

GLUCOTROL XL - glipizide tablet, extended release
Physicians Total Care, Inc.

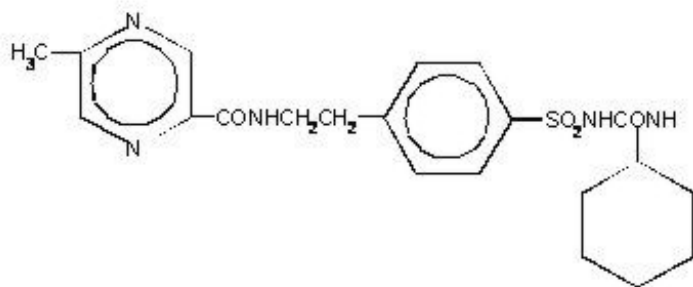
GLUCOTROL XL®
(glipizide)
Extended Release Tablets

For Oral Use

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 C₂₁H₂₇N₅O₄S; 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, hypromellose, 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. Extrapaneatic 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.

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.

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 C_{max} 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 and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

1. Known hypersensitivity to glipizide or any excipients in the GITS tablets.
2. Type 1 diabetes mellitus, 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

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUCOTROL XL or any other anti-diabetic drug.

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.

Hemolytic Anemia

Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLUCOTROL XL belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

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.

Physician Counseling Information for 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 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. Use of GLUCOTROL XL or other antidiabetic medications must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitution 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 GLUCOTROL XL or other antidiabetic medications. Maintenance or discontinuation of GLUCOTROL XL or other antidiabetic medications should be based on clinical judgment using regular clinical and laboratory evaluations.

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:

	GLUCOTROL XL (%) (N=278)	Placebo (%) (N=69)
Adverse Effect		
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.

Post-Marketing Experience

The following adverse events have been reported in post-marketing surveillance:

Gastrointestinal

abdominal pain

Hepatobiliary

Cholestatic and hepatocellular forms of liver injury accompanied by jaundice have been reported rarely in association with glipizide; GLUCOTROL XL should be discontinued if this occurs.

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 (see **PRECAUTIONS**), 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 (LD₅₀ 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	NDC 54868-
30	4420-0

5 mg tablets are white and imprinted with "GLUCOTROL XL 5" on one side.

Bottles of	NDC 54868-
15	3335-1
Bottles of	NDC 54868-
30	3335-0
Bottles of	NDC 54868-
60	3335-3
Bottles of	NDC 54868-
100	3335-2

10 mg tablets are white and imprinted with "GLUCOTROL XL 10" on one side.

Bottles of 10	NDC 54868-3334-3
Bottles of 30	NDC 54868-3334-0
Bottles of 60	NDC 54868-3334-2
Bottles of 90	NDC 54868-3334-4
Bottles of 100	NDC 54868-3334-1

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).

Rx only



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Tulsa, OK 74146

PATIENT INFORMATION

GLUCOTROL XL

(glipizide) extended release tablets

Read this information carefully before you start taking this medicine. Read the information you get with your medicine each time you refill your prescription. There may be new information. This information does not take the place of your healthcare provider's advice. Ask your healthcare provider or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What is GLUCOTROL XL?

GLUCOTROL XL (glue-kuh-troll-ex-el) is a medicine you take by mouth. It is used to treat type 2 diabetes (also called non-insulin-dependant diabetes mellitus). Your healthcare provider has prescribed GLUCOTROL XL because your current treatment, including diet and exercise, has not been able to bring your blood sugar level under good control.

Your body makes insulin to keep the amount of sugar (glucose) in your blood at the right level. With type 2 diabetes:

- your body may not be making enough insulin

- your body may not be using the insulin that you have already made
- the level of sugar in your blood is too high

If your blood sugar level is not under control, it can lead to serious medical problems, such as kidney damage, nerve damage, blindness, problems with circulation (blood movement in your body), loss of feet, legs or other limbs, high blood pressure, heart attack, or stroke.

GLUCOTROL XL works mainly by:

- helping the body release more of its own insulin
- helping the body respond better to its own insulin
- lowering the amount of sugar (glucose) made by the body

Even after you start taking GLUCOTROL XL, you must continue to follow your program of diet and exercise.

Who Should Not Use GLUCOTROL XL?

Do not use GLUCOTROL XL if you:

- have a condition called diabetic ketoacidosis
- have ever had an allergic reaction to glipizide or any of the other ingredients in GLUCOTROL XL. Ask your healthcare provider or pharmacist for a list of these ingredients.

Only your healthcare provider can decide if GLUCOTROL XL is right for you. Before you start GLUCOTROL XL, tell the healthcare provider if you:

- are taking or using **any** prescription medicines or non-prescription medicines, including natural or herbal remedies. Other medications can increase your chance of getting low blood sugar or high blood sugar. Be sure to tell your healthcare provider if you take the medicines miconazole or fluconazole, used to fight fungus infections.
- have ever had a condition called diabetic ketoacidosis
- have kidney or liver problems
- have had blockage or narrowing of your intestines due to illness or past surgery
- have chronic (continuing) diarrhea
- are pregnant or might be pregnant. Your healthcare provider may switch you to insulin injections some time during your pregnancy. You should not take GLUCOTROL XL during the last month of pregnancy.
- are breast-feeding. GLUCOTROL XL may pass to the baby through your milk and cause harm.
- have glucose-6-phosphate dehydrogenase (G6PD) deficiency. This condition usually runs in families. People with G6PD deficiency who take GLUCOTROL XL may develop hemolytic anemia (fast breakdown of red blood cells).

How Should I Take GLUCOTROL XL?

GLUCOTROL XL tablets come in three different strengths (2.5 mg, 5 mg and 10 mg). Your healthcare provider will prescribe the dose that is right for you.

- Take GLUCOTROL XL once a day with breakfast. The tablet is designed to release the medicine slowly over 24 hours. This is why you have to take it only once a day.
- Swallow the tablet whole. Never **chew, crush** or **cut** the tablet in half. This would damage the tablet and release too much medicine into your body at one time.
- After all of the medicine has been released, the empty tablet shell will pass out of the body normally in a bowel movement. Do not be concerned if you see the empty tablet shell in your stool (bowel movement).

It is important to take GLUCOTROL XL every day to help keep your blood sugar level under good

control. Your healthcare provider may adjust your dose depending on your blood glucose test results. If your blood sugar level is not under control, call your healthcare provider. Do not change your dose without your healthcare provider's approval.

In case of overdose, call the poison control center or your healthcare provider right away, or have someone drive you to the nearest emergency room.

You must continue your diet and exercise program while taking GLUCOTROL XL. You must also have your blood and urine tested regularly to be sure GLUCOTROL XL is working.

GLUCOTROL XL may not work for everyone. If it does work, you may find that GLUCOTROL XL is not working as well for you after you have used it for a while. Tell your healthcare provider if GLUCOTROL XL is not working well.

What Should I Avoid While Taking GLUCOTROL XL?

Some medicines can affect how well GLUCOTROL XL works or may affect your blood sugar level. Check with your healthcare provider or pharmacist before you start or stop taking prescription or over-the-counter medicines, including natural/herbal remedies, while on GLUCOTROL XL.

What are the Possible Side Effects of GLUCOTROL XL?

Low blood sugar. GLUCOTROL XL may lower your blood sugar to low levels that are dangerous (hypoglycemia). This can happen if you do not follow your diet, exercise too much, drink alcohol, are under stress, or get sick. This could also happen if your dose of GLUCOTROL XL is higher than you need. Your healthcare provider may need to adjust it. Do not adjust the dose on your own.

Be sure you know how to recognize your body's signs that your blood sugar is too low. These signs include:

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- | | |
|-------------------------|---------------------------------|
| • a cold clammy feeling | • hunger |
| • unusual sweating | • fast heartbeat |
| • dizziness | • headache |
| • weakness | • blurred vision |
| • trembling | • slurred speech |
| • shakiness | • tingling in the lips or hands |
-

If you notice any of these signs, eat or drink something with sugar in it right away, such as a regular (not diet) soft drink, orange juice, honey, sugar candy. You can also keep glucose tablets on hand that are available from your pharmacy. If you do not feel better shortly or your blood sugar level does not go up, call your healthcare provider. If you cannot reach your healthcare provider in an emergency, call 911 or have someone drive you to the nearest emergency room.

Other side effects. GLUCOTROL XL may cause other side effects in some people. However, the incidence of serious side effects with GLUCOTROL XL is very low. Other than the signs of low blood sugar listed above, possible side effects include:

- feeling jittery
- diarrhea
- gas

GLUCOTROL XL may cause other less common side effects besides those listed here. For a list of all side effects that have been reported, ask your healthcare provider or pharmacist.

While it has never been reported with GLUCOTROL XL, another similar type of diabetes medicine has been linked to a higher risk of heart attacks. If you have risk factors for heart disease and take

GLUCOTROL XL, be sure to see your healthcare provider for regular checkups.

How To Store GLUCOTROL XL

Keep GLUCOTROL XL and all medicines out of reach of children. Store GLUCOTROL XL in a dry place, in its original container, and at room temperature (between 59°–86°F or 15°–30°C).

General Advice About Prescription Medicines

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. If you have any concerns about GLUCOTROL XL, ask your healthcare provider. Your healthcare provider or pharmacist can give you information about GLUCOTROL XL that was written for healthcare professionals. Do not use GLUCOTROL XL for a condition for which it was not prescribed. Do not share GLUCOTROL XL with other people. For more information about GLUCOTROL XL, you can visit the Pfizer internet site at www.pfizer.com.



Distributed by

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September 2009

PRINCIPAL DISPLAY PANEL - 2.5 mg Tablet Bottle Label

Glucotrol XL[®]
(glipizide)
extended release
2.5 mg GITS



PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

Glucotrol XL[®]
(glipizide) extended release
5 mg GITS



PRINCIPAL DISPLAY PANEL - 10 mg Tablet Bottle Label

Rx only
Glucotrol XL®
(glipizide) extended release
10 mg GITS



GLUCOTROL XL
glipizide tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-4420 (NDC:0049-1620)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name		Strength
GLIPIZIDE (UNII: X7WDT95N5C) (GLIPIZIDE - UNII:X7WDT95N5C)		GLIPIZIDE 2.5 mg

Inactive Ingredients	
Ingredient Name	Strength
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	

FERRIC OXIDE RED (UNII: 1K09F3G675)				
CELLULOSE ACETATE (UNII: 3J2P07GVB6)				
Product Characteristics				
Color	blue	Score	no score	
Shape	ROUND (biconvex)	Size	8mm	
Flavor		Imprint Code	GLUCOTROL;XL;2;5	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4420-0	30 in 1 BOTTLE		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA020329	05/08/2003		

GLUCOTROL XL

glipizide tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-3335(NDC:0049-1550)
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
GLIPIZIDE (UNII: X7WDT95N5C) (GLIPIZIDE - UNII:X7WDT95N5C)		GLIPIZIDE	5 mg
Inactive Ingredients			
Ingredient Name			Strength
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)			
HYPROMELLOSES (UNII: 3NXW29V3WO)			
MAGNESIUM STEARATE (UNII: 70097M6I30)			
SODIUM CHLORIDE (UNII: 451W47IQ8X)			
FERRIC OXIDE RED (UNII: 1K09F3G675)			
CELLULOSE ACETATE (UNII: 3J2P07GVB6)			
Product Characteristics			
Color	white	Score	no score

Shape	ROUND (biconvex)	Size	8mm
Flavor		Imprint Code	GLUCOTROL;XL;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-3335-0	30 in 1 BOTTLE, PLASTIC		
2	NDC:54868-3335-1	15 in 1 BOTTLE, PLASTIC		
3	NDC:54868-3335-2	100 in 1 BOTTLE		
4	NDC:54868-3335-3	60 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020329	08/01/1994	

GLUCOTROL XL

glipizide tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-3334(NDC:0049-1560)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLIPIZIDE (UNII: X7WDT95N5C) (GLIPIZIDE - UNII:X7WDT95N5C)	GLIPIZIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	

Product Characteristics

Color	white	Score	no score
Shape	ROUND (biconvex)	Size	10mm
Flavor		Imprint Code	GLUCOTROL;XL;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-3334-0	30 in 1 BOTTLE, PLASTIC		
2	NDC:54868-3334-1	100 in 1 BOTTLE		
3	NDC:54868-3334-2	60 in 1 BOTTLE, PLASTIC		
4	NDC:54868-3334-3	10 in 1 BOTTLE, PLASTIC		
5	NDC:54868-3334-4	90 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020329	09/30/1994	

Labeler - Physicians Total Care, Inc. (194123980)**Establishment**

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel, repack

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Physicians Total Care, Inc.