GLYBURIDE TABLETS, USP  
(micronized)  
Rx Only  

DESCRIPTION

Glyburide, tablets (micronized) contain micronized (smaller particle size) glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound. Each 3 mg, 5 mg, and 6 mg tablet contains 1.5 mg, 3 mg, or 6 mg strength for oral administration. Inactive ingredients: Colloidal Silicon Dioxide, Lactose Monohydrate, Magnesium Stearate, Prefemex Blue No. 6 Alumina Lake, and the 6 mg tablet contains D&C Yellow No. 10 Alumina Lake. The chemical name for glyburide (micronized) is N-[2-(2-ethylhexyl)benzimidazol-3-yl]-N'-[ethyl (aminomethyl)-2-thienyl]-N,N-dimethylurea, and the molecular weight is 494.0. The structural formula is represented below:

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\begin{align*}
\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{C} & \text{C} \quad \text{NH} \quad \text{C} \quad \text{NH} \quad \text{CH} \quad \text{CH}_2 \quad \text{SO}_2
\end{align*}
\]

CLINICAL PHARMACOLOGY

Actions

Glyburide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in Type II diabetic patients, the blood glucose lowering effect is dependent upon continued intake of the drug, which accounts for the drug’s “secondary response to the drug.” Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs. The combination of glyburide and metformin may have a synergistic effect since both agents act to improve glucose tolerance by different but complementary mechanisms.

Some patients, who are initially responsive to oral hypoglycemic drugs, including glyburide, may become unresponsive or poorly responsive over time. Alternatively, glyburide may be effective in some patients who have become unresponsive to one or more other sulfonyluric drugs.

In addition to its blood glucose lowering actions, glyburide produces a mild diuresis and may cause a watery diarrhea. Disulfiram-like reactions have rarely been reported in patients treated with glyburide.

Pharmacokinetics

Single dose studies with glyburide tablets (micronized) in normal subjects demonstrate significant absorption of glyburide within one hour. Peak drug levels of about two to three hours, and low detectable levels at twenty-four hours.

Bioavailability studies have demonstrated that glyburide tablets (micronized) 3 mg provide serum glyburide levels that are not significantly different from those from glyburide tablets (nonmicronized) 3 mg. Therefore, the patient should be titrated in a single-dose fashion using both tablets. In a single-dose fashion study using 3 mg tablets (see figure A) in which subjects received micronized tablets (3 mg) and glyburide tablets (nonmicronized) (3 mg) with broadest, the peak of the mean serum glyburide levels (Cmax ) for the micromized tablets (micronized) (3 mg) and 87.5 ng/mL, for tablets (nonmicronized) 3 mg. The mean of the individual maxima serum concentration of glyburide (Cmax ) from tablets (micronized) (3 mg) was 106 ng/mL, and that from tablets (nonmicronized) (3 mg) was 104 ng/mL. The mean glyburide area under the serum concentration-time curve (AUC) for this study was 568 ng/mL x h, for tablets (micronized) (3 mg) and 746 ng/mL x h, for tablets (nonmicronized) (3 mg).

For Oral Use

CONTRAINdications

Glyburide tablets (micronized) are contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.
2. Diabetic ketoadiposis, with or without coma. This condition should be treated with insulin.
3. Type 1 diabetes mellitus.

SPECIAL WARNINGS AND DIRECTIONs FOR USE

The administration of oral hypoglycemic drugs has been associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus diet pill (fig. 2). However, in a 3 year follow-up of the study conducted by the University of Minnesota group (USP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study enrolled 822 patients who were randomly assigned to one of four treatment groups (diabetes, 19, (Suppl. 2):747-830, 1974).

USP 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 2.1 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued because 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 USP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glyburide tablets (micronized) 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.

PRECAUTIONS

Macrocellular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glyburide tablets (micronized) or any other anti-diabetic drug.

Bioavailability studies have demonstrated that glyburide tablets (micronized) 3 mg provide serum glyburide concentrations that are not bioequivalent to those from glyburide tablets (nonmicronized) 3 mg. Therefore, patients should be retitrated when transferred from glyburide tablets (nonmicronized) or other oral hypoglycemic agents.

General

Hypoglycemia

All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Rarer or less hypoglycemia insensitivity may cause elevated drug levels of glyburide and the latter may also impair glucogenesis capacity, both of which increase the risk of hypoglycemia in the elderly, malnourished, and malnourished, and patients with, and those with or without, insulin deficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia is more likely to occur in elderly patients, those who are taking beta-adrenergic blocking drugs.

Hypoglycemia is more likely to occur if dosage is increased, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. The risk of hypoglycemia may be increased with combination therapy.

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 or glyburide tablets (micronized) and administer insulin (micronized) or other antidiabetic therapy.

The effectiveness of any hypoglycemic drug, including glyburide tablets (micronized), in lowering blood glucose to a desired level decreases in patients over a period of time which may be due to progression of the severity of 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 glyburide tablets (micronized) is administered. Alternate adjustment of dose and administration to diet should be assessed before classifying a patient as a secondary failure.

Hematocrit Anemia

Treatment of patients with glyburide tablets (micronized) by sulfonylurea antidiabetic agents can lead to hemolytic anemia. Because glyburide tablets (micronized) belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and/or hemolytic anemia or in patients who have already been reported in patients who have not known G6PD deficiency.

Information for Patients

Patients should be informed of the potential risks and advantages of glyburide tablets (micronized) and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine glucose.

The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its occurrence should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

Physician Counseling Information for Patients

In initiating treatment for type 2 diabetes, diet should be emphasized as the primary form of treatment. Calcium restriction and weight loss is essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the hyperglycemia and diabetes. Sulfonylurea agents can lead to hypoglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrected. 

The effectiveness of any hypoglycemic drug, including glyburide tablets (micronized) or other antidiabetic medications must be judged by the physician and patient as a treatment in addition to diet and not as a substitution or as a component mechanism for avoiding dietary restraint. Furthermore, if significant blood glucose control cannot be achieved, hypoglycemia control may be transient, thus requiring only short-term administration of glyburide tablets (micronized) or other antidiabetic medications. Maintenance or discontinuance of glyburide tablets (micronized) or other antidiabetic medications should be based on clinical judgment using regular clinical and laboratory evaluations.

Laboratory Test

Therapeutic response to micrized tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurements of glycosylated hemoglobin levels may be helpful in some patients.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, misonidazole, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving glyburide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for loss of control.

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concurrently with bosentan. Therefore concomitant administration of GLYPARS ProTab and bosentan is contraindicated.

Certain drugs tend to produce hypoglycemia and may lead to loss of control. These drugs include the thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glyburide, the patient should be observed closely for loss of control. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for hypoglycemia.
A possible interaction between glyburide and cyclosporin, a fluorouracil antibiotic, has been reported, resulting in a potential increase in the risk of toxicity in patients treated with both drugs. The mechanism for this interaction is not known.

A potential interaction between oral micronized and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of micronized is not known.

Metformin

In a single-dose interaction study in NIDDM subjects, decreases in glyburide AU C and C max were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Administration of glyburide and metformin did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

Colesevelam

Concomitant administration of colesevelam and glyburide resulted in reductions in glyburide AUC and C max of 32% and 47%, respectively. The reductions in glyburide AUC and C max were 20% and 15%, respectively when administered 1 hour before, and not significantly changed (7%-4% respectively while coadministered 4 hours before colesevelam.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. In rats, the no-observed-effect level (NOEL) was 30 mg/kg/day. In a study in which 100 mg/kg/day was administered for 26 weeks, no evidence of carcinogenicity was observed. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects makes the clinical significance of this interaction uncertain.

Metabolic Reactions: Hepatic porphyria and diastase-like reactions have been reported with sulfonylureas. Hepatic porphyria has not been reported with glyburide and diastase-like reactions have been reported very rarely. Causes of hepatoxicity have been reported with glyburide and all other sulfonylureas, most often in patients who have been tested repeatedly for their effectiveness or have medical conditions known to cause hepatoxicity: a rise in alkaline phosphatase blood level, hepatomegaly, and jaundice. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and subsequent dosage should be conservative to avoid hepatoxic reactions (see DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Elderly patients are prone to develop renal insufficiency, which may put them at risk of hypoglycemia. Elderly patients may require lower doses and may need more frequent monitoring.

ADVERSE REACTIONS

Hypoglycemia

The usual maintenance dose is in the range of 0.75 to 12 mg daily, which may be given as a single dose or in divided doses (see DOSAGE AND ADMINISTRATION). Dosage increases should be made in increments of no more than 5 mg at weekly intervals based on the patient’s blood glucose response.

No exact dosage relationship exists between glyburide tablets (micronized) and the other oral hypoglycemic agents leading to severe hypoglycemia. Although patients may be transferred from the maximum dose of one sulfonylurea to the maximum starting dose of 3 mg of glyburide tablets (micronized) should be observed. A maintenance dose of 3 mg of glyburide tablets (micronized) provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 650 mg tolbutamide, or 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of glyburide tablets (micronized) 1.5 mg concomitantly with a 50% reduction in insulin dosage. Progressive withdrawal of insulin and increase of glyburide tablets (micronized) in increments of 0.75 to 1.5 mg every 2 to 3 days is then carried out until a satisfactory response is obtained. In such cases, the patient should be observed for hypoglycemia.

When both insulin and glyburide tablets (micronized) are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The presence of persistent acetonuria with glyburide may indicate the patient is a diabetic who requires insulin therapy.

CONTRAINdications

Glyburide tablets (micronized) should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks (see Initial Starting Dose and Titration to Maintenance Dose). Refer to metformin package insert.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and subsequent dosage should be conservative to avoid hypoglycemic reactions. (see PRECAUTIONS Section.)

Maximum Dose

Daily doses of more than 12 mg are not recommended.

DOSAGE INTERVAL

Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 6 mg daily, may have a more satisfactory response with twice-a-day dosage.

SPECIFIC PATIENT POPULATIONS

Glyburide tablets are not recommended for use in pregnancy or for use in pediatric patients.

Hypoglycemia may occur, particularly in elderly patients, in diabetes mellitus patients, or in patients with liver disease, since adequate lowering of blood glucose may be obtained by adjusting the dose of each drug. Hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see PRECAUTIONS Section).

HOW SUPPLIED

DOSAGE AND ADMINISTRATION

Patients should be advised to take their tablets about one hour before meals and to report all symptoms of hypoglycemia promptly. These tablets should be kept out of the reach of children.

The tablet may be easily divided in half for a more flexible dosing regimen. Press gently on the score and the tablet will split in even halves.

Write

Store at controlled room temperature 20° - 25° C (68° - 77°F). [See USP Dispense in a light, light-resistant container, as defined in the USP, with a child-resistant closure. Keep container tightly closed.

Manufactured For

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Item #: 672534600314
Rev: 06/14

Type: 5 pt. Side B
3/14/14 JB

Dava Glyburide Tabs
Rev. 3/14 Flat size: 6 x 10
Fold: 1-1/16 x 2

Flat size: 6  x 10
Fold: 1-1/16  x 2
Type: 5 pt. Side B
3/14/14 JB