechst-Roussel Pharmaceuticals, Inc. (HRPI)

February 28, 1995

MEMORANDUM OF STATUS MEETING #1

FDA Staff:

Dr. Fleming
Dr. Gueriguian
Dr. Ysern
Mr. Short (CSO)
Dr. TChen (HFD-427)
Dr. Nevius (HFD-713)
Dr. Choudhury (HFD-713)

Purpose: Internal meeting to discuss the progress of each discipline's review and projected completion dates.

Discussion and Conclusions:

Medical: Review should be completed by May 30, 1995. Reminded Dr. Gueriguian that he must also review the amendment dated January 10, 1995, which provided data for a revision of the package insert.

Pharmacology: Review complete but not yet signed by Dr. Jordan.

Chemistry: Review should be completed by April 30, 1995.

Environmental Assessment: No one attended the meeting but Mr. Jones informed me by E-Mail that the review should be completed by March 10, 1995 (outside review). Probably will require at least 1 month to obtain supervisory signature.

Biopharmaceutics: Just started. Review should be completed by June 30, 1995. Dr. Chen noted that the PK data for the secondary indication "NIDDM Failures/Combination with Insulin" were not provided, but Dr. Fleming indicated that such PK data would not be necessary for the second indication.

Statistics: Review to be completed by May 30, 1995. Considerable discussion ensued between the statistical and medical reviews. One thought conveyed was that the primary efficacy endpoint should be whether the drug demonstrates a 1.5 point difference in HbA_{1c} between the drug effect and the placebo effect (not between the drug effect and baseline).

DSI: Dr. Turner did not attend the meeting but later he said he would try his best to have the DSI investigations completed by July 30, 1995. I impressed upon him that we needed the investigations completed by June 30, 1995.

It was agreed that we would have another status meeting approximately 4/30/95.

ACTION ITEMS:

1. Everyone to complete their reviews.
2. Mr. Short to set up next status meeting ~4/30/95.

never held

NOT needed



 John R. Short, CSO

cc: NDA Arch
 HFD-510
 attendees
 HFD-005/MJones
 HFD-102/PVincent
 HFD-427/JHunt
 HFD-344/GTurner
 HFD-510/SSobel, GTroendle, YYChiu, HRhee, AJordan, EGalliers, YJohnson
 HFD-511/JShort 2/28/95/ft/js/4/21/95 \N20496MM.2JS
 Concurrence: JGueriguian 3/17, AFleming 3/20, XYsern 3/21, AChen 3/22,
 Choudhoury 3/24, ENevius 3/30/95

NDA 20-496
Amaryl (glimepiride) Tablets 1, 2, and 4 mg
Hoechst-Roussel Pharmaceuticals, Inc. (HRPI)

September 26, 1994

MEMORANDUM OF 45-DAY MEETING

FDA Staff:

Dr. Sobel
Dr. Fleming
Dr. Jordan
Dr. HRhee
Dr. Chiu
Dr. Ysern
Mr. Short (CSO)
Dr. Spires (CSO)
Dr. Turner (HFD-344)
Dr. TChen (HFD-426)
Mr. Marticello (HFD-713)

Purpose: 45-day meeting to determine if we can file the NDA and to set projected completion dates (PCD) for each discipline's review.

Discussion and Conclusions:

Medical: OK to file. PCD = Mid-January 1995. It was also discussed whether or not an advisory committee was necessary to discuss this NME. It was agreed that because it is just another sulfonylurea, it would not be necessary to hold a meeting unless a unique issue is identified.

Pharmacology: OK to file. PCD = March 31, 1995.

Chemistry: OK to file. PCD = March 31, 1995. The only issue here was that all the information for the drug substance is included in a Drug Master File (DMF), but the chemist would prefer that this information actually be included in the NDA. This is not sufficient reason to refuse to file the application. The chemist will notify the sponsor about including the DMF information in the NDA.

Environmental Assessment: Dr. Vincent did not attend the meeting. It was later learned that HFD-102 never received a copy of the EA to review. Mr. Short had delivered the chemist review copy on September 27, 1994. Ms. Good indicated that the application was OK to file but a projected completion date could not be established because a reviewer had

not been assigned. Mr. Mike Jones indicated that they will try to meet the 3/31/95 date which I requested on the consult.

Biopharmaceutics: OK to file. PCD = March 31, 1995. It was noted that the quality control specification for the specific surface area (SSA) of the drug substance is 5-8 m²/g. Because this would allow the SSA of a particular batch of tablets to be as low as 5 m²/g and as high at 8 m²/g, Dr. Chen requested HRPI to submit in vitro dissolution profiles of the three tablet strengths (employing tablets covering the range of SSAs of 5 to 8 m²/g) in simulated gastric fluid and in simulated intestinal fluid, as well as in the proposed dissolution media, using 75 rpm and 50 rpm. Mr. Short will follow up the oral request with a written request.

Statistics: OK to file. PCD = March 31, 1995.

Project Management: OK to file.

DSI: Because there is not a great disparity in the number of patients treat at various centers of the four pivotal studies, Dr. Turner wanted to know from statistics if the results are being driven by a few of the centers in the multicenter studies. This would help him decide which sites to investigate.

Advisory Committee: As indicated above (under Medical), none will be necessary unless a unique issue is identified.

This drug is rated 1S.

CONCLUSION: The application will be filed on October 29, 1994.

ACTION ITEMS:

1. Statistics to provide information to Dr. Turner as to whether the clinical results are being driven by a few of the centers in the multicenter studies.
2. Mr. Short to communicate Biopharm concerns to applicant.

*1. discuss with
long after meeting*


John R. Short, CSO

cc: NDA Arch

HFD-510

attendees

HFD-005/MJones

HFD-102/PVincent, CGood,

HFD-426/JHunt

HFD-713/ENevius

HFD-510/JGueriguan, GTroendle, EGalliers, DJenkins

HFD-511/JShort 9/28/94/ft/lp/10/31/94/N20496MM.JRS

Concurrence: Fleming, HRhee, Jordan, Ysern, Chiu 9/29/Chen, Marticello, Sobe!

10/30/94

JHunt
10/31/94

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number (908) 231-2385
Fax: (908) 231-3879

October 20, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: **Amaryl[®]** (glimepiride tablets), IND 31,759
General Correspondence - Serial No. "161"
Amaryl[®] (glimepiride tablets), NDA 20-496

Dear Dr. Sobel:

Please refer to our New Drug Application for Amaryl[®] 1, 2, and 4 mg tablets pending in your Division. Also refer to your letter dated July 19, 1995 requesting our agreement to conduct a Phase 4 study to better define the safety of Amaryl[®] therapy in the treatment of Type II diabetes under conditions of usual medical care in the United States. In a letter dated August 9, 1995, we agreed in principle to conduct such a study and to submit a draft protocol, as you requested, to the Amaryl[®] IND.

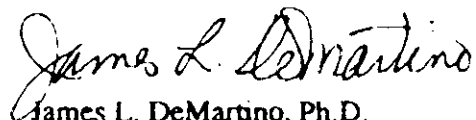
We are proposing a 1-year study to collect safety information on serious and non-serious adverse events. As stated in the protocol, the sample size of 1800 patients is adequate to detect a 4% difference in the incidence of serious adverse events, assuming a baseline incidence of 10%, and a 3% difference in the incidence of hypoglycemia assuming a baseline incidence of 5%.

We herewith submit to the above mentioned IND a protocol entitled "An Open Label, Randomized, Controlled Evaluation of the Safety of Amaryl[®] vs. Glyburide in the Real World Clinical Practice Environment". Before implementing this protocol, we welcome the opportunity to discuss your comments on the design of the study.

Three copies of this Phase 4 protocol are being submitted to the IND and copies of the cover letter are herewith submitted to the NDA cross referencing the IND.

If you have any questions regarding this material, please contact me at the above number.

Sincerely yours,



James L. DeMartino, Ph.D.
Assistant Director
Drug Regulatory Affairs

Attachment
JLD/dmc

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-208 P.O. Box 2500 Somerville, NJ 08876-1258
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Telephone (908) 231-2000



Direct Dial Number (908) 231-2385
Fax: (908) 231-3879

October 16, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD 510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
Amendment to Pending Application: Draft Labeling

Dear Dr. Sobel,

Please refer to the New Drug Application 20-496 (Amaryl 1, 2 and 4 mg tablets) submitted August 31, 1994. Also, refer to the revised labeling (package insert) submitted for review on October 6 and a page replacement submitted October 9, 1995.

We herewith submit newly revised labeling, which now provides for a change in the HOW SUPPLIED section of the labeling. The description of the tablets is revised to be consistent with the wording specified in Item 3 (Chemistry, Manufacturing and Controls) of the original NDA.

In addition to the current revision, those submitted on October 6 and 9 are again presented to consolidate the most recent changes into one submission. The revisions including those submitted on October 6 and 9 are itemized below. Page and line numbers refer to this latest edition of the labeling:

Page A.1 Line 5

Replaced the word "It" with "Glimepiride" per your request in your letter dated September 13, 1995.

Page A.2 Lines 9-15

Deleted as per 9/29 recommendation (Item 1)

Page A.3 Lines 12-21

Deleted as per 9/29 recommendation (Item 2)

Page A.4 Lines 1-5 (Item 3 of 9/29 recommendation)

Deletion of this paragraph was suggested. However, at our 10/6 teleconference, it was agreed that this paragraph would remain.

Page A.5 Line 9

Reference to glimepiride metabolite 2 (M2) has been deleted as per discussion on June 23.

Pages A.10 Lines 11 and 12, A.13 Lines 23 and 24

Sentence added as agreed at our 10/6 teleconference. (Items 4 and 6 of 9/29 recommendation)

Pages A.11 Lines 1-3, A.13 Lines 19-22, and A.14 Lines 7-9, and A.21 Lines 11-20

All references to metformin deleted per 9/29 recommendation. (Item 5)

Page A. 13 Lines 22-23

Revised sentence on combination therapy required as a result of the deletion of reference to metformin.

Page A. 13 Lines 4-6

Sentence deleted per discussion on June 23

Page A.16

Sentence added (Lines 18 and 19) to replace deleted lines A.16 Line 20 through A.17 Line 9 as agreed to at our 10/6 teleconference. (Item 7 of 9/29 recommendation)

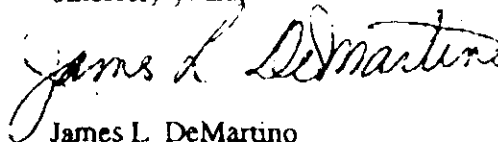
Page A.22 Lines 17-19, 23-25, and 29-31

Under HOW SUPPLIED, description of tablets changed to be consistent with the wording in the test specifications in the NDA (Original NDA Vol. 1.6 pages 216, 230, 234)

The latest edition of the labeling with revisions shown as well as the copy with revisions implemented are provided.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,



James L. DeMartino
Assistant Director
Drug Regulatory Affairs

Attachment
JLD:dmc

Hoechst-Roussel Pharmaceuticals Inc.

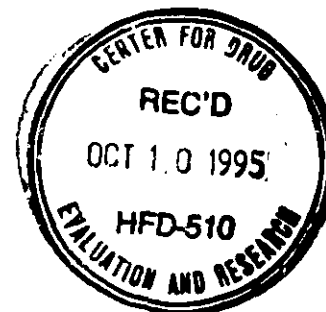
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Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

October 9, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
Amendment: Revision to labeling per September 13, 1995 FDA Letter - Page
Replacement to October 6, 1995 amendment (Revised Labeling)

Dear Dr. Sobel,

Please refer to our New Drug Application for Amaryl (glimepiride) 1, 2, and 4 mg tablets submitted on August 31, 1994. Also refer to our amendment submitted October 6, 1995, providing for revisions to the labeling (package insert).

We herewith submit an additional revision to the labeling in response to your letter dated September 13, 1995 in which a comment was conveyed concerning the package insert that was submitted on June 20, 1995. This change is being submitted as a page replacement to the October 6 amendment.

The second sentence of the DESCRIPTION section, refers to the active drug substance not the drug product. Therefore, to refer specifically to the drug substance, the sentence has been changed from "It is a white to yellowish-white. . ." to "Glimepiride is a white to yellowish-white. . ."

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph.D. D.
Senior Director
Drug Regulatory Affairs

Desk Copy: Dr. A. Fleming
Attachment
JLD:dmc

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Hoechst 

CSIG APPROVED

ORIGINAL

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

October 6, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
General Correspondence: Draft Labeling

Dear Dr. Sobel,

Please refer to the New Drug Application 20-496 (Amaryl tablets) submitted August 31, 1994. Also, refer to the revised labeling (package insert) submitted for review on June 20, 1995.

Recommendations to the June 20 proposed labeling were received on September 29, 1995. Subsequently, a teleconference was held with Dr. Alexander Fleming on October 6, 1995 to address his recommendations.

We herewith submit newly revised labeling, which incorporates the changes agreed to as a result of our teleconference. In addition, minor revisions discussed with Mr. John Short and Dr. Albert Chen at our June 23 meeting are included in this current version of the labeling. The revisions are itemized below. Page and line numbers refer to the latest edition of the labeling:

Page A.2 Lines 9-15

Deleted as per 9/29 recommendation (Item 1)

Page A.3 Lines 12-21

Deleted as per 9/29 recommendation (Item 2)

Page A.4 Lines 1-5 (Item 3 of 9/29 recommendation)

Deletion of this paragraph was suggested. However, at our 10/6 teleconference, it was agreed that this paragraph would remain.

Page A.5 Line 9

Reference to glimepiride metabolite 2 (M2) has been deleted as per discussion on June 23.

Pages A.10 Lines 11 and 12, A.13 Lines 23 and 24

Sentence added as agreed at our 10/6 teleconference. (Items 4 and 6 of 9/29 recommendation)

Pages A.11 Lines 1-3, A.13 Lines 19-22, and A.14 Lines 7-9, and A.21 Lines 11-20

All references to metformin deleted per 9/29 recommendation. (Item 5)

Page A. 13 Lines 22-23

Revised sentence on combination therapy required as a result of the deletion of reference to metformin.

Page A. 13 Lines 4-6

Sentence deleted per discussion on June 23

Page A.16

Sentence added (Lines 18 and 19) to replace deleted lines A.16 Line 20 through A.17 Line 9 as agreed to at our 10/6 teleconference. (Item 7 of 9/29 recommendation)

To assist in your review of these changes, we are providing the June 20 edition of the labeling. Your list of recommendations, also provided, cite the June 20 labeling.

The latest edition of the labeling with revisions shown as well as the latest edition with revisions implemented are provided.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Koussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,



Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Desk Copy: Dr. A. Fleming
Attachment
JLD:dmc

REVIEWS COMPLETED

CSO ACTION:

LETTER

N.A.I.

CSO INITIALS

DATE

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
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Direct Dial Number: (908) 231-2107
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October 5, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
General Correspondence: Reply to September 29, 1995 FDA Letter

Dear Dr. Sobel,

Please refer to our pending August 31, 1994 new drug application for Amaryl (glimepiride) 1, 2, and 4 mg Tablets and to your letter dated September 29, 1995 concerning the completion of your review of the August 28, 1995 amendment addressing biopharmaceutics issues.

At your request, we herewith provide a response to Items 1 and 2 of the September 29 letter.

- 1) The report for Study No. HOE490/1/YU/201/LI entitled "Safety, Pharmacokinetic and Feasibility Efficacy Study of Multiple Doses of Glimepiride (HOE 490) in Type II Diabetic Patients with Liver Impairment" will be available in the fourth quarter of 1996. When the report is available, it will be submitted to the NDA for review.
- 2) Your recommendation for in vitro inhibition studies with various concentrations of phenytoin, diclofenac, ibuprofen, naproxen, mefenamic acid and S-warfarin can be completed with final reports in about 6 months. When these reports are available, they will be submitted to the NDA for review.

If you have any questions regarding this material, please contact Dr. James DeMartino at
Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs. (908) 231-2385.

Sincerely yours,



Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Des: Copy: Dr. A. Fleming
Attachment
JLD:dmc

Hoechst-Roussel Pharmaceuticals Inc.

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Direct Dial Number: (908) 231-2107
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September 25, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
General Correspondence: Response to FDA Letter dated August 30, 1995 and September 13, 1995.

Dear Dr. Sobel,

Please refer to the pending New Drug Application for Amaryl* (glimepiride) tablets submitted August 31, 1994. Refer also to the submission dated September 13, 1995, in response to the August 30, 1995 FDA letter requesting a revised version of the Non-Confidential Environmental Assessment (EA) Report.

We herewith submit a single page replacement (page 36) to the September 13 submission in which the text is modified to be in agreement with revisions that were previously made to Items 6 and 7.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Fax copy to N. Sager
Attachment
JLD:dmc

*Send for
consult to
M. Jones #
X. Lee
4-OCT-95*

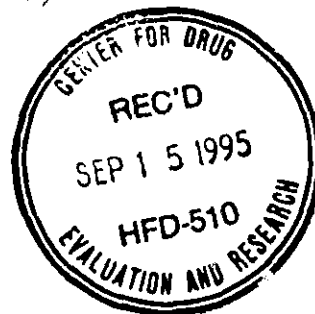
Hoechst-Roussel Pharmaceuticals Inc.



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Telephone (908) 231-2000

Direct Dial No.: (908) 231-2385
Fax No.: (908) 231-3879

*Included
in Chem Rev #3*



13 September 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Attn: Dr. S. Sobel, Director
Division of Metabolism and Endocrine Drug Products
HFD-510

Re: AMARYL® (glimepiride; HOE 490) Tablets: NDA 20-496
General Correspondence:
Reply to FDA Letters of August 30, 1995 and September 13, 1995

Dear Dr. Sobel:

Hoechst-Roussel Pharmaceuticals Inc. (HRPI) refers to the pending New Drug Application for AMARYL (glimepiride) Tablets (NDA 20-496), submitted August 31, 1994. We also acknowledge receipt of FDA's letter of August 30, 1995 (environmental assessment) and letter of September 13, 1995 (synthesis starting materials). A response to both of these FDA letters is provided as attachments to this letter, as follows:

FDA Letter of August 30, 1995:

A response to this letter is provided under Tab 1; a copy of the original FDA letter immediately follows the response for convenience in review. Under Tab 2 (Appendix I), a revised version of the Non-Confidential Environmental Assessment (EA) Report is submitted. Under Tab 3 (Appendix II), information is provided on the estimated quantity of residual glimepiride expected on farmland from use of sludge as an organic fertilizer.

AMARYL® (glimpiride; HOE 490) Tablets: NDA 20-496
Reply to FDA Letters of August 30, 1995 and September 13, 1995
Page 2 of 2

FDA Letter of September 13, 1995:

A response to this letter, including corresponding attachments, is provided under Tab 4.

If you have any questions regarding this submission, please do not hesitate to contact Dr. James DeMartino at HRPI, Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

H. Notisak for B. Reit

Barry Reit, PhD
Senior Director
Drug Regulatory Affairs

Distribution:

Desk Copy (express-mail) to Mr. John Short
FDA Consumer Safety Officer,
Division of Metabolism and Endocrine Drug Products

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus., Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number (908) 231-2107
Fax: (908) 231-3879

September 11, 1995

Department of Health and Human Services
Public Health Service
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Handwritten note:
10/11/95



ATTN: Central Document Room, RM 214
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: New Drug Application Amaryl® (glimepiride) Tablets, NDA 20-496
Safety Update 9/95**

Dear Gentlemen:

In response to a request from the Division of Metabolism and Endocrine Drug Products, in a letter dated July 12 we herewith submit a Safety Update for the New Drug Application for Amaryl® (glimepiride) tablets indicated for the treatment of patients with noninsulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet alone. The original NDA was submitted on August 31, 1994 and a 4-month Safety Update was submitted on December 29, 1994.

This submission consists of new safety data on one death, discontinuations for safety reasons, and other serious AEs. CRFs for the 22 cases presented are included.

This report supplements the last safety update with data from patients who completed between the last cut-off date (September 1, 1994) and July 1, 1995.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc. Drug Regulatory Affairs, (908) 231-2385.

REVIEWS COMPLETED

CSO ACTION
 LETTER N.A.I.

Sincerely yours,

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Attachment
JL CSO INITIALS DATE

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
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Direct Dial Number (908) 231-2107
Fax: (908) 231-3879

August 28, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: **Amaryl™ (glimepiride tablets), NDA 20-496**
General Correspondence: Response to FDA Letter dated July 12, 1995
- Biopharmaceutics Review Comments

Dear Dr. Sobel,

Please refer to your letter dated July 12, 1995 in which you conveyed comments and suggestions related to the entire biopharmaceutics data and our submission dated May 19, 1995, which included the results of the study entitled "Investigations on the Enzymes Responsible for the Main Metabolic Routes of Biodegradation of Glimepiride (HOE 490) in Man".

We herewith provide the following in response to the similarly numbered items in your July 12 letter:

1a. Discussion of Biopharmaceutical Concepts Used to Define the In Vitro Dissolution Testing Conditions and Specifications.

Text, table, and figures are attached that present our rationale why the specification and method defined in NDA 20-496 should not be altered.

1b. Use of Glimepiride in Patients With Hepatic Impairment

We are providing copies of information that appeared in Item 8 - Clinical Data of the original NDA. Safety and efficacy data of glimepiride in patients with hepatic abnormalities are summarized.

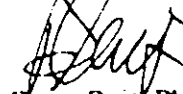
In addition, a safety, pharmacokinetic, and efficacy study in NIDDM patients is ongoing in Europe. The summary of that protocol is attached.

2. Enzymes Responsible for the Biodegradation of Glimepiride

- a) We recognize FDA's request that in vitro metabolism studies be included as part of future original NDA submissions.
- b) A study has been planned that will examine the interaction between glimepiride and ethinylestradiol.
- c) Further information is provided to explain the investigations and results of the identification and quantification of metabolites of glimepiride.

If you have any questions regarding this material, please contact Dr. James DeMarino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,



Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Desk Copy: Dr. Albert Chen (Reviewing Biopharmacist)
Dr. Xavier Ysem (Reviewing Chemist)
Attachment
JLD:dmc

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



ORIGINAL

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

August 16, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



Handwritten notes:
100
Sobel
9/8/95

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: **Amaryl™ (glimepiride tablets), NDA 20-496**
General Correspondence: Protocol 8/USA/305/DM - CRFs of Patients with Hypoglycemia

Dear Dr. Sobel,

At the request of Dr. Alexander Fleming of your division, we herewith submit CRFs for 64 patients (37 glimepiride, 27 placebo) in Protocol 8/USA/305/DM. These CRFs are the records of patients with hypoglycemia listed as an adverse event.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

REVIEWS COMPLETED

CSO ACTION:
 LETTER N.A.I.

Sincerely yours,

Handwritten signature: J. DeMartino
James DeMartino, Ph. D.
Director
Drug Regulatory Affairs

Desk copy: Dr. Alexander Fleming
Attachment
JLD:dmc

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
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Direct Dial Number: (908) 231-2107
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August 15, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
General Correspondence: Protocol 305 - Patients with the Adverse Event
Symptomatic Hypoglycemia

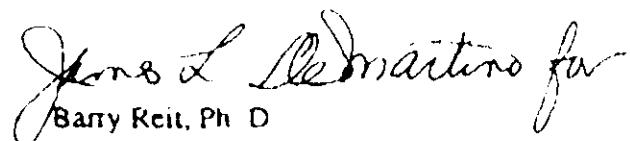
Dear Dr. Sobel:

Enclosed herewith is a table that lists all patients in Protocol 305 with symptomatic hypoglycemia reported as an adverse event. This table also lists glucometer readings collected by the patients.

This table is presented to aid in the evaluation of symptomatic hypoglycemia and concurrent blood glucose values in patients using combination therapy, Amaryl plus insulin.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph.D.
Senior Director
Drug Regulatory Affairs

Desk Copy sent directly to Dr. A. Fleming
Attachment

Orig Amend

Hoechst-Roussel Pharmaceuticals Inc.



Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-443 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

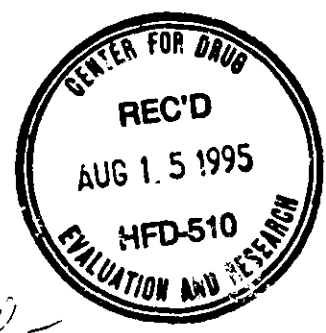
Bm

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

August 10, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

*Free:
these are
records that
you have
requested -
JLW*



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

8/16/95

Re: **Amaryl™ (glimepiride tablets), NDA 20-496**
General Correspondence: Glucose Meter Data Listing

*Under review
using desk copy
JLW
8/21/95*

Dear Dr. Sobel:

At the request of Dr. Fleming, we herewith submit subject listings of home glucose meter readings for all patients in Protocol 305. These data listings were not previously included in the original NDA.

Dr. Fleming also requested copies of data that were in the appendices to the clinical/statistical report for Protocol 305. We also submit, Appendix I.B.17 which includes the glucose meter values that were used for the determination of insulin dose adjustment and Appendix I.B.20 which lists the fasting plasma glucose values for all patients.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James L. DeMartino for
Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

*Noted
JMR
8/21/95*

Desk Copy: Dr. A. Fleming
Attachment

Hoechst-Roussel Pharmaceuticals Inc.

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Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



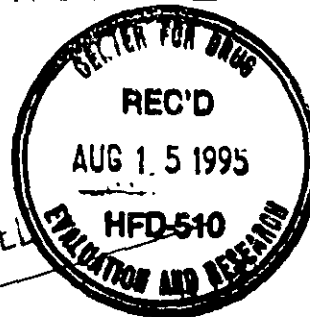
C
(NEW CORRES)

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

August 9, 1995

ORIGINAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



REVIEWS COMPLETED

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrinology Drug Products (HFD-510)

Re: **Amaryl™ (glimepiride tablets), NDA 20-496**
Response to July 19, 1995 FDA letter

CONCLUSION:
LETTER

DATE
8/24/95
12/3/95
JJL/g
8/24/95

Dear Dr. Sobel:

Please refer to your letter to Hoechst-Roussel Pharmaceuticals dated July 19, 1995 in which you notify us of the 3-months extension of the review period under the User Fee Act. You also request that you obtain our commitment to conduct a Phase 4, 1-year comparative trial. This study would collect additional data on serious adverse events in patients being treated under conditions of usual medical practice.

HRPI agrees in principle to conduct a Phase 4 study. We are currently in the process of working with members of your clinical staff to come to an agreement on the best design to satisfy our mutual goals for a post-marketing clinical trial.

As discussed with John Short in early August, HRPI also agrees to submit a Safety Update to your Division by mid-September.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

[Signature]
Barry Ren, Ph. D.
Senior Director
Drug Regulatory Affairs

Noted
JMP
8/24/95

JLD/dmc

Hoechst-Roussel Pharmaceuticals Inc.

Routes 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
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Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

July 20, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496

Dear Dr. Sobel:

Please refer to our pending August 31, 1994 new drug application submitted under section 505(b) for the Federal Food, Drug, and Cosmetic Act for Amaryl (glimepiride) 1, 2, and 4 mg Tablets. Also refer to your letter dated July 12, 1995, concerning the additional indication for Amaryl-metformin combination therapy.

We agree with your statements that "metformin" combination therapy constitutes a new indication that would require a separate NDA or a supplement following approval in order for this indication to be considered for approval. We also understand that the Division may establish a position whereby all sulfonylurea (SFU) preparations could include an SFU/metformin combination indication, and if this position is taken before an action on the pending NDA, the Amaryl package insert could be revised accordingly.

Until one of the conditions is met for the addition of the Amaryl/metformin combination indication, we agree to delete this indication from the INDICATIONS AND USAGE Section of the package insert.

If you have any questions concerning this response, please contact James DeMartino PhD at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Barry Reit", written over a circular stamp or seal.

Barry Reit, Ph.D.
Senior Director
Drug Regulatory Affairs

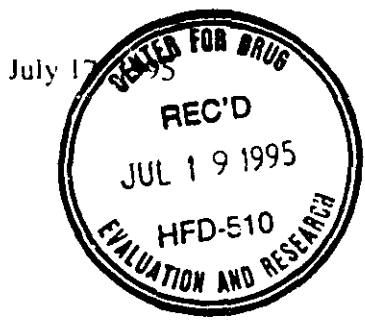
JLD/dmc

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P. O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number (908) 231-2107
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496
Item 3: Updated Stability Data - Drug Substance and Drug Product

Dear Dr. Sobel:

In fulfillment of a commitment in the original NDA to supply additional stability data to support the proposed 24-month expiration dating, we herewith submit updated drug product stability data for each dosage strength, 1-, 2-, and 4-mg tablets.

In addition, updated drug substance stability data is also provided.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

REVIEWS COMPLETED

Sincerely yours,

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

CSO ACTION:
 LETTER N.A.I.

CSO INITIALS DATE
Attachment
Desk copy to Dr. Xavier Ysern, DMEDP
JLD/dmc

*See chem
Reit #2*

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P O Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus. Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number (908) 231-2107
Fax (908) 231-3879

July 12, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496.
General Correspondence: Labels - Response to May 17, 1995 letter from FDA

Dear Dr. Sobel:

In your letter dated May 17, 1995, you requested that the labeling be revised to place the dosage form (tablets) immediately after the established: glimepiride tablets.

We herewith submit revised draft labels to comply with your request. Draft labels for bottles (100s), unit dose push-thru foil, unit dose packs, samples, and sample cartons are included. Draft labels for bottles of 30 are not included, but will be identical in design to the 100s bottle labels. The package insert, which is currently under review in your Division, has previously been modified in this respect.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-3385.

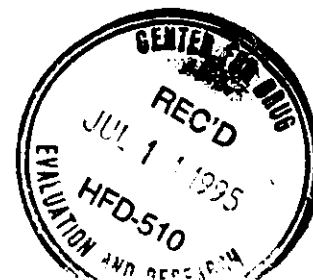
Sincerely yours,

A handwritten signature in cursive script, appearing to read "Barry Reit".

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Attachment
Desk copy to Dr. Xavier Ysern, DMEDP
JLD/dmc

1950712.DOC



Hoechst-Roussel Pharmaceuticals Inc.

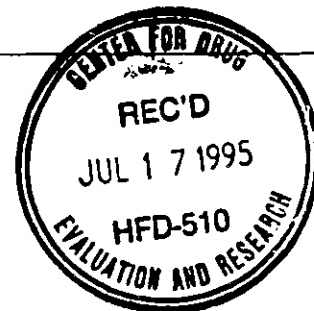
Route 202-206 P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number (908) 231-2107
Fax (908) 231-3879

July 10, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride), NDA, 20-496
General Correspondence: Response to May 31, 1995 FDA letter concerning the
Environmental Assessment section of the NDA

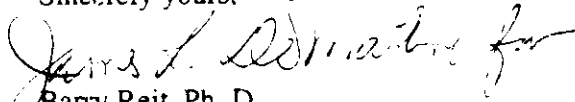
Dear Dr. Sobel:

In response to your letter dated May 31, 1995, we herewith submit a point-by-point reply to your comments on the environmental assessment (EA) section of the NDA.

A copy of your May 31st letter is included for your reference and is followed by the text of the response to FDA's comments. The non-confidential version of the EA (Appendix I) incorporates changes based on the additional information that is provided in the other responses to your questions. The remaining appendices provide supportive information as well as copies of pertinent information that was submitted with the original NDA.

If you have any questions regarding the technical content of this submission, please contact John Pandolfino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-3091. If you have any other questions, please contact James L. DeMartino, DRA, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Desk copy to John Short, CSO, DMEDP
Attachment
JLD/dmc

L950705.DOC

ORIGINAL



Hoechst-Roussel Pharmaceuticals Inc.

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ORIG AMENDMENT

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

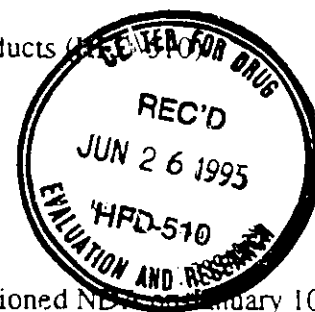
June 20, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD

Director, Division of Metabolism and Endocrine Drug Products

**Re: Amaryl™ (glimepiride tablets), NDA 20-496,
General Correspondence: Revised Package Insert**



Dear Dr. Sobel:

An updated, revised package insert was submitted to the above-mentioned ND on January 10, 1995. The Division's comments on that version of the package insert were transmitted by fax to HRPI on June 8. We herewith submit a revised version of the labeling based on those comments. In addition, we have taken this opportunity to include other changes to the insert, including reference to the combination use of Amaryl tablets and Glucophage (metformin tablets). Three pages describing the changes made to the insert precede the insert itself. Documentation supporting changes that we propose in the labeling is attached. As you requested in your cover sheet of June 8, all references have been removed.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Desk copy faxed to Mr. John Short on June 20, 1995.
Attachment
JLD/dmc

REVIEWS COMPLETED

CS
 N.A.I.
CS
DATE

Hoechst-Roussel Pharmaceuticals Inc.

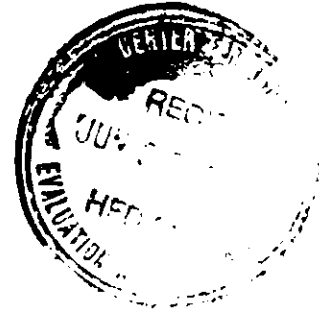
Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

June 26, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: Amaryl™ (glimepiride tablets), NDA 20-496,
General Correspondence: Response to May 17, 1995 letter from FDA**

Dear Dr. Sobel:

We hereby acknowledge receipt of your letter dated May 17, 1995 conveying the results of the reviews of the Chemistry and Pharmacology sections of the above-mentioned new drug application. We now inform you of our response to the items in that letter.

Chemistry:

Drug Substance Synthesis: In the NDA, HRPI identifies glimepiride as one of the starting materials in the synthesis of glimepiride. In your comments, you state that for regulatory purposes, the starting materials are

In attachment I, we present our position that glimepiride satisfies the criteria for a starting material.

Drug Product: The corrected dissolution specification, which you requested, was submitted to the NDA on May 10, 1995.

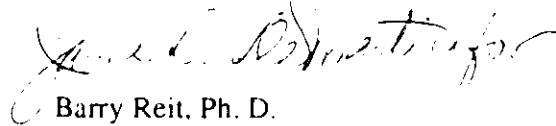
Labeling: You requested that the labeling be revised to include the dosage form immediately after the established name, ie, glimepiride tablets. Revised labeling complying with that request was reviewed by Drs. Chiu and Ysern of FDA's Metabolism Division. We expect to submit revised draft labeling by June 30.

Pharmacology

We have complied with your request to revise the appropriate sections of the labeling to express the comparison of drug exposure based on surface area instead of mg/kg. We are unable to express comparative drug exposure in terms of plasma concentration, because the requisite data for that expression are not available. The revisions have been included in the current version of the package insert that is now under discussion with your Division.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Barry Reit".

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

Attachment
JLD/dmc

Hoechst-Roussel Pharmaceuticals Inc.

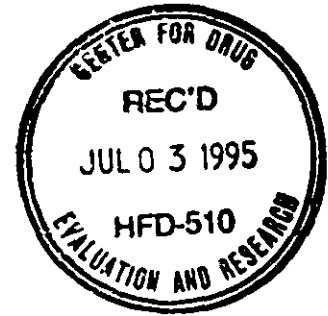
Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

June 22, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: Amaryl™ (glimepiride tablets), NDA 20-496,
General Correspondence: Item 3 - Chemistry, Manufacturing, and Controls: Section
A.4.b - Methods Validation Data section of Section A - Drug Substance**

Dear Dr. Sobel:

On June 21, 1995, Dr. Albert Chen (Division of Biopharmaceutics) requested additional information on the control of specific surface area for glimepiride drug substance. In response to that request, we herewith submit the following information:

Analytical Research Report: Validation and Technology Transfer of Specific Surface Area Method for Glimepiride (HOE 490) Drug Substance.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James L. DeMartino for
Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

*See Chen
Rw #2
8/30/96*

Desk copy faxed to Dr. Albert Chen on June 22, 1995.
Attachment
JLD/dmc

REVIEWS COMPLETED

CSO ACTION:

LETTER

N.A.I.

CSO INITIALS

DATE

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

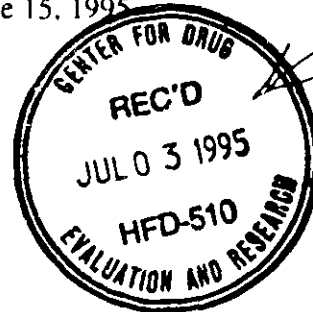


CRIG AMENDMENT

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

June 15, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



Handwritten notes:
Jules
7/25/95

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: Amaryl™ (glimepiride tablets), NDA 20-496,
General Correspondence: Item 3 - Chemistry, Manufacturing, and Controls and
Item 6 - Human Pharmacokinetics and Bioavailability**

Dear Dr. Sobel:

In response to 2 questions posed by Dr. Albert Chen (Division of Biopharmaceutics) on June 14, 1995 we herewith submit the following information.

1. The batch sizes of the 2-mg tablets (HAG Product Batch Nos. 88, 89, and 90) used in Study 1/A/124 were 100,000 tablets.
2. Dr. Chen requested content uniformity data for Product Batch RP 10602, which was used in Study USA/121. The report for USA/121 was submitted to the NDA in an amendment dated February 2, 1995. Please replace Volume 1.7, page 238 with the attached table entitled "Release Testing Data". This table now includes content uniformity data for RP 10602.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

REVIEWS COMPLETED

CSO ACTION:

LETTER N.A.I.

Sincerely yours,

James L. DeMartino for
Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

CSO INITIALS DATE

Desk copies faxed to Mr. John Short and Dr. Albert Chen on June 16, 1995.

Attachment
JLD/dmc

Handwritten notes:
Jules
7/25/95

ORIGINAL

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-125A
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



ORTO AMT...

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

June 12, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Noted

Re: Amaryl™ (glimepiride tablets), NDA 20-496,
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability

[Handwritten signature]

Dear Dr. Sobel:

7/25/95

Please refer to our General Correspondence dated June 2, 1995 in which we submitted information concerning the above-referenced new drug application following a teleconference on Thursday, June 1, 1995 with Mr. John Hunt and Dr. Albert Chen (Division of Biopharmaceutics). After review of that information, Dr. Chen asked that we clarify which formulations were used in non-US studies.

We herewith submit a revised table that presents the formulation information. Where previously this table listed formulations of tablets used in non-US studies as "N/A", the table now identifies the formulations. Specifically, the formulation of the 2-mg tablets used in Study 1/A/124 is identical to that described in Formula Code C used in the US studies of 2-mg tablets. The details of the US formulations are found in Vol 1.75, page 94 (Item 6C, Table C.2.) of the original NDA.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

[Handwritten signature]

Barry Reit, Ph. D.
Senior Director
Drug Regulatory Affairs

*Noted
HMC
6/15/95*

REVIEWS COMPLETED

CSO ACTION:

LETTER N.A.I.

Desk copy faxed to Dr. Albert Chen (Biopharmaceutics) June 12, 1995.

Attachment
JLB/dmc INITIALS

DATE

ORIGINAL

OSRO AMENDMENT

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

June 7, 1995 **REVIEWS COMPLETED**

W. Chen
July

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

CSO ACTION:

LETTER

N.A.I.

7/25/95

CSO INITIALS

DATE

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

noted

Re: **Amaryl™ (glimepiride), NDA, 20-496,**
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability
Protocol 8/USA/206 Additional Information

(Handwritten circle around "Human Pharmacokinetics and Bioavailability")

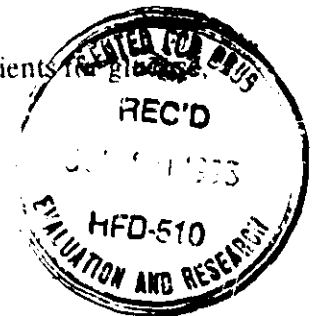
JMR
7/25/95

Dear Dr. Sobel:

At the request of Dr. Albert Chen, we herewith submit additional information concerning the analysis of young versus elderly in once daily dosing.

The pharmacodynamic data (blood glucose, insulin and C-peptide) collected at 2- and 24-h post-dose on the last day of 6 mg qd glimepiride and corresponding baselines during the placebo washout period were evaluated. Data from a total of 94 patients were available for evaluation. Two sample t-test was used for comparison. Baseline values as well as the change from baseline values at 2- and 24-h post-dose on the last day were compared.

The following are the summary results comparing "young" vs. "elderly" patients for glucose, insulin, and C-peptide for patients in the qd group.



	At 2-hour After Dose (Means)			At 24-hour After Dose (Means)		
	Young	Elderly	P-Value ¹	Young	Elderly	P-Value ¹
Glucose (mg/dl)						
N	55	38		56	38	
Baseline (BL)	301.0	309.1	0.600	238.6	239.2	0.961
Change from BL ²	-77.9	-96.0	0.159	-57.8	-68.2	0.276
Insulin (μU/ml)						
N	53	37		53	37	
Baseline (BL)	29.1	35.1	0.163	13.2	13.4	0.902
Change from BL	19.3	19.6	0.947	3.5	1.7	0.191
C-peptide (pmol/ml)						
N	50	36		53	35	
Baseline (BL)	1.73	1.95	0.238	1.03	1.32	0.299
Change from BL	0.60	0.86	0.079	0.17	-0.11	0.319

¹Two-Sample t-test was used.

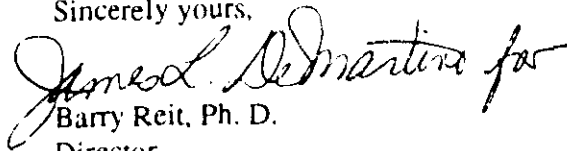
²Change from baseline = Post-dose minus Baseline

No statistically significant differences ($p > 0.05$) were found for the comparisons between "young" and "elderly" patients in the qd group for glucose, insulin, and C-peptide. These results suggest that there is no clinically significant difference in pharmacodynamic response to glimepiride therapy in "young" and "elderly" patients. These findings are consistent with the pharmacokinetic results in these two groups of patients as submitted to the agency earlier (April 26, 1995).

The dataset used in this analysis and the statistical output is included as Attachment I.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc, Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph. D.

Director
Drug Regulatory Affairs

Desk copy: Dr. Albert Chen (Biopharmaceutics)
Attachment
JLD/dmc

ORIGINAL



Hoechst-Roussel Pharmaceuticals Inc.

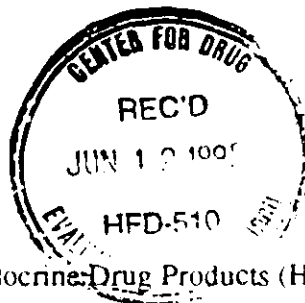
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Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

ORIG AMENDMENT

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

June 2, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



Handwritten notes:
1/22/95
Hoy
6/15/95

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine-Drug Products (HFD-510)

Re: Amaryl™ (glimepiride tablets), NDA 20-496,
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability

Dear Dr. Sobel:

Following a teleconference on Thursday, June 1, 1995 with Mr. John Hunt and Dr. Albert Chen (Division of Biopharmaceutics), we herewith submit the following information concerning the above-referenced new drug application:

1. Summary of the examination of hepatically impaired patients in a Phase I study.
2. Formulation information of the studies previously identified by Dr. Chen as "pivotal" studies.
3. Revised PK section of the package insert on WordPerfect disk and in hard copy. This revised copy will be incorporated into the package insert with other changes following comments from the Division's review of the entire insert.
4. A copy of Item 8C Summary, which contains PK/PD information. The PK/PD evaluation is summarized beginning on page 219. In addition to this summary, PK/PD data may be found in the following studies:

Study Number	Location in the NDA (Vol/Pg)
1/D/111/-	1.172/1 (Item 8)
8/USA/105/DM	1.117/a (Item 6)
8/USA/106/DM	1.119/A (Item 6)
Supplementary PK/PD Analyses:	
8/USA/205/DM	1.188/1 (Item 8)
8/USA/205/DM	1.188/34 (Item 8)
8/GB/202/DM	1.188/77 (Item 8)

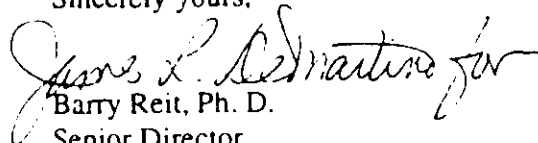
Handwritten notes:
- 11/22/95
Hoy
6/15/95

Mr. Hunt and Dr. Chen asked for a summary of the studies on drug-drug interaction and renal impairment. Tables summarizing renal impairment studies can be found in Vol 1.75/43 and a table of interaction studies is located in Vol 1.75/45 of Item 6 of the original NDA.

Additional information requested by Mr. Hunt and Dr. Chen concerning the PD data in Study USA/206 will be forthcoming within the next few days.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,



Barry Reit, Ph. D.

Senior Director

Drug Regulatory Affairs

Desk copy. Dr. Albert Chen (Biopharmaceutics)

Attachment

JLD/dmc

REVISIONS COMPLETED

COORDINATION:

LETTER

N.A.I.

CSO INITIALS

DATE

ORIGINAL



Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

May 23, 1995

REVIEWS COMPLETED

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

CSO ACTION:

LETTER

N.A.I.

CSO INITIALS

DATE

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: Amaryl™ (glimepiride), NDA, 20-496,
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability**

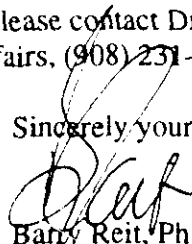
Dear Dr. Sobel:

At the request of Dr. Albert Chen, we herewith submit the following information concerning the above-referenced new drug application:

1. Study 8/USA/206/DM: Summary of PK results - QD dosing young vs elderly.
2. Special Population Studies: Responses to reviewer's questions.
3. Glimepiride Assay:
 - Summary tables of precision and accuracy
 - Statistics for quality control data

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph. D.
Director
Drug Regulatory Affairs



Desk copy: Dr. Albert Chen (Biopharmaceutics)
Attachment
JLD/dmc

ORIGINAL



Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

3B

*Noted Jimmy
6/15/95*

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

May 19, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

*Noted
H/O
6/15/95*

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: **New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets**
General Correspondence: Item 5C - Nonclinical Pharmacology and Toxicology:
ADME

*Noted
X Ysern
6/15/95*

Dear Gentlemen:

At the request of Dr. Albert Chen (Division of Biopharmaceutics), we herewith submit to the above-referenced new drug application (Item 5 - Nonclinical Pharm/Tox), a report entitled "Investigations on the enzymes responsible for the main metabolic routes of biodegradation of Glimepiride (HOE 490) in man." A desk copy of the report is being sent directly to Dr. Chen.

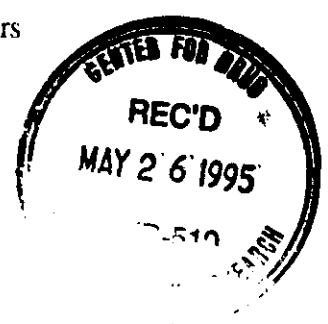
The information contained in this new report is not essential to the approval of the application and does not result in any changes to the labeling.

If you have any questions regarding this material, please contact James DeMartino, Ph.D., at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

RECEIVED
FEDERAL BUREAU OF INVESTIGATION
U.S. DEPARTMENT OF JUSTICE
WASHINGTON, D.C. 20535

Sincerely yours,

James L. DeMartino for
Barry Reit, Ph.D.
Director
Drug Regulatory Affairs



Desk copy: Dr. Albert Chen (Biopharmaceutics)
Attachment
JLD:dmc
L950519.DOC

RC

Hoechst



Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

May 10, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

This correction was requested by the agency (phone conversation)

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 3 - Chemistry, Manufacturing and Controls

Dear Gentlemen:

In reference to the above mentioned New Drug Application, we herewith submit revised pages to correct a typographical error in the dissolution specifications found in Volume 1.6, pages 216-237. Part of the second line of the S₃ specification for each tablet strength (1, 2 and 4 mg) (section I.F) now contains the correct phrase

No other changes have been made. For completeness, replacement copies of the entire specifications (Nos. 200221 [1 mg], 200222 [2 mg], and 200223 [4 mg]) are provided.

If you have any questions regarding this material, please contact James DeMartino, Ph.D., at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James DeMartino for

Barry Reit, Ph.D.
Director
Drug Regulatory Affairs

See Chem Review #2

RECEIVED	COMPLETED
☐ YES	☐ N.A.I.

Attachment
JLD



Hoechst-Roussel Pharmaceuticals Inc.

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Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



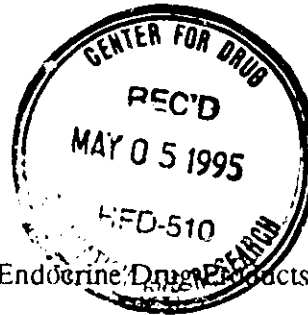
ORIG AMENDMENT

BB

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

April 26, 1995

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ORIGINAL
Noted
Jmz
5/18/95

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

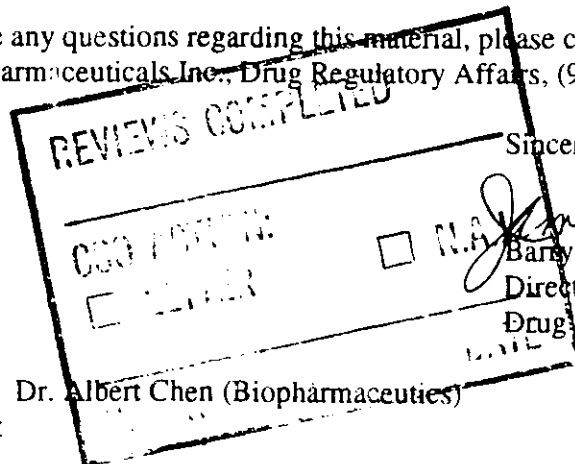
**Re: Amaryl™ (glimepiride), NDA, 20-496,
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability
Protocol 8/USA/206 Additional Information**

Dear Dr. Sobel:

At the request of Dr. Albert Chen, we herewith submit additional information concerning the analysis of young versus elderly in once daily dosing. This submission includes:

- I. Re-analysis of glimepiride data assessing the effect of age on the pharmacokinetics of glimepiride, and Metabolites 1 and 2. A diskette containing the individual parameters for once daily dosing are included. In addition, a page of revised text and statistical output replacing Appendix III.7 in the original report are provided.
- II. Concentration plots of blood glucose, insulin, and C-peptide: Young versus elderly on qd dosing.
- III. Demographic data, and glucose, insulin, and C-peptide levels for the 38 elderly and 56 young patients on qd dosing: Output and diskette are provided.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.



Sincerely yours,

James L. DeMartino for

Barry Reit, Ph. D.

Director
Drug Regulatory Affairs

Desk copy: Dr. Albert Chen (Biopharmaceutics)

Attachment

JLD/dmc

ORIGINAL



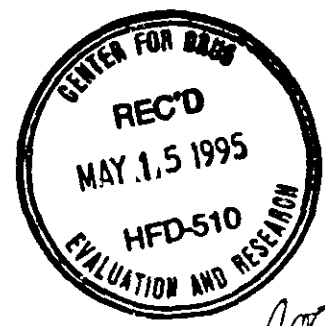
Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

April 21, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852



ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 10 - Statistical Section

W. Reed
J. J. J.
5/23/95

Dear Gentlemen:

At the request of Dr. Japobrata Choudhury (Division of Biometrics) we herewith submit a description of the pseudohomogeneity statistic and a numerical example of the statistic used in Protocol USA/205/DM. A copy of a published method is also included.

If you have any questions regarding this material, please contact James DeMartino, PhD, at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs (908) 231-2385.

Sincerely yours,

Barry Reit, PhD
Director
Drug Regulatory Affairs

Desk copy: Direct to Dr. Japobrata Choudhury (Biometrics)
Attachment
JLD:dmc

REVIEWS COMPLETED	
	☐ Final
INITIALS	DATE

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
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Telephone (908) 231-2000

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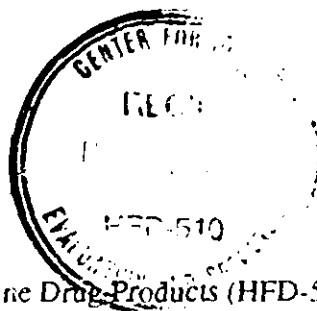
Orig AMENDMENT

ES

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

April 21, 1995



ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

CSO -

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets *Please write*
General Correspondence: Item 10 - Statistical Section *since that our Biostatistician has received this report*

Dear Gentlemen:

At the request of Dr. Masahiro Takeuchi (Division of Biometrics) on March 24, 1995, additional analyses were performed using combinations of the following data sets, approaches, and correlations structures:

1. Raw and Log HbA1c data.
2. GEE and Linear Mixed Effect Model approaches.
3. Independent, Compound Symmetry and AR(1) correlation structure.

JH
4/8/95

For all analyses, a baseline FPG stratum factor was included in the model. In addition, FPG stratum by time interaction effect was tested, and it was excluded from the model because the effect was not significant ($p > 0.20$).

Tables 1 to 4 summarize the results each of the GEE analyses. The final models for each of the subgroups are summarized in Tables 5 and 6, and in Figures 1-4. As shown in these tables, the estimated coefficients are slightly different from those faxed in draft form on February 27, 1995 for the following reasons:

1. Baseline FPG stratum was included in the analyses.
2. For noncompleter subgroups, subjects with single observations were excluded from the analyses due to the limitation of the GEE SAS macro.

The conclusions on each treatment group did not change except for the glimepiride 4 mg group. For the glimepiride 4 mg completer subgroup, a linear model with a negative coefficient, i.e., HbA1c decreases over time, was chosen. However, HbA1c remains constant over time in the noncompleter subgroup. These results suggest that the estimated values of HbA1c for the glimepiride 4 mg group, based on a Endpoint analysis, would be unbiased because the time trend for noncompleters was assumed to be the same if they had remained in the study.

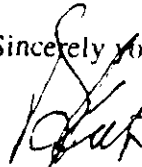
The SAS output for the GEE analyses are included in Appendix I. Tables 1-6 are repeated at the beginning of their corresponding statistical output.

The SAS output from the PROC MIXED are included in Appendix II. Tables 7-10 summarize the results from the Linear Mixed Effect Model analyses and are repeated in Appendix II.

The sample sizes by baseline FPG stratum and treatment group over time are included in Table 11.

If you have any questions regarding this material, please contact James DeMartino, Ph.D. at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,



Barry Reit, Ph.D.
Director
Drug Regulatory Affairs

Desk copy: Direct to Dr. Masahiro Takeuchi (Biometrics)
Attachment
JLD:dmc

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I.
CSO INITIALS	DATE

ORIGINAL

E 135

Hoechst



Hoechst-Roussel Pharmaceuticals Inc.

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Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

NEW COPIES

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

April 21 1995

REVIEWS	_____	_____	_____
CSO	_____	_____	_____
☐ LET	_____	_____	_____
CSO	_____	_____	DATE

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: Amaryl™ (glimepiride), NDA, 20-496,
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability
Page replacement**

Dear Dr. Sobel:

In a conversation with Dr. Albert Chen on April 19, 1995, it was brought to our attention that a table was repeated in Item 6 of the NDA. Please replace Volume 85, page 34 with the attached table entitled "Serum Concentration of M1 (ng/ml) Following Administration of 4 mg Commercial Tablet (SSA 8.9 m²/g)

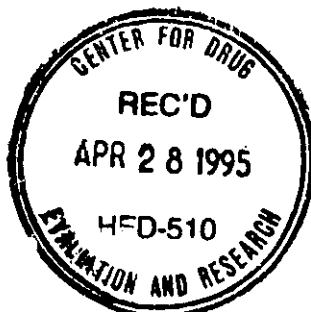
If you have any questions regarding this material, please do not hesitate to contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James L. DeMartino for
Barry Reit, Ph. D.
Director

Drug Regulatory Affairs

Attachment
JLD/dmc



ORIGINAL

Hoechst



Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

orig. amend

BB

*M. DeMartino
4/18/95*

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

April 19, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852



ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability

Dear Gentlemen:

In response to queries from Dr. Albert Chen (Division of Biopharmaceutics), we herewith submit the following information:

1. The attached pages complement the reformatted statistical output for Study 1/A/124/-- that was sent to you on April 19, 1995. This new output presents the mean values of several pharmacokinetic parameters of 3 batches of 2-mg tablets. On the new output, FORMs 1, 2, and 3 correspond to Products A, B, and C in the information supplied on April 19 and represent tablets made with drug substance with the specific surface as listed below:

FORM	Specific Surface Area (m ² /g)
1	7.9
2	5.7
3	4.9



2. The specific surface areas of 3 additional batches were given to Dr. Albert Chen over the phone on April 18. For Product Batches 27, 57, and 78 manufactured in Frankfurt, Germany, the specific surface areas are 7.8, 6.2, and 6.0, respectively.

If you have any questions regarding this material, please contact James DeMartino, Ph.D., at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours.

James A. Reiter for

Barry Reit, Ph.D.

Director

Drug Regulatory Affairs

Copy faxed to Dr. Albert Chen (Biopharmaceutics)
Attachment
JLD:dmc

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I.
CSO INITIALS	DATE

ORIGINAL

Hoechst

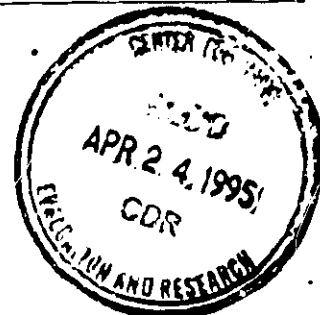


Hoechst-Roussel Pharmaceuticals Inc.

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Telex 833-449 · Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number (908) 231-2107
Fax (908) 231-3879

April 19, 1995



Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

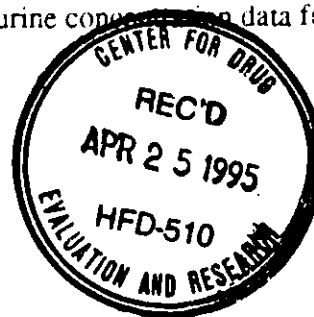
Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability

Dear Gentlemen:

At the request of Dr. Albert Chen (Division of Biopharmaceutics) in telephone contacts of March 1, 3, 8, and 15, we herewith submit the following additional information:

1.) Electronic data sets of demographic data and plasma and urine concentration data for the studies listed:

- Diskette 1 8/J/101/--
- Diskette 2 8/USA/103/--
- Diskette 3 8/USA/105/--
- Diskette 4 8/USA/106/--
- Diskette 5 8/USA/108/--
- Diskette 6 8/USA/112/--
- Diskette 7 8/USA/114/--
- Diskette 8 8/USA/118/DM
- Diskette 9 8/USA/119/DM
- Diskette 10 8/USA/205/DM
- Diskette 11 8/USA/110/DM
- Diskette 12 8/USA/120/DM
- Diskette 13 8/USA/121/DM
- Diskette 14 1/A/115/--
- Diskette 15 1/A/114/--



*Noted
HMR
5/1/95*

Diskette 16	1/A/116/--
Diskette 17	1/A/118/--
Diskette 18	1/A/122/--
Diskette 19	M1 1/A/103/--
Diskette 20	1/A/124/--
Diskette 21	1/B/203/N1
Diskette 22	1/BG/201/L1
Diskette 23	1/D/115/--
Diskette 24	1/YU/201/N1
Diskette 25	M1 1/A/102/--

2.) Time-concentration plots for the studies listed:

1/ZA/101/- (Metabolism study)

8/USA/108/DM (Multidose dose-linearity study)

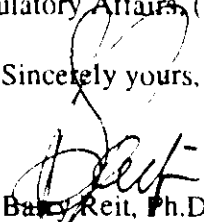
1/A/118/-- (Single-dose dose-linearity study)

3.) Reformatted statistical output for 1/A/124/--, in the same format as that used for 8/USA/110/-

4.) Diskettes in Word Perfect format containing the text of the reports of Studies 8/USA/118, 119, and 206.

If you have any questions regarding this material, please contact James DeMarino, Ph.D., at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,



Barry Reit, Ph.D.

Director

Drug Regulatory Affairs

Desk copy: Direct to Dr. Albert Chen (Biopharmaceutics)

Attachment

JLD:dmc

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I.
CSO INITIALS	DATE

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

April 13, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

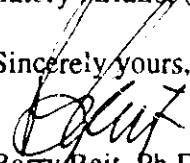
Re: **New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets**
General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability

Dear Gentlemen:

At the request of Dr. Albert Chen (Division of Biopharmaceutics), we have prepared a diskette containing parts of the text identified by Dr. Chen for the study report of Protocol 1/A/122. The diskette in WordPerfect format has been sent to Dr. Chen directly.

If you have any questions regarding this material, please contact James DeMartino, Ph.D., at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs (908) 231-2385.

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I.
INITIALS	DATE

Sincerely yours,

Barry Reit, Ph.D.
Director
Drug Regulatory Affairs

Desk copy: Director Dr. Albert Chen (Biopharmaceutics)
Attachment
JLD:dmc



BS

Hoechst-Roussel Pharmaceuticals Inc.

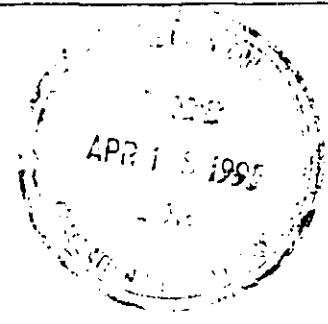
Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



ORIGINAL orig AmEroment

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

April 10, 1995



Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 10 - Statistical Section

Dear Gentlemen:

At the request of Dr. Japobrata Choudhury (Division of Biometrics) we herewith submit responses to his request for additional information from the 4 major efficacy studies, USA/201, 202, 205, and 305. A copy of the original request and a table listing the questions and identifying the responses provided precedes the data, which is grouped by protocol.

To assist Dr. Choudhury in completing his review, an identical copy of this submission has been sent to Dr. Choudhury directly.

If you have any questions regarding this material, please contact James DeMartino, PhD, at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James L. DeMartino for
Barry Reit, PhD
Director
Drug Regulatory Affairs

REVIEWS COMPLETED	
Desk copy	Direct to Dr. Japobrata Choudhury (Biometrics)
Attachment	☐ N.A.I.
JLD:dmc	DATE



Hoechst-Roussel Pharmaceuticals Inc.

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Telephone (908) 231-2000

ORIG AMENDMENT

Hoechst

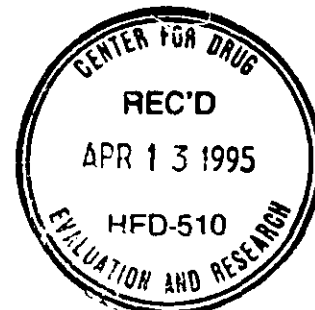


ORIGINAL

Direct Dial Number: (908) 231-2385
Fax: (908) 231-3879

April 7, 1995

Department of Health and Human Services
Center for Drugs Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



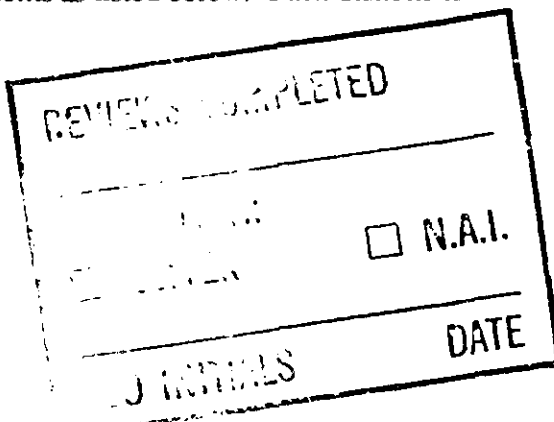
ATTN: Dr. Albert Chen, Division of Biopharmaceutics (HFD-426)

**Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
Diskettes Containing Partial Text of Various Reports in WordPerfect 5.0**

Dear Dr. Chen,

To aid in your preparation of the review of Item 6 of NDA 20-496, I herewith submit to you diskettes containing text of various documents as listed below. Each diskette is in WordPerfect 5.0 format.

1. Package Insert
Complete texts of:
2. USA/103
3. USA/105
4. USA/106
5. USA/108
6. USA/110
7. USA/112
8. USA/120
9. USA/121



If you have any questions regarding this material, please contact James DeMartino, Ph.D, at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

Jim DeMartino
James L. DeMartino, Ph.D.
Assistant Director
Drug Regulatory Affairs

*Make a submission
to the NDA.*

*Mark
4/13/95*

cc: J
Attac
JLD:

Endocrine Drug Products (HFD-510))

ORIGINAL

Hoechst



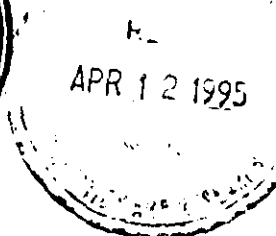
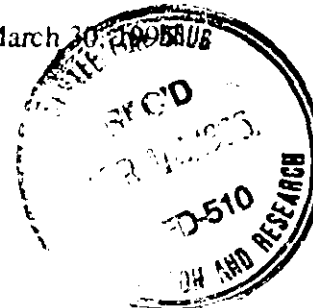
Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

March 30, 1995



ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 10 - Statistical Section

Dear Gentlemen:

At the request of Dr. Masahiro Takeuchi (Division of Biometrics) we herewith submit a diskette containing 2 SAS datasets (Windows 6.08) for the longitudinal analysis of HbA1c data for Protocol 8/USA/201/DM. Both datasets are in the format provided to HRPI by Dr. Takeuchi. The description of the contents of the diskette and a print out of the first 50 records for each dataset are included with the diskette.

An identical copy of this submission has been sent to Dr. Takeuchi directly.

If you have any questions regarding this material, please contact James DeMartino, Ph.D, at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James L. DeMartino for
Barry Reit, Ph.D.
Director
Drug Regulatory Affairs

Desk copy: Direct to Dr. Masahiro Takeuchi (Biometrics)
Attachment
JLD:dmc

REVIEWS COMPLETED	
CSD ACTION:	
☐ LETTER	☐ N.A.I.
CSD INITIALS	DATE

ORIGINAL

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

(BB)

Hoechst



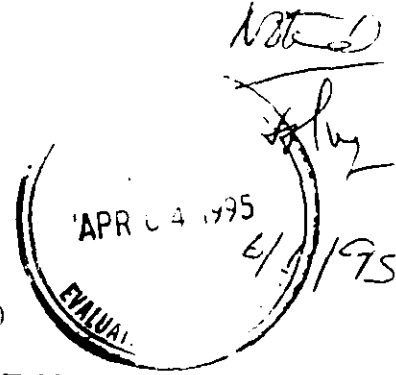
ORIG ALMTDPTNT

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

March 28, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)



Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 6 - Human pharmacology and bioavailability

Dear Gentlemen:

Dr. Albert Chen, Division of Biopharmaceutics, has requested data from studies in which NON-MEM analyses were conducted. In response to that request, we herewith submit a diskette containing ASCII files of data from study 8/USA/106/DM. Data from Study 8/USA/206/DM in ASCII format were previously submitted to the NDA and Dr. Chen on February 21, 1995.

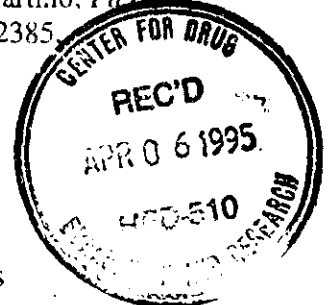
The files on the diskette in this submission contain plasma and urine concentration data, demographic data, and glucose and parent compound concentration data. Corresponding hard copy is also included. The full report of Study 8/USA/106/DM is found in Vol 1.119 of the original NDA.

An identical copy of this submission has been sent to Dr. Chen directly.

If you have any questions regarding this material, please contact James DeMartino, Ph.D. at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

[Signature]
Barry Reit, Ph.D.
Director
Drug Regulatory Affairs



REVIEWS COMPLETED

RECOMMENDED ACTION:

APPROVED N/A

Desk copy: Direct to Dr. Albert Chen (Biopharmaceutics)

Attachments

JLD:dmc

INITIALS

DATE

ORIGINAL

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



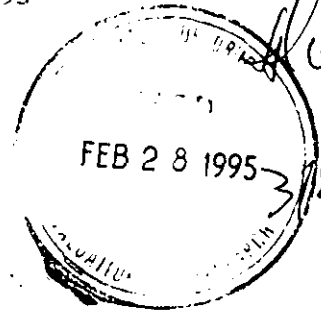
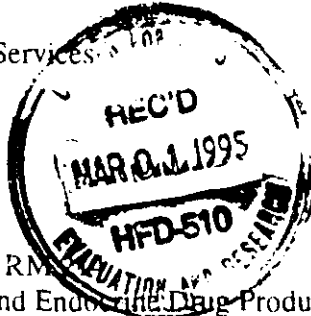
Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

ORIG AMENDMENT

February 21, 1995

Noted

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852



Noted
3/8/95

ATTN: Central Document Room, RMA
Division of Metabolism and Endocrine Drug Products (HFD-510)

Noted
3/8/95

Re: New Drug Application 20-496 Amaryl™ (HOE 490, glimepiride) Tablets
General Correspondence: Item 6 - Human pharmacology and bioavailability

Dear Gentlemen:

At the request of Dr. Albert Chen, Division of Biopharmaceutics, we herewith submit a diskette containing ASCII files of pharmacokinetic and pharmacodynamic (PK/PD) data on HOE 490. Corresponding hard copy is also included. The data submitted are taken from study 8/USA/206/DM. The full report of this study begins at Vol 1.123 of the original NDA.

An identical copy of this submission has been sent to Dr. Chen directly.

If you have any questions regarding this material, please contact James DeMartino, PhD, at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

Barry Reit, Ph. D.
Director
Drug Regulatory Affairs

Attachments
JLD:dmc

L950221.DOC

BZ

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

DRUG AMENDMENT



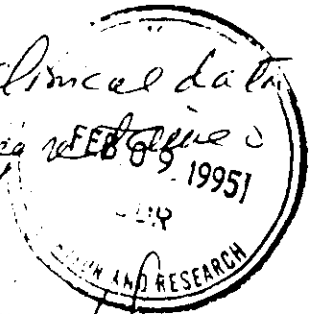
Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

ORIGINAL

February 2, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

1350 - the clinical data section is being reviewed for future review



file

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: New Drug Application 20-496 Amaryl™ (glimepiride) Tablets
NDA Amendment - Other Information**

*clinical data has been reviewed 2/26/95
Doesn't alter the NO original review & its conclusion*

Dear Gentlemen:

In accordance with the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Section 314.60(a) of 21 CFR, we herewith submit an amendment to the above referenced New Drug Application.

The information contained in this amendment does not change the assessment of effectiveness and safety of the drug as presented in the original NDA and the Safety Update. Therefore, no revisions to the previously submitted labeling are needed.

This submission comprises the following information:

Item 5. Nonclinical Pharmacology and Toxicology: Amendments to previously submitted reports, one new reproduction Segment II report, 4 mutagenicity reports, and a GLP statement.

Item 6. Human Pharmacokinetics and Bioavailability: Final report of a bioequivalence study comparing clinical and commercial scale 1 mg tablets.

*file
6/2/95*



Item 8. Clinical Data:

8.D Controlled Studies (also Item 10.C Controlled Studies):
Study synopsis completed since submission of the original NDA.

8.F Other Studies and Information:

3 synopses of new studies from which safety data was reported in the Safety Update submitted December 29, 1994; 1 final report completed since submission of the original NDA.

If you have any questions regarding this material, please contact Dr. James DeMarino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph. D.
Director
Drug Regulatory Affairs

Attachments
JLD:dmc

REVIEWS COMPLETED

CSO ACTION: LETTER N.A.I.

CSO INITIALS _____ DATE _____

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

January 10, 1995

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

**Re: New Drug Application 20-496 Amaryl™ (glimepiride) Tablets
NDA Amendment - Package Insert Revisions**

Dear Gentlemen: -

In accordance with the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Section 314.60(a) of 21 CFR, we herewith submit an amendment to the above referenced New Drug Application.

This submission comprises 3 copies of the package insert: the original insert, the revised insert with changes underscored, and the insert with the changes implemented.

In addition, the final report of a completed US active-controlled study (USA/301, completed after submission of the NDA) is included. This study is the source of the data accounting for the revisions to the clinical information in the insert. The safety data from this study was incorporated into the Safety Update that was submitted to the Agency on December 28, 1994.

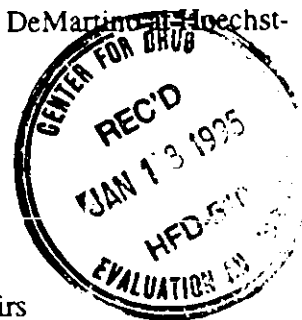
If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Barry Reit".

Barry Reit, Ph. D.

Director
Drug Regulatory Affairs



JD/dc

L950110.DOC

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P O Box 2500 Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus. Somerville, NJ
Telephone (908) 231-2000

*Not on C&H card
received at 11:30 AM
1/6/95*

Hoechst



Direct Dial Number (908) 231-2107
Fax (908) 231-3879

January 6, 1995

Dr. Gurston Turner
Division of Scientific Investigations
Clinical Investigations Branch FDA (HFD-344)
Metro Park North
7520 Standish Place
Rockville, MD 20855

Re: NDA 20-496 Amaryl™ Tablets - Request for Copies of Information Submitted to the Original NDA

Dear Dr. Turner:

We herewith submit copies of the material from the above referenced NDA that you requested in our conversation on January 3, 1995. That information is:

1. List of investigators, including full mailing addresses, for the 3 placebo-controlled trials 8/USA/201, 202 and 205/DM.
2. Tables from each study showing number of patients enrolled in each treatment group by investigator.
3. Copies of the synopses and protocols for the 3 studies.

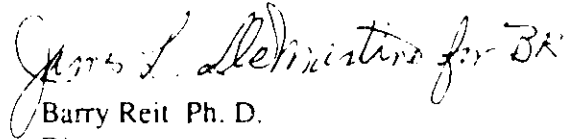
In addition, to facilitate any future requests from you for CRFs, we are providing a list of the CRFs from Protocols 201, 202, and 205, that were included in the NDA.

4. A copy of Vol 1.1 of the NDA, which includes the Item 2 Overall Summary of the NDA.

No new information, which was not already submitted with the original NDA, is included in this package.

If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

A handwritten signature in black ink that reads "James L. DeMartino for Barry Reit". The signature is written in a cursive style.

Barry Reit Ph. D.
Director
Drug Regulatory Affairs

cc: John Short, CSO, Metabolism

JD/dc

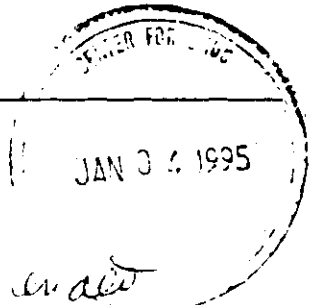
Hoechst-Roussel Pharmaceuticals Inc.



Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000

Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

*This safety update request
seems to reveal an important
concern (has recent request in NDA)
December 29, 1994.
Glimepiride would seem to still be recommended
for approval.*

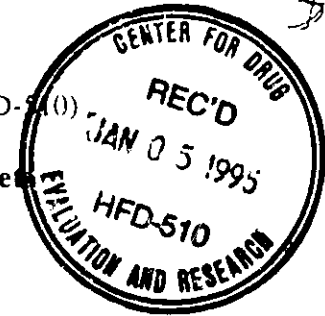


Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ORIGINAL

3/2/95

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)



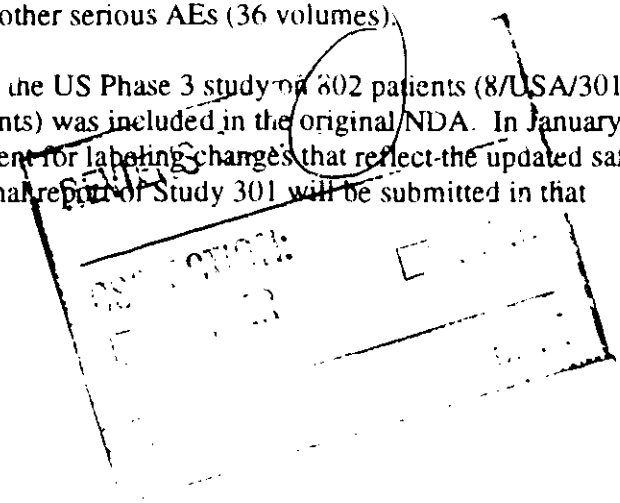
**Re: New Drug Application 20-496 Amaryl™ (glimepiride) Tablets
Item 9 – Safety Update**

Dear Gentlemen:

In accordance with the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Section 314.50(d)(5)(vi)(b) of 21 CFR, we herewith submit Item 9 – Safety Update for the New Drug Application for Amaryl™ (glimepiride) tablets indicated for the treatment of patients with noninsulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet alone. The original NDA was submitted on August 31, 1994 and filed on October 29, 1994.

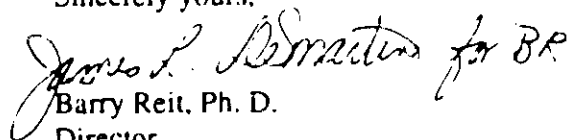
This submission consists of the Item 9 Safety Update (4 volumes) and CRFs for deaths, discontinuations for safety reasons, and other serious AEs (36 volumes).

Most of the new safety data comes from the US Phase 3 study of 802 patients (8/USA/301/DM). An interim report of that trial (130 patients) was included in the original NDA. In January 1995, we will be submitting an NDA amendment for labeling changes that reflect the updated safety information. The recently completed final report of Study 301 will be submitted in that amendment.



If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

Handwritten signature of Barry Reit in cursive script, appearing to read "James L. DeMartino for BR".

Barry Reit, Ph. D.
Director
Drug Regulatory Affairs

JD/dc

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P.O. Box 2500 Somerville, NJ 08876-1258
Telax 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
Fax: (908) 231-3679

December 21, 1994

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

*in total
K. Y. Scm
27 APR 1995*

**Re: Amaryl™ (glimepiride), NDA 20-496, Item 6
General Correspondence - Response to FDA Letter of October 6, 1994**

Dear Dr. Sobel:

Reference is made to your letter of October 6, 1994 in which you requested in vitro dissolution profiles for 1, 2, and 4 mg tablet strengths (n = 12) covering the proposed bulk drug surface area of 5 to 8 m²/g in simulated gastric fluid, simulated intestinal fluid, and the proposed dissolution medium (pH 7.8) using 50 and 75 rpm.

We herewith submit data showing the dissolution behavior of each tablet strength as a function of different active ingredient surface areas within our proposed surface area specification.

If you have any other questions regarding this material, please do not hesitate to contact Dr. James L. DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

RECEIVED
DEC 27 1994
Drug Regulatory Affairs

Sincerely yours,

[Signature]
James L. DeMartino, Ph.D.
Director
Drug Regulatory Affairs



Attachment
JLD/dmc
L94, 208.DOC

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 P O Box 2500 Somerville, NJ 08876 1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231 2000

BS

Hoechst



Direct Dial Number (908) 231-2107
Fax (908) 231 3879

November 10, 1994

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

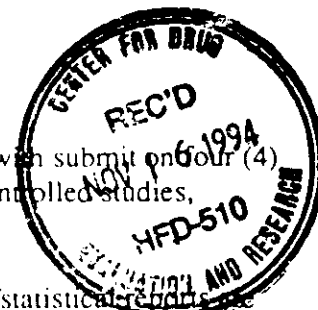
ORIGINAL *K. Reed*
S. H. L.
11/11/94

ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride), NDA 20-496
NDA Amendment: Item 10 - Statistics
Diskettes, SAS programs requested by Dr. Jabo Choudhury

Dear Dr. Sobel:

At the request of Dr. Jabo Choudhury, reviewing statistician, we herewith submit our (4) diskettes, demographic and primary efficacy data from the placebo-controlled studies, Protocols 201, 202, 205, and 305



The SAS programs used to generate the efficacy output in the clinical/statistical records are included on the diskettes. Documentation for the records, decodes for variables, and hard copy of the SAS files, which include the derived variables, are also attached. This material was not included in the original NDA submission. Diskettes are not included in the archival copy of this submission.

If you have any questions regarding this material, please contact Dr. James L. DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

James L. DeMartino for BR
Barry Reit, Ph.D.
Director
Drug Regulatory Affairs

Attachment
JLD/dmc

C w/box

Hoechst-Roussel Pharmaceuticals Inc.

Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 · Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Working on pers.

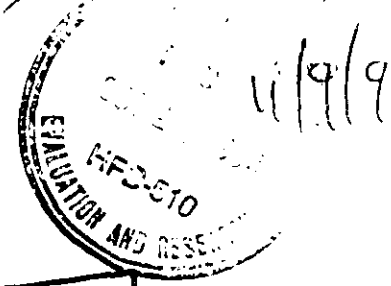
ORIGINAL

file copy
11/9/94

Direct Dial Number: (908) 231-2582
Fax: (908) 231-3879

October 14, 1994

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ATTN: S. Sobel, MD
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Amaryl™ (glimepiride), NDA 20-496
General Correspondence

EVENTS COMPLETED	
DISPATCHED	☐ MAIL
FILED	☐ FILE

Dear Dr. Sobel:

At the request of Dr. John Gueriguian, we herewith submit the annotated "Outline for Clinical Review" in hard copy and on diskettes in Word Perfect 5.1.

	File Name	Contents
Text for "Outline for Clinical Review"		
Disk 1	FLA1.doc	pages 1-37
	FLA2.doc	pages 38-95
Disk 2	FLAB1.doc	pages 96-122
	FLAB2.doc	pages 123-171

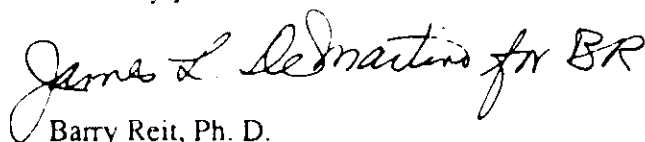
Hard copies without annotations (September 1 and 13) and diskettes (September 13) without annotations were previously submitted to the Amaryl™ IND 31,759 on the dates indicated. Now that we have been informed by Mr. John Short on October 5, 1994 by telephone contact with Dr. James DeMartino of Hoechst-Roussel Pharmaceuticals, that the Amaryl™ NDA 20-496 is fileable, we submit this information to the NDA.

^ desk copy of the text and diskettes are being sent directly to Dr. John Gueriguian.

If you have any questions or problems with the WordPerfect disk, please call Dr. Don Costello, Director, Medical Writing at (908)231-3149 for assistance.

If you have any other questions regarding this material, please do not hesitate to contact Dr. James L. DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

A handwritten signature in cursive script that reads "James L. DeMartino for BR". The signature is written in black ink and is positioned above the typed name.

Barry Reit, Ph. D.
Director
Drug Regulatory Affairs

Desk Copy (text and diskettes): Dr. John Gueriguan

Desk copy (text only): Dr. Alexander Fleming

Attachment

JLD/dmc

Hoechst-Roussel Pharmaceuticals Inc.

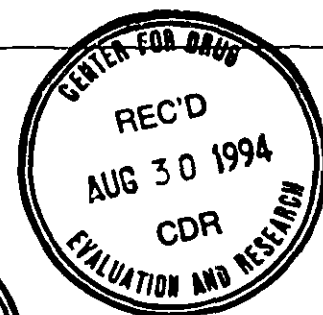
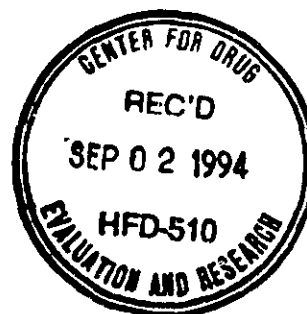
Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 · Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
Fax: (908) 231-3879

August 31, 1994

Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852



ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)

Re: Original New Drug Application
Amaryl™ (glimepiride) Tablets

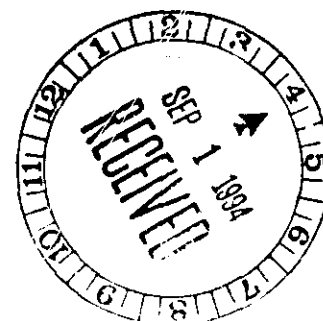


Dear Gentlemen:

In accordance with the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Section 314.50 of 12 CFR, we herewith submit a New Drug Application for Amaryl™ (glimepiride) tablets indicated for the treatment of patients with noninsulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet alone.

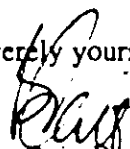
In addition, we are seeking approval for treatment with Amaryl™ (glimepiride) tablets in combination with insulin in NIDDM patients who do not respond to diet and oral hypoglycemic agents alone. At a meeting with the Agency on June 9, 1992, it was agreed that the results of a single adequate, well-controlled study (Protocol 305) would suffice to permit evaluation of this second indication.

This NDA consists of 786 volumes (Volumes 1.1-1.786). A signed FD Form 356h, patent information, debarment certification, a copy of the letter that accompanies the District's copy of the Chemistry section of the NDA, and an introduction to the organization of the NDA follow. A copy of the signed User Fee Cover Sheet is also included.



If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Barry Reit", written over the printed name below.

Barry Reit, Ph. D.
Director
Drug Regulatory Affairs

JD/dc

Hoechst-Roussel Pharmaceuticals Inc.

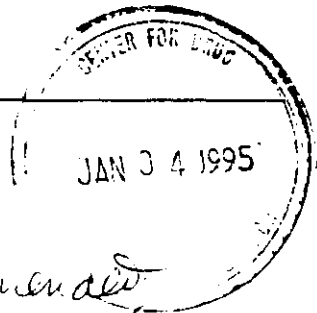
Route 202-206 · P.O. Box 2500 · Somerville, NJ 08876-1258
Telex 833-449 Cable Hoechstus, Somerville, NJ
Telephone (908) 231-2000



Direct Dial Number: (908) 231-2107
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This safety update does not seem to reveal any novel concern (that wasn't raised in the NDA) & glimepiride would seem to still be recommended for approval.

December 29, 1994

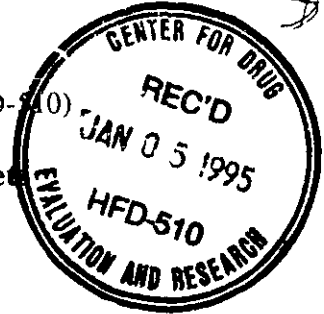


Department of Health and Human Services
Center for Drugs and Biologics
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ORIGINAL

HKG
3/2/95

ATTN: Central Document Room, RM 214
Division of Metabolism and Endocrine Drug Products (HFD-510)



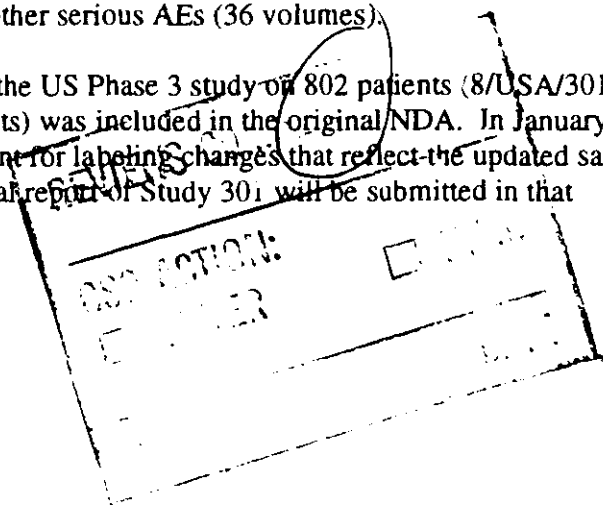
**Re: New Drug Application 20-496 Amaryl™ (glimepiride) Tablets
Item 9 – Safety Update**

Dear Gentlemen:

In accordance with the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Section 314.50(d)(5)(vi)(b) of 21 CFR, we herewith submit Item 9 – Safety Update for the New Drug Application for Amaryl™ (glimepiride) tablets indicated for the treatment of patients with noninsulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet alone. The original NDA was submitted on August 31, 1994 and filed on October 29, 1994.

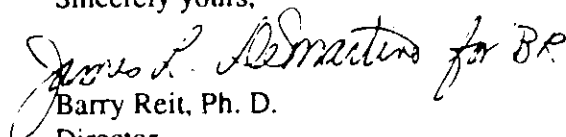
This submission consists of the Item 9 Safety Update (4 volumes) and CRFs for deaths, discontinuations for safety reasons, and other serious AEs (36 volumes).

Most of the new safety data comes from the US Phase 3 study of 802 patients (8/USA/301/DM). An interim report of that trial (130 patients) was included in the original NDA. In January 1995, we will be submitting an NDA amendment for labeling changes that reflect the updated safety information. The recently completed final report of Study 301 will be submitted in that amendment.



If you have any questions regarding this material, please contact Dr. James DeMartino at Hoechst-Roussel Pharmaceuticals Inc., Drug Regulatory Affairs, (908) 231-2385.

Sincerely yours,


Barry Reit, Ph. D.
Director
Drug Regulatory Affairs

JD/dc

**ADVISORY COMMITTEE
MEETING MINUTES**

Not Taken to an Advisory Committee

FEDERAL REGISTER NOTICES

N/A

ADVERTISING MATERIAL

Requested in Approval Letter

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END

DD