GLIPIZIDE

Minidiab®

℞

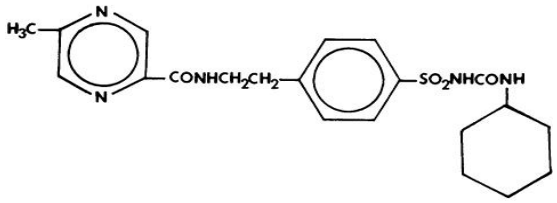
5 mg Tablet

1.0 PHARMACOLOGIC CATEGORY

Oral Hypoglycemic

2.0 DESCRIPTION

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.

3.0 FORMULATION/ COMPOSITION

5 mg Tablet: Each tablet contains 5 mg glipizide, EP.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Glipizide 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.

Short-term administration of glipizide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

In general, glipizide should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose

The recommended starting dose is 5 mg/day, given before breakfast or the mid-day meal. Elderly patients and other patients at risk for hypoglycemia may be started on 2.5 mg (See Use in Elderly and High-Risk Patients).

Titration

Dosage adjustments should ordinarily 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.

Maintenance

Some patients may be effectively controlled on a once-a-day regimen. The maximum recommended single dose is 15 mg. If this is not sufficient, splitting the daily dosage may prove effective. Doses above 15 mg should ordinarily be divided. Total daily dosage above 15 mg should ordinarily be divided. Total dosage above 30 mg has been safely given on a twice-a-day basis to long-term patients. Patients can usually be stabilized on a dosage ranging from 2.5 mg to 30 mg daily. The maximum recommended daily dosage is 40 mg.

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 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 Initial Dose and section **4.4. - Special Warnings and Precautions for Use**).

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. When transferring patients from insulin to glipizide, the following general guidelines should be considered.

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and glipizide 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 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 sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to glipizide due to potential overlapping of drug effect.

Combination Use

When adding other blood-glucose-lowering agents to glipizide 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 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. Hypersensitivity to glipizide or any excipients in the tablets i.e. lactose monohydrate, maize starch, cellulose, microcrystalline, 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 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 sulfonylurea agents, including glipizide 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 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 blood glucose 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. This may be due to progression of the severity of the diabetes or due 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.

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 should also be explained.

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. 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, the patient should be observed closely for hypoglycemia (or loss of blood glucose 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/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 blood 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, the patient should be observed closely for hypoglycemia (or loss of blood glucose control).

4.6 Pregnancy and Lactation

Pregnancy

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

Glipizide 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 drug at the time of delivery. If glipizide 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 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 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

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 < 1/10000**	**Not known (cannot be estimated from available data)**
Blood and lymphatic system disorders						Agranulocytosis Leukopenia Thrombocytopenia Hemolytic Anemia Pancytopenia
Metabolism and nutrition disorders		Hypoglycemia				Hyponatremia
Psychiatric disorders						Confusional state[#]
Nervous system disorders			Dizziness[#] Somnolence[#] Tremor[#]			Headache[#]
Eye disorders			Vision blurred[#]			Diplopia[#] Visual impairment[#] Visual acuity reduced[#]
Gastrointestinal disorders		Nausea[$] Diarrhea[$] Abdominal pain upper[$] Abdominal pain	Vomiting			Constipation[$]
Hepatobiliary disorders			Jaundice cholestatic[†]			Hepatic function abnormal Hepatitis

Skin and subcutaneous tissue disorders			Eczema‡			Dermatitis allergic‡ Erythema‡ Rash morbilliform‡ Rash maculopapular‡ Urticaria‡ Pruritus‡ Photosensitivity reaction
Congenital, familial and genetic disorders						Porphyria non-acute
General disorders and administration site conditions						Malaise#
Investigations						Aspartate amino transferase increased§ Blood lactate dehydrogenase increased§ Blood alkaline phosphatase increased§ Blood urea increased§ Blood creatinine increased§

This is usually transient and does not require discontinuance of therapy; however, it may also be a symptom of hypoglycemia.
$ Appear to be dose related and generally disappear when the dose is divided or reduced.
† Discontinue treatment if cholestatic jaundice occurs.
‡ They frequently disappear with continued therapy. However, if they persist, the drug should be discontinued.
§ The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

Aplastic anemia and disulfiram-like reactions have been reported with other sulfonylureas.

4.9 Overdose

Overdosage of sulfonylureas, including glipizide can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a 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 (5.55 mmol/L). Patients should be closely monitored for a minimum of 24 to 48 hours, and depending on the status of the patient at this time, the physician should decide whether further monitoring is required. Clearance of glipizide from plasma may be prolonged in people 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 is an oral blood-glucose-lowering drug of the sulfonylurea class.

The primary mode of action of glipizide is the stimulation of insulin secretion from the beta cells of pancreatic islet tissue. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. There is

also increasing evidence that extrapancreatic effects involving potentiation of insulin action form a significant component of the activity of glipizide.

Blood sugar control persists for up to 24 hours after a single dose of glipizide, even though plasma levels have declined to a small fraction of peak levels by that time (See section **5.2. - Pharmacokinetic Properties**).

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylureas, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Other Effects

One study has shown that glipizide 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.

In a 3-year, placebo-controlled study of low-dose glipizide in chemical diabetics, muscle capillary basement membrane width was used as an index of early diabetic vasculopathy. The glipizide group had a significant decrease in membrane width, while the control group showed a significant increase. In a placebo-controlled crossover study in normal volunteers, glipizide had no antidiuretic activity and, in fact, led to a slight increase in free water clearance.

5.2 Pharmacokinetic Properties

Gastrointestinal absorption of glipizide in humans is uniform, rapid and essentially complete. Peak plasma concentrations occur 1 to 3 hours after a single oral dose. The half-life of elimination ranges from 2 to 4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose were unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus, glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98% to 99% 1 hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 L, indicative of localization within the extracellular fluid compartment. In mice, no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant

females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labeled drug.

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine.

5.3 Preclinical Safety Data

Acute toxicity studies showed no specific susceptibility. The acute oral toxicity of glipizide was extremely low in all species tested (LD_{50} greater than 4 g/kg). Chronic toxicity tests in rats and dogs at doses up to 8.0 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 maximum human dose showed no effects on fertility.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

See attached outer package for the expiry date.

6.2 Storage Condition

Store at temperatures not exceeding 30°C.

6.3 Availability

Glipizide (Minidiab) 5 mg tablet: White, round, convex tablets, scored with breakline on both sides. Box of 100's.

7.0 FDA REGISTRATION NUMBER

Glipizide (Minidiab) 5mg tablet: DR – XY31426

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Glipizide (Minidiab) 5mg tablet: 20 January 1975

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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