GLIPIZIDE- glipizide tablet, film coated, extended release
Preferred Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GLIPIZIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for GLIPIZIDE EXTENDED-RELEASE TABLETS.

GlipiZIDE Extended-Release Tablets, for oral use
Initial U.S. Approval: 1994

INDICATIONS AND USAGE

Glipizide extended-release tablets are a sulfonylurea indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
Limitations of Use: Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 5 mg once daily. Dose adjustment can be made based on the patient's glycemic control. Maximum recommended dose is 20 mg once daily **(2.1)**.
- Administer with breakfast or the first meal of the day **(2.1)**.
- For combination therapy with other blood-glucose-lowering agents, initiate the agent at the lowest recommended dose, and observe patients for hypoglycemia **(2.2)**.

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg **(3)**.

CONTRAINDICATIONS

- Known hypersensitivity to glipizide or any of the product's ingredients **(4)**
- Hypersensitivity to sulfonamide derivatives **(4)**

WARNINGS AND PRECAUTIONS

- Hypoglycemia: May be severe. Ensure proper patient selection, dosing, and instructions, particularly in at-risk populations (e.g., elderly, renally impaired) and when used with other anti-diabetic medications **(5.1)**.
- Hemolytic Anemia: Can occur if glucose 6-phosphate dehydrogenase (G6PD) deficient. Consider a non-sulfonylurea alternative **(5.2)**.
- Potential Increased Risk of Cardiovascular Mortality with Sulfonylureas: Inform patient of risks, benefits and treatment alternatives **(5.3)**.
- Macrovascular Outcomes: No clinical studies have established conclusive evidence of macrovascular risk reduction with glipizide extended-release tablets or any other anti-diabetic drug **(5.4)**.

ADVERSE REACTIONS

Most common adverse reactions (incidence > 3%) are dizziness, diarrhea, nervousness, tremor, hypoglycemia and flatulence **(6.1)**.
To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

DRUG INTERACTIONS

- Certain medications may affect glucose metabolism, requiring glipizide extended-release tablets dose adjustment and close monitoring of blood glucose **(7.1)**
- Miconazole: Monitor patients closely. Severe hypoglycemia can occur when glipizide and oral miconazole are used concomitantly **(7.2,12.3)**.
- Fluconazole: Monitor patients closely. An increase in glipizide AUC was seen after fluconazole administration **(7.3, 12.3)**.
- Colesevelam: glipizide extended-release tablets should be administered at least 4 hours prior to colesevelam **(7.4, 12.3)**.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm **(8.1)**.
- Nursing Mothers: Discontinue glipizide extended-release tablets or nursing taking into consideration the importance of glipizide extended-release tablets to the mother **(8.3)**.
- Geriatric, Hepatically Impaired Patients: At risk for hypoglycemia with glipizide extended-release tablets. Use caution in dose selection and titration, and monitor closely **(8.5, 8.6)**.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Glipizide extended-release tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.1 Limitations of Use

Glipizide extended-release tablets are not recommended for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Glipizide extended-release tablets should be administered orally with breakfast or the first main meal of the day.

The recommended starting dose of glipizide extended-release tablets is 5 mg once daily. Start patients at increased risk for hypoglycemia (e.g., the elderly or patients with hepatic insufficiency) at 2.5 mg *[see Use in Specific Population (8.5, 8.6)]*.

Dosage adjustment can be made based on the patient's glycemic control. The maximum recommended dose is 20 mg once daily. Patients receiving immediate release glipizide may be switched to glipizide extended-release tablets once daily at the nearest equivalent total daily dose.

2.2 Use with Other Glucose Lowering Agents

When adding glipizide extended-release tablets to other anti-diabetic drugs, initiate glipizide extended-release tablets at 5 mg once daily. Start patients at increased risk for hypoglycemia at a lower dose.

When colesevelam is coadministered with glipizide ER, maximum plasma concentration and total exposure to glipizide is reduced. Therefore, glipizide extended-release tablets should be administered at least 4 hours prior to colesevelam.

3 DOSAGE FORMS AND STRENGTHS

Glipizide Extended-Release Tablets:

5 mg, pink, film-coated, round tablets, with an indentation hole on one side, with "C" and "745" in black on one side and plain on the other side.

10 mg, white, film-coated, round tablets, with an indentation hole on one side, with "C" and "746" in black on one side and plain on the other side.

4 CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

- Known hypersensitivity to glipizide or any of the product's ingredients.
- Hypersensitivity to sulfonamide derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

All sulfonylurea drugs, including glipizide extended-release tablets, are capable of producing severe hypoglycemia *[see ADVERSE REACTIONS (6)]*.

Concomitant use of glipizide extended-release tablets with other anti-diabetic medication can increase the risk of hypoglycemia. A lower dose of glipizide extended-release tablets may be required to minimize the risk of hypoglycemia when combining it with other anti-diabetic medications.

Educate patients to recognize and manage hypoglycemia. When initiating and increasing glipizide extended-release tablets in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications) start at 2.5 mg. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of anti-diabetic medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

5.2 Hemolytic Anemia

Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents, including glipizide extended-release tablets, can lead to hemolytic anemia. Avoid use of glipizide extended-release tablets in patients with G6PD deficiency. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

5.3 Increased Risk of Cardiovascular Mortality with Sulfonylureas

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 mellitus. The study involved 823 patients who were randomly assigned to one of four treatment groups.

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.

5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glipizide extended-release tablets or any other anti-diabetic drug.

5.5 Gastrointestinal Obstruction

There have been reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug with this non-dissolvable extended release formulation. Avoid use of glipizide extended-release tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic).

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail below and elsewhere in the labeling:

- Hypoglycemia *[see Warnings and Precautions (5.1)]*
- Hemolytic anemia *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 580 patients from 31 to 87 years of age received glipizide extended-release tablets in doses from 5 mg to 60 mg in both controlled and open trials. The dosages above 20 mg are not recommended dosages. In these trials, approximately 180 patients were treated with glipizide extended-release tablets for at least 6 months.

Table 1 summarizes the incidence of adverse reactions, other than hypoglycemia, that were reported in pooled double-blind, placebo-controlled trials in ≥3% of glipizide extended-release tablet-treated patients and more commonly than in patients who received placebo.

Table 1: Incidence (%) of Adverse Reactions Reported in ≥3% of Patients Treated in Placebo-Controlled Clinical Trials and More Commonly in Patients Treated with GlipizideExtended-Release Tablets (Excluding Hypoglycemia)

	Glipizide Extended-Release Tablets (%)	**Placebo (%)**
	(N=278)	**(N=69)**
Adverse Effect		
Dizziness	6.8	5.8
Diarrhea	5.4	0.0
Nervousness	3.6	2.9
Tremor	3.6	0.0
Flatulence	3.2	1.4

Hypoglycemia:

Of the 580 patients that received glipizide extended-release tablets in clinical trials, 3.4% had hypoglycemia documented by a blood-glucose measurement <60 mg/dL and/or symptoms believed to be associated with hypoglycemia and 2.6% of patients discontinued for this reason. Hypoglycemia was not reported for any placebo patients.

Gastrointestinal Reactions

In clinical trials, the incidence of gastrointestinal (GI) side effects (nausea, vomiting, constipation, dyspepsia), occurred in less than 3% of glipizide extended-release tablet-treated patients and were more common in glipizide extended-release tablet-treated patients than those receiving placebo.

Dermatologic Reactions

In clinical trials, allergic skin reactions, i.e., urticaria occurred in less than 1.5% of treated patients and were more common in glipizide extended-release tablet-treated patients than those receiving placebo. These may be transient and may disappear despite continued use of glipizide XL; if skin reactions persist, the drug should be discontinued.

Laboratory Tests: Mild to moderate elevations of ALT, LDH, alkaline phosphatase, BUN and creatinine have been noted. The relationship of these abnormalities to glipizide is uncertain.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of glipizide extended-release tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Abdominal pain
- Cholestatic and hepatocellular forms of liver injury accompanied by jaundice
- Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia *[see Warnings and Precautions (5.2)]*, aplastic anemia, pancytopenia
- Hepatic porphyria and disulfiram-like reactions
- Hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- Rash
- There have been reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug with this non-dissolvable extended release formulation.

7 DRUG INTERACTIONS

7.1 Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require glipizide extended-release tablets dose adjustment and close monitoring for hypoglycemia or worsening glycemic control.

The following are examples of medication that may increase the glucose lowering effect of glipizide extended-release tablets, increase the susceptibility to and/or intensity of hypoglycemia: antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), sulfonamide antibiotics, nonsteroidal anti-inflammatory agents, chloramphenicol, probenecid, coumarins, voriconazole, H2 receptor antagonists, and quinolones. When these medications are administered to a patient receiving glipizide extended-release tablets, monitor the patient closely for hypoglycemia. When these medications are discontinued from a patient receiving glipizide extended-release tablets, monitor the patient closely for worsening glycemic control.

The following are examples of medication that may reduce the glucose-lowering effect of glipizide extended-release tablets, leading to worsening glycemic control: atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), thyroid hormones, phenytoin, nicotinic acid, and calcium channel blocking drugs. When such drugs are administered to patients receiving glipizide extended-release tablets, monitor the patients closely for worsening glycemic control. When these medications are discontinued from patients receiving glipizide extended-release tablets, monitor the patient closely for hypoglycemia.

Alcohol, beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of the

glucose-lowering effect. Increased frequency of monitoring may be required when glipizide extended-release tablets is coadministered with these drugs.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine. Increased frequency of monitoring may be required when glipizide extended-release tablets is coadministered with these drugs.

7.2 Miconazole

Monitor patients closely for hypoglycemia when glipizide extended-release tablets are coadministered with miconazole. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported *[see Clinical Pharmacology (12.3)]*.

7.3 Fluconazole

Monitor patients closely for hypoglycemia when glipizide extended-release tablets are coadministered with fluconazole. Concomitant treatment with fluconazole increases plasma concentrations of glipizide, which may lead to hypoglycemia *[see Clinical Pharmacology (12.3)]*.

7.4 Colesevelam

Glipizide extended-release tablets should be administered at least 4 hours prior to the administration of colesevelam. Colesevelam can reduce the maximum plasma concentration and total exposure of glipizide when the two are coadministered *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5 to 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. There are no adequate and well controlled studies in pregnant women. Glipizide extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

8.3 Nursing Mothers

It is not known whether glipizide extended-release tablets are 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.

8.4 Pediatric Use

Safety and effectiveness in children have not been established.

8.5 Geriatric Use

There were no overall differences in effectiveness or safety between younger and older patients, but greater sensitivity of some individuals cannot be ruled out. Elderly patients are particularly susceptible to the hypoglycemic action of anti-diabetic agents. Hypoglycemia may be difficult to recognize in these patients. Therefore, dosing should be conservative to avoid hypoglycemia. *[see Dosage and*

Administration (2.1), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

8.6 Hepatic Impairment

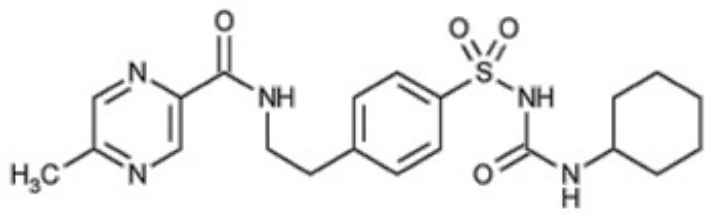
There is no information regarding the effects of hepatic impairment on the disposition of glipizide. However, since glipizide is highly protein bound and hepatic biotransformation is the predominant route of elimination, the pharmacokinetics and/or pharmacodynamics of glipizide may be altered in patients with hepatic impairment. If hypoglycemia occurs in such patients, it may be prolonged and appropriate management should be instituted. *[see Dosage and Administration (2.1), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

Overdosage of sulfonylureas including glipizide can produce severe hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated with oral glucose. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment are medical emergencies requiring immediate treatment. The patient should be treated with glucagon or intravenous glucose. 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.

11 DESCRIPTION

Glipizide extended-release tablets are an oral sulfonylurea. 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_5 O_4 S; the molecular weight is 445.55; the structural formula is shown below:



Molecular Structure

Glipizide, USP 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.

Inert ingredients in the 5 mg and 10 mg formulations are: anhydrous lactose, butylated hydroxytoluene, cellulose acetate, colloidal silicon dioxide, glyceryl monostearate, hypromellose, magnesium stearate, methacrylic acid copolymer (Type B Powder), polyethylene glycol, polyethylene oxide, polysorbate 80, propylene glycol, sodium chloride, sodium starch glycolate (Type A), iron oxide black, titanium dioxide and triacetin. Additionally, the 5 mg strength also contains FD&C yellow #6 aluminum lake and FD&C red #40 aluminum lake.

System Components and Performance

Glipizide extended-release tablets are 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 function of the glipizide extended-release tablets depends upon the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Glipizide primarily lowers blood glucose by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

12.2 Pharmacodynamics

The insulinotropic response to a meal is enhanced with glipizide extended-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 two randomized, double-blind, dose-response studies comprising a total of 347 patients, there was no significant increase in fasting insulin in all glipizide extended-release tablet-treated patients combined compared to placebo, although minor elevations were observed at some doses.

In studies of glipizide extended-release tablets in subjects with type 2 diabete mellitus, once daily administration produced reductions in hemoglobin A1c, fasting plasma glucose and postprandial glucose. The relationship between dose and reduction in hemoglobin A1c was not established, however subjects treated with 20 mg had a greater reduction in fasting plasma glucose compared to subjects treated with 5 mg.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of glipizide was 100% after single oral doses in patients with type 2 diabetes mellitus. Beginning 2 to 3 hours after administration of glipizide extended-release tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6 to 12 hours after dosing. With subsequent once daily dosing of glipizide extended-release tablets, 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 mellitus after administration of 20 mg glipizide extended-release tablets, compared to immediate release glipizide (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 extended-release tablets in 21 males with type 2 diabetes mellitus and patients younger than 65 years. No accumulation of drug was observed in patients with type 2 diabetes mellitus during chronic dosing with glipizide extended-release tablets.

Administration of glipizide extended-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 extended-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 extended-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 mellitus, the pharmacokinetics of glipizide were linear with glipizide extended-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 extended-release tablets were bioequivalent. In a separate single dose study in 36 healthy subjects, four 2.5-mg glipizide extended-release tablets were bioequivalent to one 10 mg glipizide extended-release tablets.

Distribution

The mean volume of distribution was approximately 10 liters after single intravenous doses in patients with type 2 diabetes mellitus. Glipizide is 98 to 99% bound to serum proteins, primarily to albumin.

Metabolism

The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite, an acetylamino-ethyl benzene derivative, which accounts for less than 2% of a dose, is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound.

Elimination

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 mean total body clearance of glipizide was approximately 3 liters per hour after single intravenous doses in patients with type 2 diabetes mellitus. 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 mellitus.

Specific Populations

Pediatric:

Studies characterizing the pharmacokinetics of glipizide in pediatric patients have not been performed.

Geriatric:

There were no differences in the pharmacokinetics of glipizide after single dose administration to older diabetic subjects compared to younger healthy subjects. *[see Use in Specific Populations (8.5)]*

Renal Impairment:

The pharmacokinetics of glipizide has not been evaluated in patients with varying degree of renal impairment. Limited data indicates that glipizide biotransformation products may remain in circulation for a longer time in subjects with renal impairment than that seen in subjects with normal renal function.

Hepatic Impairment:

The pharmacokinetics of glipizide has not been evaluated in patients with hepatic impairment.

Drug-drug Interactions

Miconazole

A potential interaction between oral miconazole and oral glipizide leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. *[see Drug Interactions (7.2)]*

Fluconazole

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

Interactions (7.3)]

Colesevelam

Colesevelam can reduce the maximum plasma concentration and total exposure of glipizide when the two are coadministered. In studies assessing the effect of colesevelam on the pharmacokinetics of glipizide ER in healthy volunteers, reductions in glipizide $AUC_{0-\infty}$ and C_{max} of 12% and 13%, respectively were observed when colesevelam was coadministered with glipizide ER. When glipizide ER was administered 4 hours prior to colesevelam, there was no significant change in glipizide $AUC_{0-\infty}$ or C_{max}, -4% and 0%, respectively. *[see Drug Interactions (7.4)]*

13 NONCLINICAL TOXICOLOGY

13.1 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.

15 REFERENCES

1. *Diabetes,* 19, SUPP. 2: 747 to 830, 1970

16 HOW SUPPLIED/STORAGE AND HANDLING

Glipizide Extended-Release Tablets are supplied as 5 mg and 10 mg film-coated, round tablets and imprinted in black as follows:

Table 2. Glipizide Extended-Release Tablets Presentations

Tablet Strength	**Tablet Color/ Shape**	**Tablet Markings**	**Package Size**	**NDC Code**
10 mg	White, Film-coated, Round	Indentation hole on one side, with “C” and “746” in black on one side and plain on the other side	Bottles of 30	NDC 68788-7230-3
			Bottles of 60	NDC 68788-7230-6
			Bottles of 90	NDC 68788-7230-9
			Bottles of 100	NDC 68788-7230-1

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. PROTECT FROM MOISTURE AND HUMIDITY. Dispense in a tight, light-resistant container as defined in the USP. Do not crush.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the potential adverse reactions of glipizide extended-release tablets including hypoglycemia. Explain the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development to patients and responsible family members. Also inform patients about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of glycemic control.

Inform patients that glipizide extended-release tablets should be swallowed whole. Inform patients that they should not chew, divide or crush tablets and they may occasionally notice in their stool something that looks like a tablet. In the glipizide extended-release tablets, the medication is contained within a

non-dissolvable shell that has been specially designed to slowly release the drug so the body can absorb it.

Advise patients with diabetes to inform their healthcare provider if they are pregnant, contemplating pregnancy, breastfeeding, or contemplating breastfeeding.

This product's label may have been updated. For full prescribing information, please contact Par Pharmaceutical at 1-800-828-9393 or visit www.parpharm.com.

PATIENT INFORMATION

GlipiZIDE (glip' i zide) Extended-Release Tablets

What is Glipizide Extended-Release Tablets?

- Glipizide extended-release tablets is a prescription medicine you take by mouth used along with diet and exercise to lower blood sugar in adults with type 2 diabetes mellitus.
- Glipizide extended-release tablets is not for people with type 1 diabetes or people with diabetic ketoacidosis. It is not known if glipizide extended-release tablets are safe and effective in children under 18 years of age.

Who Should Not Take Glipizide Extended-Release Tablets? Do not use glipizide extended-release tablets if you:

- have a condition called diabetic ketoacidosis
- have ever had an allergic reaction to glipizide or any of the other ingredients in glipizide extended-release tablets. See the end of this Patient Information for a complete list of ingredients in glipizide extended-release tablets.

What should I tell my doctor before taking glipizide extended-release tablets?

Before you take glipizide extended-release tablets, tell your healthcare provider if you:

- Have ever had a condition called diabetic ketoacidosis.
- Have kidney or liver problems.
- Have had a blockage or narrowing of your intestines due to illness or past surgery.
- Have chronic (continuing) diarrhea.
- Have glucose-6-phosphate dehydrogenase (G6PD) deficiency. This condition usually runs in families. People with G6PD deficiency who take glipizide extended-release tablets may develop hemolytic anemia (fast breakdown of red blood cells).
- Are pregnant or might be pregnant. It is not known if glipizide extended-release tablets will harm your unborn baby. If you are pregnant, talk to you healthcare provider about the best way to control your blood sugar while you are pregnant. You should not take glipizide extended-release tablets during the last month of pregnancy.
- Are breastfeeding or plan to breastfeed. It is not known if glipizide extended-release tablets passes into your breast milk. You and your healthcare provider should decide if you will take glipizide extended-release tablets or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Glipizide extended-release tablets may affect the way other medicines work, and other medicines may affect how glipizide extended-release tablets works.

Some medicines can affect how well glipizide extended-release tablets works or may affect you blood

sugar level.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take glipizide extended-release tablets?

- Take glipizide extended-release tablets exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much glipizide extended-release tablets to take and when to take it.
- Take glipizide extended-release tablets by mouth, 1 time each day with breakfast or your first meal of the day.
- Each glipizide extended-release tablets will release the medicine slowly over 24 hours. This is why you take it only 1 time each day.
- Swallow the glipizide extended-release tablets whole. Do not break, crush, dissolve, chew, or cut the tablet in half. This will damage the tablet and release too much medicine into your body at one time.
- When you take glipizide extended-release tablets you may see something in your stool that looks like a tablet. This is the empty shell from the tablet. It is normal for the empty shell to pass with your bowel movement after medicine has been absorbed by your body.
- It is important to take glipizide extended-release tablets every day to help keep your blood sugar level under good control. Your healthcare provider may change your dose depending on your blood sugar test results. If your blood sugar level is not under control, call your healthcare provider. Do not change your dose unless your healthcare provider tells you to.
- If you take too much glipizide extended-release tablets, call your healthcare provider or go to the nearest emergency room right away. Your healthcare provider may tell you to take glipizide extended-release tablets with other diabetes medicines. Low blood sugar can happen more often when glipizide extended-release tablets is taken with other diabetes medicines. See **"What are the possible side effects of glipizide extended-release tablets?"**
- Check your blood sugar as your healthcare provider tells you to.
- Stay on your prescribed diet and exercise program while taking glipizide extended-release tablets.

What should I avoid while taking glipizide extended-release tablets?

- Do not drink alcohol while taking glipizide extended-release tablets. It can increase your chances of getting serious side effects.
- Do not drive, operate machinery, or do other dangerous activities until you know how glipizide extended-release tablets affects you.

What are the possible side effects of glipizide extended-release tablets? Glipizide extended-release tablets can cause serious side effects, including:

- Low blood sugar. Glipizide extended-release tablets may cause low blood sugar. Signs and symptoms of low blood sugar may include:

• 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 have signs or symptoms of low blood sugar, eat or drink something with sugar in it right away. If you do not feel better or your blood sugar level does not go up, call your healthcare provider or go to the nearest emergency room.

The most common side effects of glipizide extended-release tablets include: dizziness, diarrhea, nervousness, tremor, and gas.

These are not all the possible side effects of glipizide extended-release tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How to store glipizide extended-release tablets?

- Store glipizide extended-release tablets at 68° to 77°F (20° to 25°C).
- Store glipizide extended-release tablets in a dry place, in its original container.

Keep glipizide extended-release tablets and all medicines out of reach of children. General information about the safe and effective use of glipizide extended-release tablets.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use glipizide extended-release tablets for a condition for which it was not prescribed. Do not give glipizide extended-release tablets to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about glipizide extended-release tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about glipizide extended-release tablets that is written for healthcare professionals.

For more information about glipizide extended-release tablets, you can contact Par Pharmaceutical at 1-800-828-9393 or visit the Par internet site at www.parpharm.com.

What are the ingredients in glipizide extended-release tablets? Active ingredient: glipizide

Inactive ingredients: anhydrous lactose, butylated hydroxytoluene, cellulose acetate, colloidal silicon dioxide, glyceryl monostearate, hypromellose, magnesium stearate, methacrylic acid copolymer (Type B Powder), polyethylene glycol, polyethylene oxide, polysorbate 80, propylene glycol, sodium chloride, sodium starch glycolate (Type A), iron oxide black, titanium dioxide and triacetin. Additionally, the 5 mg strength also contains FD&C yellow #6 aluminum lake and FD&C red #40 aluminum lake.

This Patient Information has been approved by the U.S. Food and Drug Administration

Rx Only

Manufactured by:

Par Pharmaceutical

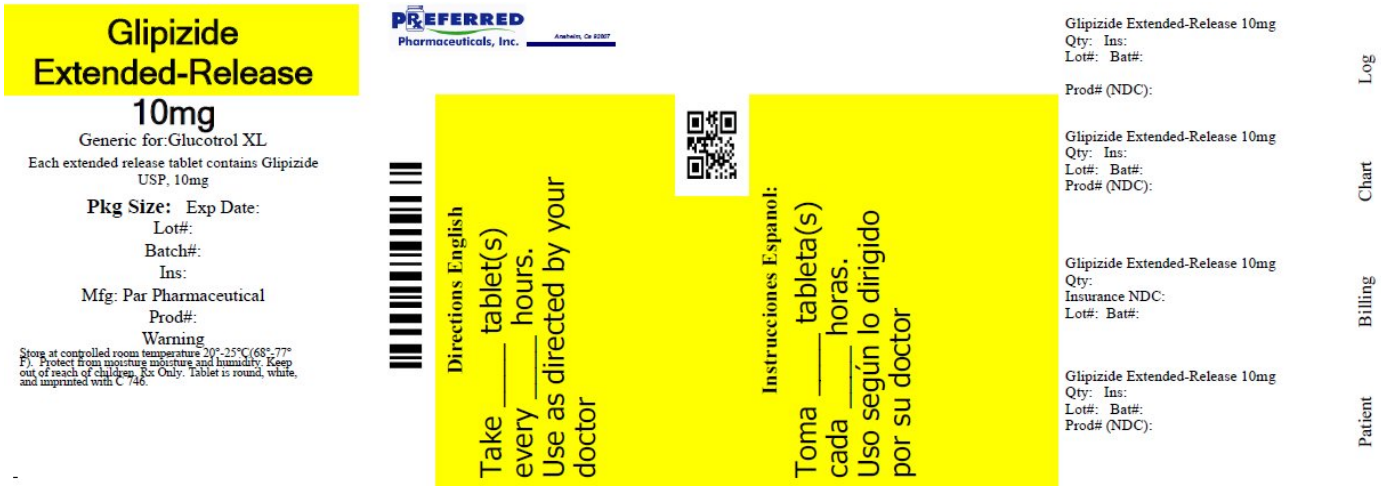
Chestnut Ridge, NY 10977

Revised 09/2017 OS744A-01-50-05

Repackaged By: Preferred Pharmaceuticals Inc.

PACKAGE LABEL PRINCIPAL DISPLAY PANEL

NDC 68788-7230
GlipiZIDE
Extended-Release Tablets
10 mg
Rx Only



GLIPIZIDE

glipizide tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68788-7230(NDC:10370-746)
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**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	

CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:2) (UNII: 5KY68S2577)	
CETEARETH-8 (UNII: 4W0XA5SY57)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM STARCH GLYCOLATE TYPE A CORN (UNII: AG9B65PV6B)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	746
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68788-7230-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	08/06/2018	
2	NDC:68788-7230-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	08/06/2018	
3	NDC:68788-7230-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	08/06/2018	
4	NDC:68788-7230-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	08/06/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076159	08/06/2018	

Labeler - Preferred Pharmaceuticals Inc. (791119022)

Registrant - Preferred Pharmaceuticals Inc. (791119022)

Establishment

Name	Address	ID/FEI	Business Operations
Preferred Pharmaceuticals Inc.		791119022	REPACK(68788-7230)

Revised: 6/2020 Preferred Pharmaceuticals Inc.