For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

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Amaryl® / Semi-Amaryl®

Glimepiride Tablets IP

DESCRIPTION

Active Ingredient
Glimepiride IP

Therapeutic or Pharmacological Class
Antidiabetic. Sulfonylurea.

Pharmaceutical Form(s)
Semi-Amaryl 0.5mg
Tablets for oral administration

Amaryl 1mg/2mg/3mg
Tablets for oral administration. The tablets can be divided into two equal doses along the score line.

COMPOSITION

Semi-Amaryl® 0.5mg
Each uncoated tablet contains
Glimepiride IP 0.5mg

Amaryl® 1mg
Each uncoated tablet contains
Glimepiride IP 1mg

Amaryl® 2mg
Each uncoated tablet contains
Glimepiride IP 2 mg

Amaryl® 3mg
Each uncoated tablet contains
Glimepiride IP 3 mg

INDICATIONS

Non-insulin dependent (type II) diabetes mellitus, whenever blood glucose levels cannot be controlled adequately by diet, physical exercise and weight reduction alone.

Glimepiride may be combined with other, non-betacytotropic, oral antidiabetics.

Glimepiride may also be used together with insulin (see dosage and administration).

Glimepiride is not suitable for the treatment of insulin–dependent (type I) diabetes mellitus (e.g., for the treatment of diabetics with a history of ketoacidosis), of diabetic ketoacidosis, or of diabetic precoma or coma.

DOSAGE AND ADMINISTRATION

General

Dosage

In principle, the dosage of glimepiride is governed by the desired blood glucose level. The dosage of glimepiride must be the lowest which is sufficient to achieve the desired metabolic control.

During treatment with glimepiride, glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycated haemoglobin be carried out.

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.

Initial dose and dose titration

Usual initial dose : 0.5mg to1mg glimepiride once daily.

If necessary, the daily dose can be increased. It is recommended that the increase be guided by regular blood glucose monitoring, and that the dose be increased gradually, i.e. at intervals of one to two weeks and according to the following dose steps:0.5mg- 1 mg - 2 mg- 3mg – 4 mg – 6mg (-8 mg)

Dose range in patients with well controlled diabetes

Usually daily doses in patients with well controlled diabetes are 1 to 4 mg glimepiride. Daily doses of more than 6 mg are more effective only in a minority of patients.

Distribution of doses

Timing and distribution of doses are to be decided by the physician, taking into consideration the patient's current life-style.

Normally a single daily dose of glimepiride is sufficient.

It is recommended that this dose be taken immediately before a substantial breakfast or – if none is taken – immediately before first main meal.

It is very important not to skip meals after the tablets have been taken.

As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glimepiride requirements may fall as treatment proceeds. To avoid hypoglycaemia timely dose reduction or cessation of glimepiride therapy must therefore be considered.

Correction of dosage must also be considered, whenever

- the patient's weight changes.
- the patient's life-style changes.
- Other factors arise which cause an increased susceptibility to hypoglycaemia or hyperglycaemia (See Precautions).

Duration of treatment

Treatment with glimepiride is normally a long-term therapy.

Changeover from other oral antidiabetics to Amaryl® /Semi- Amaryl®

There is no exact dosage relationship between glimepiride and other oral antidiabetics. When substituting glimepiride for other oral antidiabetics, it is recommended that the procedure be the same as for initial dosage starting with daily doses of 0.5mg to 1 mg. This applies even in cases where the patient is being switched from the maximum dose of another oral antidiabetic

Consideration must be given to the potency and duration of action of the previous antidiabetic agent. A break from medication may be required to avoid any summation of effects entailing a risk of hypoglycaemia

Use with metformin

In patients not adequately controlled with the maximum daily dose of either glimepiride or metformin, combination therapy with both oral antidiabetic agents may be initiated. As the established therapy with either glimepiride or metformin progresses at the same dose level, the additional metformin or glimepiride treatment is started with a low dose, which is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

Use with insulin

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

Administration

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

Special Populations

Children

Data are insufficient to recommend pediatric use of glimepiride.

Elderly

Renal Impairment

There is limited information available on the use of glimepiride in renal insufficiency. Patients with impaired renal function may be more sensitive to the glucose- lowering effect of glimepiride.

Contraindications
Semi-Amaryl® / Amaryl®, must not be used :
- in patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, or any of the excipients.
- in pregnant women.
- in breast-feeding women.

No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of hepatic function, change over to insulin is indicated, not least to achieve optimal metabolic control.

Warnings
In exceptional stress situations (e.g trauma, surgery, febrile infections) blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

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

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to co-operate.
- undernourishment, 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,
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal insufficiency).
- concurrent administration of certain other medicines (See Interactions).
- treatment with glimepiride in the absence of any indication.

If such risk factors for hypoglycemia 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.

Those symptoms of hypoglycaemia which reflect the body's adrenergic counter-regulation (See Adverse Reactions) may be milder or absent where hypoglycaemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs.

Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar).

It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.

Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Interactions
Take into account
Based on experience with glimepiride, and what is known of other sulfonylureas, the following interactions must be considered:

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP 2C9.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:
Insulin and other oral antidiabetics; ACE inhibitors; anabolic steroids and male sex hormones; chloramphenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors ; miconazole; fluconazole; para-aminosalicylic acid ; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenecid; quinolones; salicylates; sulfinpyrazone; clarithromycin sulfonamide antibiotics; tetracyclines; tritoqualine; trofosfamide.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example:
Acetazolamide;barbiturates;corticosteroids;
Diazoxide; diuretics; epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (after protracted use) ; nicotinic acid (in high doses); oestrogens and progestogens; phenothiazines; phenytoin ; rifampicin; thyroid hormones.

H_2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Under the influence of sympatholytic drugs 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 intake may potentiate or weaken the blood-glucose-lowering action of glimepiride in an unpredictable fashion.

The effect of coumarin derivatives may be potentiated or weakened.

Bile acid sequestrant: 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.

Pregnancy
Glimepiride must not be taken during pregnancy. Otherwise there is risk of harm to the child. The patient must change over to insulin during pregnancy.

Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

Lactation
To prevent possible ingestion with the breast milk and possible harm to the child, glimepiride must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast- feeding.

Driving a vehicle or performing other hazardous tasks
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, for example, affect the ability to drive or to operate machinery.

Adverse Reactions
Metabolism and Nutrition disorders
As a result of the blood – glucose – lowering action of glimepiride, hypoglycaemia may occur, which – based on what is known of other sulfonylureas – may also be prolonged.

Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness upto 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 nearly always subside when hypoglycaemia is corrected.

Eye disorders
Especially at the start of treatment, there may be temporary visual impairment 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.

Gastrointestinal disorders
Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur.

In isolated cases, there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may progress to life – threatening liver failure but can regress after withdrawal of glimepiride.

Dysgeusia (frequency not known)

Blood and lymphatic system disorders
Changes in the blood picture may occur: Rarely, thrombocytopenia and, in isolated cases, leucopenia, haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop. Cases of severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura have been reported in post-marketing experience (frequency not known).

Skin and subcutaneous tissue disorders
Alopecia (Frequency not known)

General disorders
Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such mild reactions may develop into serious 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 and allergic vasculitis or hypersensitivity of the skin to light may occur.

Investigations
Glimepiride,like all sulfonylureas,can cause weight gain (frequency not known)

Overdose
Signs and Symptoms
Acute overdosage as well as long-term treatment with too high a dose of glimepiride may lead to severe life-threatening hypoglycaemia.

Management
As soon as an overdose of glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose.

Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycaemia may recur after initial recovery.

Admission to hospital may sometimes be necessary-even as a precautionary measure. In particular, significant overdoses and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.

If, for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting with 40 ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1 mg i.v., s.c.or i.m., may be considered.

In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous hyperglycaemia, and must be controlled by close monitoring of blood glucose.

Patients who have ingested life-threatening amounts of glimepiride require detoxification (e.g. by gastric lavage and medicinal charcoal).

After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days.

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