1.1 THERAPEUTIC CATEGORY

Oral Hypoglycemic

2.0 DESCRIPTION

Minidiab OD (Glipizide) is an oral blood-glucose-lowering drug of the sulfonylurea class.

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

![Structural formula of glipizide](image)

Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethylformamide. Glipizide (Minidiab OD) tablets for oral use are available in 5 and 10 mg strengths.

Inert ingredients are: colloidal silicon dioxide; lactose; microcrystalline cellulose; starch; stearic acid.

3.0 FORMULATION

Each tablet contains 5 mg or 10 mg of glipizide as the active ingredient.
4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Dosage and Method of Administration

As for any hypoglycemic agent, dosage must be adapted for each individual case.

The Gastrointestinal Therapeutic System (GITS) tablets should be swallowed whole with a sufficient amount of liquid. Patients should not chew, divide or crush the tablets. (See section 4.4 – Special Warnings and Special Precautions for Use: Information for Patients.)

Initial Dose:

The recommended starting dose of glipizide GITS is 5 mg/day, given with breakfast. For elderly patients and other patients at risk for hypoglycemia, see “Use In Elderly and In High Risk Patients”

Titration:

Dosage adjustments should ordinarily be in increments of 5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. Steady-state plasma glipizide levels were achieved by the fifth day of dosing with glipizide GITS. Elderly patients may require 1 to 2 days longer.

Maintenance:

Patients are effectively controlled on a once-a-day regimen. The maximum recommended dosage is 20 mg since the maximum blood glucose lowering effect is observed at this level.

Patients receiving immediate release glipizide between 5 and 20 mg daily may be switched safely to glipizide GITS once-a-day at the nearest equivalent or lower total daily dose.

Use In Children

Safety and effectiveness in children have not been established.
Use In Elderly and In High Risk Patients

To decrease the risk of hypoglycemia in patients at risk including elderly patients, debilitated, malnourished or patients with irregular caloric intake and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See 4.4 Special Warnings and Special Precautions for Use.)

Studies in approximately 200 patients aged 65 years or over indicate that glipizide is as safe and effective in this age group as in those patients under 65 years old.

Patients Receiving Insulin

As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be transferred safely to treatment with glipizide GITS. When transferring patients from insulin to glipizide GITS, the following general guidelines should be considered:

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

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

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

Patients Receiving Other Oral Hypoglycemic Agents

As with other sulfonylureas, when switching patients to glipizide GITS from another sulfonylurea, they should be observed carefully for hypoglycemia (e.g., by symptoms or by blood glucose monitoring) for at least two weeks. When switching patients to glipizide GITS a conservative dose is recommended.

Combination Use

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

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

4.3 Contraindications

Glipizide is contraindicated in patients with:

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

4.4 Special Warnings and Special Precautions for Use

G6PD-deficiency: Since glipizide GITS belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency. Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anemia and a non-sulfonylurea alternative should be considered.

Hypoglycemia: All sulfonylurea drugs, including glipizide GITS, are capable of producing severe hypoglycemia which may result in coma, and may require hospitalization. As with any long-acting sulfonylurea, the hypoglycemia associated with glipizide GITS therapy may be prolonged. Patients experiencing severe hypoglycemia should be managed with appropriate glucose therapy and should be monitored for a minimum of 24-48 hours.

Renal or hepatic insufficiency may affect the disposition of glipizide and 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.

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 glucose should be monitored periodically. Measurement of glycosylated hemoglobin should be performed and goals assessed by the current standard of care.

**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 glipizide GITS may influence the pharmacokinetic profile and hence the clinical efficacy of the drug. As with any other nondeformable material, caution should be used when administering glipizide GITS in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic).

There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this nondeformable sustained release formulation.

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

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

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

**4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**
The following products are likely to increase the hypoglycemic effect:

**Antifungals:**

_Miconazole:_ Increase in hypoglycemic effect, possibly leading to symptoms of hypoglycemia or even coma.

_Fluconazole:_ There have been reports of hypoglycemia following the co-administration of glipizide and fluconazole, possibly the result of an increased half-life of glipizide.

_Voriconazole:_ Although not studied, voriconazole may increase the plasma levels of sulfonylureas, (e.g. tobutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Careful monitoring of blood glucose is recommended during co-administration.

**Nonsteroidal anti-inflammatory agents (NSAIDS) (e.g. phenylbutazone):** Increase in hypoglycemic effect of sulfonylureas (displacement of sulfonylurea binding to plasma proteins and/or decrease in sulfonylurea elimination).

_Salicylates (acetylsalicylic acid):_ Increase in hypoglycemic effect by high doses of acetylsalicylic acid (hypoglycemic action of the acetylsalicylic acid).

_Alcoholic:_ Increase in hypoglycemic reaction which can lead to hypoglycemia or coma.

_Beta-blockers:_ All beta-blockers mask some of the symptoms of hypoglycemia, e.g., palpitations and tachycardia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycemia.

_Angiotensin converting enzyme inhibitors:_ The use of angiotensin converting enzyme inhibitors may lead to an increased hypoglycemic effect in diabetic patients treated with sulfonylureas, including glipizide GITS. Therefore, a reduction in glipizide dosage may be required.

_H₂ Receptor Antagonists:_ The use of H₂ receptor antagonists (i.e., cimetidine) may potentiate the hypoglycemic effects of sulfonylureas, including glipizide.

The hypoglycemic action of sulfonylureas in general may also be potentiated by monoamine oxidase inhibitors and drugs that are highly protein bound, such as sulfonamides, chloramphenicol, probenecid and coumarins.

When such drugs are administered to a patient receiving glipizide GITS, the patient should be observed closely for hypoglycemia (or 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.

The following products could lead to hyperglycemia:

Phenothiazines (e.g. chlorpromazine) at high doses (>100 mg per day of chlorpromazine): elevation in blood glucose (reduction in insulin release).

Corticosteroids: elevation in blood glucose.

Sympathomimetics (e.g. ritodrine, salbutamol, terbutaline): elevation in blood glucose due to beta-2-adrenoceptor stimulation.

Other drugs that may produce hyperglycemia and lead to a loss of control include the thiazides and other diuretics, thyroid products, estrogens, progestogens, oral contraceptives, phenytoin, nicotinic acid, calcium channel blocking drugs and isoniazid.

When such drugs are withdrawn from (or administered to) a patient receiving glipizide GITS, the patient should be observed closely for hypoglycemia (or loss of control).

4.6 Pregnancy and Lactation

Pregnancy

Glipizide GITS was found to be mildly fetotoxic in rat reproductive studies. No teratogenic effects were found in rat or rabbit studies.

Because data suggest 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.

Glipizide GITS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. If glipizide GITS is used during pregnancy, it should be discontinued at least one month before the expected delivery date and other therapies instituted to maintain blood glucose levels as close to normal as possible.
Lactation

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.

4.7 Effects on Ability to Drive and Use Machines:

The effect of glipizide on the ability to drive or operate machinery has not been studied. However, there is no evidence to suggest that glipizide may affect these abilities. Patients should be aware of the symptoms of hypoglycemia and be careful about driving and the use of machinery.

4.8 Undesirable Effects

As with other sulfonylureas, there is a possibility of the following events:

Blood and Lymphatic System Disorders: Leucopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia.

Metabolism and Nutrition Disorders: Hypoglycemia may be severe, prolonged and may result in coma. (See section 4.4 Special Warnings and Special Precautions for Use and section 4.9 – Overdoes). Hyponatremia has been reported. Disulfiram-like reactions have been reported with sulfonylureas.

Psychiatric Disorders: Confusion

Nervous System Disorders: Headache, tremor have been reported in patients treated with glipizide GITS.

Eye Disorders: Visual disturbances such as blurred vision and decreased vision have been reported in patients treated with glipizide GITS.

Gastrointestinal Disorders: Abdominal pain, nausea, constipation, diarrhea, epigastric discomfort and vomiting.

Hepatobiliary Disorders: Cholestatic jaundice, toxic hepatitis, and hepatic porphyria. Discontinue treatment if cholestatic jaundice occurs. Hepatic porphyria has been reported with sulfonylureas.

Skin and Subcutaneous Tissue Disorders: Allergic skin reactions including mucocutaneous eruptions, pruritus, urticaria and maculopapular eruptions.
General Disorders and Administration Site Conditions: Malaise

Investigations: Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN, and creatinine. The relationship to glipizide GITS is uncertain.

This is usually transient and does not require discontinuation of therapy; however, it may also be a symptom of hypoglycemia.

4.9 Overdose

There is no well-documented experience with glipizide GITS overdosage in humans.

Overdosage of sulfonylureas including glipizide GITS can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustment 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Glipizide GITS 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. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. The insulintropic response to a meal is enhanced with glipizide GITS administration in diabetic patients. The postprandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment. Reductions in HbA1c and fasting plasma glucose were similar in younger and older patients.
**Other Effects** One study has shown that glipizide GITS therapy is effective in controlling blood glucose without deleterious effects on the plasma lipoprotein profiles of patients treated for type 2 diabetes. These changes were well correlated with the reduction achieved in fasting glucose levels.
5.2 Pharmacokinetic Properties

Beginning 2 to 3 hours after administration of glipizide GITS plasma drug concentrations gradually rise reaching maximum concentrations within 6-12 hours after dosing. With subsequent once daily dosing of glipizide GITS 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 NIDDM after administration of 20 mg glipizide GITS, 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 GITS. Approximately 1 to 2 days longer were required to reach steady-state in patients over 65 years of age. No accumulation of drug was observed in patients with NIDDM during chronic dosing with glipizide GITS. Administration of glipizide GITS with food has no effect on the 2- to 3-hour lag time in drug absorption.

In a single dose, food effect study, the administration of glipizide GITS immediately before a high fat breakfast resulted in a 40% increase in the glipizide mean C\text{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 glipizide GITS 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 NIDDM, the pharmacokinetics of glipizide were linear over the dose range of 5 to 60 mg of glipizide GITS 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 GITS tablets were bioequivalent. 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%). Glipizide is 98-99% bound to serum proteins, primarily to albumin. In a placebo-controlled, crossover study in normal volunteers, glipizide showed no antidiuretic activity and in fact, led to a slight increase in free water clearance.

5.3 Preclinical Safety Data

In nonclinical studies the acute oral toxicity of glipizide was extremely low in all species tested (LD\text{50} greater than 4 g/kg).

Acute toxicity studies showed no specific susceptibility. Chronic toxicity tests in rats and dogs at doses up to 8 mg/kg did not show any evidence of toxic effects.
A 20-month study in rats and an 18-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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities (major)

None.

6.2 Shelf Life

Please see outer package for the expiry date of the product.

6.3 Special Precautions for Storage

Glipizide (Minidiab OD) 5 mg – Store at a temperature not exceeding 30°C
Glipizide (Minidiab OD) 10 mg - Store at a temperature not exceeding 25°C.

Protect from moisture and humidity.

6.4 Nature and Contents of Container

Glipizide GITS tablets will be packed in high density polyethylene bottles.

6.5 Instructions for Use/Handling

No special instructions.

6.6 Availability

Glipizide (Minidiab OD) 5 mg Controlled-Release Tablet: White coated, biconvex tablet with an orifice on one side and printed GXL 5 in HDPE bottles of 30’s.

Glipizide (Minidiab OD) 10 mg Controlled-Release Tablet: White coated, biconvex tablet with an orifice on one side and printed GXL 10 in HDPE bottles of 30’s.