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GLIPIZIDE

MINIDIAB OD

5 mg and 10 mg Controlled-release Tablet

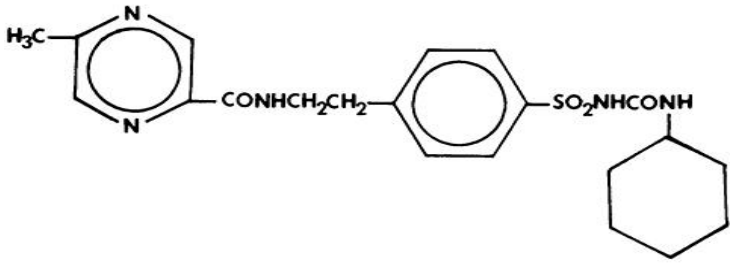
1.0 PHARMACOLOGIC CATEGORY

Oral Hypoglycemic (Sulfonylurea)

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:



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/COMPOSITION

Each controlled release tablet contains 5 mg or 10 mg of Glipizide, EP.

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 Glipizide (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 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 High–risk Patients.

Titration

Dosage adjustments may be in increments of 2.5 mg or 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 mg 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 High-risk Patients

To decrease the risk of hypoglycemia in patients at risk, including elderly, debilitated and malnourished 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 Initial dose and section **4.4 Special Warnings and Precautions for Use**).

Studies in approximately 200 patients aged 65 years or over indicate that glipizide (GITS) 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 type 2 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 self-monitor glucose levels. 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 2 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.

When colesevelam is co-administered with glipizide GITS, maximum plasma concentration and total exposure to glipizide is reduced. Therefore, glipizide GITS should be administered at least 4 hours prior to colesevelam (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

4.3 Contraindications

Glipizide GITS is contraindicated in patients with:

1. Known hypersensitivity to glipizide or any excipients in the glipizide GITS tablets, i.e., colloidal silicon dioxide, lactose, microcrystalline cellulose, starch, stearic acid.

2. Type 1 diabetes mellitus, diabetic ketoacidosis, diabetic coma.

4.4 Special Warnings and Precautions for Use

Glucose-6-Phosphate Dehydrogenase-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 hemolytic anemia, and a non-sulfonylurea alternative should be considered.

Hypoglycemia

All sulfonylureas, including glipizide GITS, are capable of producing severe hypoglycemia, which may result in coma and may require hospitalization. Patients experiencing severe hypoglycemia should be managed with appropriate glucose therapy and monitored for a minimum of 24 to 48 hours.

Renal or hepatic insufficiency may affect the disposition of glipizide GITS 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 a 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 GITS and administer insulin.

The effectiveness of any oral hypoglycemic drug, including glipizide GITS, in lowering blood glucose to a desired level decreases in many patients over a period of time. This 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 GITS 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.

Gastrointestinal Disease

Markedly reduced gastrointestinal (GI) retention times of glipizide GITS may influence the pharmacokinetic profile and hence the clinical efficacy of the drug. As with any other non-deformable material, caution should be used when administering glipizide GITS in patients with pre-existing severe GI narrowing (pathologic or iatrogenic).

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

Information for Patients

The risks of hypoglycemia, its symptoms and treatment, and conditions that pre-dispose 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 non-absorbable 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.

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., tolbutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Careful monitoring of blood glucose is recommended during co-administration.

Non-steroidal Anti-inflammatory Drugs (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).

Alcohol

Increase in hypoglycemic reaction, which can lead to hypoglycemic 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.

H_2 Receptor Antagonists

The use of H_2 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, quinolones and drugs that are highly protein bound, such as sulfonamides, chloramphenicol, probenecid and coumarins.

When such drugs are administered to (or withdrawn from) 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.

<u>The following products could lead to hyperglycemia:</u>

Phenothiazines (e.g., chlorpromazine) at High Doses (>100 mg/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 administered to (or withdrawn from) a patient receiving glipizide GITS, the patient should be observed closely for hypoglycemia (or loss of control).

Colesevelam: In studies assessing the effect of colesevelam on the pharmacokinetics of glipizide GITS in healthy volunteers, reductions in glipizide $AUC_{0-\infty}$ and C_{max} of 12% and 13%, respectively, were observed when colesevelam was co-administered with glipizide GITS. When glipizide GITS was administered 4 hours prior to colesevelam, there was no significant change in glipizide $AUC_{0-\infty}$ or C_{max}, -4% and 0%, respectively. Therefore, glipizide GITS

should be administered at least 4 hours prior to colesevelam to ensure that colesevelam does not reduce the absorption of glipizide.

4.6 Fertility, 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.

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

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.

Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea at the time of delivery. If glipizide GITS is used during pregnancy, it should be discontinued at least 1 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 GITS is excreted in human milk, some sulfonylureas 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 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 GITS on the ability to drive or operate machinery has not been studied; however, there is no evidence to suggest that glipizide GITS 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

Adverse Reactions Table						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10000 to <1/1000**	**Very Rare <1/10 000**	**Not Known (cannot be estimated from available data)**
Blood and lymphatic system disorders						Leukopenia Agranulocytosis Thrombocytopenia Hemolytic anemia Aplastic anemia Pancytopenia
Metabolism and nutrition disorders		Hypoglycemia[‡]				Hyponatremia
Psychiatric disorders			Confusional state[#]			
Nervous system disorders		Headache[#] Tremor[#]				
Eye disorders		Visual impairment				Vision blurred[#] Visual acuity reduced[#]
Gastrointestinal disorders		Abdominal pain Nausea Constipation Diarrhea Vomiting				Epigastric discomfort
Hepatobiliary disorders						Jaundice cholestatic[†] Hepatitis toxic
Skin and subcutaneous tissue disorders		Pruritus	Urticaria			Dermatitis allergic Mucocutaneous rash Rash maculopapular
Congenital, familial and genetic disorders						Porphyria non-acute

Adverse Reactions Table						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10000 to <1/1000**	**Very Rare <1/10 000**	**Not Known (cannot be estimated from available data)**
General disorders and administration site conditions						Malaise[#]
Investigations		Aspartate amino transferase increased[§] Blood alkaline phosphatase increased[§] Blood creatinine increased[§]				Blood lactate dehydrogenase increased[§] Blood urea increased[§]
# This is usually transient and does not require discontinuance of therapy; however, it may also be a symptom of hypoglycemia. ‡ May be severe, prolonged and may result in coma. † Discontinue treatment if cholestatic jaundice occurs. § The relationship to glipizide GITS is uncertain.						

Disulfiram-like reactions have been reported with other sulfonylureas.

4.9 Overdose and Treatment

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 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.

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 insulinotropic response to a meal is enhanced with the administration of glipizide GITS in diabetic patients. The post-prandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment. Reductions in HbA_{1c} 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 mellitus. These changes were well correlated with the reduction achieved in fasting glucose levels.

5.2 Pharmacokinetic Properties

Beginning 2 to 3 hours after the administration of glipizide GITS, plasma drug concentrations gradually rise, reaching maximum concentrations within 6 to 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 type 2 diabetes mellitus after administration of 20 mg of 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 aged 65 years or over. No accumulation of drug was observed in patients with type 2 diabetes mellitus 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_{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 states. 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 type 2 diabetes mellitus, the pharmacokinetics of glipizide were linear over the dose range of 5 mg to 60 mg of glipizide GITS in that the plasma drug concentrations increased proportionately with the 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 the dose is excreted as unchanged drug in the urine and feces; approximately 90% of the dose is excreted as biotransformation products in the urine (80%) and feces (l0%). Glipizide is 98% to 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 non-clinical studies, the acute oral toxicity of glipizide was extremely low in all species tested (LD_{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 Shelf-Life

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

6.2 Storage Condition(s)

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.

6.3 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.

6.4 Special Precautions for Disposal and Other Handling

No special instructions.

7.0 FDA REGISTRATION NUMBER

5 mg Controlled-release tablet: DRP – 3420

10 mg Controlled-release tablet: DRP – 3621

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

5 mg Controlled-release tablet: 31 May 2004

10 mg Controlled-release tablet: 31 May 2004

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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