SAFETY DATA SHEET

GLIPIZIDE EXTENDED-RELEASE TABLETS.

Strength: 2.5 mg, 5 mg, 10 mg **Revision No.:** 00

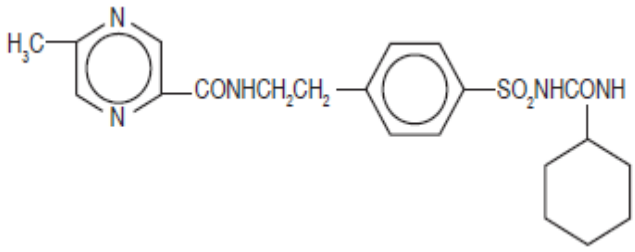
Pack Style: Refer NDC Number Section

EMERGENCY OVERVIEW

Each glipizide extended-release tablets intended for oral administration contains **:** 2.5 mg, 5 mg, 10 mg of glipizide and excipients generally considered to be non- toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

Section 1. IDENTIFICATION OF THE PRODUCT

Product Name:	Glipizide extended-release tablets 2.5 mg, 5 mg, 10 mg
Active Pharmaceutical Ingredient	Glipizide
Formula:	C 21 H27N5O4S
Chemical Name:	1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido) ethyl] phenyl] sulfonyl] urea



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.

Manufacturer / supplier identification

Company:	Cadila Healthcare Ltd. Ahmedabad, India
Address:	Plot no 417,419 and 420 , Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand. Dist. Ahmedabad – 382210. State: Gujarat. India
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Emergency Telephone No.	Tel.: +91 79 6868100

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Strength: 2.5 mg, 5 mg, 10 mg **Revision No.:** 00

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Therapeutic Category: Type 2 diabetes mellitus

Indications : Glipizide extended-release tablets are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

Contraindications Glipizide is contraindicated in patients with:
- Known hypersensitivity to Glipizide or any of the product's Ingredients.
- Hypersensitivity to sulphonamide derivatives.

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

Restriction on Use / Contraindications:
1.Glipizide extended-release tablets is not recommended for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
2.Glipizide is contraindicated in patients with
- Known hypersensitivity to Glipizide or any of the product's Ingredients.
- Hypersensitivity to sulphonamide derivatives.

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WARNINGS AND PRECAUTION:

Hypoglycemia

All sulfonylurea drugs, including glipizide extended-release tablets, are capable of producing severe hypoglycemia. 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.

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.

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.

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.

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).

The 2.5 mg tablets contain FD&C Yellow No.5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No.5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

SECTION 2. HAZARD(S) IDENTIFICATION

Dosage and Administration

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

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 once daily at the nearest equivalent total daily dose.

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 extended-release tablets, 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.

Adverse Effects:

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

• Hypoglycemia
• Hemolytic anemia

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 tablets 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 glipizide extended-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 tablets treated patients and were more common in glipizide extended-release tablets 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 tablets 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.

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, 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.

Over Dose Effect

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.

Pregnancy Comments

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. 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.

Nursing Mothers

It is not known whether glipizide is 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.

Pediatric Use

Safety and effectiveness in children have not been established.

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.

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.

Drug Interactions:

Miconazole

Monitor patients closely for hypoglycemia when glipizide extended-release tablets are co-administered with miconazole. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported

Fluconazole

Monitor patients closely for hypoglycemia when glipizide extended-release tablets are co-administered with fluconazole. Concomitant treatment with fluconazole

increases plasma concentrations of glipizide, which may lead to hypoglycemia.

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.

Section 3. COMPOSITION / INFORMATION ON INGREDIENTS

Component	Exposure limit	CAS No.
Principle component		
Glipizide	Not found	29094-61-9
Inactive ingredients		
Acetyltributyl citrate	Not found	77-90-7
Colloidal silicon dioxide	Not found	7631-86-9
Hydroxyethyl cellulose	Not found	9004-62-0.
Hydroxypropyl cellulose	Not found	9004-64-2
Hypromellose	Not found	9004-65-3
Lactose monohydrate	Not found	5989-81-1
Magnesium stearate	Not found	557-04-0
Acid copolymer	Not found	40623-75-4
Polyethylene glycol.	Not found	25322-68-3
Additionally each 2.5 mg tablet contains.		
FD&C yellow #5 aluminum lake	Not found	12225-21-7
Titanium dioxide	Not found	13463-67-7
Additionally each 5 mg tablet contains.		
FD&C yellow #6 aluminum lake	Not found	15790-07-5
Titanium dioxide	Not found	13463-67-7
Ammonium hydroxide	Not found	1336-21-6
Iron oxide black	Not found	1309-38-2
Isopropyl alcohol	Not found	67-63-0
N-butyl alcohol	Not found	71-36-3
Propylene glycol	Not found	57-55-6
Shellac	Not found	9000-59-3

Section 4. FIRST -AID MEASURES

Eye Contact: Check for and remove any contact lenses. Do not use an eye ointment. Seek medical attention

Skin Contact:	After contact with skin, wash immediately with plenty of water. Gently and thoroughly wash the contaminated skin with running water and non-abrasive soap. Be particularly careful to clean folds, crevices, creases and groin. Cover the irritated skin with an emollient. If irritation persists, seek medical attention. Wash contaminated clothing before reusing.
Serious Skin Contact:	Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek medical attention.
Inhalation:	Allow the victim to rest in a well ventilated area. Seek immediate medical attention.
Serious Inhalation:	Not available.
Ingestion:	Do not induce vomiting. Loosen tight clothing such as a collar,tie, belt or waistband. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek immediate medical attention.
Serious Ingestion:	Not available.

Section 5. FIRE FIGHTING MEASURES

Flammability of the Product:	May be combustible at high temperature.
Auto-Ignition Temperature:	Not available.
Flash Points:	Not available.
Flammable Limits:	Not available.
Products of Combustion:	These products are carbon oxides (CO, CO2), nitrogen oxides (NO, NO2...).
Fire Hazards in Presence of Various Substances:	Not available.
Explosion Hazards in Presence of Various Substances:	Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.
Fire Fighting Media and Instructions:	SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use water spray, fog or foam. Do not use water jet.
Special Remarks on Fire Hazards:	Not available.
Special Remarks on Explosion Hazards:	Not available.

Section 6. ACCIDENTAL RELEASE MEASURES

Small Spill: Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill: Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7. HANDLING AND STORAGE

Precautions: Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. Do not breathe dust. Wear suitable protective clothing In case of insufficient ventilation, wear suitable respiratory equipment If you feel unwell, seek medical attention and show the label when possible. Avoid contact with skin and eyes.

Storage: Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed. Keep in a cool, well-ventilated place. Combustible materials should be stored away from extreme heat and away from strong oxidizing agents.

Section 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Engineering Controls: Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection: Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill: Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product.Suggested

	protective clothing might not be sufficient; consult a specialist BEFORE handling this product.
Exposure Limits:	Not available.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Description Glipizide Extended-release Tablets 2.5 mg

Glipizide extended-release tablets, 2.5 mg are yellow colored, round, biconvex film-coated tablets imprinted with "2" on one side with black ink and plain on the other side.

Description Glipizide Extended-release Tablets 5 mg

Glipizide extended-release tablets, 5 mg are orange colored, round, biconvex film-coated tablets imprinted with "3" on one side with black ink and plain on the other side.

Description Glipizide Extended-release Tablets 10 mg

Glipizide extended-release tablets, 10 mg are white colored, round, biconvex film-coated tablets imprinted with "4" on one side and plain on the other side.

NDC No.	**Glipizide Extended-release Tablets 2.5 mg** NDC 68382-335-06 in bottle of 30 tablets NDC 68382-335-14 in bottle of 60 tablets NDC 68382-335-16 in bottle of 90 tablets NDC 68382-335-01 in bottle of 100 tablets NDC 68382-335-05 in bottle of 500 tablets NDC 68382-335-10 in bottle of 1000 tablets NDC 68382-335-77 in cartons of 100 tablets (10 x 10 unit-dose) **Glipizide Extended-release Tablets 5 mg** NDC 68382-336-06 in bottle of 30 tablets NDC 68382-336-14 in bottle of 60 tablets NDC 68382-336-16 in bottle of 90 tablets NDC 68382-336-01 in bottle of 100 tablets NDC 68382-336-05 in bottle of 500 tablets NDC 68382-336-10 in bottle of 1000 tablets NDC 68382-336-77 in cartons of 100 tablets (10 x 10 unit-dose) **Glipizide Extended-release Tablets 10 mg** NDC 68382-337-06 in bottle of 30 tablets NDC 68382-337-14 in bottle of 60 tablets NDC 68382-337-16 in bottle of 90 tablets NDC 68382-337-01 in bottle of 100 tablets

NDC 68382-337-05 in bottle of 500 tablets
NDC 68382-337-10 in bottle of 1000 tablets
NDC 68382-337-77 in cartons of 100 tablets (10 x 10 unit-dose)

State: Mixture

Section 10. STABILITY AND REACTIVITY

Product is stable.

Section 11. TOXICOLOGICAL INFORMATION

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.

Section 12. ECOLOGICAL INFORMATION

Ecotoxicity: Not available.
BOD5 and COD: Not available.
Products of Biodegradation: Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13. DISPOSAL CONSIDERATION

DISPOSAL Whatever cannot be saved for recovery or recycling should be managed in an appropriate and approved waste disposal facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Follow handling guidance

appropriate for OEB-2 potent compounds. Dispose of container and Unused contents in accordance with federal, state and local requirements.

Section 14. TRANSPORT INFORMATION

DOT Classification: Not a DOT controlled material (United States).
Identification: Not applicable.
Special Provisions for Transport: Not applicable.

Section 15. REGULATORY INFORMATION

ANDA No.: 203499

Section 16. OTHER INFORMATION

NFPA (National Fire Protection Association (U.S.A).) Rating:
These ratings are based on NFPA code 704 and are intended for use by emergency personnel to determine the immediate hazards of a material
Health: 2
Flammability: 1
Reactivity: 0
Specific hazard:
Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Splash goggles.

HMIS (U.S.A.):
Health Hazard: 2
Fire Hazard: 1
Reactivity: 0
Personal Protection: E

Date of issue: January 22, 2018 **Supersedes edition:** New Edition

The information presented in the safety data sheet is, to the best our knowledge, accurate and reliable. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.