Approved Date: December 19th, 2008
Revision Date: February 05th, 2015
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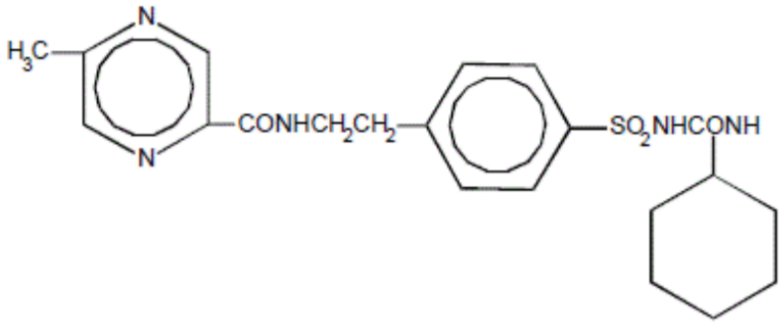
Package Insert of Glipizide Controlled Release Tablets

Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]
Generic Name: Glipizide Controlled Release Tablets
Chinese Pinyin: Geliebiqin Kongshi Pian

[Active Ingredients]
The active pharmaceutical ingredient (API) of this product is Glipizide
Chemical Name of the API: 1-cyclohexyl-3-[[p-[2-(5- methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea.
Chemical structure:



Molecular Formula: $C_{21}H_{27}N_5O_4S$
Molecular Weight: 445.5

[Inactive Ingredient]
Polyvinylpyrrolidone, Copovidone, Iron(III) oxide-hydroxide, Iron(III) oxide, Alcohol, Purified Water, Magnesium Stearate, Carboxymethyl Starch Sodium, Hydroxypropylmethylcellulose, Carbomer, Sodium Chloride, Cellulose acetate, Diethyl-o-Phthalate, Acetone, Spectrablend Pink, Gastrolysis Film Coating Premix.

[Properties]
This product is a white film-coated tablets and the core inside is a yellow-red double layer.

[Indications]
Glipizide controlled release tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

[Strength]
5 mg.

[Dosage and Administration]
There is no fixed dosage regimen for the management of diabetes mellitus with Glipizide Extended Release Tablet or any other hypoglycemic agent. Glycemic control should be monitored with hemoglobin A1C 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 Glipizide Extended Release Tablet may be sufficient during periods of transient loss of control in patients usually controlled on diet.
In general, LOTOFIER should be given with breakfast.

[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 Glipizide 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
Only 3.4% of patients receiving Glipizide 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 Glipizide Extended Release Tablets and Glipizide Tablets, 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 Glipizide - 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 Glipizide controlled-release tablets 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: hinitis
Special senses: blurred vision Urogenital–polyuria

Other adverse experiences occurred with an incidence of less than 1% in Glipizide Controlled Release Tablets 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 Glipizide Controlled Release Tablets, 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.
In post-marketing experience of Glipizide Controlled Release Tablets, the additional adverse reaction of abdominal pain has been reported.
The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with Glipizide Controlled Release Tablets:

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.

[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.

[Precautions]
General

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Glipizide Controlled Release Tablets 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 Glipizide Controlled 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 A1C may be useful.

[Use in Pregnant and Lactation]
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 pediatric patients have not been established.

[Geriatric Use]
Of the total number of patients in clinical studies of Glipizide Controlled Release Tablets, 33 percent were 65 and over. Approximately 1–2 days longer were required to reach steady-state in the elderly. 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.

[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%).

[OverDosage]
There is no well-documented experience with Glipizide Controlled Release Tablets overdosage in humans. There have been no known suicide attempts associated with purposeful overdosing with Glipizide Controlled Release Tablets. 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.

[Pharmacology and Toxicology]

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 Glipizide Controlled Release Tablets 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 Glipizide Controlled Release Tablets - 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 Glipizide Controlled 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 A1C, 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 Glipizide Controlled Release Tablets' effect of reducing hemoglobin A1C 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 A1C and fasting plasma glucose were similar in younger and older patients. Efficacy of Glipizide Controlled Release Tablets was not affected by gender, race or weight (as assessed by body mass index). In long term extension trials, efficacy of Glipizide Controlled Release Tablets 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 Glipizide Controlled Release Tablets for 8 weeks and then crossed over to the other drug for an additional 8 weeks. Glipizide Controlled Release Tablets administration resulted in significantly lower fasting plasma glucose levels and equivalent hemoglobin A1C levels, as compared to immediate-release Glipizide.

In 12 week, well-controlled studies there was a maximal average net reduction in hemoglobin A1c of 1.7% in absolute units between placebo-treated and Glipizide Controlled Release Tablets-treated patients.

[Pharmacokinetics]

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 Glipizide Controlled Release Tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6 to 12 hours after dosing. With subsequent once daily dosing of Glipizide Controlled 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 Glipizide Controlled 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 Glipizide Controlled 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 ($\geqslant$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 Glipizide Controlled Release Tablets. Administration of Glipizide Controlled Release Tablets 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 Glipizide Controlled Release Tablets 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 Glipizide Controlled Release 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 Glipizide Controlled Release Tablets 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 Glipizide Controlled Release Tablets were bioequivalent. In a separate single dose study in 36 healthy subjects, four 2.5-mg Glipizide Controlled Release Tablets were bioequivalent to one 10 mg Glipizide Controlled Release Tablets.
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.

[Storage]
Seal and store away from direct sunlight and prevent from moisture. Do not exceed 25°C.

[Packaging]
Aluminum-Aluminum blister packaging, 7 tablets/plate, two plates/carton
Aluminum-Aluminum blister packaging, 7 tablets/plate, three plates/carton
Aluminum-Aluminum blister packaging, 7 tablets/plate, four plates/carton
Aluminum-Aluminum blister packaging, 7 tablets/plate, six plates/carton

[Shelf-Life]
24 months

[Executive Standard]
National Medical Products Agency Standard YBH14872008

[Approval Number]
Guo Yao Zhun Zi H20084634

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