CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-329/s-003

Trade Name: Glucotrol XL Extended Release Tablets, 2.5 mg

Generic Name: Glipizide

Sponsor: Pfizer Pharmaceuticals

Approval Date: August 10, 1999

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APPLICATION NUMBER:

20-329/s003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-329/s003

APPROVAL LETTER

AUG 10 1999

NDA 20-329/S-003

Pfizer Pharmaceuticals
Attention: Craig M. Audet
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Audet:

Please refer to your supplemental new drug application dated February 10, 1999, received February 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucotrol XL (glipizide) Extended Release Tablets, 2.5 mg, 5 mg, and 10 mg's.

This supplemental new drug application provides for a new dosage strength, 2.5 mg tablets.

We have completed the review of this supplemental 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 proposed labeling changes submitted on February 10, 1999, with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. Global Change: Replace NIDDM with type 2 diabetes.

2. Under **DESCRIPTION** section: Add 2.5 mg tablet.

3. Under **CLINICAL PHARMACOLOGY** section: Add "In a separate single dose study in 36 healthy subjects, four 2.5 mg GLUCOTROL XL Extended Release Tablets were bioequivalent to one 10 mg GLUCOTROL XL Extended Release Tablet."

4. Under **DOSAGE AND ADMINISTRATION** section: Changed section to note that if the most patients will be controlled with 5 mg to 10 mg

5. Under **HOW SUPPLIED** section: Add 2.5 mg tablet.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert, immediate container and carton labels submitted February 10, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-329/S-003." Approval of this submission by FDA is not required before the labeling is used.

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

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

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

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

Sincerely,

10/29

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

cc:
Archival NDA 20-329
HFD-510/Div. Files
HFD-510/JWeber
HFD-510/RKavanagh/HYAhn/XYsern/SMoore/RMisbin/SMalozowski
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: jmw/August 4, 1999
Initialed by:XYsern 8/4/SMoore 8/4/HYAhn 8/9/RMisbin 8/10/SMalozowski/8/10/EGalliers 8/10/99
final:JWeber 8/10/99
filename: N20329.003

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-329/s003

APPROVED LABELING

GLUCOTROL XL®

(glipizide)

Extended Release Tablets

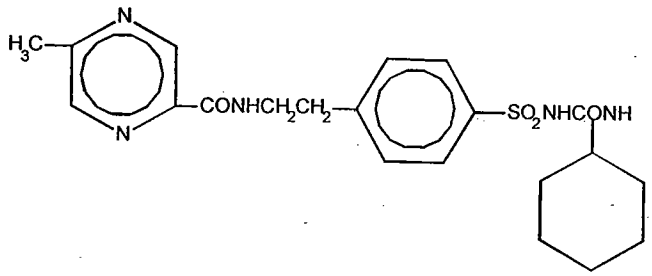
For Oral Use

Rx only

DESCRIPTION

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl] phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. GLUCOTROL XL® is a registered trademark for glipizide GITS. Glipizide GITS (Gastrointestinal Therapeutic System) is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 2.5, 5, or 10 mg of glipizide.

Inert ingredients in the 2.5 mg, 5 mg and 10 mg formulations are: polyethylene oxide, hydroxypropyl methylcellulose, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, opadry blue (OY-LS-20921)(2.5 mg tablets), opadry white (YS-2-7063)(5 mg and 10 mg tablet) and black ink (S-1-8106).

System Components and Performance

GLUCOTROL XL Extended Release Tablet is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet.

The GLUCOTROL XL Extended Release Tablet is designed to provide a controlled rate of delivery of glipizide into the gastrointestinal lumen which is independent of pH or gastrointestinal motility. The function of the GLUCOTROL XL Extended Release Tablet depends upon the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Mechanism of Action: Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Extrapancreatic effects also may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. Two extrapancreatic effects shown to be important in the action of glipizide are an increase in insulin sensitivity and a decrease in hepatic glucose production. However, the mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. The insulinotropic response to a meal is enhanced with GLUCOTROL XL administration in diabetic patients. The postprandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment. In 2 randomized, double-blind, dose-response studies comprising a total of 347 patients, there was no significant increase in fasting insulin in all GLUCOTROL XL-treated patients combined compared to placebo, although minor elevations were observed at some doses. There was no increase in fasting insulin over the long term.

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Effects on Blood Glucose

The effectiveness of GLUCOTROL XL Extended Release Tablets in type 2 diabetes at doses from 5-60 mg once daily has been evaluated in 4 therapeutic clinical trials each with long-term open extensions involving a total of 598 patients. Once daily administration of 5, 10 and 20 mg produced statistically significant reductions from placebo in hemoglobin A_{1c}, fasting plasma glucose and postprandial glucose in patients with mild to severe type 2 diabetes. In a pooled analysis of the patients treated with 5 mg and 20 mg, the relationship between dose and GLUCOTROL XL's effect of reducing hemoglobin A_{1c} was not established. However, in the case of fasting plasma glucose patients treated with 20 mg had a statistically significant reduction of fasting plasma glucose compared to the 5 mg-treated group.

The reductions in hemoglobin A_{1c} and fasting plasma glucose were similar in younger and older patients. Efficacy of GLUCOTROL XL was not affected by gender, race or weight (as assessed by body mass index). In long term extension trials, efficacy of GLUCOTROL XL was maintained in 81% of patients for up to 12 months.

In an open, two-way crossover study 132 patients were randomly assigned to either GLUCOTROL XL or Glucotrol® for 8 weeks and then crossed over to the other drug for an additional 8 weeks. GLUCOTROL XL administration resulted in significantly lower fasting plasma glucose levels and equivalent hemoglobin A_{1c} levels, as compared to Glucotrol.

Other Effects: It has been shown that GLUCOTROL XL therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for type 2 diabetes.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics and Metabolism: Glipizide is rapidly and completely absorbed following oral administration in an immediate release dosage form. The absolute bioavailability of glipizide was 100% after single oral doses in patients with type 2 diabetes. Beginning 2 to 3 hours after administration of GLUCOTROL XL Extended Release Tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6 to 12 hours after dosing. With subsequent once daily dosing of GLUCOTROL XL Extended Release Tablets, effective plasma glipizide concentrations are maintained throughout the 24 hour dosing interval with less peak to trough fluctuation than that observed with twice daily dosing of immediate release glipizide. The mean relative bioavailability of glipizide in 21 males with type 2 diabetes after administration of 20 mg GLUCOTROL XL Extended Release Tablets, compared to immediate release Glucotrol (10 mg given twice daily), was 90% at steady-state. Steady-state plasma concentrations were achieved by at least the fifth day of dosing with GLUCOTROL XL Extended Release Tablets in 21 males with type 2 diabetes and patients younger than 65 years. Approximately 1 to 2 days longer were required to reach steady-state in 24 elderly (≥65 years) males and females with type 2 diabetes. No accumulation of drug was observed in patients with type 2 diabetes during chronic dosing with GLUCOTROL XL Extended Release Tablets. Administration of GLUCOTROL XL with food has no effect on the 2 to 3 hour lag time in drug absorption. In a single dose, food effect study in 21 healthy male subjects, the administration of GLUCOTROL XL immediately before a high fat breakfast resulted in a 40% increase in the glipizide mean Cmax value, which was significant, but the effect on the AUC was not significant. There was no change in glucose response between the fed and fasting state. Markedly reduced GI retention times of the GLUCOTROL XL tablets over prolonged periods (e.g., short bowel syndrome) may influence the pharmacokinetic profile of the drug and potentially result in lower plasma concentrations. In a multiple dose study in 26 males with type 2 diabetes, the pharmacokinetics of glipizide were linear over the dose range of 5 to 60 mg of GLUCOTROL XL in that the plasma drug concentrations increased proportionately with dose. In a single dose study in 24 healthy subjects, four 5 mg, two 10 mg, and one 20 mg GLUCOTROL XL Extended Release Tablets were bioequivalent. In a separate single dose study in 36 healthy subjects, four 2.5-mg GLUCOTROL XL Extended Release Tablets were bioequivalent to one 10-mg GLUCOTROL XL Extended Release Tablet.

Glipizide is eliminated primarily by hepatic biotransformation: less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite which accounts for

less than 2% of a dose, an acetylamino-ethyl benzene derivative, is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound. The mean total body clearance of glipizide was approximately 3 liters per hour after single intravenous doses in patients with type 2 diabetes. The mean apparent volume of distribution was approximately 10 liters. Glipizide is 98-99% bound to serum proteins, primarily to albumin. The mean terminal elimination half-life of glipizide ranged from 2 to 5 hours after single or multiple doses in patients with type 2 diabetes. There were no significant differences in the pharmacokinetics of glipizide after single dose administration to older diabetic subjects compared to younger healthy subjects. There is only limited information regarding the effects of renal impairment on the disposition of glipizide, and no information regarding the effects of hepatic disease. However, since glipizide is highly protein bound and hepatic biotransformation is the predominant route of elimination, the pharmacokinetics and/or pharmacodynamics of glipizide may be altered in patients with renal or hepatic impairment.

In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

INDICATIONS AND USAGE

GLUCOTROL XL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with type 2 diabetes formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory. GLUCOTROL XL is indicated when diet alone has been unsuccessful in correcting hyperglycemia, but even after the introduction of the drug in the patient's regimen, dietary measures should continue to be considered as important. In 12 week, well-controlled studies there was a maximal average net reduction in hemoglobin A_{1c} of 1.7% in absolute units between placebo-treated and GLUCOTROL XL-treated patients.

In initiating treatment for type 2 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 blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, 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 should be considered. If additional reduction of symptoms and/or blood glucose is required, the addition of insulin to the treatment regimen should be considered. Use of GLUCOTROL XL 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 also may be transient, thus requiring only short-term administration of glipizide.

Some patients fail to respond initially or gradually lose their responsiveness to sulfonylurea drugs, including GLUCOTROL XL. In these cases, concomitant use of GLUCOTROL XL with other oral blood-glucose-lowering agents can be considered. Other approaches that can be considered include substitution of GLUCOTROL XL therapy with that of another oral blood-glucose-lowering agent or

insulin. GLUCOTROL XL should be discontinued if it no longer contributes to glucose lowering. Judgment of response to therapy should be based on regular clinical and laboratory evaluations.

In considering the use of GLUCOTROL XL in asymptomatic patients, it should be recognized that controlling blood glucose in type 2 diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes. However, in insulin-dependent diabetes mellitus controlling blood glucose has been effective in slowing the progression of diabetic retinopathy, nephropathy, and neuropathy.

CONTRAINDICATIONS

Glipizide 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 type 2 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 glipizide 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.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS

General

Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may affect the disposition of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Therapy with a combination of glucose-lowering agents may increase the potential for hypoglycemia.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

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

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1C} may be useful.

Information for Patients: Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the GLUCOTROL XL Extended Release Tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.

Patients should be informed of the potential risks and advantages of GLUCOTROL XL and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

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

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving glipizide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

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

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. The effect of concomitant administration of Diflucan® (fluconazole) and Glucotrol has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received Glucotrol alone and following treatment with 100 mg of Diflucan® as a single daily oral dose for 7 days. The mean percentage increase in the Glucotrol AUC after fluconazole administration was 56.9% (range: 35 to 81%).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood-glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood-glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

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

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL, 33 percent were 65 and over. Approximately 1-2 days longer were required to reach steady-state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) There were no overall differences in effectiveness or safety between younger and older patients, but greater sensitivity of some individuals cannot be ruled out. As such, it should be noted that elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly. In addition, in elderly, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.

ADVERSE REACTIONS

In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Only 3.4% of patients receiving GLUCOTROL XL Extended Release Tablets had hypoglycemia documented by a blood-glucose measurement < 60 mg/dL and/or symptoms believed to be associated with hypoglycemia. In a comparative efficacy study of GLUCOTROL XL and Glucotrol, hypoglycemia occurred rarely with an incidence of less than 1% with both drugs.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients include:

Adverse Effect	GLUCOTROL XL (%) (N=278)	Placebo (%) (N=69)
Asthenia	10.1	13.0
Headache	8.6	8.7
Dizziness	6.8	5.8
Nervousness	3.6	2.9
Tremor	3.6	0.0
Diarrhea	5.4	0.0
Flatulence	3.2	1.4

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients:

Body as a whole–pain
Nervous system–insomnia, paresthesia, anxiety, depression and hypesthesia
Gastrointestinal–nausea, dyspepsia, constipation and vomiting
Metabolic–hypoglycemia
Musculoskeletal–arthralgia, leg cramps and myalgia
Cardiovascular–syncope
Skin–sweating and pruritus
Respiratory–rhinitis
Special senses–blurred vision
Urogenital–polyuria

Other adverse experiences occurred with an incidence of less than 1% in GLUCOTROL XL-treated patients:

Body as a whole–chills
Nervous system–hypertonia, confusion, vertigo, somnolence, gait abnormality and decreased libido
Gastrointestinal–anorexia and trace blood in stool

Metabolic–thirst and edema
Cardiovascular–arrhythmia, migraine, flushing and hypertension
Skin–rash and urticaria
Respiratory–pharyngitis and dyspnea
Special senses–pain in the eye, conjunctivitis and retinal hemorrhage
Urogenital–dysuria

Although these adverse experiences occurred in patients treated with GLUCOTROL XL, a causal relationship to the medication has not been established in all cases.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with GLUCOTROL XL:

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

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with glipizide and other sulfonylureas.

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE

There is no well-documented experience with GLUCOTROL XL overdosage in humans. There have been no known suicide attempts associated with purposeful overdosing with GLUCOTROL XL. In nonclinical studies the acute oral toxicity of glipizide was extremely low in all species tested (LD_{50} greater than 4 g/kg). Overdosage of sulfonylureas including glipizide 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 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 hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL XL Extended Release Tablet or any other hypoglycemic agent. Glycemic control should be monitored with hemoglobin A_{1c} and/or blood-glucose levels 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 an adequate blood-glucose-lowering response after an initial period of effectiveness. Home blood-glucose monitoring may also provide useful information to the patient and physician. Short-term administration of GLUCOTROL XL Extended Release Tablet may be sufficient during periods of transient loss of control in patients usually controlled on diet.

In general, GLUCOTROL XL should be given with breakfast.

Recommended Dosing: The usual starting dose of GLUCOTROL XL as initial therapy is 5 mg per day, given with breakfast. Those patients who may be more sensitive to hypoglycemic drugs may be started at a lower dose.

Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood-glucose levels generally reach steady-state following initiation or change in GLUCOTROL XL dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases, hemoglobin A_{1c} level measured at three month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1c} should be measured as GLUCOTROL XL therapy is initiated and repeated approximately three months later. If the result of this test suggests that glycemic control over the preceding three months was inadequate, the GLUCOTROL XL dose may be increased. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1c} levels measured at three month intervals. If no improvement is seen after three months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust GLUCOTROL XL therapy should be based on at least two or more similar, consecutive values obtained seven days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg to 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1c} beyond what was achieved with the 10 mg dose.

Based on the results of a randomized crossover study, patients receiving immediate release glipizide may be switched safely to GLUCOTROL XL Extended Release Tablets once-a-day at the nearest equivalent total daily dose. Patients receiving immediate release Glucotrol also may be titrated to the appropriate dose of GLUCOTROL XL starting with 5 mg once daily. The decision to switch to the nearest equivalent dose or to titrate should be based on clinical judgment.

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

Combination Use: When adding other blood-glucose-lowering agents to GLUCOTROL XL for combination therapy, the agent should be initiated at the lowest recommended dose, and patients should be observed carefully for hypoglycemia. Refer to the product information supplied with the oral agent for additional information.

When adding GLUCOTROL XL to other blood-glucose-lowering agents, GLUCOTROL XL can be initiated at 5 mg. Those patients who may be more sensitive to hypoglycemic drugs may be started at a lower dose. Titration should be based on clinical judgment.

Patients Receiving Insulin: As with other sulfonylurea-class hypoglycemics, many patients with stable type 2 diabetes receiving insulin may be transferred safely to treatment with GLUCOTROL XL Extended Release Tablets. When transferring patients from insulin to GLUCOTROL XL, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and GLUCOTROL XL therapy may begin at usual dosages. Several days should elapse between titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and GLUCOTROL XL therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between titration steps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least three times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when the patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

Patients Receiving Other Oral Hypoglycemic Agents: As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to GLUCOTROL XL Extended Release Tablets. Patients should be observed carefully
(1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to GLUCOTROL XL due to potential overlapping of drug effect.

HOW SUPPLIED

GLUCOTROL XL® (glipizide) Extended Release Tablets are supplied as 2.5 mg, 5 mg, and 10 mg round, biconvex tablets and imprinted with black ink as follows:

2.5 mg tablets are blue and imprinted with "GLUCOTROL XL 2.5" on one side.
Bottles of 30: NDC 0049-1620-30

5 mg tablets are white and imprinted with "GLUCOTROL XL 5" on one side.
Bottles of 100: NDC 0049-1550-66
Bottles of 500: NDC 0049-1550-73

10 mg tablets are white and imprinted with "GLUCOTROL XL 10" on one side.
Bottles of 100: NDC 0049-1560-66
Bottles of 500: NDC 0049-1560-73

Recommended Storage: The tablets should be protected from moisture and humidity and stored at controlled room temperature, 59° to 86°F (15° to 30°C).

U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017

Printed in U.S.A.

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/s/

David Orloff
4/1/02 05:14:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-329/s003

CHEMISTRY REVIEW(S)

JUN 29 1999

CHEMIST'S REVIEW

1. Organization CDER/HFD-510
Division of Metabolism and Endocrine Drug Products

2. NDA # 20-329
Approved: 26-APR-1994

3. Name and address of Applicant
Pfizer Pharmaceutical Group

Pfizer Inc.
235 East 42nd. Street P.O. Box 9627
New York, NY10017-5755 (212) 733-6866
Fax (212) 573-1563

4. Supplement SCS-003
Doc. 10-FEB-1999 Rec. 11-FEB-1999

5. Name of the Drug
Glucotrol XL (Glipizide GITS)

6. Nonproprietary Name
Glipizide Extended Release Tablet

7. Supplement provides for a new dosage strength, 2.5-mg, Glucotrol XL (glipizide) Extended Release tablets.

8. AMENDMENT
--

9. Pharmacological category
Hypoglycemic Agent, treatment of NIDDM.

10. How dispensed
Oral

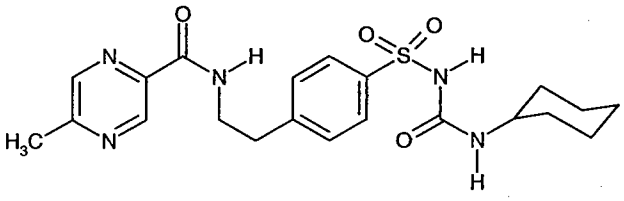
11. Related
DMF [illegible]

12. Dosage Form Tablet

13. Potency 2.5-, 5.0- and 10.0-mg

14. Chemical Name and Structure

Glipizide
$C_{21}H_{27}N_5O_4S$
M.W. = 445.5
CAS 29094-61-9



1-cyclohexyl-3-[[*p*-2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulphonyl]urea or

[illegible]

15. Comments: Supplement, SCS-003, provides for a new dosage strength of Glucotrol XL Tablets. The manufacture procedure, in-process controls, packaging, and specifications of proposed new dosage strength, 2.5-mg, are similar to that of the approved higher strengths. The District Office has found the manufacturing facilities acceptable. Bioequivalence issues will be evaluated by the Biopharm Division..

16. Conclusions and Recommendations Adequate CMC information has been provided to judge the quality of the proposed new strength, 2.5-mg, of Glucotrol XL Tablets. From the chemistry viewpoint this supplement can be approved. Evaluation of the appropriateness of the Bioequivalence data will be evaluated by the Biopharm Division.

17. Reviewer name (and signature)
Xavier Ysern, PhD

Date completed 28-JUN-1999

Xavier Ysern

R/D Init. by

filename: \nda\20329s03.doc

DISTRIBUTION: Original: NDA 20-329 cc: HFD-510 Division File/ SMoore/ JWeber/ XYsern

AP

Stephen L. Moore
6/29/99

7 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20329/003**
Stamp: **11-FEB-1999** Regulatory Due: **11-JUN-1999**
Applicant: **PFIZER**
235 EAST 42ND ST 5TH FLOOR
NEW YORK, NY 10017

Priority: **3S** Org Code: **510**
Action Goal: District Goal: **07-MAY-1999**
Brand Name: **GLUCOTROL EXTENDED RELEASE TABLETS**
Established Name:
Generic Name: **GLIPIZIDE**
Dosage Form: **EXT (EXTENDED-RELEASE TABLET)**
Strength: **2.5-, 5.0- AND 10.0-MG**

FDA Contacts: **X. YSERN (HFD-510) 301-827-6420 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 23-JUN-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1211022**
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUN-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: **2410924**
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUN-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-329/s003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 30 1999

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-329
Type of Submission:	SCS - 003 (Supplement - Control Supplement)
Generic Name:	Glipizide
Formulation(s);	GITS Tablet
Strength(s);	2.5 mg
Route(s)	PO
Brand Name:	Glucotrol XL® Extended Release Tablets 2.5 mg
Sponsor:	Pfizer, Inc. New York, NY
Submission Date(s):	February 10, 1999
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. SYNOPSIS

Glipizide is a second-generation sulfonylurea that assists in the secretion of insulin by the pancreas.

Glucotrol XL 2.5 mg is a modified (extended) release tablet formulation intended to deliver 2.5 mg glipizide over approximately 16 - 20 hours. This allows once daily dosing of glipizide. The extended release characteristics are achieved through a Gastro-Intestinal Therapeutic System (GITS). This is an osmotic delivery system. The tablet absorbs fluid from the gastrointestinal tract through a semi-permeable layer. An osmotic gradient results and forces drug to be released at a zero order release rate.

The original NDA submission in 1993 requested approval of 5, 10, and [redacted] GITS tablet formulations. In the original 1993 submission efficacy studies 0491 and 0591 were consistent in demonstrating greater decreases in mean fasting blood sugars (FBS) and hemoglobin A_{1c} (HbA_{1c}) with the 5 mg GITS formulation taken daily compared to placebo. Both of these studies indicated that there was no improvement in HbA_{1c} at higher dosages of 10 and [redacted] daily compared with 5 mg daily, although mean FBS was lower. In the end, the 5 and the 10 mg formulations were approved, as some patients are titrated to 10 mg daily with the immediate release formulation, and a 10 mg GITS formulation would allow switching to a single daily dosing. [redacted] increased benefit to dosages above 10 mg daily, although the incidence of side effects increases. [redacted] dosages of up to 20 mg are approved, as indicated in the approved labeling, as some patients may derive benefit at dosages above 10 mg daily.

The current 2.5 mg GITS tablet formulation is intended to allow greater flexibility in dosage titration. This will allow the use of a 7.5 mg daily dose (5 mg + 2.5 mg or 3 x 2.5 mg), an intermediate dose within the usual dosage range of 5 - 10 mg of Glucotrol XL daily. It will also allow additional narrower titration of dosage at doses above 10 mg daily.

Glucotrol XL 2.5 mg is very similar in qualitative-quantitative composition to Glucotrol XL 5 mg tablets. The total tablet weight of the 2.5 mg tablet is similar to the 5 mg formulation and is [redacted] of the weight of the 10 mg formulation. Consequently, the amount of active ingredient as a % of total tablet weight is quite different from both of the currently approved formulations. In addition, there are some differences in the composition of the coatings. Thus, an *in vivo* dosage formulation bioequivalence study is needed for approval.

In the present NDA submission, four Glucotrol XL 2.5 mg tablets were demonstrated to be bioequivalent to one Glucotrol XL 10 mg tablet. The geometric mean ratios and 90% confidence intervals of the 2.5 mg tablets to the 10 mg tablets were 1.10 (102 - 119) for Cmax and 1.01 (96 - 106) for $AUC_{0-\infty}$.

Utilizing a slightly modified dissolution procedure, Glucotrol XL 2.5 mg tablets meet the same *in vitro*

dissolution specifications currently approved for the 5 and 10 mg tablets. The modifications for the dissolution procedure for the 2.5 mg tablets are inconsequential and include a decrease in the volume of media and a change in the analytical method used for drug analysis.

II. RECOMMENDATION

The Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE-2) has reviewed NDA # 20-329 SCS - 003, submitted February 10, 1999. The overall Human Pharmacokinetic Section is acceptable to OCPB. This recommendation, comments and labeling comments should be sent to the sponsor as appropriate.

Table of Contents

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PROTOCOL INDEX

Protocol Numbers	Title	Page
125-004 and L0354	A comparative, Single-Dose Bioavailability Study of Four 2.5 mg Glipizide GITS (Gastrointestinal Therapeutic System) Tablets and One 10 mg Glipizide GITS Tablet in Healthy Subjects.	21

III. TERMS AND ABBREVIATIONS

AE ..... adverse effect
AUCa-b ..... area under the plasma-concentration-time curve from time a to time b
Cmax ..... maximum measured concentration
CV ..... coefficient of variation
DPEII ..... Division of Pharmaceutical Evaluation II
FBS ..... fasting blood sugars
GITS ..... Gastrointestinal Intestinal Therapeutic System
HbA_{1c} ..... hemoglobin A_{1c}
LLOQ ..... lower limit of quantitation
NF ..... National Formulary
OCPB ..... Office of Clinical Pharmacology and Biopharmaceutics
PO ..... per os
STP ..... Standard Test Protocol
$t_{1/2}$ ..... half-life
Tmax ..... time to maximum concentration
USP ..... United States Pharmacopeia
UV ..... ultraviolet

IV. ASSAY VALIDATION

Compound of Interest:	Glipizide			
Type of Analytical Method	HPLC with UV Detection			
Internal Standard	Chlorpropamide			
Sponsor:	Pfizer			
Contract Organization:	[redacted]			
Species	Human			
Matrices	Serum - Primary Validation Plasma - Cross Matrix Validation			
Validation Reports	**Report**	**Study Number**	**Report Number**	**Dates of Validation**
	Initial Validation	6139-151		June 22, '90
	Addendum 1 - Stability in plasma	6139-264	6348-197MVD	July 3, '91

A. Limit of Detection

Variously listed as 2.5 or 4 ng/ml based on 2 times the background noise.

B. Specificity

1. Matrix

Serum
Plasma - cleaner chromatograms than serum - see cross matrix calibration.

C. Dynamic Response

Linear with weighting 1/concentration
$R^2 > 0.999$
Range 10 - 1000 ng/ml
Y intercept did not deviate significantly from zero
Precision and accuracy at each standard concentration was very good

D. Limits of Quantitation

	Lower	**Upper**
Nominal Concentrations (ng/ml)	10	1000
Mean	10.3	1003
N	6	6
S.D.	0.08	8
Precision (CV %)	0.8	0.8
Bias (%)	2.5	0.3
Range (%)	[redacted]	

E. Accuracy and Precision

1. Total Accuracy and Precision

Table 1 Total Accuracy and Precision

Nominal Concentrations (ng/ml)	15	150	800.00
Mean	15.6	153	815
N	18	18	18
S.D.	0.55	0.60	11.0
Precision (CV %)	3.5	3.5	1.3
Bias (%)	4.3	2.3	1.9
Range (%)	[redacted]		

(2 curves, 3 samples/curve, 3 days)

2. Intra-day Accuracy and Precision

Table 2 Intra-day Accuracy and Precision

Nominal Concentrations (ng/ml)	15	150	800.00
Mean	16	155	820
N	0.65	6	6
S.D.	0.39	3.8	11.5
Precision (CV %)	4.1	2.4	1.4
Bias (%)	6.4	3.6	2.5

(2 curves, 3 samples/curve) (Worst Data Shown)

F. Ruggedness

[redacted]

G. Stability

1. Stock Solution Stability

Reference and internal standards are claimed to be stable for [redacted]. No are data provided.

2. Sample Handling

A variety of conditions were assessed. However stress testing at high temperatures was not performed. Samples were stable under all conditions tested. Drug is stable in blood both with and without contact to [redacted] It's stable in plasma at room temperature up to 7 days.

3. Freeze-Thaw Stability

Assessment not provided.

4. Post Extraction Stability

Not Provided.

5. Long Term Stability

Stable at -20 °C for 3 months.

H. Cross Matrix Validation

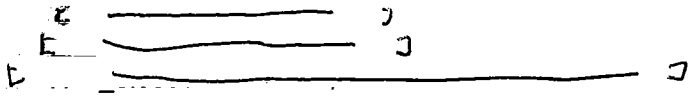
Accuracy and precision are very similar to serum. Plasma is an acceptable matrix.

I. Partial Validation

Since the assay had not been used for several years, a partial validation should have been performed. No information was provided to indicate that a partial re-validation was performed.

J. Glipizide Assay of Clinical Samples - In Process Controls

1. Dynamic Response



2. LLOQ

10 ng/ml CV(%) 8.5%

3. Total Overall Accuracy & Precision

Table 3 Total Overall Accuracy and Precision Over All Runs

	Low	Medium	High
Nominal Concentration (ng/ml)	15	150	800 ng/ml
Mean Measured Concentration (ng/ml)	15.1	150	780
SD	1.28	9.6	47.4
% CV	8.5	6.4	6.1
Accuracy (%)	100.7	100	97.5
Bias (%)	0.7	0.0	-2.5
N	49	49	49

K. Reviewer's Comments & Assessment

The assay validation was initially performed several years ago. This assay validation is acceptable. Since the assay had not been used for several years, a partial validation should have been performed. No information was provided to indicate that a partial re-validation was performed.

Post-extraction stability data would be nice, but it appears that the compound is quite stable.

Thirty-three standard curves were run for the analysis of clinical samples. Of these 8 were rejected for the following reasons.

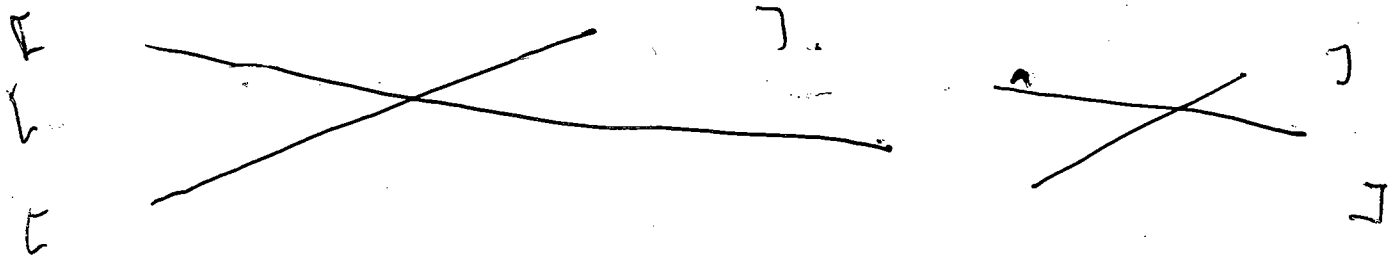
Standard curve failed acceptance criteria	3
Standard curve and QC samples failed acceptance criteria	1
Instrument failure	3
Poor Chromatography	1

In addition there were a limited number of QC samples that fell outside of the range of ± 20% of the nominal concentrations and these were not included in the calculations of accuracy and precision. However, the analytical runs used appear acceptable.

V. FORMULATION

Neither the 2.5, 5 or 10 mg tablets are true dose multiples. Except for the coatings and amount of active ingredient the 2.5, 5, and 10 mg tablets have very similar compositions when expressed as a percentage of tablet weight. However all strengths have very different coatings (See Table 4 and Table 5)

The major differences between the 2.5 mg tablet and the 5 mg tablet include,



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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

VI. DISSOLUTION

A. *Proposed Dissolution Procedure - Glucotrol XL 2.5 mg Tablets*

STP No.	STANDARD TEST PROCEDURE (STP) TITLE
R 38.65	Determination of Release Rate of Glipizide from 2.5 mg Glipizide GITS Tablets Using USP Dissolution Apparatus with Rotating Paddles and HPLC Quantitation
Apparatus	USP Apparatus II (Rotating Paddle)
Media	Simulated Intestinal Fluid without Pancreatin
Volume	500 ml
pH	7.5 ± 0.1
Temperature	37 ± 2 °C
Rotation Speed	50 ± 2 RPM
Drug Analysis	HPLC with UV detection @ [redacted] external standard method
Sampling	Every 2 hours x 9 sampling times (2 - 18 hours)
Reference	(NDA 20-329 Pages 3 101-109)

B. *Currently Approved Dissolution Procedure - Glucotrol XL 5 and 10 mg Tablets*

STP No.	STANDARD TEST PROCEDURE (STP) TITLE
R 38.6	(no title available - for 5 and 10 mg tablets)
Apparatus	USP Apparatus II (Rotating Paddle)
Media	Simulated Intestinal Fluid without Pancreatin
Volume	*900 ml*
pH	7.5 ± 0.1
Temperature	37 ± 2 °C
Rotation Speed	50 ± 2 RPM
Drug Analysis	UV Spectrophotometer @ [redacted]
Reference	(Chemistry Review - April 23, 1993)

According to the sponsor, the reason for the difference in wavelength is to eliminate the effect of the absorbance of the excipients in the non-HPLC method. All HPLC methods used for manufacturing controls use [redacted] and is a USP method (USP XXIII).1

C. *Proposed Specifications for Glucotrol XL 2.5 mg Tablets*

Cumulative Amount Released

4 hours	Q ≤ [redacted] of label claim
8 hours	Q = [redacted] % of label claim
16 hours	Q ≥ [redacted] of label claim

Average Release Rate

4-8 hours (R1)	[redacted] label claim/hour
8-12 hours (R2)	[redacted] of label claim/hour

1 Teleconference with Sponsor July 30, 1999

The sponsor states that Glucotrol XL 2.5 mg tablets "meets USP acceptance criteria for extended release articles". Although not explicitly stated, it appears that these acceptance criteria are from USP 23 <724> Drug Release: Extended-release Articles—General Drug Release Standard, Acceptance Table 1 - page 1796.

D. Dissolution Data

Data was provided for 3 biobatch lots, (N8013, N8030, and N8038). Data in Table 6 was generated immediately after manufacture without long term storage. Lot N8030 was used in the bioequivalence study.

Table 6 Mean Dissolution Data for Glucotrol XL 2.5 mg Tablets

Manufacturing Information			
Lot No.	N8013	N8030	N8038
Manufacturing Date	June 1998	May 1998	June 1998
Manufacturing Site	Brooklyn, NY	Brooklyn, NY	Brooklyn, NY
Batch Size	[redacted]		
Specifications			
Content [redacted]			
Cumulative Amount Released			
4 hours Q < [redacted] of Label Claim			
8 hours Q [redacted] % of Label Claim			
16 hours Q ≥ [redacted] of label claim			
Average Release Rate			
4-8 hours (R1) [redacted] of Label Claim			
8-12 hours (R2) [redacted] of Label Claim			
Used in Bioequivalence Study			

Table 7 contains the initial dissolution data for Glucotrol XL 2.5 mg Tablets - Lot N8030, the lot used in the bioequivalence trial. This was the only set of dissolution data to fail at the L1 level. It did pass at the L2 level.

Table 7 Initial Dissolution Data from Glucotrol XL 2.5 mg Tablets - Lot N8030

Tab #	Percent Released @ 4 hours	Fraction Released Relative to Mean	Percent Released @ 8 hours	Fraction Released Relative to Mean	Percent Released @ 16 hours	Fraction Released Relative to Mean	Percent Released over 4-8 Hours	Rate of Release per Hour (4-8 Hours)
Descriptive Statistics								
Mean	13.46	1.0	47.88	1.0	101.08	1.0	—	8.60
SD	4.44	0.3301	8.13	0.1697	3.90	0.0386	—	1.15
CV	***33.01***	33.01	***16.97***	16.97	3.86	3.86	—	13.33
min								
max								
% deviation from mean								
min								
max								

Data in ***bold italics*** is for emphasis.

Data was also provided after long term storage and included stability data for up to 12 weeks (See Table 8). All dissolution tests after storage for 6 and 12 weeks under all storage conditions met the L1 acceptance criteria.

Table 8 Long Term Storage Conditions with Dissolution Data Submitted

Temp(°C)	RH (%)	Duration (Weeks)		
		0	6	12
30	Not mentioned - assume ambient	Initial Baseline Data	d.a.	d.a.
40	Not mentioned - assume ambient	N/A	d.a.	d.a.
50	Not mentioned - assume ambient	N/A	d.a.	d.a.
40	75	N/A	d.a.	d.a.

N/A not applicable - initial time 0 dissolution dissolution data was available for 30 °C.
d.a. Data available in application. For each lot, data is available upon storage in [redacted] containers containing [redacted] tablets.

E. Reviewer Comments

The dissolution procedure for the 2.5 mg tablet is very similar to the procedure for the 5 and 10 mg tablets. The main differences are that the volume is 500 ml instead of 900 ml and that the analytical method is different (i.e. UV absorption wavelength differs). The volume difference should not matter, as the final drug concentration is similar for the two procedures. **The difference in analytical method is also not important.**

The FDA Guidance for Industry—Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. September 1997 suggests a number of considerations when setting dissolution criteria for extended release oral dosage form, including:

- At least three time points for pharmacopeial purposes.
  - Early time point (1 - 2 hours) to show dose dumping is not a problem
  - Intermediate time point to define *in vitro* release
  - Final time point to show essentially complete release
- Additional sampling times may be required for approval purposes.
- The dissolution specification range should generally be ± 10% of the mean observed value from the clinical/bioavailability lots. [2]
- For drugs with zero order release rates the guidance suggests that a release rate specification may be used either alone in combination with other dissolution specifications.[3]

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2 FDA Guidance for Industry—Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. September 1997
VII. Applications of an IVIVC
B. Setting Dissolution Specifications
1. Setting Dissolution Specifications Without an IVIVC - pg 17

3 FDA Guidance for Industry—Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. September 1997
VII. Applications of an IVIVC
B. Setting Dissolution Specifications
3. Setting Specifications Based on Release Rate - page 19

- Test times and specifications chosen are based on drug release profile data.
- Specifications are generally set so that some lots fail at level 1 testing but are acceptable at level 2 testing.

The current specification of [redacted], released at 8 hours is ±17.5% and is wider than the ±10% recommended in the guidance. However, the data from the 8 hour time point (See Table 9) support using the wider critera, as this will allow acceptance at the L2 level. The increased variance is due to a tablet that dissolved more slowly than most of the others. This may be why one or two subjects in the bioequivalence trial had a delayed Tmax. In spite of this delayed absorption, four 2.5 mg tablets had comparable bioavailability to one 10 mg tablet (See VII Bioequivalence).

Table 9 Descriptive Statistics from Initial Dissolution Data from Glucotrol XL 2.5 mg Tablets - Lot N8030

Tab #	Percent Released @ 4 hours	Fraction Released Relative to Mean	Percent Released @ 8 hours	Fraction Released Relative to Mean	Percent Released @ 12 hours	Fraction Released Relative to Mean	Percent Released over 4-8 Hours	Rate of Release per Hour (4-8 Hours)
Mean	13.46	1.0	47.88	1.0	101.08	1.0	—	8.60
SD	4.44	0.3301	8.13	0.1697	3.90	0.0386	—	1.15
CV	***33.01***	33.01	***16.97***	16.97	3.86	3.86	—	13.33
min								
max								
% deviation from mean								
min								
max								

Bold italicized data is for emphasis.

The data from the 4 hour time point suggest that the specifications for this time point could be more stringent. Specifically the percent released at 4 hours might be lowered.

Based upon the 4 - 8 hour release rate data, this release rate specification might also be more stringent. The data to calculate release rate over 8 - 12 hours was not provided and so can't be evaluated.

In light of the above information and since the specifications for dissolution are currently approved and in use for the 5 and 10 mg tablets; the dissolution procedures, specifications and acceptance criteria are acceptable.

VII. BIOEQUIVALENCE

The pivotal bioequivalence trial was a randomized, open-label, single-dose, 2-treatment, 2-period, 2-way crossover study with a 7-day washout between treatment periods.

In this study the bioavailability of 4 x 2.5 mg Glucotrol XL tablets was compared to the bioavailability of 1 x 10 mg Glucotrol XL tablet in 35 healthy male and female subjects between 18 - 45 yo. The study results demonstrate that 4 x 2.5 mg Glucotrol XL tablets are bioequivalent to 1 x 10 mg Glucotrol XL tablet.

A. Pharmacokinetic Metrics

The formulations have similar dose adjusted bioavailability (See **Table 10**)

Table 10 Pharmacokinetic Metrics from Single Dose Biocomparison Trial

Metric	4 x 2.5 mg Tablets	1 x 10 mg Tablet	p-Value	Ratio 4 x 2.5 mg : 10 mg or Difference	Upper and Lower Limits of 90% Confidence Interval
Cmax[1] (ng/ml)	376	342	N/A	1.10	102 & 119
AUC0-∞[1] (ng/ml x hr^{-1})	6084	6030	N/A	1.01	96 & 106
AUC0-t[2] (ng/ml x hr^{-1})	6067 ± 1751 29% (4022 - 10965)	5853 ± 1627 28% (3171 - 11206)			
Tmax[2] (hours)	10.3 ± 1.7 16% (8 - 12)	11 ± 2.9 26% (8 - 24)	0.179	- 0.7	-1.5461 & 0.1605
$t_{1/2}$[2] (hours)	8.4 ± 2.8 33% (3.8 - 13.4)	9.3 ± 4.3 46% (3.7 - 22.3)	0.184	- 0.9	-2.1228 & 0.2341

1 - Geometric Mean
2 - Arithmetic Mean, SD, CV and Range
N/A - not applicable

The half-life of glipizide reported in the original NDA review with the immediate release formulation was 2 - 4 hours. This half-life, the half-life of approximately 9 hours with the GITS formulation, the time to Cmax and the nature of the formulation indicate that 'flip-flop' kinetics is likely occurring. Consequently, the reported half-life with the GITS formulation is reflective of the half-life of absorption and is not an elimination half-life.

B. Plasma Concentration vs. Time Profiles

The profiles of the arithmetic mean concentrations from the 2 treatment arms are very similar with the 4 x 2.5 mg tablets having a slightly later and larger peak (See Figure 1). In contrast the geometric mean data show an earlier and larger peak.

Individual absorption data for the 2.5 mg tablets demonstrate that Tmax is slightly earlier in a few subjects and that Cmax's tend to be higher. For example 13/35 subjects (37.8%) in the 4 x 2.5 mg group vs. 5/36 subjects (13.8%) in the 1 x 10 mg group had Cmax's >450 ng/ml. (See Figure 2 and Figure 3.) On average there is a higher mean Cmax in the 4 x 2.5 mg group

Most subjects did not begin to absorb drug until 4 hours post ingestion. The 10 mg tablets had a delayed Tmax in one subject. The earlier absorption with multiple tablets and the single incident of significantly delayed absorption with a 10 mg tablet may reflect differences in GI transit with multiple tablets vs. a single tablet (See Figure 2 and Figure 3 - Appendix 1).

C. Adverse Effects

There was a difference in adverse effects (AE's) between groups in treatment emergent AE's. There were

13 AE's (12 treatment related) in 8/36 subjects receiving the 1 x 10 mg treatment and 17 AE's (16 treatment related) in 9/35 subjects receiving the 4 x 2.5 mg treatment. It's difficult to say whether there is a real difference or not due to the small numbers. When broken down by body system, in most systems the number of AE's between groups differed by one. The largest difference was in the 'nervous' category.

	4 x 2.5 mg	1 x 10 mg
Nervous	7	4
Dizziness	1	3
Tremor	7	2

Within the 'nervous' category, the primary difference in AE's is in the incidence of tremor in the 2.5 mg group. Tremor and dizziness can both be associated with hypoglycemia. There is no information provided in the sNDA regarding time of onset, duration, or concurrent plasma drug or glucose concentrations. Thus it's impossible to determine the relationship between intraindividual plasma concentrations and hypoglycemia. Although on average, there is a higher mean Cmax in the 4 x 2.5 mg group. As mentioned previously 13/35 (37.1%) vs. 5/36 (13.8%) of Cmax's in the 4 x 2.5 mg and 1 x 10 mg groups respectively were >450 ng/ml. The sponsor also attributed the tremor to higher drug concentrations and hypoglycemia.

There were no serious AE's and virtually all AE's were classified as mild in severity.

Although there is some indication toward faster and more extensive absorption with the 2.5 mg tablets, there were not major differences and those seen may have been spurious

VIII. COMMENTS TO THE SPONSOR

These comments are for informational purposes only and are intended to assist the sponsor with future submissions. They do not require a response.

- Since the glipizide assay had not been used for several years, a partial validation of the analyst utilizing this assay should have been performed prior to assaying clinical samples. These data should have been included in the submission.

- The dissolution data, information on the lots used, and their batch sizes were difficult to find. This slows the review. As we move to electronic submissions this becomes an even greater difficulty as electronic submissions are more difficult to navigate. The importance of well laid out submissions and easily navigated tables of contents can not be stressed enough.

- Complete dissolution profiles were generated, however the data was not provided. Data from a complete dissolution profile, specifically the worst data, i.e. the batch that failed at the L1 level, should have been provided. This would also have allowed verification of the 8 - 12 hour release rate. In addition, dissolution data and certificates of analysis from the 10 mg formulation used in the bioequivalence trial would have been appreciated for comparative purposes.

IX. LABELING COMMENTS FOR SPONSOR

The following labeling changes requested by the sponsor are acceptable.

Table 11 Proposed Labeling Modifications

Section	Description of Change
CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism	Add "In a separate single dose study in 36 healthy subjects, four 2.5 mg GLUCOTROL XL Extended Release Tablets were bioequivalent to one 10 mg GLUCOTROL XL Extended Release Tablet."

X. SIGNATURES

Ronald C. Kavanagh

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — 7/30/99 Date

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD - Hae-Young Ahn, Ph.D., Team Leader — Date

7/30/99

~~FD~~ - Hae-Young Ahn, Ph.D., Team Leader — Date
~~FT~~

OCPB Briefing Meeting: None

CC: **NDA 20-329 (orig., 1 copy)**
HFD-510 (Misbin, Weber)
HFD-850 (Lesko, Huang)
HFD-870 (M. Chen, Kavanagh, Ahn)
HFD-340 (Vish)
Central Document Room (Barbara Murphy)

Appendix 1

PROTOCOL REVIEWS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
Protocol Number:	125-004 and L0354
Title:	A comparative, Single-Dose Bioavailability Study of Four 2.5 mg Glipizide GITS (Gastrointestinal Therapeutic System) Tablets and One 10 mg Glipizide GITS Tablet in Healthy Subjects.
Objectives:	**Primary:** To assess whether four 2.5 mg Glipizide GITS is bioequivalent to one 10 mg Glipizide GITS tablet.
Study Design:	Randomized, open-label, single-dose, 2-treatment, 2-period, 2-way crossover study with a 7-day washout between treatment periods..
Subjects:	35 healthy (36 enrolled - one discontinued due to conflict with dental appointment), male and female subjects between 18 - 45 yo less than 200 lbs. and within 15 % of IBW. According to the protocol subjects could be replaced, however none were. Female subjects had to be either of non-child bearing potential or using a protocol approved contraceptive method.

Demographics

	Group A 4 x 2.5 mg - Period 1			Group B 10 mg - Period 1		
	Male	Female	Total	Male	Female	Total
Number	7	11	18	6	12	18
Age						
Mean	27.4	27.5	27.5	23.7	28.4	26.8
SD	8.2	8.7	8.3	2.9	8.6	7.5
Range	18-37	18-44	18-44	19-27	18-44	18-44
Race						
White	6	6	12	4	6	10
Black	1	5	6	2	5	7
Other	0	0	0	0	1	1
Weight						
Mean	75.1	62.5		77.7	64.1	
SD	4.8	10.4		9.0	8.9	
Range	66-79	46-76		70-90	50-80	
Height						
Mean	179.3	166.4		183.3	167.9	
SD	6.7	6.5		7.3	10.1	
Range	168-188	152-177		173-193	152-180	

Significant Inclusion / Exclusion Criteria:	Significant inclusion and exclusion criteria included habitual tobacco or nicotine use within 3 months of the study.
Drug Administration:	Drug was administered after a 10 hour overnight fast with [illegible] solution. Subjects then received [illegible] solution every 15 minutes for 4 hours. Subjects were not allowed to lie down for 4 hours post-dosing.

Drug Product:	2.5 mg Glucotrol XL tablets Lot No. N8030-G1 10 mg Glucotrol XL tablets Lot No. ED-O-290-798
Meals:	Standardized meals that excluded xanthines and alcohol were served beginning 4 hours post-dosing.
PK Blood sampling:	Day 1 and Day 8 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-administration.
Analytical Method:	HPLC - UV method. Plasma concentrations were measured. Concentrations below the lower limit of detection were set to 0.0 ng/ml.
Pharmacokinetic / Pharmacodynamic Data Analysis:	**PK:** Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$ Cmax and Tmax were determined directly from the observed concentrations. The AUC_{0-t} was determined using the linear trapezoidal rule and the $AUC_{0-\infty}$ was determined by AUC_{0-t} + Cpt estimated/kel.
Statistical Plan / Data Analysis:	Descriptive statistics including mean and standard deviations for each pharmacokinetic metric. The LSMeans statement of SAS was used to calculate geometric means for Cmax and AUC and arithmetic means for Tmax and $t_{1/2}$. Ratios of means and arithmetic means as appropriate were compared using ANOVA for a 2-period, 2-treatment crossover design. Sequence effect of subject(sequence) was tested with a claim that other main effects would be tested. 90% confidence intervals were constructed for the ratios of the means of the test and reference products. Sample size was based on an estimated within-subject CV of 30% for Cmax obtained from Gluctrol XL study 90CK04-0505. A sample size of 36 was estimated to provide at least 80% power to determine if the ratio of the geometric means lies within 0.8 to 1.25 using a 5% level of significance.

Results:

Metric	4 x 2.5 mg Tablets	1 x 10 mg Tablet	p-Value	Ratio 4 x 2.5 mg : 10 mg or Difference	Upper and Lower Limits of 90% Confidence Interval
Cmax[1] (ng/ml)	376	342	N/A	1.10	102 & 119
AUC0-∞[1] (ng/ml x hr^{-1})	6084	6030	N/A	1.01	96 & 106
AUC0-t[2] (ng/ml x hr^{-1})	6067 ± 1751 29% (4022 - 10965)	5853 ± 1627 28% (3171 - 11206)			
Tmax[2] (hours)	10.3 ± 1.7 16% (8 - 12)	11 ± 2.9 26% (8 - 24)	0.179	- 0.7	-1.5461 & 0.1605
$t_{1/2}$[2] (hours)	8.4 ± 2.8 33% (3.8 - 13.4)	9.3 ± 4.3 46% (3.7 - 22.3)	0.184	- 0.9	-2.1228 & 0.2341

1 - Geometric Mean
2 - Arithmetic Mean, SD, CV and Range
N/A - not applicable

Sponsor's Conclusions:	Four 2.5 mg tablets are bioequivalent to one 10 mg tablet.
Reviewer's Comments:	**Concomitant Medications** 8/35 subjects in the 4 x 2.5 mg group and 6/36 subjects in the 1 x 10 mg group received concomitant medications during the stud. The difference in the two treatment groups is due to a single dose of an analgesic and use of a dietary supplement during only 1 of the 2 treatment periods, thus causing an imbalance. These medications however would not be expected to alter the kinetics between treatment periods. Other medications taken includedan antifungal agent, an oral contraceptive, and a female hormone. These did not imbalance the treatments arms as they were taken throughout the study. However, they could hypothetically increase the variability in the kinetics. **ANOVA** LN Cmax showed no sequence effect and no period effect, although there was a treatment effect ($p = 0.0497$). This is expected based on the confidence intervals (lower limit = 102%) LN AUC0-∞ showed no sequence effect, and no treatment effect, although there was a period effect ($p = 0.0131$). Tmax showed no sequence effect, no period effect, and no treatment effect. $t_{1/2}$ showed a sequence effect ($p=0.0219$), no period effect, and no treatment effect.

AE's

There was a difference in AE's between groups in treatment emergent AE's. There were 13 AE's (12 treatment related) in 8/36 subjects receiving the 10 mg treatment and 17 AE's (16 treatment related) in 9/35 subjects receiving the 4 x 2.5 mg treatment. It's difficult to say whether there is a real difference or not due to the small numbers. When broken down by body system in most systems there was only a difference of 1 in the number of AE's between groups The largest difference was in the 'nervous' category.

	4 x 2.5 mg	1 x 10 mg
Nervous	7	4
Dizziness	1	3
Tremor	7	2

The primary difference is in the incidence of tremor in the 2.5 mg group. Tremor and dizziness can both be associated with hypoglycemia. There is no information provided in the sNDA regarding time of onset, duration, and concurrent plasma drug or glucose concentrations to determine the relationship to intraindividual plasma concentrations and hypoglycemia. Although, on average there is a higher mean Cmax in the 4 x 2.5 mg group. In addition 13/35 vs. 5/36 Cmax's in the 4 x 2.5 mg and 1 x 10 mg groups respectively were >450 ng/ml. The sponsor also attributed the tremor to higher drug concentrations and hypoglycemia.

There were no serious AE's and virtually all AE's were classified as mild in severity.

Plasma Concentration vs. Time Profiles

The mean profiles from the 2 treatment arms are very similar with the 4 x 2.5 mg tablets having a slightly later and larger peak (See figure 1). Absorption for the 2.5 mg tablets began slightly earlier in a few subjects and had higher Cmax's in a number of subjects (*vide supra*). The 10 mg tablets had a delayed Tmax in one subject. The earlier absorption with multiple tablets and the single incident of significantly delayed absorption with a single 10 mg tablet may reflect differences in GI transit with multiple tablets vs. a single tablet (See figures 2 and 3). Most subjects did not begin to absorb drug until 4 hours post ingestion.

Pharmacokinetic Metrics

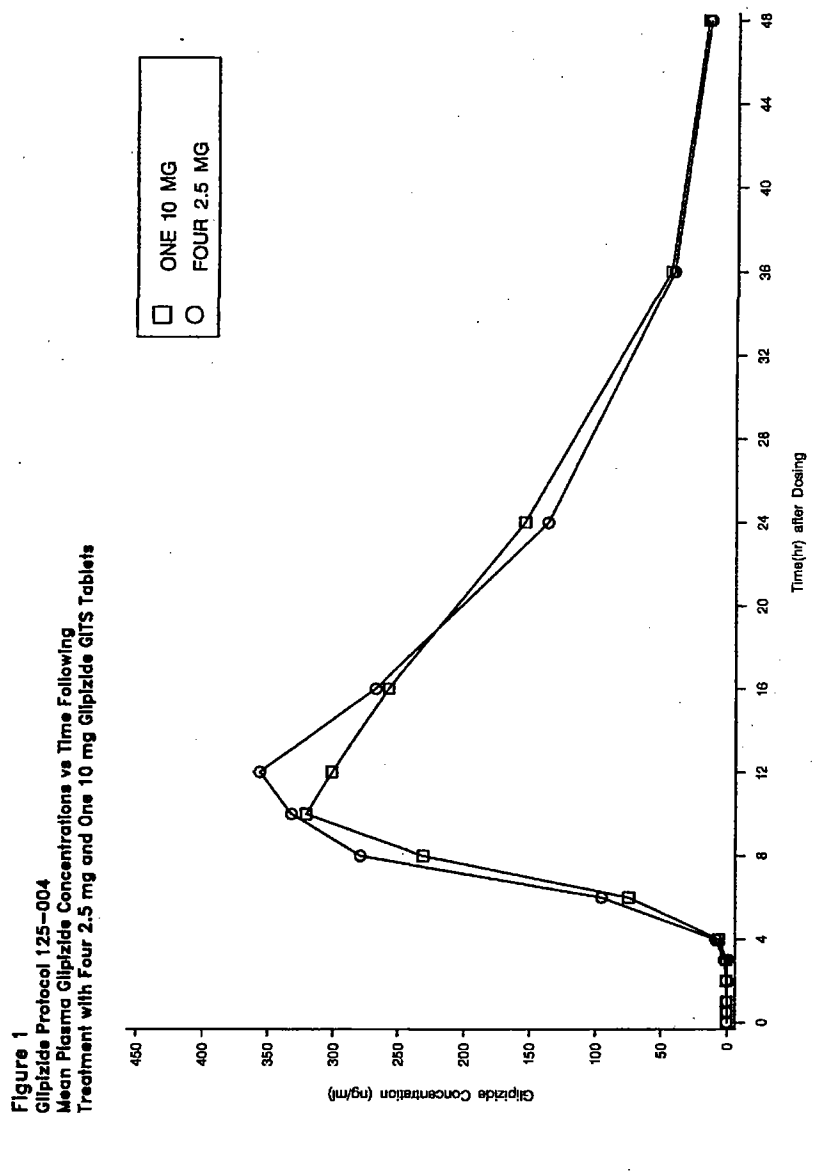
The half-life of glipizide reported in the original NDA review is 2 - 4 hours. This half-life, the time to Cmax and the nature of the formulation indicate that 'flip-flop' kinetics is likely occurring and that the reported half-life is reflective of the half-life of absorption, and is not an elimination half-life.

Reviewer's Conclusions:

Concur with the sponsor, the formulations have similar dose adjusted bioavailability. (I'm not using the term bioequivalent because they're different dosages.)

Although there may be a slightly greater absorption with the 2.5 mg tablets, their intended use is to make a 7.5 mg dose intermediate between the 5 and 10 mg doses. Consequently the use of a single 2.5 mg tablet should further minimize the slight difference in bioavailability.

Figure 1 Mean Glipizide Plasma Concentration vs. Time Profiles



4 52

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-329/s-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-329/S-003

FEB 19 1999

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: Rita A. Wittich
Director, Regulatory Affairs

Dear Ms. Wittich:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Glucotrol XL (glipizde) Extended Release Tablets
NDA Number:	20-329
Supplement Number:	S-003
Date of Supplement:	February 10, 1999
Date of Receipt:	February 11, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 12, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

Completed 7/30 REIC OCPB

Sincerely,

Enid Galliers

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

cc:
Original NDA 20-329/S-003
HFD-510/Div. Files
HFD-510/CSO/J. Weber

filename: C:\DATA\WPFILES\20329

SUPPLEMENT ACKNOWLEDGEMENT / PA

Regulatory Affairs Division
Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 733 6866 Fax 212 573 1563

ORIGINAL

Pfizer Pharmaceuticals

NDA NO. 20329 REF. NO. 003
NDA SUPPL FOR SE2
SCS

Craig M. Audet
Director
Regulatory Affairs

February 10, 1999

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

HFD 510
FEB 11 1999

Re: Glucotrol XL (glipizide) Extended Release Tablets
NDA #20-329

Dear Dr. Sobel:

Please refer to Pfizer Inc's approved New Drug Application for Glucotrol XL (glipizide) Extended Release Tablets (Glipizide GITS), NDA #20-329.

Pursuant to 21 CFR 314.70, Pfizer submits this supplemental application to NDA #20-329 for a 2.5 mg dosage strength of Glucotrol XL. Contained within this supplemental application is the relevant pharmacokinetics and manufacturing, chemistry and control data to support this request.

The currently approved Glucotrol XL commercial dosage forms are 5 and 10 mg tablets, approved by the FDA in a letter dated April 26, 1994. Pfizer incorporates the relevant portions of NDA #20-329 in this submission by reference.

Pfizer commits to place the first three commercial lots into our ongoing stability program, to periodically submit the stability data as it becomes available, and to withdraw from the market any lot that fails to meet the required specifications.

Additionally, as required by 21 CFR 314.70(a), a field copy of this supplemental application has been provided to Pfizer's home FDA district office.

Should you have any questions regarding this submission, please do not hesitate to contact me at (212) 733-6866.

Please include this supplement in the subject file.

Sincerely,

Craig M. Audet

Enclosure (1)

REVIEWER INITIALED
AP
8/10/99
DATE

RECORD OF TELEPHONE CONVERSATION

20-329

NDA#:	20-329 SCS-003
Product Name:	Glucotrol XL 2.5 mg tablets
Generic Name:	Glipizide
Sponsor:	Pfizer Groton, CT
Date:	July 30, 1999
Telecon/Meeting initiated by:	Applicant/Sponsor ✓ FDA
Name and Title of Person(s) with whom conversation was held:	**Sponsor:** Craig Audet — Regulatory Affairs Pareen Gamper — CMC **FDA:** Ron Kavanagh — OCPB Hae Young Ahn — OCPB

This phone call was initiated to clarify the discrepancy in the UV wavelength between the different dissolution methods for the 2.5 mg tablets and the 5 &10 mg tablets.

According to the sponsor,

The dissolution method for the 5 and 10 mg tablets use a spectrophometer at [redacted] nm without HPLC separation.

The dissolution method for the 2.5 mg tablets use an HPLC method with UV absorbance at [redacted] nm.

The reason for the difference in wavelength is to eliminate the effect of the absorbance of the excipients in the non-HPLC method.

All HPLC methods used for manufacturing controls use [redacted] nm and is a USP method (USP XXIII).

Post T-con note: Bioanalytical HPLC-UV method uses a wavelength of [redacted] nm.

Signatures:

Ronald E. Kavanagh

Ronald E. Kavanagh, BS Pharm, PharmD, PhD — 7/30/99 Date

Hae Young Ahn

Hae Young Ahn, PhD (Team Leader) — 7/30/99 Date

CC: NDA File 20-329
HFD-870 (Ahn, Ysern)