EVOPRIDE®
(Glimepiride USP)

ایوو پرائڈ

COMPOSITION

Each tablet of Evopiride 1mg, 2mg, 3mg & 4mg contains:
Glimepiride USP.....1mg, 2mg, 3mg & 4mg respectively.
(USP Specs.)

DESCRIPTION

EVOPRIDE tablets contain glimepiride, an oral hypoglycemic agent belonging to the sulfonylurea group used in the treatment of Type II diabetes mellitus.

CLINICAL PHARMACOLOGY

Mechanism of action
Glimepiride is an insulin secretagogue belonging to the sulfonylurea group that primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane leading to closure of the ATP-sensitive potassium channel which induces depolarization of the beta cell and results (by opening of calcium channels) in an increased influx of calcium into the cell. This leads to insulin release through exocytosis. As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus.

In addition, glimepiride seems to have pronounced extra-pancreatic effects also postulated for other sulfonylureas. The extra pancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

Pharmacokinetics

Absorption
The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (Cmax) are reached approximately 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both Cmax and AUC (area under the time/concentration curve).

Distribution
Glimepiride has a very low distribution volume (approximately 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approximately 48 ml/min).

Metabolism
Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes.

Elimination
Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives have been noted. After a single dose of radiolabelled glimepiride, approximately 58% of the radioactivity is recovered in the urine, and 35% in the feces. No unchanged substance was detected in the urine. Two metabolites most probably resulting from hepatic metabolism (major enzyme is CYP2C9) - were identified both in urine and feces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing has revealed no significant differences in pharmacokinetics, and the intra-individual variability is found to be very low. There is no relevant accumulation.

INDICATIONS

EVOPRIDE (Glimepiride) tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type II diabetes mellitus whose hyperglycemia cannot be controlled by diet and exercise alone.
Glimepiride is also used in combination with other oral hypoglycemic drugs or with insulin, if required.

Limitations of use:
Glimepiride should not be used for the treatment of Type I diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these conditions.

DOSAGE AND ADMINISTRATION

The recommended starting dose of EVOPRIDE (Glimepiride) is 1 mg or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should be started on 1 mg once daily.
After reaching a daily dose of 2 mg, further dose increases can be made in increments of 1 mg or 2 mg based upon the patient's glycemic response. Uptitration should not occur more frequently than every 1-2 weeks. A conservative titration scheme is recommended for patients at increased risk for hypoglycemia.
A dose of more than 4 mg glimepiride per day is generally not needed. However, dose may be titrated to a maximum recommended dose of 8 mg daily.

Dose adjustment and dosing considerations in Special populations:

Elderly (65 years and older)
No dosage adjustment is needed in the elderly. However, upward titration of dosage should be performed slowly and cautiously because elderly population may be more prone to develop hypoglycemia.

Renal impairment
A starting dose of not more than 1 mg daily is suggested to minimize the risk of hypoglycemia for all diabetic patients with renal impairment.

Administration requirements:
EVOPRIDE tablets should be administered with breakfast or the first main meal of the day.

CONTRAINDICATIONS

• Glimepiride is contraindicated in patients with a history of a hypersensitivity reaction to Glimepiride or to other sulfonamide derivatives.
• Glimepiride should not be used in patients with Type I diabetes mellitus, ketoacidosis, diabetic coma or severe renal and hepatic function disorders.

WARNINGS AND PRECAUTIONS

Hypoglycemia
Treatment with Glimepiride may lead to hypoglycemia. This may be severe. The clinical picture of a severe hypoglycemic attack may resemble that of a stroke. Hypoglycemia symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect. It is known from other sulfonylureas that, despite initially successful counter measures, hypoglycemia may recur. Severe or prolonged hypoglycemia, which is only temporarily controlled by the usual amounts of sugar, may require immediate medical treatment and occasionally hospitalization.
Factors favoring hypoglycemia include under-nutrition, irregular mealtimes or missed meals or periods of fasting, alterations in diet, imbalance between physical exertion and carbohydrate intake, consumption of alcohol, especially in combination with skipped meals, impaired renal function, serious liver dysfunction, overdose with Glimepiride, certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency), concurrent administration of certain other medicinal products and failure to adjust the dose of concomitant anti-diabetic drugs (see section DRUG INTERACTIONS).
Treatment with Glimepiride requires regular monitoring of glucose levels in the blood and urine. Patients should be encouraged to use self-monitoring devices to keep a track of their blood glucose levels.

G6PD Deficiency and Hemolytic Anemia

Treatment of patients with G6PD-deficiency with sulfonylurea agents including Glimepiride can lead to hemolytic anemia. Caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered. There have also been post-marketing reports of hemolytic anemia in patients receiving Glimepiride who did not have known G6PD deficiency.

Severe Renal and Hepatic Impairment

No experience has been gained concerning the use of Glimepiride in patients with dialysis or severe hepatic impairment. In patients with severe impairment of renal or hepatic function change over to insulin is indicated. Monitoring of renal and hepatic function may be needed during therapy with Glimepiride.

Hypersensitivity reactions

There have been post-marketing reports of hypersensitivity reactions in patients treated with Glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens - Johnson syndrome. If a hypersensitivity reaction is suspected Glimepiride should be discontinued at once with assessment for other potential causes for the reaction, and alternative antidiabetic therapy should be used.

Effects related to lactose used in formulation

EVOPRIDE tablet formulation contains lactose as an inactive ingredient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

Glimepiride may induce hypoglycemia. Symptoms of hypoglycemia such as somnolence, lassitude, impaired concentration, alertness and reaction time, confusion, visual disturbances and dizziness etc. may impair a person's ability to drive and operate machines.

ADVERSE REACTIONS

The following adverse reactions from clinical investigations are based on experience with Glimepiride and listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, erythropenia, hemolytic anemia and pancytopenia, which are in general reversible upon discontinuation of medication.

Not known: severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.

Immune system disorders

Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnea, fall in blood pressure and sometimes shock.

Not-known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

Metabolism and nutrition disorders

Rare: hypoglycemia.

These hypoglycemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycemic therapies, on individual factors such as dietary habits and dose.

Eye disorders
Not known: visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

Gastrointestinal disorders
Very rare: nausea, vomiting, diarrhea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.

Hepato-biliary disorders
Not know: hepatic enzymes increased.

Very rare: hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure.

Skin and subcutaneous tissue disorders
Not known: hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.

Investigations
Very rare: blood sodium decrease.

The following adverse reactions have been identified during **post-approval use** of Glimepiride.
• Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens Johnson Syndrome
• Hemolytic anemia in patients with and without G6PD deficiency
• Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.
• Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis
• Leucopenia, agranulocytosis, aplastic anemia, and pancytopenia
• Thrombocytopenia (including severe cases with platelet count less than 10,000/µL) and thrombocytopenic purpura
• Hepatic porphyria reactions and disulfiram-like reactions
• Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone

DRUG INTERACTIONS

Drugs predisposing to hypoglycemia/potentiating the effects of Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, undesired increases in the hypoglycemic action of glimepiride can occur. For this reason, other medicinal products should only be used with caution. These include the following:

Insulin, pramlintide and oral antidiabetic drugs, phenylbutazone, azapropazone and oxyfenbutazone NSAIDs, salicylates and p-amino-salicylic acid, somatostatin analogs, anabolic steroids and male sex hormones, chloramphenicol, long acting sulfonamides, tetracyclines, quinolone antibiotics & clarithromycin, coumarin anticoagulants, fenfluramine, disopyramide, fibrates, H2-receptor antagonists ACE inhibitors, fluoxetine, MAO-inhibitors, allopurinol, probenecid, sulfinpyrazone, sympatholytics, cyclophosphamide, trophosphamide and iphosphamides, pentoxifylline (high dose parenteral) and tritoqualine.

Fluconazole and Micoconazole
Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inhibitors (e.g. fluconazole). Results from an in vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors. This may also lead to hypoglycemia.
A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has also been reported.

Drugs reducing the pharmacological effect of Glimepiride
Weakening of the blood-glucose-lowering effect and thus worsening glycemic control may occur when one of the following medicinal products is taken with glimepiride:

Estrogens and progestogens, oral contraceptives, danazol, protease inhibitors, saluretics, thiazide diuretics and other diuretics, thyroid stimulating agents, glucocorticoids, phenothiazine derivatives, chlorpromazine, adrenaline and sympathomimetics, nicotinic acid (high doses) and nicotinic acid derivatives, laxatives (long term use), phenytoin, diazoxide, glucagon, barbiturates, rifampicin and isoniazid, acetazolamide, atypical antipsychotics (olanzapine, clozapine) and phenothiazines.

Drugs and substances that may potentiate or weaken the hypoglycemic effect of Glimepiride

Beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the effect of glimepiride in an unpredictable way, the signs and symptoms of hypoglycemia may also be reduced or absent in patients taking these drugs.

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride.

Colesevelam
Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

USE IN SPECIAL POPULATIONS

Hepatic Impairment:
Glimepiride is not recommended in patients with severe hepatic impairment.

Renal Impairment:
Dosing considerations should be followed in patients with renal impairment. (See section DOSAGE AND ADMININSTRATION)

Pregnancy:
There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycemia) of glimepiride. Consequently, glimepiride should not be used during the whole pregnancy. In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy. Glimepiride belongs to FDA pregnancy category C.

Breast feeding:
The excretion of glimepiride in human milk is unknown. Glimepiride is excreted in rat milk. Offspring of rats exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period.
As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycemia in nursing infants, breast-feeding is not advised during treatment with glimepiride.

Geriatric Use:
Elderly patients may be more prone to hypoglycemia therefore, dosing considerations should be followed and dose titration should be done slowly. (See DOSAGE AND ADMINISTRATION)

OVERDOSE

Symptoms
After ingestion of an overdose of glimepiride, hypoglycemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general, observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycemia may in general, be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Management of overdose
In case of overdose with glimepiride component, treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate.
Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose.
Intravenous glucose is generally administered by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.
Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery

PRESENTATION

Evopride Tablets 1 mg: Pack of 30 tablets
Evopride Tablets 2 mg: Pack of 30 tablets
Evopride Tablets 3 mg: Pack of 30 tablets
Evopride Tablets 4 mg: Pack of 30 tablets

INSTRUCTIONS
As advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from heat, light and moisture.
Store below 30°C.
For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

ہدایات:
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