United Pharmaceuticals

AMEPRIDE®

Glimepiride

Description:

AMEPRIDE® (Glimepiride) is a sulfonylurea hypoglycaemic agent. The decrease in blood glucose level is achieved mainly by means of the stimulation of Insulin release from pancreatic beta cells. This effect is predominantly based on improved responsiveness of these cells to the physiological glucose stimulus. Glimepiride augments the normal action of Insulin on peripheral glucose uptake. Moreover, it mimics such action as well as the glucose output of the liver. Good metabolic control over 24 hours can be achieved with a single dose of **AMEPRIDE®**.

In patients with insufficient response to the maximum dose, combined use with an additional oral antidiabetic, containing Metformin, or with Insulin improves metabolic control.

Properties:

After oral administration, Glimepiride is absorbed completely from the gastrointestinal tract. Food intake has no relevant influence on Glimepiride absorption, only absorption rate is slightly diminished. Maximum serum concentrations are reached approximately 2.5 hours after oral intake. Glimepiride has very low distribution volume, high protein binding (>99%) and low clearance. After a single dose of Glimepiride, 58% of the dose is recovered in the urine and 35% in the faeces.

Indications:

AMEPRIDE® is indicated for the treatment of non-insulin dependent diabetes mellitus (Type II), when diet, physical exercise and weight reduction alone are not adequate to control blood glucose levels.

Dosage and administration:

AMEPRIDE® tablets must be swallowed without chewing and with sufficient amount of liquid, immediately before breakfast or the first main meal. It is very important not to skip meals after taking **AMEPRIDE®**.

Initial dose and dose titration: The usual initial dose is 1 mg 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 1 - 2 weeks, and carried out stepwise as follows: 1 mg - 2 mg - 3 mg - 4 mg - 6 mg, and, in exceptional cases, 8 mg.

Secondary dosage adjustment: The sensitivity to Insulin increases with the improvement of diabetes control; therefore, as treatment proceeds, **AMEPRIDE®** requirements may fall. To avoid an excessive reduction in blood glucose level (hypoglycaemia), a timely dose reduction or cessation of **AMEPRIDE®** therapy must be considered.

Changeover from other oral anti-diabetics to AMEPRIDE®: There is no exact dosage relationship between **AMEPRIDE®** and other oral blood-sugar-lowering agents. When substituting **AMEPRIDE®** for such an agent, the initial daily dose is 1 mg; this applies even in changeover from the maximum dose of the other anti-diabetic, taking into consideration the potency and duration of action of the previous anti-diabetic agent. It may be necessary to interrupt treatment to avoid additive effects which would increase the risk of hypoglycaemia.

Use of AMEPRIDE® in combination with Metformin or Insulin: Whenever blood sugar levels can't be controlled adequately with the maximum daily dose of **AMEPRIDE®**, Metformin or Insulin may be given concomitantly with **AMEPRIDE®**. In these cases, the current dose of **AMEPRIDE®** remains unchanged. Metformin or 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.

Patient notes:

• For the optimal blood glucose control, it is important to consider a correct diet, regular and sufficient physical exercise and, if necessary, reduction of body weight. These are just as important as regular intake of **AMEPRIDE®**.

• When starting treatment, the patient must be informed about the effects and risks of **AMEPRIDE®** and about its role in conjunction with dietary measures and physical exercise.

• Treatment with **AMEPRIDE®** must be initiated and monitored by a physician and based upon the results of regular checks of glucose in blood and urine as should, additionally, the proportion of glycated haemoglobin.

• **AMEPRIDE®** 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 physician and patient beforehand.

• Treatment with **AMEPRIDE®** must be at the lowest dose which is sufficient to achieve the desired metabolic control.

• The usual dose range in patients with well controlled diabetes is 1 - 4 mg **AMEPRIDE®** daily. Only some patients benefit from daily doses at more than 6 mg.

• Normally, a single daily dose of **AMEPRIDE®** is sufficient.

• Treatment with **AMEPRIDE®** is normally a long term therapy.

Contraindications:

Glimepiride is contraindicated in the following cases:

• Treatment of insulin dependent diabetes mellitus (Type I).

• Diabetic ketoacidosis.

• Diabetic pre-coma or coma.

• Hypersensitivity to Glimepiride, other sulfonylureas or sulfonamides.

• Severe impairment of renal or hepatic function. Changeover to Insulin is indicated in these cases.

Precautions:

• In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates especially careful monitoring.

Factors favoring hypoglycaemia include:

- Unwillingness.
- Under-nutrition, irregular mealtimes, or skipped meals.
- Imbalance between physical exertion and carbohydrate intake.
- Alterations of diet.
- Consumption of Alcohol, especially in combination with skipped meals.
- Impaired renal function.
- Severe impairment of liver function.
- Overdosage with Glimepiride.
- Concurrent administration with other certain medicines.

The physician must be informed about such factors and about hypoglycaemic episodes, since these require particularly careful monitoring.

If such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of Glimepiride or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life-style changes.

Hypoglycaemia can almost always be promptly controlled by immediate intake of sugar. Severe hypoglycaemia requires, in addition, immediate treatment and follow-up by a physician and, in some circumstances, hospitalization.

If treated by different physicians (upon, e.g., admission to hospital after an accident, illness while on holiday), the patients must inform them about their diabetes and previous treatment.

• In exceptional stress situations (e.g. trauma, surgery, infections with fever) blood sugar control may deteriorate, and a temporary change to Insulin may be necessary.

• The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia, especially when beginning or after altering treatment or when the treatment doses are not taken regularly. This may affect the ability to operate a vehicle or machinery.

Use during pregnancy and lactation:

Pregnancy category **C**.

Glimepiride must not be taken during pregnancy to avoid the risk of harming the fetus. A changeover to Insulin is indicated.

Sulfonylurea derivatives including Glimepiride passes into the breast milk, therefore Glimepiride must not be taken by breast-feeding women. A changeover to Insulin or discontinuation of breast-feeding is necessary.

Drug interactions:

• Potentiation of the hypoglycaemic effect of Glimepiride: Hypoglycaemia, in some instances, may occur when one of the following drugs is taken concomitantly with Glimepiride, for example: Insulin and other oral anti-diabetics, ACE inhibitors, Allopurinol, anabolic steroids and male sex hormones, Chloramphenicol, coumarin derivatives, Cyclophosphamide, Disopyramide, Fenfluramine, Fenyramidol, fibtates, Fluoxetine, Guanethidine, Ifosfamide, MOA inhibitors, Miconazole, Para-aminosalicylic acid, Pentoxifylline (high dose parenteral), Phenylbutazone, Azapropazone, Oxyphenbutazone, Probenecid, quinolones, tetracyclines, salicylates, Sulfinpyrazone, sulfonamides, Tritoqualine, Trofosfamide.

• Weakening of the hypoglycaemic effect of Glimepiride: Raised blood sugar levels may occur when one of the following drugs is taken concomitantly with Glimepiride, for example: Acetazolamide, barbiturates, corticosteroids, Diazoxide, diuretics, Epinephrine (adrenaline) and other sympathomimetic agents, Glucagon, laxatives (after protracted use), Nicotinic acid (in high doses), estrogens and progestogens, phenothiazines, Phenytoin, Rifampicin, thyroid hormones.

• H_2 receptor antagonist, Clonidine and Reserpine may lead to either potentiation or weakening of the hypoglycaemic effect.

• Beta-blockers decrease glucose tolerance. In patients with diabetes mellitus this may lead to deterioration of metabolic control. In addition, beta-blockers may increase the tendency to hypoglycaemia (due to impaired counter-regulation). Under the influence of sympatholytic medicines such as beta-blockers, Clonidine, Guanethidine and Reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.

• Both acute and chronic Alcohol intakes may be potentiate or weaken the hypoglycaemic action of Glimepiride unpredictably.

• The effect of coumarin derivatives may be potentiated or weaken.

Side effects:

The side effects of Glimepiride and possibly the other sulfonylureas include:

• Hypoglycaemia: As a result of the blood-sugar-lowering action of Glimepiride, hypoglycaemia may occur, and may also be prolonged.

Possible symptoms of hypoglycaemia include: Headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, depression, confusion, difficulty in speaking and even speech loss, visual disorders, tremor, sensory disturbances, dizziness, helplessness, loss of self control, delirium, loss of consciousness up to and including coma, shallow respiration and slow heart rate (bradycardia). In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, rapid heart rate (tachycardia), hypertension, angina pectoris and cardiac arrhythmias.

The symptoms of hypoglycaemia nearly always subside when hypoglycaemia is corrected.

• Eye disorders: Transient visual disturbances may occur especially on initiation of the treatment, due to changes in blood glucose levels.

• Digestive tract: Occasionally, gastrointestinal symptoms such as the following may occur: Nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain, and diarrhea.

In rare cases, liver enzyme levels may increase.

In isolated cases, impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis may develop, possibly leading to liver failure.

• Blood: Severe changes in haematology may occur during treatment.

In rare cases, thrombocytopenia, and in isolated cases, leucopenia, haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis and pancytopenia (e.g. due to myelosuppression) may develop.

• Other side effects: Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such reactions may be mild, but also may become more serious and may be accompanied by dyspnoea and a fall in blood pressure, sometimes progressing to shock. If urticaria occurs, a physician must be notified immediately.

In isolated cases, a decrease in serum Sodium, inflammation of blood vessels (allergic vasculitis) and hypersensitivity of the skin to light may occur.

Overdosage:

Glimepiride overdosage may lead to severe and sometimes life-threatening hypoglycaemia and may require hospitalization even as a precautionary measure.

Significant overdosage with severe reactions is a medical emergency and will necessitate immediate treatment and hospitalization.

Overdosage treatment:

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dosage, meal patterns or physical activity may be necessary.

More severe episodes with coma, seizure or neurologic impairment may be treated with Glucagon (intramuscular or/and subcutaneous) or concentrated glucose solution (intravenous).

If life-threatening amounts have been ingested, detoxification (by, e.g., gastric lavage, activated charcoal) will be necessary.

Sustained administration of carbohydrates and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

Storage conditions:

Store up to 30º C.

Presentation:

AMEPRIDE® 1: Each tablet contains Glimepiride 1 mg EP in packs of 30 tablets.
AMEPRIDE® 2: Each tablet contains Glimepiride 2 mg EP in packs of 30 tablets.
AMEPRIDE® 3: Each tablet contains Glimepiride 3 mg EP in packs of 30 tablets.
AMEPRIDE® 4: Each tablet contains Glimepiride 4 mg EP in packs of 30 tablets.
Hospital packs are also available.

Excipients:

AMEPRIDE® 1: Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, Red Iron Oxide, Magnesium Stearate and Polyvinyl Pyrrolidinone.
AMEPRIDE® 2: Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, Eurolake Green, Magnesium Stearate and Polyvinyl Pyrrolidinone.
AMEPRIDE® 3: Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, Yellow Iron Oxide, Magnesium Stearate and Polyvinyl Pyrrolidinone.
AMEPRIDE® 4: Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, Blue No. 2, Magnesium Stearate and Polyvinyl Pyrrolidinone.

This is a medicament

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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