INTASZORYL-1, 2, 3 & 4

(Glimepiride Tablets 1 mg, 2 mg, 3 mg & 4 mg)

DESCRIPTION

Glimepiride is an oral hypoglycaemic agent belonging to sulfonylurea class. Chemically, glimepiride is identified as trans-3-Ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4-methylcclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-1H-pyrrole-1 -carboxamide.

COMPOSITION

1. INTASZORYL-1 mg Tablets
Each uncoated tablet contains: Glimepiride 1 mg
2. INTASZORYL-2 mg Tablets
Each uncoated tablet contains:Glimepiride 2 mg
3. INTASZORYL-3 mg Tablets
Each uncoated tablet contains:Glimepiride 3 mg
4. INTASZORYL-4 mg Tablets
Each uncoated tablet contains: Glimepiride 4 mg

PRODUCT DESCRIPTION

INTASZORYL-1mg Tablets: Pink coloured round, flat uncoated tablets with bevelled edges and score line on one side and plain on other side of tablet.
INTASZORYL-2mg Tablets: Green coloured oval shaped, uncoated tablets with score line on one side and plain on other side of tablet.
INTASZORYL-3mg Tablets: Pale yellow, oval shaped, uncoated tablets with score line on one side and plain on other side of tablet.
INTASZORYL-4mg Tablets: Blue coloured, oval shaped, uncoated tablets with score line on one side and plain on other side.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Glimepiride primarily acts by stimulating the release of insulin from functional pancreatic beta cells. Also it has been found that glimepiride increases sensitivity of peripheral tissues to insulin.
Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for non-insulin dependent diabetes mellitus (NIDDM).

Pharmacokinetics:

Absorption:
Following oral administration, glimepiride is completely (100%) absorbed from the GI tract[1]. The drug is significantly absorbed within 1 hour after oral administration and peak drug levels (C_{max}) reach at 2 to 3 hours.
Distribution:
After intravenous (IV) dosing in normal subjects, the volume of distribution was 8.8 L (113 ml/kg), and the total body clearance was 47.8 ml/min. Protein binding was greater than 99.5%.
Metabolism:
Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes.
Excretion:
Glimepiride when given orally, approximately 60% of the total dose was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80% to 90% of that recovered in the urine. Approximately 40% of the total dose was recovered in the feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.
In pharmacokinetic studies carried out, glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride was not different in healthy volunteers and in NIDDM patients.

INDICATIONS

As an adjunct to diet and exercise in non-insulin-dependent (type II) diabetes, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise and weight reduction alone.
Glimepiride may also be used in combination with an oral antidiabetic containing metformin or with insulin.

DOSAGE AND ADMINISTRATION

In principle, the dosage of Glimepiride is governed by the desired blood sugar level. The dosage of glimepiride must be the lowest which is sufficient to achieve the desired metabolic control.
Treatment with Glimepiride must be initiated and monitored by a doctor. Glimepiride must be taken at the times and in the doses prescribed. Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose. Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or situations where a dose cannot be taken at the prescribed time must be discussed and agreed between doctor and patient beforehand. A doctor must be notified immediately if the dose taken is too high, or an extra dose has been taken.

The initial and the maintenance doses are set based on the results of regular checks of glucose in blood and urine. Monitoring of glucose levels in blood and urine also serves to detect either primary or secondary failure of therapy.

Initial dose and dose titration: The usual initial dose is 1 mg Glimepiride once daily. If necessary, the daily dose can be increased. Any increase should be based on regular blood sugar monitoring, and should be gradual, i.e., at intervals of one to two weeks, and carried out stepwise, as follows: 1 mg - 2 mg - 3 mg - 4 mg - 6 mg, and - in exceptional cases - 8 mg.

Dose range in patients with well controlled diabetes: The usual dose range in patients with well controlled diabetes is 1 to 4 mg Glimepiride daily. Only some patients benefit from daily doses of more than 6 mg.

Distribution of doses: Timing and distribution of doses are to be decided by the doctor, taking into consideration the patient's current life-style. Normally, a single daily dose of Glimepiride is sufficient. This dose should be taken immediately before a substantial breakfast or - if none is taken - immediately before the first main meal. It is very important not to skip meals after taking Glimepiride.

Secondary dosage adjustment: As the control of diabetes improves, sensitivity to insulin increases; therefore, glimepiride requirements may fall as treatment proceeds. To avoid an excessive reduction in blood sugar (hypoglycaemia), a timely dose reduction or cessation of Glimepiride therapy must be considered.

A dose adjustment must also be considered whenever the patient's weight or life-style changes, or other factors causing an increased susceptibility to hypoglycaemia or to an excessive increase in blood sugar levels (hyperglycaemia) arise (see under 'Special warnings and precautions').

Duration of treatment: Treatment with Glimepiride is normally a long-term therapy.

Changeover from other oral antidiabetics to Glimepiride: There is no exact dosage relationship between Glimepiride and other oral blood-sugar-lowering agents. When substituting Glimepiride for other such agents, the initial daily dose is 1 mg; this applies even in changeovers from the maximum dose of another oral blood-sugar-lowering agent. Any Glimepiride dose increase should be in accordance with guidelines given above in 'Initial dose and dose titration'.

Consideration must be given to the potency and duration of action of the previous blood-sugar-lowering agent. It may be necessary to interrupt treatment to avoid additive effects which would increase the risk of hypoglycaemia.

Use in combination with insulin: Whenever blood sugar levels cannot be controlled adequately with the maximum daily dose of Glimepiride , insulin may be given concomitantly. In this case, the current dose of Glimepiride remains unchanged. Insulin treatment is started at a low dose, which is subsequently increased stepwise according to the desired blood sugar level. Combined treatment should be initiated under close medical supervision.

Administration

Glimepiride tablets must be swallowed without chewing and with sufficient amounts of liquid (approximately ½ glass).

CONTRAINDICATIONS

Glimepiride is contraindicated in patients with:
1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma.
3. In pregnant or breast-feeding women.

WARNINGS

Special Warning on Increased Risk of Cardiovascular Mortality
The administration of oral hypoglycemic drugs belonging to sulfonylurea group has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Considering similarities in mode of action and chemical structure, it is advised from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class.

PRECAUTIONS

Hypoglycemia: All sulfonylurea drugs have propensity of producing severe hypoglycemia.
Patients with impaired renal function may be more sensitive to the hypoglycaemic effect of glimepiride. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

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Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Combined use of glimepiride with insulin or metformin may increase the potential for hypoglycemia.
Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with glimepiride or even use insulin monotherapy. Should secondary failure occur with glimepiride or metformin monotherapy, combined therapy with glimepiride and metformin or glimepiride and insulin may result in a response. Should secondary failure occur with combined glimepiride/metformin therapy, it may be necessary to initiate insulin therapy.
Laboratory Tests
Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Pregnancy
Teratogenic Effects: Pregnancy Category C: Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.
There are no adequate and well-controlled studies in pregnant women. It is recommended that glimepiride tablets should not be used during pregnancy.

Nursing Mothers
In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. There is no data whether glimepiride is excreted in human milk. Since other sulfonylureas are excreted in human milk, it is recommended that glimepiride should be discontinued in nursing mothers. If glimepiride is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS
• The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.
• Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diurectics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.
When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.
• Caution should be exercised while administering glimepiride with beta blockers and patients should be warned about the potential for hypoglycemia.
• Glimepiride treatment has been found to result in a slight, but statistically significant, decrease in the pharmacodynamic response of warfarin.[2]
• Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.
• Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

ADVERSE REACTIONS[3]
Hypoglycemia:
Hypoglycemia (sometimes life-threatening) may occur as a result of the blood-glucose lowering action of glimepiride. This happens when there is an imbalance between glimepiride dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism.
Possible symptoms of hypo glycemic include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, sleep disorders, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia.
In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias.
The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke. The symptoms of hypo glycaemia may persist even if hypoglycaemia is corrected.
Eyes:
There may be a temporary visual impairment during the initiation of therapy, due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.
Digestive tract:
Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness of the epigastrium, abdominal pain and diarrhoea may occur.
In isolated cases, there may be elevation of liver enzyme levels, impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which may also lead to lifethreatening liver failure.
Blood:
Potentially life-threatening changes in the blood profile may occur, such as thrombocytopenia and, in isolated cases, leucopenia. In addition to the above mentioned, glimepiride may cause haemolytic anaemia or erythrocytopenia, granulocytopenia, agranulocytosis and (e.g. due to myelosuppression) pancytopenia.
Allergic or pseudoallergic reactions may occur such as itching, urticaria or rashes. These mild reactions may develop into serious and even life-threatening reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must therefore be notified immediately.
In isolated cases, a decrease in serum sodium concentration has been seen and allergic vasculitis or hypersensitivity of the skin to light may occur. If any of these reactions occur a doctor should be consulted. Alertness and reactions may be impaired due to hypo- or hyperglycaemia, especially when beginning or after altering treatment, or when glimepiride is not taken regularly. This may affect the ability to drive or to operate machinery.

OVERDOSAGE
Overdosage of sulfonylureas, including glimepiride, 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. Patient should be closely monitored and the dose of glimepiride should be carefully titrated. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dl. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

PRESENTATION
PVC/PVDC - Alu Blister of 10 tablets. Each Carton contains 3 such blister. (3 x 10T)

Storage
Store below 30°C.

SHELF LIFE
Two years from the date of the manufacturing.

Manufactured by:
INTAS
INTAS PHARM LTD.
PLOT NO 457/458, VILLAGE MATODA,
TALIKA:SANAND 382 210, INDIA

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References
1. Drug Metab Drug Interact 1994; 11(4): 331-9.
2. Drugs 1998; 55(4): 563-84.
3. Horm Metab Res1996; 28: 413-8.

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