PRODUCT MONOGRAPH

[Pr]ratio-GLYBURIDE
(glyburide)

2.5 and 5 mg Tablets
House Standard

Oral Hypoglycaemic

ratiopharm inc.
Canada, J7J 1P3

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PHARMACOLOGIC CLASSIFICATION

Oral hypoglycaemic

ACTION AND CLINICAL PHARMACOLOGY

The principal action of glyburide results in an increased insulin release from the beta cells of the pancreas. Other mechanisms leading to a reduction of blood glucose are also believed to be influenced by glyburide[8]. The insertion of an alkylene chain on the benzene nucleus results in a product of very high potency.

Schulz and Schmidt[12] indicated that the presence of a sulfonamide (sulphaphenazole) decreased the distribution volume of [Pr]ratio-GLYBURIDE (glyburide) without influence on the half-life of the oral hypoglycaemic agent. As a result, insulin and serum concentrations of [Pr]ratio-GLYBURIDE were higher and hypoglycaemic attacks could be expected.

Hirn and Konigstein[6] have observed hypoglycaemia when phenylbutazone and oxyphenbutazone were added to [Pr]ratio-GLYBURIDE . Schulz and Schmidt confirmed that phenylbutazone has an enhancing effect on the blood sugar lowering effect of [Pr]ratio-GLYBURIDE and found higher insulin levels. The plasma half-life of [Pr]ratio-GLYBURIDE did not change with phenylbutazone administration. However, a significant decrease in the renal excretion of the main metabolite of [Pr]ratio-GLYBURIDE was observed, suggesting that the elimination in the bile may compensate for the amount not excreted in the urine.

Glyburide micronized powder is well absorbed from the intestinal tract[1,2]. Glyburide is highly bound to plasma proteins after absorption from the gastrointestinal tract[2,5]. It is completely metabolized by hydroxylation of the cyclohexyl ring into 3-cis and 4-trans derivatives in the liver[1,2,9] and the kidneys play only a minor role in their biotransformation and elimination from plasma[1]. The metabolites have no essential hypoglycaemic effect and they are not stored in the body, but they are eliminated via the bile, and in approximately the same amounts in the urine conjugated to glucoronic acid and in the faeces[1,2].

Maximal plasma levels of insulin, after an oral dose of 5 mg [Pr]ratio-GLYBURIDE in normal subjects were reached 90 minutes after dosing[10,11].

Minimal blood levels of glucose, after an oral dose of 5 mg [Pr]ratio-GLYBURIDE in normal subjects were reached 120 minutes after dosing corresponding to a reduction of about 35%[10,11].

Raptis et al.[8] found that the effect of an intravenous injection of 1 mg of [Pr]ratio-GLYBURIDE on blood glucose and serum insulin levels of healthy subjects was slower in onset and lasted longer than that of 1 gm of tolbutamide. Furthermore, when a second injection of [Pr]ratio-GLYBURIDE was given one hour later, the effects were undiminished. When [Pr]ratio-GLYBURIDE was injected at 4-hour intervals in patients with adult-onset diabetes, the effects of [Pr]ratio-GLYBURIDE were not diminished.

INDICATIONS AND CLINICAL USE

To control hyperglycaemia in [Pr]ratio-GLYBURIDE (glyburide) -responsive diabetes mellitus of stable, mild, non- ketosis-prone, maturity-onset or adult-type which cannot be controlled solely by proper dietary management, exercise and weight reduction or when insulin therapy is not appropriate.

CONTRAINDICATIONS

[Pr]ratio-GLYBURIDE (glyburide) should not be given to patients with known hypersensitivity or allergy to the active ingredient or any other component of the formulation. [Pr]ratio-GLYBURIDE should not be given to patients with: unstable and/or insulin-dependent diabetes mellitus; ketoacidosis; diabetic precoma; coma; in the presence of pre-existing complications peculiar to diabetes; during stress conditions such as severe infections, trauma or surgery; in the presence of liver disease or renal impairment; or frank jaundice.

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

The use of [Pr]ratio-GLYBURIDE (glyburide) will not prevent the development of complications peculiar to diabetes mellitus.

The use of [Pr]ratio-GLYBURIDE must be considered as treatment in addition to a proper dietary regimen and not as a substitute for diet.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycaemic agents because of deterioration of their diabetic state. If a loss of adequate blood glucose lowering response to [Pr]ratio-GLYBURIDE is detected, the drug should be discontinued.

PRECAUTIONS

Patient Selection and Follow-Up

Careful selection of patients is important. It is imperative that there be rigid 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.

Since the effects of oral hypoglycaemic agents on the vascular changes and other long-term sequelae of diabetes mellitus are not fully known, patients receiving such drugs must be closely observed for both short and long-term complications.

Periodic assessment of cardiovascular, ophthalmic, haematologic, renal and hepatic status is advisable.

In patients stabilized on [Pr]ratio-GLYBURIDE (glyburide) therapy, loss of blood sugar control may occur in cases of acute intercurrent disease or in stressful situations such as trauma or surgery. Under these conditions, discontinuation of [Pr]ratio-GLYBURIDE and administration of insulin should be considered.

Oral hypoglycaemic agents should be administered with caution to patients with Addison's disease.

The use [Pr]ratio-GLYBURIDE is not recommended for women planning a pregnancy (see CONTRAINDICATIONS); these patients should be changed over to insulin therapy.

Hypoglycaemic Reactions

Severe hypoglycaemia can be induced by all sulfonylurea drugs. Particularly susceptible are elderly subjects, patients with impaired hepatic and renal function, those who are

debilitated or malnourished, and patients with primary or secondary adrenal insufficiency. Hypoglycaemia is more likely to occur when the caloric intake is inadequate or after strenuous or prolonged exercise.

Drug Interactions

Patients who receive or discontinue certain medications while undergoing treatment with [Pr]ratio-GLYBURIDE may experience changes in blood glucose control.

Hypoglycaemia may be potentiated when a sulfonylurea is used concurrently with agents such as: insulin and other oral antidiabetics, anabolic steroids and androgens, azapropazone, chloramphenicol, clofibrate, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fibrates, fluoxetine, ifosfamide, miconazole, monoamine oxidase inhibitors, oxyphenbutazone, para-aminosalicylic acid, phenylbutazone, probenecid, propanolol, quinolones, salicylates, sulphinpyrazone, sulphonamides, sympatholytic agents (e.g. beta-blockers, guanethidine), tetracyclines, tuberculostatics.

Certain drugs tend to produce hyperglycaemia and may lead to loss of blood sugar control; these include: acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics (thiazides, furosemide), glucagon, laxatives (after protracted use), nicotinic acid (in pharmacologic doses), oral contraceptives (oestrogen plus progestogen), phenothiazines, phenytoin, rifampicin, sympathomimetic agents (e.g. epinephrine) and thyroid hormones.

Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.

Concurrent use of H_2-receptor antagonists, clonidine or reserpine with [Pr]ratio-GLYBURIDE may lead to either a potentiation or an attenuation of the blood-glucose-lowering effect.

Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of 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 oral hypoglycaemic drugs. These reactions can be prevented by avoiding the use of alcohol.

Barbiturates should be used cautiously in patients receiving an oral hypoglycaemic agent since their action may be prolonged.

[Pr]ratio-GLYBURIDE may potentiate or weaken the effects of coumarin derivatives.

Impairment of Alertness and Reaction Time

Until optimal control has been achieved, when changing the antidiabetic preparation, or when the tablets have not been taken regularly, alertness and reaction time may be altered to such an extent that the patient cannot safely cope with road traffic or operate machinery.

ADVERSE REACTIONS

Hypoglycaemia (see PRECAUTIONS)

Severe hypoglycaemia, which may be prolonged and has occasionally been life-threatening, may occur and mimics acute CNS disorders (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). Hepatic and/or renal disease, malnutrition and/or irregular meals, exercise without adequate caloric supplementation, debility, advanced age, patient non-compliance, alcoholism, 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 may be predisposing factors.

Gastrointestinal Reactions

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

Dermatologic and Sensitivity Reactions

Allergic and pseudoallergic skin reactions such as pruritus, erythema, urticaria, morbilliform, or maculopapular eruptions have been reported in a number of patients. These may subside on continued use of ^{Pr}ratio-GLYBURIDE (glyburide), but if they persist the drug should be discontinued. Mild reactions such as urticaria may very rarely develop into serious and life-threatening reactions including dyspnea, hypotension or shock. Porphyria cutanea tarda and photosensitivity reactions have been associated with the use of oral hypoglycaemic drugs. Allergic vasculitis have been observed very rarely in patients receiving ^{Pr}ratio-GLYBURIDE and in some circumstances may be life-threatening.

Cross-sensitivity to sulphonamides or their derivatives may occur in patients treated with oral sulphonylurea hypoglycaemic agents.

Haematologic Reactions

Rare cases of mild to severe thrombocytopenia which can manifest itself as purpura have been reported. Leukopenia, agranulocytosis, pancytopenia (which may be due to myelosuppression), erythrocytopenia, granulocytopenia, haemolytic anemia and aplastic anemia have been observed very rarely with [Pr]ratio-GLYBURIDE therapy. These reactions may be reversible following discontinuation of the sulphonylurea antidiabetic agent.

Metabolic Reactions

Hepatic porphyria and disulfiram-like reactions have been observed in patients treated with oral hypoglycaemic drugs. 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.

Endocrine Reactions

Reduced radioactive iodine uptake by the thyroid gland has been reported with oral hypoglycaemic therapy.

Other Adverse Reactions

Transient visual disturbances may occur at the commencement of treatment due to fluctuations in blood glucose levels.

In isolated cases, reduction of serum sodium concentrations has been observed in patients receiving [Pr]ratio-GLYBURIDE.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with sulfonylureas may result in hypoglycaemia, but it should be noted that the dosage which causes hypoglycaemia varies widely, and may be within the accepted therapeutic range in sensitive individuals.

The manifestations of hypoglycaemia include: flushing or pallor, chilliness, excessive hunger, trembling, headache, dizziness, nausea, vomiting, restlessness, aggressiveness, depression, speech disorders, 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, or patients who receive concurrent treatment with sympatholytic agents (e.g. beta blockers, clonidine, reserpine, guanethidine).

Discontinue medication and treat hypoglycaemia by giving dextrose promptly and in sufficient quantity.

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. Continuous dextrose infusions for hours to days have been necessary.

DOSAGE AND ADMINISTRATION

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

If the maximal recommended dose fails to lower blood glucose adequately in patients on initial trial, [Pr]ratio-GLYBURIDE (glyburide) should be discontinued. During the course of therapy a loss of effectiveness may occur. It is advisable to ascertain the contribution of the drug in the control of blood glucose by discontinuing the medication semi-annually or at least annually with careful monitoring of the patient. If the need for the drug is not evident, the drug should not be resumed. In some diabetic subjects, short-term administration of the drug may be sufficient during periods of transient loss of blood sugar control.

Adjustment of glyburide dosage should be considered whenever factors predisposing the patient to the development of hypo- or hyperglycaemia, such as weight or life-style changes, are present (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS AND ADVERSE REACTIONS).

<u>Newly-Diagnosed Diabetics</u>

The initial dose is 5 mg daily (2.5 mg in patients over 60 years of age) and it should be continued for 5 to 7 days. Depending on the response, the dosage should then be either increased or decreased by steps of 2.5 mg. The maximum daily dose of [Pr]ratio-GLYBURIDE is 20 mg (because higher doses normally have no additional effect on control of metabolic state). Occasionally, control is maintained with 2.5 mg daily. The majority of cases can be controlled by 5 to 10 mg (1 to 2 tablets) 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. If more than 10 mg (2 tablets) daily is required, the excess

should be taken with the evening meal.

Changeover From Other Oral Hypoglycaemic Agents

There is no exact dosage relationship between [Pr]ratio-GLYBURIDE and other oral antidiabetic agents. Discontinue previous oral medication and start [Pr]ratio-GLYBURIDE 5 mg daily (2.5 mg in patients over 60 years of age). This also applies to patients changed over from the maximum dose of other oral antidiabetic medication. Determine maintenance dosage as in newly diagnosed diabetics.

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 hypoglycaemia.

Changeover From Insulin

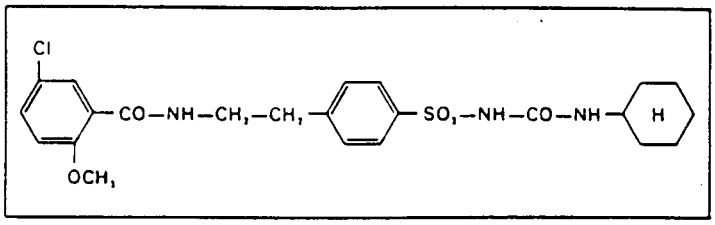
If a change from insulin to [Pr]ratio-GLYBURIDE is contemplated in a patient with stable, mild, maturity-onset diabetes, treatment with insulin should be discontinued for a period of two or three days to determine whether any therapy other than dietary regulation and exercise is needed. During this insulin-free 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 - 24 hours after the withdrawal of insulin strongly suggests that the patient is ketosis-prone and precludes the change from insulin to [Pr]ratio-GLYBURIDE.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: glyburide

Structural Formula:



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

Molecular Weight: 494

Chemical Name: N4-[2-(5-chloro-2-methoxybenzamido)-ethyl-phenyl-sulfonyl-N'-cyclohexylurea

Description:

White, crystalline, tasteless, odorless powder practically insoluble in water and dilute acids, very sparingly soluble in ethanol and chloroform, sparingly soluble with salt formation in alkali and readily soluble in dimethylformamide, with a melting range of 172-174°C.

Dosage Forms

Composition:

[Pr]ratio-GLYBURIDE (glyburide) 2.5 mg and 5 mg tablets contain 2.5 mg and 5.0 mg of the medicinal ingredient, glyburide, respectively.

The qualitative formulation of [Pr]ratio-GLYBURIDE tablets is: glyburide, colloidal silicon dioxide, corn starch, lactose hydrous, magnesium stearate, purified water, talc.

Availability:

White, oblong, uncoated, bevelled tablet with score-break, number 5 and ALBERT® logo trademark on obverse each containing 5.0 mg glyburide. Available in cartons of 30 (3 x 10 blister packed) or plastic bottles of 300 tablets.

White, round, uncoated, bevelled tablet with score-break, and code letters GLY (imprinted both above and below the score-break) on obverse and ALBERT® logo trademark on reverse, each containing 2.5 mg glyburide. Available in plastic bottles of 300 tablets.

Storage:

[Pr]ratio-GLYBURIDE should be stored at room temperature, below 25°C, and not beyond the expiry date indicated on the package.

PHARMACOLOGY

Animal

In the isolated, perfused rat pancreas, glyburide produced a sustained rise in insulin output[7]. In the presence of 0.5 mcg/mL of glyburide, isolated rat pancreatic islets released insulin continuously[3]. When isolated pieces of rat pancreas were repeatedly exposed to glucose or glyburide for brief periods of time at intervals of 30 minutes, they consistently released insulin[3]. In the presence of 300 mg% of glucose, glyburide (2.5 mcg/min.) increased effectively insulin output from isolated rat pancreas[3,4].

Sirek et al.[13] found that the beta adrenergic blocker propranolol inhibits sulphonylurea-stimulated insulin secretion in the dog and that the hypoglycaemia produced by glyburide in the presence of propranolol could be the result of extra-pancreatic effects.

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 is given orally. The LD_{50} in rats following intraperitoneal injection is 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 hypoglycaemic dose in man. Organ function tests were carried out continuously. Haematological examination, blood sugar tests and urinary analyses were performed every three months. None of the rats showed any abnormal findings in the function tests or 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 the experiment. There was no vomiting or diarrhoea, and their weights remained unchanged. Subsequent post-mortem examination and histological investigations showed no abnormality.

Teratological tests were carried out in rats and rabbits. Rats were given 0.2, 20 and 2,000 mg/kg body weight of glyburide from day 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 12 suspension by gastric tube. Examination of the intact fetuses, followed by examination of transverse sections and of the stained skeleton, showed no evidence of teratogenic action.

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