PRODUCT MONOGRAPH

pms-GLYBURIDE

(Glyburide Tablets)

2.5 mg & 5 mg

Oral Hypoglycemic Agent

Pharmascience Inc
8400 Darnley Road
Montreal, Quebec
H4T 1M4

#053067

Date of Preparation:
October 23, 1997

NAME OF DRUG

pms-GLYBURIDE

(Glyburide Tablets)

2.5 mg & 5 mg

THERAPEUTIC CLASSIFICATION

Oral Hypoglycemic Agent

CLINICAL PHARMACOLOGY

The principal action of glyburide is to increase the amount of insulin released from the pancreas.

The insertion of an alkyline chain on the benzene nucleus results in a product of very high potency. The hypoglycemic activity of 5 mg of glyburide is approximately equal to that of 1 g of tolbutamide, 500 mg of acetohexamide or 250 mg chlorpropamide.

glyburide is largely absorbed from the intestinal tract (Rupp et al. 1972; Balant et al. 1975). It is extensively metabolized in the liver, the principal metabolites resulting from hydroxylation of the cyclohexyl ring to the 3-cis- and 4-trans-derivatives. The metabolites, which have essentially no hypoglycemic effect, are not stored in the body, but are eliminated via the bile and urine (Christ et al. 1969). The role of the kidneys in the biotransformation of the drug appears to be minimal.

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Known hypersensitivity or allergy to the drug, unstable and/or insulin-dependent diabetes mellitus; ketoacidosis; coma; stress conditions such as severe infections, trauma or surgery; in the presence of jaundice, liver disease, or renal disease or impairment; during pregnancy; in the presence of

important preexisting complications peculiar to diabetes, such as retinopathy or neuropathy, for which no oral antidiabetic drugs should be given.

WARNINGS

The use of glyburide will not prevent the development of complications peculiar to diabetes mellitus.

Use of glyburide must be considered as treatment in addition to a proper dietary regimen, and not as a substitute for diet. Patients may, over a period of time, become progressively less responsive to therapy with oral hypoglycemic agents because of a deterioration of their diabetic state. If a loss of adequate blood glucose-lowering response to 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, careful adjustment of dosage, instruction of the patient on hypoglycemic reactions and their control, as well as regular, thorough follow-up examinations.

Since the effects of oral hypoglycemic 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, renal and hepatic status is advisable.

In patients stabilized on 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 glyburide and administration of insulin should be considered.

Hypoglycemic reactions

Severe hypoglycemia can be induced by all sulfonylurea drugs. Particularly susceptible are elderly subjects, patients with impaired hepatic or renal functions, those who are debilitated or malnourished, and patients with primary or secondary adrenal insufficiency. Hypoglycemia is more likely to occur when the caloric intake is inadequate or after strenuous or prolonged exercise.

Drug interactions

As a result of drug interaction, hypoglycemia may be potentiated when a sulfonylurea is used concurrently with agents such as: long-acting sulfonamides, tuberculostatics, phenylbutazone,

clofibrate, monoamine oxidase inhibitors, coumarin derivatives, salicylates, probenecid or propranolol and other beta adrenergic receptor blockers.

Certain drugs tend to produce hyperglycemia and may lead to loss of blood sugar control; these include diuretics (thiazides, furosemide), corticosteroids, oral contraceptives (estrogen plus progestogen) phenothiazines, calcium channel blocking drugs and nicotinic acid in pharmacological doses.

Barbiturates and other sedatives and hypnotics should be used cautiously in patients receiving an oral hypoglycemic agent, since their action may be prolonged.

Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea, and occasionally tachycardia) may occur in patients treated with a sulfonylurea, including glyburide. This reaction can be prevented by avoiding the use of alcohol.

ADVERSE REACTIONS

Hypoglycemia

Severe hypoglycemia which mimics acute CNS disorders may occur (see PRECAUTIONS). Hepatic and/or renal disease, malnutrition, debility, advanced age, alcoholism, adrenal or pituitary insufficiency may be predisposing factors.

Gastrointestinal

Nausea, epigastric fullness, heartburn, are common reactions to sulfonylurea therapy. These tend to be dose related and may disappear when dosage is reduced. Jaundice has been reported rarely in conjunction with some sulfonylureas.

Dermatological

Allergic skin reactions such as pruritus, erythema, urticaria, mobilliform or maculopapular eruptions have been observed following sulfonylurea therapy. These may subside on continued use of drug, but if they persist, the drug should be discontinued. Porphyria cutanea tardis and photosensitivity reactions have also been reported. In one patient, a severe skin reaction 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 (Clark et al. 1974).

Hematological

Thrombocytopenia has occasionally been observed in patients receiving glyburide. Leukopenia, agranulocytoses, hemolytic anemia and aplastic anemia have been noted as a results of therapy with other sulfonylureas.

Metabolic

Hepatic prophyria and disulfiram-like reactions have been observed.

Endocrinological

Reduced radioactive iodine uptake by the thyroid gland has been reported.

Miscellaneous

Headache, tints, fatigue, malaise, weakness and dizziness have been reported in a small number of patients.

SYMPTOMS AND TREATMENT OF OVERDOSE

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

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. However, symptoms of hypoglycemia 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 the hypoglycemia by giving dextrose promptly and in sufficient quantity.

Some sulfonylurea-induced hypoglycemias may be refractory to treatment and susceptible to relapse, and may be fatal, 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 the management of blood glucose levels. Individual determination of the minimum dose that will lower the blood glucose adequately should be made.

In patients where, on initial trial, the maximal recommended dose fails to lower blood glucose adequately, the drug 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, therapy 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.

Usual starting dose

In newly-diagnosed diabetics, the initial dose is 5 mg daily (2.5 mg in patients over 60 years of age) and it 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.

Maximal daily dose

The maximum daily dosage of pms-GLYBURIDE (glyburide) is 20 mg.

Usual maintenance dose

Occasionally, 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. If more than 10 mg daily is required, the excess should be taken with the evening meal.

Changeover from other oral hypoglycemic agents

Discontinue previous oral medication and start pms-GLYBURIDE 5 mg daily (2.5 mg in patients over 60 years of age) . Determine maintenance dosage as in newly-diagnosed diabetics.

Changeover from insulin

In a change from insulin to 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 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.

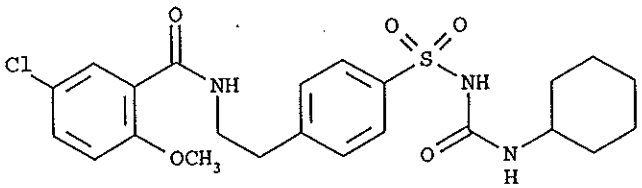
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: glyburide (USAN)

Chemical Name: 5-chloro-N-[2-[4-[[[(cyclohexylamino)carbonyl] amino]sulfonyl]phenyl]ethyl]-2-methoxy benzamide.

Structure



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

Molecular Weight: 494.00

Physical Form: White to almost white, odorless to almost odorless, fine crystalline powder.

Solubility:

Water.....practically insoluble
Ether.....practically insoluble
Ethanol.....slightly soluble
Methanol.....slightly soluble
Chloroform .....sparingly soluble
Alkaline solution.....sparingly soluble (with salt formation)
Dimethylformamide...freely soluble

Melting Point: 172° - 174° C

COMPOSITION

Non-medicinal ingredients: Lactose, Maize Starch, Talc, Colloidal Silicon Dioxide, Magnesium Stearate.

STORAGE CONDITIONS

Store at room temperature.

AVAILABILITY OF DOSAGE FORMS

White oblong scored 5 mg tablets of pms-GLYBURIDE coded BM/EU on the face and EU/BM on the reverse, and white cylindrical biplane tablets of pms-GLYBURIDE 2.5 mg with a logo consisting of a "T" superimposed on a smaller "O" printed on one face; it is single scored on the other face, with Al printed above and below the score line.

pms-GLYBURIDE 5 mg tablet is available in bottles of 300 tablets and blister packs of 30 tablets. The blister format is 3 x 5 tablets per blister sheet; 2 blister sheets per carton.

pms-GLYBURIDE 2.5 mg tablet is available in blister packs of 30 tablets. The blister format is 3 x 5 tablets per blister sheets; 2 blister sheets per carton.

PHARMACOLOGY

Animal

In rabbits, the oral administration of 0. 2 mg/kg of 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 (Baender et al. 1969). In the isolated rat pancreas, glyburide produced a long-lasting rise in insulin output while tolbutamide had an effect of a faster onset and a shorter duration (Mariani, 1969). A short period of exposure of isolated rat pancreas to tolbutamide caused a brief release of insulin, but the effect of glyburide lasted longer and exceeded the time of exposure (Grodsky et al. 1969). In the presence of 0.5 ug/ml of glyburide, isolated rat pancreatic islets released insulin continuously; in contract, the effect of 0.3 mg/ml of tolbutamide could not be maintained (Fussganger et al. 1969).

Clinical Pharmacology

The pharmacokinetics of glyburide, which is largely bound to plasma protein, have been studied by Balant et al. (1975) using orally-administered ^{14}C-labeled glyburide in two subjects, and were shown to follow a complex multicompartmental pattern. Plasma concentrations showed a steep rise and fall immediately before and after reaching the peak value. Reported biological half-lives ranged from 1.9 to 16.0 hours. Experimental evidence show that glyburide has a longer action than tolbutamide with regard to both insulin release and lowering of the blood sugar.

Improved glucose tolerance levels and random blood sugar levels over diet alone were described by Doar et al. (1976); the improvement in glucose tolerance was ascribed to a combination of a reduce fasting plasma sugar level and an improved tolerance to the glucose load.

In a study comparing the effects of phenformin, metformin and glyburide on six patients with maturity-onset diabetes, Nattrass et al. (1977) 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 hypoglycemic dose in man. organ f unction 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 postmortem 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 hypoglycemic dose in man. Regular checks of blood status, blood glucose, urine, electrolytes, electrophoresis, BUN and enzyme levels (GPT, GOT, LDH, AP) in the serum 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 postmortem 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 0.35, 3.5 and 350 mg/kg given from days 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 stained skeletons, showed no evidence of teratogenic action.

BIBLIOGRAPHY

Asplund k; Niholm BE; Lithner F
Glibenclamide-associated hypoglycaemia; A report of 57 cases. DIABETOLOGIA; 24/6 (412-417)/1983/

Baender, A., Pfaff, W., Schmidt, F.H., Stork, H. and Schroeder, H.B.;
Zur Pharmakologie von HB 419, einem neuen, stark wirksamen oralen Anti-diabeticum. Arzneim Forsch 19: 1362-1368, 1969.

Balant, L., Fabre, J. and Zahnd, G.R.:
Comparison of the pharmacokinetics of glipizide and glibenclamide in man. Europ. J. Clin. Pharmacol. 8 :63-69, 1975.

Christ, O.E., Heptner, W. and Rupp, W.:
Investigations on absorption, excretion, and metabolism in man after administration of 14C-labelled HB 419. Hormone Metab. Res. 1 (Suppl.): 51-54, 1969.

Clark, B.F., Campbell, I.W., Ewing, D.J., Beveridge, G.W. and MacDonald, M.K.:
Generalized hypersensitivity reaction and visceral arteritis with fatal outcome during glibenclamide therapy. Diabetes 23:739-742 (Sept.) 1974.

Doar, J.W.H., Thompson, M.E., Wilde, C.E. and Sewell, P.F.J.:
Diet and oral antidiabetic drugs and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. Brit. Med. J. 1:498-500 (Feb. 28) 1976.

Feldman, Jerome M. M.D.
Glyburide: A second-generation sulfonylurea hypoglycemic agent History, Chemistry, Metabolism, Pharmacokinetics, Clinical Use and Adverse Effects.

Fussganger, R.D., Goberna, R., Hinz, M., et al.
Comparative studies on the dynamics of insulin secretion following HB 419 and tolbutamide of the perfused isolated rat pancreas and the perfused isolated pieces and islets of rat pancreas. Hormone Metab. Res. 1 (Suppl.):34-40, 1969.

Grodsky, G.M., Curry, D., Landahl, H. and Bennett, L.:
Further studies on the dynamic balance of insulin release in vitro with evidence of a two-compartmental storage system. Acta Diabetologia Lat. 6 (Suppl.): 554-579, 1969.

Jackson, J.E.; Bressler, R.
Clinical pharmacology of sulphonylurea hypoglycaemic agents. I. Drugs; 22/3 (211-245)/1981/

Mariani, M.M.:
The action of sulfonylureas on the insulin secretion of the perfused rat pancreas. Acta Diabetologia Lat. 6 (Suppl.):256270, 1969.

Muller, R., Dauer, G., Schroder, R. and Saito, S.:
Summary report of clinical investigation of the oral antidiabetic drug HB 419 (glibenclamide). Hormone Metab. Res. 1(Suppl.):88-92, 1969.

Nattrass, M., Todd, P.G., Hinks, L., Lloyd, B. and Alberti, K.G.M.M.:
Comparative effects of phenformin, metformin and glibenclamide on metabolic rhythms in maturity-onset diabetics. Diabetologia 13:145-152, 1977.

Peacock, I., Tattersall, R.B.
The difficult choice of treatment of poorly controlled maturity onset of diabetes: Tablets or insulin? BR. Med. J.; 288/6435 (1956-1959)/1984/

Raptis, S., Rau, R.M. Schroder, K.E., Faulhaber, J.D. and Pfeiffer, E.F.:
Comparative study of insulin secretion following repeated administration of glucose, tolbutamide and glibenclamide (HB 419) in diabetic and non-diabetic human subjects. Hormone Metab. Res. 1 (Suppl.):65-72, 1969.

Rupp, W., Christ, 0. and Fulberth, W.:
Studies on the bioavailability of glibenclamide. Arzneim Forsch 22:471-473, 1972.

Schmidt, H.A.E. and Petridge, P.:
Glukose-und HB 419-Konzentration im Blut sowie HB 419-Ausscheidung im Urin nach einmaliger oraler Applikation von HB 41914-C. Arzneim Forsch 19:1422-1428, 1969.

Taylor, K.G., John, W.G., Matthews, K.A., Wright, A.D.
A prospective study of the effect of 12 months treatment on serum lipids and apolipoprotiens A-I and B in type 2 (non-insulin dependent diabetes). Diabetologia; 23/6 (507-510)/1982/