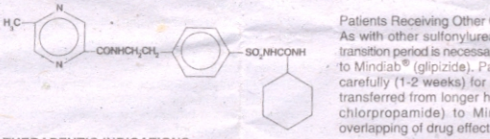
Pfizer

مِنی دیاب

Minidiab®
(Glipizide)

DESCRIPTION

Minidiab® (glipizide) is an oral blood-glucose-lowering drug of the sulfonylurea class. Minidiab® (glipizide) is available as 5 mg scored tablets containing Glipizide as the active ingredient. 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:



THERAPEUTIC INDICATIONS

Minidiab® (glipizide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

POSOLOGY AND METHOD OF ADMINISTRATION

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

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

In general, Minidiab® 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 in High Risk Patients.)

Titration

Dosage adjustments should ordinarily be in increments of 2.5 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 have 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 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 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 Initial Dose and section **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 Minidiab®. When transferring patients from insulin to Minidiab® the following general guidelines should be considered:

- For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and Minidiab® (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 Minidiab® (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 Minidiab® (glipizide). Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to Minidiab® due to potential overlapping of drug effect.

Combination Use

When adding other blood-glucose-lowering agents to Minidiab® 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 Minidiab® (glipizide) to other blood-glucose-lowering agents, Minidiab® 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.

CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

1. Hypersensitivity to glipizide or any excipients in the tablets.
2. Type 1 diabetes, diabetic ketoacidosis, diabetic coma.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

G6PD-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 haemolytic anemia and a non-sulfonylurea alternative should be considered.

Hypoglycemia: All sulfonylurea drugs 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 be 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 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 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The following products are likely to increase the hypoglycemic effect:

Anti-fungals:

- 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.

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).

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

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 to 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 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.

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.

UNDESIRABLE EFFECTS

The majorities of side effects have been dose related, transient, and have responded to dose reduction or withdrawal of the medication. However, clinical experience thus far has shown that, as with other sulfonylureas, some side effects associated with hypersensitivity may be severe and deaths have been reported in some instances.

Blood and Lymphatic System Disorders:
Agranulocytosis, leucopenia, Thrombocytopenia, hemolytic anemia and pancytopenia have been reported. Aplastic anemia has been reported with other sulfonylureas.

Metabolism and Nutrition Disorders - Hypoglycemia (see section **Special Warnings and Precautions for Use** and section **Overdose**). Hyponatremia has been reported. Disulfiram-like reactions have been reported with other sulfonylureas.

Psychiatric Disorders: Confusion*.

Nervous System Disorders: Dizziness*, drowsiness*, headache*, and tremor* have been reported in patients treated with glipizide.

Eye Disorders: Visual disturbances such as blurred vision*, diplopia*, and abnormal vision* including visual impairment* and decreased vision*, have each been reported in patients treated with Mindiab® (glipizide).

Gastrointestinal Disorders: Nausea, diarrhea, constipation and gastralgia. They appear to be dose related and usually disappear when the dosage is divided or reduced. Abdominal pain and vomiting.

Hepatobiliary Disorders: Cholestatic jaundice, impaired hepatic function, and hepatitis have been reported. Discontinue treatment if cholestatic jaundice occurs. Hepatic porphyria and porphyria cutanea tarda have been reported.

Skin and Subcutaneous Tissue Disorders: Allergic skin reactions including erythema, morbilliform or maculopapular reactions, urticaria, pruritus and eczema have been reported. They frequently disappear with continued therapy. However, if they persist, the drug should be discontinued. As with other sulfonylureas, photosensitivity reactions have been reported.

General Disorders and Administration Site Conditions: Malaise*.

Investigations: Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. The relationship of these abnormalities to Mindiab® (glipizide) is uncertain, and they have rarely been associated with clinical symptoms.

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

PHARMACOLOGICAL PROPERTIES

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 **Pharmacokinetic Properties**.)

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, 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. 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.

Pharmacokinetic Properties

Gastrointestinal absorption of glipizide in man is uniform, rapid and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 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 was 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 98-99% 1 hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 liters, 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.

OVERDOSAGE

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 persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

SHELF LIFE

36 Months

HOW SUPPLIED

Mindiab® (glipizide) 5 mg tablet is available as box of 30 scored tablets.

DOSAGE

Use as directed by the physician.

INSTRUCTIONS

Avoid exposure to heat & sunlight.
Store below 30°C.
Keep out of the reach of children.

CAUTION

To be sold on the prescription of a registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دوا کو گرمی اور سورج کی روشنی سے بچائیں۔
دوا کو ۳۰°C گرمی سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

تاکید: صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔

Pfizer

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