CTD MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION	
Product Name :	**GLYCOREN TABLETS (Glibenclamide Tablets 5mg)**

Pack Insert:

GLYCOREN TABLETS

Glibenclamide 5mg tablets BP

GLYCOREN TABLETS
Glibenclamide 5mg tablets BP

Composition:
Each uncoated tablet contains Glibenclamide 5 mg.

Actions:
Glibenclamide is a potent oral sulphonylurea hypoglycaemic agent. It lowers blood glucose concentration in diabetic and non diabetic patients by stimulating the release of insulin from the pancreas which requires functioning beta cells. It acts in concert with glucose (improved sensitivity of beta cells to physiological glucose stimulus) and leads to an insulin secretion in the rhythm of meals. Other mechanisms of the hypoglycaemic action associated with short-term therapy appear to include reduction of basal hepatic glucose production and enhancement of peripheral insulin action at postreceptor sites.

With prolonged therapy there tends to be a gradual decline in insulin secretion but the glibenclamide-induced improvement in glucose tolerance persists. Extrapancreatic effects appear to substantially contribute to the hypoglycaemic action during long term therapy. The principle mechanism appears to be due to inhibition of hepatic glucose production and enhanced peripheral sensitivity to insulin.

Glibenclamide also exerts a direct inhibitory effect on glucagon producing alpha cells of the pancreas and increases the release of somatostatin. These two pancreatic non-beta cell actions may only play a minor clinical role. Glibenclamide can also produce a mild diuresis by enhancing renal free water clearance through an unclearly defined action.

Pharmacokinetics:
Glibenclamide is readily and almost completely absorbed (approximately 86%) from the gastrointestinal tract after oral administration. Food does not appear to affect the rate and extent of absorption. Glibenclamide is 99% bound to plasma proteins. Binding is non-ionic so that unlike many other sulphonylureas glibenclamide is unlikely to be displaced from binding sites by other highly protein bound agents. The volume of distribution of glibenclamide at steady state averages 0.125L/kg. Glibenclamide is completely metabolised and the break down takes place by the hydroxylation of the cyclohexyl group. The major metabolite is the 4-transhydroxy derivative and the 3-cis-hydroxy derivative also occurs. A third metabolite has been isolated but not identified. The mean metabolism half-life and the mean elimination half-life are very similar and it can be concluded that the metabolites are not stored in the body and are promptly excreted. This conclusion is confirmed by the high renal clearance of the principle metabolite. The metabolites have practically no hypoglycaemic action.

The elimination half-life from the serum can be divided in a rapid phase (2.1+0.7 hours) and a slow phase (10+2 hours). After oral administration of 5mg of glibenclamide, peak serum concentrations are reached in 2 to 4 hours and within 24hours the concentration falls in keeping with the elimination rate in less than 4% of the maximum level. Accumulation of glibenclamide is not observed after repeated doses. The hypoglycaemic effect lasts for 24 hours. Approximately 50% of a dose is excreted in urine and 50% via the bile into the faeces. In patients with renal insufficiency depending upon the degree of the renal excretion disorder there is increased elimination of the metabolites via the bile.
Glibenclamide is only minimally removed by haemodialysis.

Indications:
Non-insulin dependent diabetes mellitus (type II): glibenclamide is used as an adjunct in patients whose hyperglycaemia cannot be controlled by diet alone.

Dosage and Administration:
Glibenclamide is usually administered as a single daily dose preferably given 30 minutes before breakfast or the first main meal. For requirements of greater than 10 mg daily, divided doses may be prescribed usually as a twice-daily regimen. The doses and scheduling should be individualized according to the patient's meal pattern and blood or urine glucose response.
Regular monitoring is required.
Initial Dosage in Previously Untreated Patients:
Adult Dose: Initially one 2.5mg tablet daily before breakfast should be given. If necessary the dose may be increased by 2.5mg increments until the diabetes is under control. As a rule, maximum effect is obtained with a daily dose of three 5mg tablets. Daily doses of up to two 5mg tablets can be taken as a single dose before breakfast, but any excess over this should be taken before the evening meal. A dose of four 5mg tablets should be divided into two tablets before breakfast, one tablet before lunch and one tablet before the evening meal.
Debilitated, malnourished or elderly patients, or those with impaired renal or hepatic function:
One 2.5mg tablet daily is recommended initially. Patients should have their blood or urine glucose monitored every 3 to 5 days and if a dosage increase is deemed necessary increments of not more than 2.5mg daily should be prescribed at weekly intervals.
Initial dosage in patients transferred from other antidiabetic agents:
Sulphonylureas: the switch to glibenclamide can be immediate. An initial dose of 10 mg should not be exceeded. Subsequent dosage adjustments are based on the patient's blood or urine glucose response. If patients were on chlorpropamide they should be closely monitored for hypoglycaemia for the first 2 weeks of the transition.
Insulin: on rare occasions, Type II diabetic patients receiving insulin may be transferred to glibenclamide. For doses less than 40 units daily, 2.5mg to 5mg is prescribed initially and insulin can be discontinued abruptly. For doses greater than 40 units daily, 5mg of glibenclamide may be prescribed whilst the insulin dose is reduced by 50%. Insulin is then withdrawn gradually and glibenclamide increased by 1.25mg to 2.5mg daily every 2 to 10 days as necessary.
Biguanides: 2.5mg glibenclamide can be substituted for the biguanide initially and adjusted as required after 3 to 5 days. On occasion, glibenclamide may be prescribed together with metformin if control is not adequate with either agent alone. Clinical benefit of the combination should be monitored from time to time.
Maintenance dose: Dosage usually ranges from 1.25 mg to 15 mg. The maximum daily dose is 20 mg.
Children:
Glibenclamide is not indicated in children, as Type II diabetes mellitus is not usual in this age group. Dosage or effectiveness has not been established.

Contraindications:
➢Glibenclamide should not be given as sole therapy to patients with unstable and/or insulin dependent diabetes mellitus (Type I)
➢Patients with ketoacidosis or diabetic coma
➢Trauma or surgery
➢Severe infection
➢Obvious jaundice
➢In the presence of severe hepatic or renal impairment.
➢Glibenclamide is also contra-indicated in patients with known hypersensitivity or allergy to the drug.
➢Pregnancy
Warnings and Precautions:
Dietary management with or without weight reduction is the principal therapy for the management of Type II diabetes mellitus. Oral hypoglycaemic agents or insulin should only be used after these measures have failed by themselves.

Hypoglycaemia: may be severe and has occasionally been fatal thus necessitating careful monitoring and selection of both patient and dosage. Hypoglycaemia is more likely in elderly patients, those who are debilitated or who have impaired hepatic or renal function. Alcohol, severe or prolonged exercise, inadequate caloric intake, certain medicines (see drug interactions), severe endocrine disorders, and adrenal or pituitary insufficiency may also predispose patients to hypoglycaemia. It may be necessary to institute insulin during illness, stress or surgery.

Regular monitoring of blood and/or urine glucose: It is necessary to determine the minimum effective dose; to detect primary failure (inadequate lowering of blood glucose concentration at the maximum recommended dosage); or secondary failure (loss of control of blood glucose following an initial period of effectiveness). If secondary failure occurs, glibenclamide should usually be discontinued. However, some clinicians may initially evaluate the addition of a low dose insulin regimen.

Use in Pregnancy

Category C.

It is important to achieve strict normoglycaemia during pregnancy. Oral hypoglycaemic agents should be replaced by insulin. The sulphonylureas may enter the foetal circulation and cause neonatal hypoglycaemia. In animal studies embryotoxicity and/or birth defects have been demonstrated. If glibenclamide is used during pregnancy it should be discontinued at least two weeks before the expected delivery date to avoid severe hypoglycaemia in the neonate following delivery.

Use in Lactation

It is not known whether glibenclamide is excreted in breast milk or whether it has a harmful effect on the newborn infant. Other sulphonylureas have been found in breast milk and therefore glibenclamide is not recommended for nursing mothers unless the expected benefits outweigh any potential risks.

Effects on ability to drive and use machines

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 Effects

Adverse effects serious enough to require discontinuation of therapy are uncommon however of adverse effects persist glibenclamide should be discontinued.

Hypoglycaemia.

May be not only severe but also prolonged and fatal (see Warnings and Precautions).

Gastrointestinal:

Gastrointestinal effects e.g. nausea, vomiting, epigastric fullness or sensation of pressure, heartburn, anorexia, dyspepsia and diarrhoea are the most common adverse reactions and occur in 1-2% of patients. Effects tend to be dose related and may disappear when dosage is reduced. Pancreatitis has been reported rarely.

Dermatological:

Allergic skin reactions to sulphonylureas such as pruritus, erythema, urticaria, and erythematous, maculopapular and bullous skin eruptions or psoriasiform drug eruption occur in 1.5% of treated patients. These may be transient and may disappear despite continued use of glibenclamide. If they persist glibenclamide should be discontinued. Porphyria cutanea tarda, pellagra-like changes and photosensitivity reactions have been reported with sulphonylureas.

Haematological:

Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis, pancytopenia, eosinophilia, haemolytic anaemia, aplastic anaemia, bone marrow aplasia and coagulation disorders have been reported with sulphonylureas.

Hepatic:

Increased hepatic enzymes (AST, ALT), abnormal hepatic function, cholestasis, cholestatic hepatitis, granulomatous hepatitis and bilirubinaemia have been reported with sulphonylureas.

Miscellaneous:

Although a causal relationship has not been established, the following adverse effects have been reported in patients receiving glibenclamide; paraesthesia, blindness, deafness, diplopia, visualdisturbances, tremor, convulsions, encephalopathy, confusion, acute psychosis, abnormal renal function, acute renal failure, ocular disturbances, lactic acidosis, alopecia/hypotrichosis, hyponatraemia, syndrome of inappropriate secretion of antidiuretic hormone, arthralgia, arthritis, cerebrovascular disorders, headache, facial oedema, angioedema, hypersensitivity vasculitis and increased sweating.

Interactions

Other medicines given at the same time as sulphonylureas may cause undesirable depression or elevation of the blood sugar level.

The hypoglycaemic action of glibenclamide may be potentiated by ACE inhibitors, aminosalicylic acid, anabolic steroids, ß-receptor blockers, bezafibrate, biguanides, chloramphenicol, clofibrate,clonidine, co-trimoxazole, coumarin derivatives, disopyramide, fenfluramine, fluoxetine, gemfibrozil, guanethidine, heparin, MAOI's, miconazole, parenteral high dose aspantifylline, phenylbutazone, phenyramidol, phosphamides, probenecid, quinolone antibiotics, ranitidine, reserpine, salicylates, sulphinpyrazone, tritoqualine, tetracycline compounds and certain long acting sulphonamides. Highly protein bound agents may also potentiate the hypoglycaemic action due to glibenclamide displacement from plasma proteins including oral anticoagulants, hydantoins, salicylates and other NSAIDs.

Medicines which may produce hyperglycaemia or diminish the hypoglycaemic effect of glibenclamide include alcohol, acetazolamide, calcium channel blockers, cimetidine, clonidine, diazoxide, corticosteroids, glucagon, isoniazid, high dose nicotinic acid, oestrogens, progestogens, phenothiazine derivatives, phenytoin, ranitidine, rifampicin, ritodrine, saluretics, sympathomimetic agents, thyroid hormones and large doses of laxatives. Concomitant treatment with ß-receptor blockers or clonidine may mask the warning symptoms of a hypoglycaemic attack.

Potentiation or attenuation of the blood sugar lowering effect of glibenclamide has been observed during concomitant therapy with H2-receptor antagonists.

Intolerance to alcohol may occur. Excessive alcohol ingestion by people who drink occasionally may attenuate the hypoglycaemic effect of glibenclamide or dangerously potentiate it by delaying its metabolic inactivation. Disulfiram-like reactions have occurred very rarely following the concomitant use of alcohol and glibenclamide.

Overdosage:

Overdosage of sulphonylureas including glibenclamide can produce hypoglycaemia. In acute poisoning, the stomach should be emptied by aspiration and lavage. Hypoglycaemia may be treated with glucose tablets or powder or 3 to 4 teaspoons of sugar mixed with a little water. This should be followed by a snack of complex carbohydrate e.g. a sandwich. Alternatively, 1 mg glucagon may be administered subcutaneously or intramuscularly in the absence of oral glucose. If the patient is comatose or the hypoglycaemia is severe, glucose should be given as an intravenous infusion. The patient should be observed over several days in case hypoglycaemia recurs.

Pharmaceutical Precautions:

Store below 30°C.

Protect from heat, light and moisture.

Medicine Classification: Prescription only medicine.

Presentation: Blister pack of 10x10's tablets
Jar of 1000's tablets

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