ORBIDE 1 mg /2 mg /3 mg /4 mg Tablets
(Glimepiride)

Orbide contains Glimepiride, an oral hypoglycemic agent belonging to the sulfonylurea group which is used widely for the treatment of type-2 diabetes mellitus.

DESCRIPTION

Chemically, Glimepiride is 1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) - ethyl]phenyl]sulfonyl] -3-(trans-4-methylcyclohexyl) urea. It has a chemical formula of C24 H34 N4 O5 S and a molecular weight of 490.62.

PHARMACOLOGY

Orbide is a sulfonylurea antihyperglycemic agent that may be given in a single daily dose. It acts by stimulating insulin release from pancreatic beta-cells and possibly also via extrapancreatic mechanisms. The major site of activity of Orbide is thought to be membrane receptors on pancreatic ß cells, where it acts via ATP-regulated potassium (KATP) channels, resulting in membrane depolarisation and release of insulin. Orbide decreases blood glucose and increases blood insulin levels, with maximum effects during the first 4 hours after the dose.

PHARMACOKINETICS

Orbide is rapidly and completely absorbed after oral administration. Oral bioavailability is approximately 100%. Peak serum concentrations occur 2-3 hours after oral administration, are proportional to dose and are similar in healthy volunteers and in patients with Type 2 diabetes. After multiple doses, there is no evidence of accumulation in serum. Meals have only modest effect on fasting pharmacokinetic data. When Orbide is administered with meals, the time to reach peak concentration is delayed by approximately 10%; decrease in both peak concentration and AUC is also about 10%.

After intravenous (i.v.) dosing in normal subjects, the volume of distribution (Vd) is 8.8L (113mL/kg) and the total body clearance (CL) is 47.8 mL/min. More than 99% of Orbide is bound to plasma proteins. Orbide is completely biotransfered by hepatic oxidative metabolism. The CYP2C9 enzyme transforms Orbide to the cyclohexylhydroxymethyl derivative (M1), which is further metabolized to form carboxyl derivative (M2) by cytosolic enzymes,

After a single dose, the elimination half-life of Orbide is 5 hours and increases to 9 hours after multiple doses. Urinary excretion of metabolites accounts for 60% of the dose; the remainder is found as metabolites in faeces. M1 is the predominant urinary metabolite and M2 is predominant faecal metabolite.

INDICATIONS

Orbide is indicated for the treatment of type-2 diabetes mellitus in association with dietary measures and with physical exercise, when these measures alone are not sufficent to normalize the blood glucose levels.

DOSAGE & ADMINISTRATION

The usual starting dose of Orbide as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. No exact dosage relationship exists between Orbide and the other oral hypoglycemic agents. The maximum starting dose of Orbide should not be more than 2 mg. The usual maintenance dose of Orbide is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dose increase should be made in increments of not more than 2 mg at 1-2 week intervals, based on the patient's blood glucose response. Long term efficacy should be monitored by measurment of HbA1c levels, for example every 3 to 6 months.

CONTRAINDICATIONS

Orbide is contraindicated in the following situations:

- Type-1 diabetes mellitus
- Hypersensitivity to sulfonylureas
- Severe hepatic and renal failure
- Pregnancy and Lactation
- Patients with ketoacidosis
- Patients undergoing surgery, after severe trauma or during severe infections

WARNINGS & PRECAUTIONS

All sulfonylureas, including Orbide, can cause episodes of hypoglycemia. Hypoglycemia may present with sweating, intense hunger, trembling, pallor, visual disturbances, feeling of malaise and abnormal behaviour. If untreated it can lead to drowsiness, convulsions or coma. Hypoglycemic coma can be fatal. Hence all patients given sulfonylureas must be taught to recognise the symptoms of hypoglycemia and if it occurs, be told to take either sugar or food containing sugar immediately and inform the doctor.

Hypoglycemia can occur because of irregular meal times, missed meals, changes in diet, prolonged or strenous exercise, by intake of alcohol or other hypoglycemic drugs. The patient should be told to avoid these situations which are likely to cause hypoglycemia. The patient should be warned about the dangers of hypoglycemia while driving or operating machinery. Patients who develop frequent episodes of hypoglycemia should not drive or operate machinery.

DRUG INTERACTIONS

An increased hypoglycemic effect can occur on co-administration of sulfonylureas, including Orbide, with the following drugs:

Salicylates, Sulfonamides, Alcohol, Betablockers, Azole antifungals like Fluconazole, Ketoconazole and Miconazole, ACE Inhibitors, MAO Inhibitors, Tricyclic anti-depressants, Chloramphenicol, Tetracyclines, Thyroid hormones, Cimetidine, Ranitidine, Clofibrate, Allopurinol and oral anti-coagulants. Care should be taken when Orbide is administered with these drugs.

A diminished hypoglycemic effect, possibly requiring an increase in Orbide dose may occur with drugs like Danazol, Chlorpromazine, Glucocorticoids, Oral Contraceptives, Rifamycins, Thiazide diuretics and Epinephrine.

Co-administration of Aspirin and Orbide led to a 34% decrease in the mean Orbide AUC and, therfore, a 34% increase in the mean CL/f. The mean Cmax had a decrease of 4%. Blood glucose and serum C-peptide concentrations were uneffected and no hypoglycemic symptoms were reported. Co-administration of either cimetidine (800mg once daily) or ranitidine (150mg bid) with a single 4-mg oral dose of Orbide did not significantly alter the absorption and disposition of Orbide.

Concomitant administration of propranolol (40mg tid) and Orbide significantly increased Cmax, AUC, and t ½ of Orbide by 23%, 22% and 15% respectively, and it decreased CL/f by 18%. Concomitant administration of Orbide (4mg once daily) did not alter the pharmacokinetic characteristics of R- and S- warfarin enantiomers following administration of a single dose (25mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2mg Orbide were unaffected by co-administration of ramipril (an ACE inhibitor) 5mg once daily in normal subjects. No hypoglycemic symptoms were reported.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies in rats showed no evidence of carcinogenesis.

Orbide was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies.

Orbide had no effect on the fertility of male and female rats.

USE IN SPECIAL POPULATION

Pregnancy : Orbide is contraindicated in pregnancy.

Nursing Mothers : Orbide is contraindicated in a mother who is breast feeding her baby.

Pediatric Use : No studies were performed in pediatric patients.

Geriatric Use : Comparison of Orbide pharmacokinetics in NIDDM patients ≤ 65 years and those > 65 years was performed an a study using a dosing regimen of 6mg daily. There were no significant differences in Orbide pharmacokinetics between the two age groups.

Use in Renal Impairment : A single-dose, open-label study was conducted in 15 patients with renal impairment. The results showed that Orbide serum levels decreased as renal function decreased. The apparent terminal half-life (t ½) for Orbide did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excreation of M1 plus M2 as percent of dose, however, decreased.

Use in Hepatic Impairment : No studies have been performed in patients with hepatic insufficinency. There were no important differences in Orbide metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine. The pharmacokinetics of Orbide in morbidly obese patients were similar to those in the normal weight group, except for a lower Cmax and AUC.

ADVERSE REACTIONS

Vomiting, gastrointestinal pain and diarrhoea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas. Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients.

Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and pancytopenia have been reported with sulfonylureas. Hepatic porphyria reactions and disulfiram-like reaction have been reported with sulfonylurea; however, no cases have yet been reported with Glimpiride. Cases of hyponatremia have been reported with Orbide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. Change in accommodation and/or blurred vision may occur with the use of Orbide. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. Overdosage of sulfonylureas, including Orbide, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24-48 hours, because hypoglycemia may recur after apparent clinical recovery.

PACKING

Box of 30 tablets

STORAGE INSTRUCTIONS

Store in a cool, dry place. Protect from light.

ORBUS PHARMA INC

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