PRODUCT MONOGRAPH

[Pr] PRO-GLYBURIDE

Glyburide

Tablets, 5 mg

Manufacturer's Standard

Oral Hypoglycaemic Agent
ATC Code: A10BB01

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Oral Hypoglycaemic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 5 mg	Lactose monohydrate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

PRO-GLYBURIDE (glyburide) is indicated:

- To control hyperglycemia in glyburide-responsive diabetes mellitus of stable, mild, non-ketosis prone, maturity-onset or adult type (Type 2) which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.

Geriatrics:
Elderly with type 2 diabetes when treated with PRO-GLYBURIDE (glyburide) may be more prone to hypoglycaemia[8] (see WARNINGS and PRECAUTIONS, Special Populations).

Pediatrics (< 18 years of age):
Safety and effectiveness of PRO-GLYBURIDE (glyburide) have not been established in this population. Use in patients under 18 years of age is not recommended (see WARNINGS and PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

PRO-GLYBURIDE (glyburide) is contraindicated in patients with:

- Known hypersensitivity or allergy to glyburide, to any sulfonylurea or sulfonamides or any other component of the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Unstable and/or Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus).
- Diabetic ketoacidosis with or without coma. This condition should be treated with insulin.
- Diabetic precoma or coma.
- Severe liver disease or frank jaundice.
- Severe renal impairment (creatinine clearance less than 30 mL/min).
- Patients treated with bosentan (see DRUG INTERACTIONS).
- Pregnancy and lactation.
  During pregnancy, no oral antidiabetic agent should be given.
  Due to the possible excretion in human milk, the patient should discontinue nursing or discontinue taking the drug depending on the importance of the drug to the mother. If glyburide is discontinued, the patient should be transferred to insulin therapy.

WARNINGS AND PRECAUTIONS

General

Use of PRO-GLYBURIDE must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as a substitute for proper dietary management, exercise and weight reduction or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of PRO-GLYBURIDE. As is necessary during treatment with any blood-glucose-lowering drug, the patient and the physician must be aware of the risk of hypoglycaemia.

In initiating treatment for Type 2 diabetes, non-pharmacologic therapy (proper dietary management, exercise and weight reduction) should be emphasized as the initial form of treatment. Caloric restriction, weight loss and exercise are essential in the obese diabetic patient.

Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycaemia. If non-pharmacologic therapy fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered.

Patient Selection and Follow-Up
Careful selection of patients is important.

It is imperative that there be careful ongoing attention to diet, adherence to regular exercise, reduction of body weight in obese patients, careful adjustment of dosage, instruction of the patient on hypoglycaemic reactions and their control, as well as regular, thorough follow-up examinations. Cardiovascular risk factors should be identified.

The effectiveness of any oral hypoglycaemic drug, including PRO-GLYBURIDE, 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, known as secondary failure, is distinctive of primary failure, in which the drug is ineffective in an individual patient when given for the first time.

Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (A_{1C}) determinations, to determine the minimum effective dosage and to detect primary failure (inadequate lowering of blood glucose concentrations at the maximum recommended dosage) or secondary failure (progressive deterioration in blood sugar control following an initial period of effectiveness). The rate of primary failure will vary greatly depending upon patient selection and adherence to diet and exercise. The etiology of secondary failure is multifactorial and may involve progressive β-cell failure as well as exogenous diabetogenic factors such as obesity, illness, drugs, or tachyphylaxis to the sulfonylurea.

Cardiovascular
Some literature studies have suggested an association between the use of sulfonylureas and the risk of cardiovascular events including cardiovascular mortality, since these agents may potentially impair cardioprotective processes. Although, there is inconsistency in the literature regarding a definite conclusion for this association, a cautious approach is nevertheless warranted. All patients on sulfonylureas, particularly high risk patients with cardiovascular disease, should be closely monitored for cardiovascular complications.

Some literature studies have suggested an association between glyburide and QTc interval prolongation. Particular caution should be observed in patients who have risk factors for torsade de pointes, such as QTc prolongation at baseline, cardiovascular disease, or electrolyte abnormalities, or who are receiving other QTc interval prolonging drugs (see DRUG INTERACTIONS).

Endocrine and Metabolism

Hypoglycaemia

Hypoglycaemia, sometimes prolonged and even life-threatening, may occur as a result of the blood-glucose-lowering action of PRO-GLYBURIDE. Severe hypoglycaemia can be induced by all sulfonylurea drugs. Thus, proper patient selection, dosage, and instructions are important to avoid hypoglycaemic episodes. Hepatic and/or renal disease, inadequate caloric intake, malnutrition and/or irregular meals, exercise without adequate caloric supplementation, debility, advanced age, patient non-compliance, when alcohol is ingested (especially in combination with skipped meals), certain disorders of thyroid function, adrenal or pituitary insufficiency, excessive glyburide dosage, treatment with glyburide in the absence of indication or concurrent use with other agents with blood glucose lowering potential (see DRUG-DRUG INTERACTIONS) may be predisposing factors. Oral hypoglycaemic agents should be administered with caution to patients with Addison's disease.

The patient should be questioned about such factors, as well as about pertinent lifestyle changes, concomitant illnesses and hypoglycemic episodes as these may indicate the need for particularly careful monitoring. If necessary, the dosage of PRO-GLYBURIDE may need to be modified.

The manifestations of hypoglycaemia include: flushing or pallor, chilliness, excessive hunger, trembling, headache, dizziness, nausea, vomiting, restlessness, aggressiveness, depression, speech disorders, aphasia, sensory and/or visual disturbances, helplessness, lassitude, shallow respiration or bradycardia. In more severe cases, the clinical symptoms of a stroke or coma appear. However, symptoms of hypoglycaemia are not necessarily as typical as described above and sulphonylureas may cause insidious development of symptoms mimicking cerebrovascular insufficiency (e.g., disordered sleep, somnolence, impaired alertness and reactions, confusion, delirium, cerebral convulsions, paralytic symptoms or loss of consciousness).

Signs of adrenergic counter-regulation to hypoglycaemia include: sweating, damp skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias. However, these symptoms may be milder or absent in patients who develop hypoglycaemia gradually, patients with autonomic neuropathy, elderly or patients who receive concurrent treatment with sympatholytic agents (e.g., beta blockers, clonidine, reserpine, guanethidine) (see DRUG-DRUG INTERACTIONS).

Mild to moderate episodes of hypoglycaemia can usually be treated by immediate intake of oral carbohydrates. Patients should be advised to carry an adequate amount of glucose with them at all times. Patients may require the assistance of other persons. Artificial sweeteners are ineffective in controlling hypoglycaemia. The symptoms of hypoglycaemia nearly always subside when hypoglycaemia is corrected. Despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation after an episode of hypoglycemia.

Severe hypoglycaemia, which may be prolonged and has occasionally been life-threatening, may occur and mimics acute CNS disorders. Signs of severe hypoglycaemia can include disorientation, loss of consciousness, and seizures. Severe hypoglycaemia, or a protracted episode, which can only be temporarily controlled by usual amounts of sugar requires in-patient hospital care.

Drug interactions: Severe hypoglycemia has been reported following coadministration of clarithromycin and glyburide. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has also been reported. See DRUG INTERACTIONS.

Loss of control of blood glucose
If loss of adequate blood glucose lowering response to sulfonylurea is detected, treatment must be reassessed.

When a patient stabilized on any diabetic regimen is exposed to stress such as illness during therapy, fever, trauma, infection, or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to adjust the dosage of PRO-GLYBURIDE or consider discontinuation of PRO-GLYBURIDE and administration of insulin.

Lactose
PRO-GLYBURIDE tablets contain lactose monohydrate. Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product.

Hematologic
Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency with sulfonylurea agents can lead to haemolytic anemia. Since PRO-GLYBURIDE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.[29,55]

Hepatic/Biliary/Pancreatic
The metabolism and excretion of sulfonylureas including PRO-GLYBURIDE may be slowed in patients with impaired hepatic function (see MONITORING AND LABORATORY TESTS below). PRO-GLYBURIDE is contraindicated in patients with severe liver disease or frank jaundice. Patients with liver disease may be more susceptible to glyburide-induced hypoglycaemia. Elevation of liver enzyme levels has been reported very rarely in patients treated with glyburide (see Monitoring and Laboratory Tests; ADVERSE REACTIONS - Adverse Drug Reaction Overview).

Immune
Persons allergic to sulfonamide derivatives may also develop an allergic reaction to glyburide.

Peri-operative considerations
See *Endocrine and Metabolism section - Loss of control of blood glucose*.

Renal
PRO-GLYBURIDE is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min).[19] In patients with mild to moderate renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycaemic reactions. See Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARMACOLOGY, Special Populations.

Special Populations
Pregnant Women: The use of PRO-GLYBURIDE is contraindicated in pregnancy (see CONTRAINDICATIONS). PRO-GLYBURIDE should be discontinued in patients who become pregnant or who are planning a pregnancy. These patients should be changed over to insulin. Recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Experts, including the Canadian Diabetes Association and the Canadian Medical Association recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.[8]

Nursing Women: The use of PRO-GLYBURIDE is contraindicated in lactating women (see CONTRAINDICATIONS).

Pediatrics (< 18 years of age): Safety and effectiveness of PRO-GLYBURIDE (glyburide) have not been established in this population. Use in patients under 18 years of age is not recommended.

Geriatrics: Elderly patients with Type 2 diabetes are more susceptible to hypoglycaemia.[8]

Monitoring and Laboratory Tests
Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin (HbA_{1C}) should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycaemic control. Blood glucose self-monitoring is also recommended.

Periodic assessment of cardiovascular, ophthalmic, hematologic, renal and hepatic status is recommended.

PRO-GLYBURIDE is contraindicated in patients with severe liver disease and frank jaundice. Glyburide is extensively metabolized by the liver (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics), thus patients with liver disease may be more susceptible to glyburide-induced hypoglycaemia. Patients with mild to moderately impaired hepatic function should be monitored carefully for hypoglycaemia and should have their hepatic function reassessed periodically.

Elderly patients, particularly those who are malnourished or who have mild to moderate hepatic or renal insufficiency or impaired adrenal function, will require special care.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypoglycemia and weight gain are common side effects of treatment with glyburide.[8]

Blood and lymphatic system disorders: Potentially life-threatening hematological changes may occur. Rare cases of mild to severe thrombocytopenia which can manifest as purpura have been reported. Leukopenia, agranulocytosis, pancytopenia (which may be due to myelosuppression), erythrocytopenia, granulocytopenia, hemolytic anemia (immune, G6PD-deficiency) and aplastic anemia have been observed very rarely with glyburide therapy. These reactions may be reversible following discontinuation of the sulphonylurea antidiabetic agent.[1,29,30,36,55]

Endocrine disorders: Reduced radioactive iodine uptake by the thyroid gland has been reported.
Eye disorders: Transient visual disturbances may occur at the commencement of treatment due to fluctuations in blood glucose levels.

Gastrointestinal disorders: Nausea, epigastric fullness and heartburn are common reactions. Vomiting, diarrhea and abdominal pain have also been reported. These tend to be dose-related and may disappear when dosage is reduced.

General disorders and administration site conditions: Fatigue, malaise, and weakness have been reported.

Hepatobiliary disorders: Elevation of liver enzyme levels has been reported very rarely in patients treated with glyburide. In isolated cases, impairment of liver function (e.g. cholestasis and jaundice) and hepatitis have been observed, which can regress after withdrawal of the drug or may lead to life-threatening liver failure.

Immune system disorders: Allergic skin reactions such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions have been observed following sulfonylurea therapy. These may subside with continued use of the drug, but if they persist, the drug should be discontinued.

Reactions such as urticaria may very rarely develop into serious and life-threatening reactions including dyspnea, hypotension or shock. The patient should be advised to contact a physician immediately if urticaria develop.

Allergic vasculitis has been observed very rarely in patients receiving glyburide and in some circumstances may be life-threatening, including a severe skin reaction in one patient that occurred as a result of a generalized hypersensitivity to glyburide; hepatic, splanchnic and renal complications, followed by bronchopneumonia and renal failure resulted in a fatal outcome.[10]

A hypersensitivity reaction may occur in response to exposure to glyburide or to any of the excipients in PRO-GLYBURIDE. Cross-sensitivity to sulfonamides or their derivatives may occur in patients treated with oral sulphonylurea hypoglycaemic agents.

Metabolism and nutrition disorders: Severe hypoglycemia which mimics acute central nervous system disorders may occur (see WARNINGS AND PRECAUTIONS).

Hepatic porphyria and disulfiram-like reactions have been observed.

Cases of hyponatremia have been reported with sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increased release of antidiuretic hormones. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increased release of ADH.

Nervous system disorders: Headache, tinnitus, and dizziness have been reported.
Skin and subcutaneous tissue disorders: Porphyria cutanea tardis and photosensitivity reactions have been reported.

Clinical Trial Adverse Drug Reactions

No clinical trial adverse drug reaction data available.

Post-Market Adverse Drug Reactions

The following serious and unexpected adverse events not previously listed in the Adverse Drug Reaction Overview section of the Product Monograph have been reported. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: anaemia, neutropenia

Cardiac disorders: cardiac arrest, cardiac failure acute, myocardial infarction, torsade de pointes

Eye disorders: blindness

Gastrointestinal disorders: ascites, constipation, large intestinal obstruction, lower gastrointestinal haemorrhage, melaena, pancreatitis acute, varices oesophageal

General disorders and administration site conditions: death, drug ineffective, drug interaction, general physical health deterioration, ill-defined disorder, multi-organ failure, oedema peripheral

Hepatobiliary disorders: cryptogenic cirrhosis, hepatic cirrhosis, hepatitis acute, hepatitis toxic, hepatocellular injury, liver disorder, liver injury

Infections and infestations: Acinetobacter infection, candiduria, cytomegalovirus enteritis, gastroenteritis, staphylococcal infection, zygomycosis

Injury, poisoning and procedural complications: accidental exposure, drug toxicity, fall, overdose, poisoning, therapeutic agent toxicity, traumatic brain injury

Investigations: antinuclear antibody positive, blood creatinine increased, blood glucose increased, electrocardiogram QT prolonged, Glasgow coma scale abnormal, haemoglobin decreased, transaminases increased

Metabolism and nutrition disorders: decreased appetite, dehydration, diabetes mellitus, failure to thrive, hypoglycaemic unconsciousness, lactic acidosis, metabolic acidosis

Musculoskeletal and connective tissue disorders: myalgia, polymyalgia rheumatica, rheumatoid arthritis

Neoplasms benign, malignant and unspecified (including cysts and polyps): neoplasm malignant, rectal adenoma

Nervous system disorders: altered state of consciousness, coma, depressed level of consciousness, dysarthria, haemorrhagic stroke, hemiparesis, hypoglycaemic coma, hypoglycaemic encephalopathy, motor dysfunction, neurological symptom

Psychiatric disorders: abnormal behaviour, confusional state, delirium, disorientation, hallucination, intentional drug misuse, mental disorder, mental status changes

Renal and urinary disorders: anuria, glomerulonephritis membranous, renal failure, renal failure acute, renal vein thrombosis

Respiratory, thoracic and mediastinal disorders: hypoxia, lung disorder, pneumonia aspiration, pulmonary arterial hypertension, respiratory failure, tachypnoea

Skin and subcutaneous tissue disorders: dermatitis exfoliative, hyperhidrosis, linear IgA disease, toxic skin eruption

Vascular disorders: circulatory collapse, hypertension, hypotension

DRUG INTERACTIONS

Serious Drug Interactions

The concomitant use of bosentan and PRO-GLYBURIDE (glyburide) is contraindicated (see CONTRAINDICATIONS and DRUG-DRUG INTERACTIONS, Table 1).

Overview

Glyburide is extensively metabolized in the liver by cytochrome P450. The isoforms 2C9, 2C19 and 3A4 are involved, each to an unknown extent. Glyburide is also a substrate for p-glycoprotein. [25-27,30,35,38,39,54] Blood glucose should be monitored carefully if PRO-GLYBURIDE is administered with other drugs whose metabolism is dependent upon CYP 2C9, 2C19, 3A4 and p-glycoprotein. In addition, the hypoglycaemic action of sulfonylureas is potentiated when used with insulin and other oral antidiabetics. Patients should be monitored accordingly. See Table 1, below. See also ACTION AND CLINICAL PHARMACOLOGY, *Metabolism*.

Drug-Drug Interactions

Patients who take or discontinue taking certain other medicines while undergoing treatment with PRO-GLYBURIDE may experience changes in blood glucose control.

A study in 12 healthy volunteers showed that the concomitant administration of clarithroymycin increases plasma concentrations of glyburide. Severe hypoglycemia has been reported following coadministration of these two drugs. [6,26,27,47] See Table 1, below.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known. See Table 1, below.

Table 1 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical Comment
ACE-inhibitors	T	The hypoglycaemic action of sulfonylureas may be potentiated.	When these drugs are administered to a patient receiving PRO-GLYBURIDE, the patient should be observed closely for hypoglycaemia. When these drugs are withdrawn from a patient receiving PRO-GLYBURIDE, the patient should be observed closely for loss of glycaemic control.
Anabolic steroids and androgens	T		
Azapropazone	T		
Chloramphenicol	T		
Clarithromycin [6,26,27,47]	CT, C		
Coumarin derivatives	T		
Cyclophosphamide	T		
Disopyramide[52]	T		
Fenfluramine	T		
Fenyramidol (phenyramidol)	T		
Fibrates (clofibrate)	T		
Fluconazole[2]	T		
Fluoxetine	T		
Ifosfamide	T		
Insulin and other (oral) antidiabetics	T		
Miconazole[2]	T		
Monoamine oxidase inhibitors	T		
Nonsteroidal anti-inflammatory drugs	T		
Oxyphenbutazone	T		
Para-aminosalicylic acid	T		
Pentoxifylline (high dose parenteral)	T		
Phenylbutazone	T		
Probenecid	T		
Propranolol	T		
Quinolones	T		
Salicylates	T		
Sulfonamides (e.g., sulphaphenazole)	T		
Sulphinpyrazone	T		
Sympatholytic agents (e.g., beta-blockers, guanethidine	T		
Tetracyclines	T		
Tritoqualine	T		
Trofosfamide	T		
Tuberculostatics	T		
Acetazolamide	T	These drugs tend to produce hyperglycaemia and may lead to loss of blood sugar control.	When these drugs are administered to a patient receiving PRO-GLYBURIDE, the patient should be observed closely for loss of glycaemic control. When these drugs are withdrawn from a patient receiving PRO-GLYBURIDE, the patient should be observed closely for hypoglycaemia.
Barbiturates	T		
Calcium channel blockers	T		
Corticosteroids	T		
Danazol[52]	T		
Diazoxide	T		
Diuretics (thiazides, furosemide)	T		
Epinephrine (e.g., adrenaline) and other sympathomimetic agents	T		
Estrogen and progestogen	T		
Glucagon	T		
Isoniazid	T		
Laxatives (after protracted use)	T		
Nicotinic acid (in pharmacologic doses)	T		
Phenothiazines	T		
Phenytoin	T		
Thyroid products	T		

Proper name	Ref	Effect	Clinical Comment
Rifampicin (Rifampin) [38]	CT	Co-administration of rifampin has been shown to reduce glyburide plasma levels.	When rifampin is administered to a patient receiving PRO-GLYBURIDE, the patient should be observed closely for loss of glycemic control. When rifampin is withdrawn from a patient receiving PRO-GLYBURIDE, the patient should be observed closely for hypoglycemia.
Barbiturates (and other sedatives and hypnotics)	T	PRO-GLYBURIDE may prolong the action of barbiturates (and other sedatives and hypnotics).	To be used cautiously in patients receiving an oral hypoglycaemic agent.
Bosentan	CT	Potentiation of the risk of cholestatic liver injury and an increased incidence of elevated liver enzymes was observed in patients receiving glyburide concomitantly with bosentan. Both glyburide and bosentan inhibit the bile salt export pump (Bsep), leading to intracellular accumulation of cytotoxic bile salts.[7, 13 ,51]	This combination should not be used (see CONTRAINDICATIONS).
Coumarin derivatives	T	PRO-GLYBURIDE may potentiate or weaken the effects of coumarin derivatives.	
Cyclosporine	C	PRO-GLYBURIDE may increase cyclosporine plasma levels, with potentially increased toxicity.[20]	Monitoring and dosage adjustment of cyclosporine are recommended when both drugs are coadministered.
Drug containing alcohol	C	Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose lowering action of PRO-GLYBURIDE in an unpredictable fashion.	Intolerance to alcohol (disulfiram-like reaction; flushing, sensation of warmth, giddiness, nausea, and occasionally tachycardia) may occur in patients treated with a sulfonylurea. Caution should be exercised with the concomitant use with alcohol-containing drugs.
H_2-receptor antagonists, beta-blockers, clonidine or reserpine	T		Concurrent use with PRO-GLYBURIDE may lead to either a potentiation or an attenuation of the blood-glucose-lowering effect.
Nicorandil	T	Some *in vitro* and *in vivo* experimental animal data indicate a potential impairment of the activity of nicorandil by glyburide.[31,43]	The clinical relevance of this interaction is unknown.
Sympatholytic drugs (such as beta-blockers, clonidine, guanethidine, and reserpine)	T		The signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent in case of concomitant use with PRO-GLYBURIDE.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

QTc Prolonging Drugs: Some literature studies have suggested an association between glyburide and QTc interval prolongation. Caution should be observed if glyburide is to be used concomitantly with QT/QTc-prolonging drugs. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide); Class 1C antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antitibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxazin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-hydroxytryptamine (5-HT) 3 receptor antagonists (e.g., dolasetron, ondansetron); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Caution should be exercised if using PRO-GLYBURIDE with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Alertness and reactions may be impaired due to hypoglycaemic or hyperglycaemia episodes, especially when beginning or after altering treatment or when PRO-GLYBURIDE is not taken regularly. This may, for example, affect the ability to drive a vehicle or to operate machinery.

Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of PRO-GLYBURIDE in an unpredictable fashion. Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea, and occasionally tachycardia) may occur in patients treated with a sulfonylurea. These reactions can be prevented by avoiding the use of alcohol.

DOSAGE AND ADMINISTRATION

Dosing Considerations

In diabetic subjects, there is no fixed dosage regimen for the management of blood glucose levels. Individual determination of the minimum dose that will lower the blood glucose adequately should be made.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycaemic agents because of deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (A_{1C}) measurements, to determine the minimum effective dosage and to detect primary failure or secondary failure (see WARNINGS AND PRECAUTIONS).

Adjustment of glyburide dosage should be considered whenever factors predisposing the patient to the development of hypo- or hyperglycaemia are present (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS). As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glyburide requirements may fall as treatment proceeds. To avoid hypoglycaemia, timely dose reduction or cessation of PRO-GLYBURIDE therapy must therefore be considered.

Timing of doses should be decided by the prescriber, taking into consideration the patient's current lifestyle.

The first dose should be given during or immediately after breakfast. Patients who eat only a light breakfast should defer the first dose of the day until lunchtime. If a second daily dose is required, the second dose should be taken with the evening meal.

It is very important not to skip meals after the tablets have been taken.

Renal: PRO-GLYBURIDE is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min). In patients with mild to moderate renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycaemic reactions.

Pediatrics (< 18 years of age): Safety and effectiveness of PRO-GLYBURIDE (glyburide) have not been established in this population. Use in patients under 18 years of age is not recommended.

Geriatrics (>60 years of age): Elderly patients with Type 2 diabetes are more susceptible to hypoglycaemia. Caution should be applied when initiating or escalating doses of PRO-GLYBURIDE in patients over 60 years of age. It is recommended that treatment be started with the smallest dose (2.5mg) in this population. See *Usual Starting Dose*, below.

Recommended Dose and Dosage Adjustment

Usual Starting Dose

In newly-diagnosed diabetics, the initial dose is 5 mg daily; however, it is recommended that treatment be started with the smallest dose (2.5 mg) in patients over 60 years of age, and in patients who have a tendency to hypoglycemia (see WARNINGS AND PRECAUTIONS) or who weigh less than 50 kg. The initial dose should be administered with breakfast or a first meal of the day and should be continued for five to seven days. Depending on the response, the dosage should then be either increased or decreased in steps of 2.5 mg. The increases or decreases should be guided by regular blood glucose monitoring.

Usual Maintenance Dose

Occasionally, glycemic control is maintained with 2.5 mg daily. The majority of cases can be controlled by 5 mg to 10 mg daily given as a single dose during or immediately after breakfast. Patients who eat only a light breakfast should defer the first dose of the day until lunchtime. A single dose of 10 mg must not be exceeded. If more than 10 mg daily is required, the excess should be taken with the evening meal.

Maximum Daily Dose

The maximum daily dose of PRO-GLYBURIDE is 20 mg. A single dose of 10 mg must not be exceeded. Large daily doses must be divided into at least 2 separate single doses.

Changeover From Other Oral Hypoglycaemic Agents

There is no exact dosage relationship between PRO-GLYBURIDE and other oral antidiabetic agents. Discontinue previous oral medication and start PRO-GLYBURIDE 5 mg daily (2.5 mg in patients over 60 years of age, and in patients who have a tendency to hypoglycaemia (see WARNINGS AND PRECAUTIONS) or who weigh less than 50 kg). This also applies to patients changed over from the maximum dose of another oral antidiabetic medication. Consideration must be given to the potency and duration of action of the previous antidiabetic agent. A break from medication may be required to avoid any summation of effects entailing a risk of hypoglycemia.

Determine maintenance dosage as in newly-diagnosed diabetics.

Changeover From Insulin

If a change from insulin to glyburide is contemplated in a patient with stable, mild, maturity-onset (Type 2) diabetes, treatment with insulin should be discontinued for a period of two or three days to determine whether any therapy other than dietary regulation and exercise is needed.

During this insulin-free interval, the patient's urine should be tested at least three times daily for glucose and ketone-bodies, and the results monitored carefully by a physician. The appearance of significant ketonuria accompanied by glucosuria within 12 to 24 hours after the withdrawal of insulin strongly suggests that the patient is ketosis prone and precludes the change from insulin to sulfonylurea therapy.

Missed Dose

The missed dose should be taken as soon as possible, unless it is almost time for the next dose. Forgetting to take a dose must never be corrected by subsequently taking a larger dose.

Prior to starting treatment with PRO-GLYBURIDE, the physician and patient should discuss how to address missed doses or skipped meals.

If it is discovered that too high a dose or an extra dose of PRO-GLYBURIDE has been taken, a physician must be notified immediately (see OVERDOSAGE).

Method of Administration

PRO-GLYBURIDE tablets must be swallowed whole with sufficient amounts of liquid; half a glass to one glass of water is recommended.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Acute overdosage as well as long-term treatment with too high a dose of glyburide may lead to severe, protracted, life-threatening hypoglycaemia. The dosage which causes hypoglycaemia varies widely, and may be within the accepted therapeutic range in sensitive individuals. Significant overdoses and severe reactions with serious neurological signs and/or loss of consciousness are medical emergencies that require immediate treatment and admission to hospital.

Symptoms

The manifestations of hypoglycemia include sweating, flushing or pallor, numbness, chilliness, hunger, trembling, headache, dizziness, increased pulse rate, palpitations, increase in blood pressure and apprehensiveness in mild cases. In more severe cases, coma occurs. Symptoms of hypoglycaemia are not necessarily as typical as described above and sulfonylureas may cause insidious development of symptoms which mimic cerebrovascular insufficiency.

Treatment

Discontinue medication and treat hypoglycaemia by giving dextrose promptly and in sufficient quantity. After acute glucose replacement has been completed, it may be necessary to give an intravenous glucose infusion to ensure that the hypoglycaemia does not recur. Continuous dextrose infusions for hours to days have been necessary. The patient's blood-glucose level should be carefully monitored for at least 24 hours. Admission to hospital may sometimes be necessary as a precautionary measure.

The symptoms of hypoglycaemia nearly always subside when blood glucose control is attained; however, some sulfonylurea-induced hypoglycaemias may be refractory to treatment and susceptible to relapse, especially in elderly or malnourished patients. In severe cases with a protracted course, hypoglycaemia or the danger of slipping back into hypoglycaemia may persist for several days. Patients must therefore remain under close observation.

Patients who have ingested life-threatening amounts of glyburide require detoxification (for instance by gastric lavage and medicinal charcoal).[24,50]

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The principal action of PRO-GLYBURIDE is to increase the amount of insulin released from the pancreas. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycaemic drugs. The insertion of an alkyl chain on the benzene nucleus results in a product of very high potency. The hypoglycaemic activity of 5 mg of EUGLCON is approximately equal to that of 1g of tolbutamide, 500mg of acetohexamide or 250mg chlorpropamide.

Pharmacodynamics

Cardiac Electrophysiology: A clinical trial was performed in which patients with type 2 diabetes were randomised to receive glibenclamide (N=15) or metformin (N=15). ECG recordings were performed at baseline and after two months of treatment. Glibenclamide was associated with a significant increase in QTc (433±24 to 467±24 ms, $p < 0.001$) from baseline to month 2 of treatment, whilst metformin was associated with a decrease in QTc (444±15 to 432±15 ms, $p < 0.01$).[34]

Pharmacokinetics

Absorption: PRO-GLYBURIDE is largely absorbed from the intestinal tract.[4,45] The pharmacokinetics of glyburide have been studied using orally administered ^{14}C-labelled glyburide in two subjects, and were shown to follow a complex multicompartmental pattern.[4] Plasma concentrations showed a steep rise and fall immediately before and after reaching the peak value.

Distribution: Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycaemic action.

Metabolism: Glyburide is extensively metabolized in the liver by cytochrome P450. The isoforms 2C9, 2C19 and 3A4 are involved, each to an unknown extent. Glyburide is also a substrate for p-glycoprotein.[25-27,30,35,38,39,54] Blood glucose should be monitored carefully if PRO-GLYBURIDE is administered with other drugs dependent on CYP 2C9, 2C19, and 3A4 and p-glycoprotein for metabolism.

The principal metabolites of glyburide result from hydroxylation of the cyclohexyl ring to the 4-trans-hydroxyl (major metabolite) and 3-cis-hydroxy (minor metabolite) derivatives. In rabbits, these metabolites contribute no significant hypoglycemic action as they are only weakly active ($1/400^{th}$ and $1/40^{th}$ respectively, as glyburide).[14] However, the results of one small (n=8) placebo-controlled cross-over study in humans in which these two metabolites were administered by the intravenous route suggest that these metabolites may contribute to the blood-glucose-lowering effect in humans.[22,46] The role of the kidneys in the biotransformation of the drug appears minimal.

Excretion: Glyburide is excreted as metabolites in the bile and urine.[9,14,15,41,46] Reported biological half-lives ranged from 1.9 to 16.0 hours.

Special Populations and Conditions

Renal Insufficiency: In a study of diabetic patients with impaired renal function (n=13) administered a single oral dose of glyburide as a solution, there was no relationship between creatinine clearance (CL_{CR}) and glyburide clearance in patients with normal to moderately impaired renal function (CL_{CR} 29 – 131 mL/min). In one patient with severe renal impairment (CL_{CR} of 5mL/min), however, glyburide clearance was significantly reduced, resulting in an elimination half-life of 11 hours compared to 2 – 5 hours in patients without severe renal impairment.[41]

In another study of diabetic patients administered a single oral dose of glyburide, there were decreased levels of metabolites excreted in the urine of renally impaired patients (n=11) compared with patients with normal renal function (n=11), suggesting that in renal impairment, the metabolites of glyburide may be eliminated via the complementary non-renal route of biliary excretion.[23]

STORAGE AND STABILITY

PRO-GLYBURIDE should be stored at room temperature between 15 and 30^{o}C, and not beyond the expiry date indicated on the package.

Keep in a safe place out of the reach of children and pets.

Unused medication should not be disposed of down the drain or in household garbage.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PRO-GLYBURIDE 5 mg contains 5 mg glyburide (non-micronised). Each tablet also contains as non-medicinal ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, starch (corn starch, and pre-gelatinized corn starch) and talc.

PRO-GLYBURIDE (glyburide) 5 mg tablets are white to off-white, oblong tablets, with bilateral break-marks. They are debossed "BM/EU" on both faces. PRO-GLYBURIDE 5 mg tablets are available in bottles of 100 and 500 tablets and blister packs of 30 tablets. The blister format is 3 x 5 tablets per blister sheet; 2 blister sheets per carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

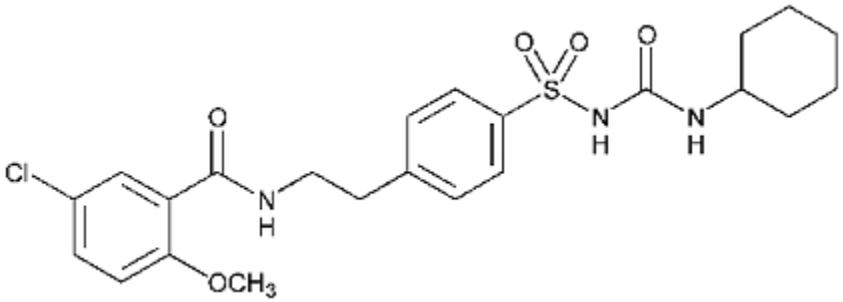
Proper name: Glyburide (as per USP), Glibenclamide (as per Ph.Eur.)

Chemical name: 1-[[4-[2-[(5-Chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulphonyl]-3-cyclohexylurea

Molecular formula: $C_{23}H_{28}ClN_3O_5S$

Molecular mass: 494

Structural formula:



Physiochemical properties:

Description: White or almost white, odourless to almost odourless, crystalline powder.

Melting Point: 169 – 174°C

Solubility: Practically insoluble in: water, ether
Slightly soluble in: ethanol, methanol
Sparingly soluble in: chloroform, methylene chloride
Sparingly soluble (with salt formation) in: alkaline solution
Freely soluble in: dimethylformamide

CLINICAL TRIALS

No clinical data available.

DETAILED PHARMACOLOGY

Animals

In rabbits, the oral administration of 0.2 mg/kg of PRO-GLYBURIDE lowered the blood sugar level 25%, an effect which occurred 3 hours after administration of the drug and lasted longer than 24 hours. The duration of action of 200 mg/kg of tolbutamide was much shorter.[5] In the isolated rat pancreas, PRO-GLYBURIDE produced a long-lasting rise in insulin output while tolbutamide had an effect of a faster onset and a shorter duration.[28] A short period of exposure of isolated rat pancreas to tolbutamide caused a brief release of insulin, but the effect of PRO-GLYBURIDE lasted longer and exceeded the time of exposure.[18] In the presence of 0.5 ug/mL of PRO-GLYBURIDE, isolated rat pancreatic islets released insulin continuously; in contrast, the effect of 0.3 mg/ml of tolbutamide could not be maintained.[16]

Safety Pharmacology

Glibenclamide has been reported to block the ATP-sensitive potassium channels in cardiac myocytes and pancreatic beta cells [56] and the neural and cardiac delayed rectifier potassium current (IKr) channels.[44] In post-infarcted anaesthetised dogs (N=10/treatment), glibenclamide (0.3 to 10 mg/kg iv) had proarrhythmic effects, as reflected by increased inducibility, lowered ventricular fibrillation threshold, and reduced survival.[11]

Humans

Improved glucose tolerance levels and random blood sugar levels over diet alone were described; the improvement in glucose tolerance was ascribed to a combination of a reduced fasting plasma sugar level and an improved tolerance to the glucose load.[12]

In a study comparing the effects of phenformin, metformin and glyburide on six patients with maturity-onset diabetes[37], it was found that the greatest reduction of the blood glucose concentration was obtained following treatment with glyburide, and corresponded with the observed higher serum insulin levels. Although gross and moderate elevation of blood lactate concentrations were observed in the patients treated with phenformin and metformin respectively, normal blood lactate levels were observed in the patients treated with glyburide. Similar effects were observed on the lactate/pyruvate ratios, and on the levels of alanine, glycerol and ketone bodies; only phenformin administration resulted in significantly increased levels of serum triglycerides.

TOXICOLOGY

The LD_{50} for white mice, rats and guinea pigs was found to be more than 15 g/kg body weight and for rabbits and beagles more than 10 g/kg body weight when glyburide was given orally. The LD_{50} in rats following intraperitoneal injection was found to be from 6.3 to 8.4 g/kg body weight.

Long-term feeding experiments were carried out in rats and dogs over the course of one year. Rats were given glyburide in their food in doses of approximately 0.2, 1.0 and 5.0 mg/kg body weight daily. The highest dose is equivalent to 350 times the minimal effective hypoglycaemic dose in man. Organ function tests were carried out continuously. Hematological examinations, blood sugar tests and urine analyses were performed every three months. None of the rats showed any abnormal findings in the function tests, or in the blood and urine studies. Subsequent post-mortem examination revealed no macroscopic or histological changes attributable to a toxic effect of glyburide.

Dogs were given glyburide by mouth at dose levels of 0.4, 2.0 and 10.0 mg/kg body weight daily. The highest dose is equivalent to 650 times the minimal effective hypoglycaemic dose in man. Regular checks of blood cell counts, blood glucose, urine, electrolytes, electrophoresis, BUN and serum enzyme levels (GPT, GOT, LDH, AP) showed no abnormalities. All the animals behaved normally during the period of experiment. There was no vomiting or diarrhea, and their weights remained unchanged. Subsequent post-mortem examination and histological investigation showed no abnormality.

Teratological tests were carried out in rats and rabbits. Rats were given 0.2, 20 and 2000 mg/kg body weight of glyburide from days 7 to 16 of gestation. For rabbits, the doses were 0.035, 3.5 and 350 mg/kg given from day 7 to 17 of gestation, in a starch suspension by gastric tube. Examination of the intact fetuses, followed by examination of transverse sections and of the stained skeletons, showed no evidence of teratogenic action.

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PART III: CONSUMER INFORMATION

[Pr]PRO-GLYBURIDE

Glyburide 5 mg Tablets

This leaflet is part III of a three-part "Product Monograph" published when PRO-GLYBURIDE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PRO-GLYBURIDE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PRO-GLYBURIDE (glyburide) is used to control high blood sugar in patients with stable, mild Type 2 diabetes (maturity-onset or adult type) which cannot be controlled by proper diet and exercise, or when insulin therapy is not appropriate.

What it does:
PRO-GLYBURIDE lowers blood sugar by stimulating the pancreas to secrete insulin. The pancreas must produce insulin for this medication to work.

In addition to taking PRO-GLYBURIDE, you should continue to exercise and follow the diet recommended for you by your doctor.

When it should not be used:
Do not take PRO-GLYBURIDE
- If you have Type 1 diabetes.
- If you have known hypersensitivity or allergy to glyburide, to any sulfonylurea or sulfonamides, or to any ingredient in the formulation or component of the container.
- If you have diabetic ketoacidosis (an emergency condition with high blood glucose levels, a lack of insulin and an accumulation of ketones (chemicals) in the blood and urine). This condition should be treated with insulin.
- In the presence of diabetic precoma or coma.
- If you have severe liver disease or frank jaundice. (yellowing of the skin and/or eyes).
- If you have severe kidney disease.
- If you are taking bosentan.
- If you are pregnant or breastfeeding.

What the medicinal ingredient is:
Glyburide

What the nonmedicinal ingredients are:
Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, starch (corn starch, and pre-gelatinized corn starch) and talc.

What dosage forms it comes in:
Tablets. Each tablet contains 5 mg glyburide.

WARNINGS AND PRECAUTIONS

PRO-GLYBURIDE may cause low blood sugar (hypoglycaemia), especially if you miss a meal, exercise for a long time, drink alcohol or also take another antidiabetic medication.

You should ask your doctor, pharmacist or diabetes educator about symptoms of low blood sugar and what to do if you experience these symptoms. You should tell your friends, co-workers, or family members what they can do to help if you have a low blood sugar. You should also test your blood sugar as instructed by your doctor.

Before you use PRO-GLYBURIDE talk to your doctor or pharmacist if:
- You have or have had liver, kidney, or heart disease.
- You have low blood electrolyte (e.g., potassium, magnesium, or calcium) levels or conditions that could lead to low electrolyte levels (e.g., vomiting, diarrhea, dehydration).
- You are pregnant or planning to get pregnant.
- You are breastfeeding.
- You have a blood disease called G6PD-deficiency.
- You are over 60 years of age.
- You are taking clarithromycin (an antibiotic) or miconazole (an antifungal).

Lactose monohydrate is a non-medicinal ingredient in PRO-GLYBURIDE. Do not take PRO-GLYBURIDE if a doctor has told you that you have one of the following hereditary diseases: galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Your blood sugar may get too high (hyperglycaemia) if you have fever, infection, surgery, or trauma (stress conditions). In such cases contact your doctor as your medication may need to be adjusted.

PRO-GLYBURIDE is not recommended for use in children under 18 years of age.

Driving and Operating Machinery
Alertness, reaction time and vision may be impaired due to low or high blood sugar (hypo- or hyperglycaemia), especially when beginning or after changing treatment or when PRO-GLYBURIDE is not taken regularly. This may affect your ability to drive or to operate machinery.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

PRO-GLYBURIDE (glyburide) should not be taken if you are also taking bosentan. See "**When it should not be used**" section of this leaflet.

Other drugs that may interact with PRO-GLYBURIDE include:

- other oral antidiabetic drugs and insulin
- antibiotics (sulphonamides/sulfa drugs, clarithromycin, rifampin, quinolones, tetracyclines)
- anti-tuberculosis drugs (e.g. isoniazid)
- anti-fungal drugs (miconazole, fluconazole)
- cyclosporine (an immunosuppressant drug)
- non-steroidal anti-inflammatory drugs (NSAIDs) including phenylbutazone (used to treat inflammation and pain)
- corticosteroids (used to treat inflammation)
- salicylates (e.g. acetylsalicylic acid)
- angiotensin converting enzyme (ACE) inhibitors (used to treat high blood pressure and certain heart conditions)
- coumarin derivatives (blood thinners such as warfarin)
- beta blockers (used to treat high blood pressure and certain heart conditions)
- calcium channel blockers (used to treat high blood pressure)
- diuretics (thiazides, furosemide) (used to treat high blood pressure and certain heart conditions)
- fibrates (clofibrate), nicotinic acid (used to treat high levels of fats in the blood)
- nicorandil (used to treat angina)
- H_2-receptor antagonists (used to treat acid reflux/heartburn)
- monoamine oxidase inhibitors (used to treat depression)
- fluoxetine (used to treat depression)
- probenecid (used to treat high levels of uric acid in the blood and gout)
- barbiturates (sedatives, anti-seizure medications)
- phenytoin (anti-seizure medication)
- estrogen and progestogen
- anabolic steroids and androgens (male hormones)
- danazol (used to treat breast cysts and endometriosis)
- thyroid products
- laxatives
- alcohol. Avoid drinking alcoholic beverages and taking medicines containing alcohol while you are taking PRO-GLYBURIDE as this can lead to a drop in blood sugar (hypoglycaemia).

This is not a complete list of possible drug interactions. Tell your doctor if you have recently taken any of the medicines listed above or any other medicines, including those obtained without a prescription. Do not take other medicines unless prescribed or approved by your doctor. Tell any health care professionals that you see that you are taking PRO-GLYBURIDE.

PROPER USE OF THIS MEDICATION

Take PRO-GLYBURIDE exactly as prescribed by your doctor. Never exceed the prescribed dose.

Usual dose:
The usual dose is 2.5 to 10 mg daily. The maximum daily dose is 20 mg. A dose of more than 10 mg should be taken in two divided doses.

Tablets should be taken during or immediately after meals.

Overdose:
Overdosage with this medication may result in hypoglycaemia.

If you take more than the recommended number of tablets, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take PRO-GLYBURIDE tablets, take your missed dose as soon as possible, unless it is almost time for your next dose. Do not take a double dose to make up for the forgotten dose.

Discuss with your health care practitioner how you should address missed doses or skipped meals, or in the event a dose cannot be taken at the prescribed time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect:

- low blood sugar. If your blood sugar gets too low, you may feel shaky, weak, drowsy, confused, or very hungry. You may sweat or have blurred vision, abnormal heartbeats, trouble concentrating, or a headache that does not go away. Signs of severe hypoglycaemia can include disorientation, loss of consciousness, and seizures.

Other side effects:

- nausea, heartburn, feeling "full", vomiting, diarrhea and abdominal pain
- allergic skin reactions (itchiness, rash, eruption), sensitivity to light
- temporary problems with the eye sight (transient visual disturbances).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking PRO-GLYBURIDE and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Low blood sugar (hypoglycaemia)		√	
Uncommon	Skin reactions (itchiness, rash, eruption)		√	
Rare	Blood disorders (unusual bruising or bleeding)		√	
Very rare	Liver problem (yellowing of the eyes or skin)			√
	Allergic reaction (difficulty breathing, decreased blood pressure)			√

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting, or seizures, you should seek immediate medical attention.

This is not a complete list of side effects. For any unexpected effects while taking PRO-GLYBURIDE, contact your doctor or pharmacist.

HOW TO STORE IT

PRO-GLYBURIDE should be stored between 15-30°C, and not beyond the expiry date indicated on the package.

Keep out of reach of children and pets.

Medicines should not be disposed of down the drain or in household garbage. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Pro Doc Ltée at 1-800-361-8559, http://www.prodoc.qc.ca or info@prodoc.qc.ca.

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