

Module 1.3 Summary of Product Characteristics, Labeling and Package Leaflet

Module 1.3.1 Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Trade Name:

INN: Glimpiride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition

Each uncoated tablet contains:

Glimpiride USP 1 mg

Colour : Red Oxide of Iron

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimpiride is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

4.2 Posology and method of administration

For oral administration

The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin cannot compensate if the patient does not keep to the recommended diet.

Dosage is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg glimepiride per day. If good control is achieved this dosage should be used for maintenance therapy.

If control is unsatisfactory the dosage should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3 or 4 mg glimepiride per day.

A dosage of more than 4 mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6 mg glimepiride per day.

In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and 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.

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated if necessary. 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.

Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or if none is taken - shortly before or during the first main meal.

If a dose is forgotten, this should not be corrected by increasing the next dose.

If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone.

In the course of treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycaemia timely dose reduction or cessation of therapy must therefore be considered. Change in dosage may also be necessary, if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo-or hyperglycaemia.

Switch over from other oral hypoglycaemic agents to glimepiride

A switch over from other oral hypoglycaemic agents to glimepiride can generally be done. For the switch over to glimepiride the strength and the half life of the previous medication has to be taken into account. In some cases, especially in antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect.

The recommended starting dose is 1 mg glimepiride per day.

Based on the response the glimepiride dosage may be increased stepwise, as indicated earlier.

Switch over from Insulin to glimepiride

In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to glimepiride may be indicated.

The changeover should be undertaken under close medical supervision.

Use in renal or hepatic impairment

In case of severe renal or hepatic function disorders, a change over to insulin is required.

Children and Elderly

Safety and efficacy of glimepiride in children younger than 16 years of age have not been established. Although no overall differences were observed between geriatric and younger adults in safety or efficacy in clinical studies, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out.

4.3 Contraindications

Glimepiride should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulphonylureas or sulphonamides.

In case of severe renal or hepatic function disorders, a change over to insulin is required.

Glimepiride is contraindicated in pregnancy and lactation.

4.4 Special warnings and special precautions for use

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with glimepiride may lead to hypoglycaemia. Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulphonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.

Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:

- undernutrition, 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
- 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 adrenocortical insufficiency)
- concurrent administration of certain other medicines (see Interactions)

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended.

Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride.

In stress-situations (e.g. accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.

No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.

4.5 Interaction with other medicinal products and other forms of interaction

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 CYP2C9.

Potentialiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

- phenylbutazone, azapropazon and oxyfenbutazone, sulphinpyrazone,
- insulin and oral antidiabetic products, certain long acting sulphonamides,
- metformin, tetracyclines,
- salicylates and p-aminosalicylic acid, MAO inhibitors,
- anabolic steroids and male sex hormones, quinolone antibiotics,
- chloramphenicol, probenecid,
- coumarin anticoagulants, miconazol,
- fenfluramine, pentoxifylline (high dose parenteral),
- fibrates, tritoqualine,
- ACE inhibitors, fluconazole.
- fluoxetine,
- allopurinol,
- sympatholytics,

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:

- oestrogens and progestagens,
- saluretics, thiazide diuretics,
- thyroid stimulating agents, glucocorticoids,
- phenothiazine derivatives, chlorpromazine,

- adrenaline and sympathicomimetics,
- nicotinic acid (high dosages) and nicotinic acid derivatives,
- laxatives (long term use),
- phenytoin, diazoxide,
- glucagon, barbiturates and rifampicin,
- Acetazolamide,
- H₂ 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 counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Pregnancy and lactation

Pregnancy

On the basis of results from animal studies, glimepiride should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Lactation

Because no information is available on the use of glimepiride during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

4.8 Undesirable effects

Based on experience with glimepiride and with other sulphonylureas the following side effects have to be mentioned.

Organ class	Uncommon (>1/1,000 and <1/100)	Rare (>1/10,000 and <1/1,000)	Very rare (<1/10,000, incl. isolated reports)
Blood and lymphatic System disorders		Changes in the blood picture*, including: moderate to severe thrombocytopenia, leukopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia	
Immune system disorders			Mild hypersensitivity reactions may develop to severe reactions with dyspnoea, fall in blood pressure and possibly shock. Allergic vasculitis. Cross allergy with sulfunylureas, sulphonamide and related substances.
Metabolism and nutrition disorders			Hypoglycaemic reactions**
Eye disorders	Visual disturbances***		
Gastrointestinal disorders			Gastrointestinal discomforts such as nausea, vomiting, diarrhoea, epigastric pressure or fullness and abdominal pain****
Hepato-biliary disorders		Increased hepatic enzymes	Hepatic impairment e.g. with cholestasis and icterus. Hepatitis*****
Skin and subcutaneous tissue disorders	Allergic skin reactions such as pruritus, rash, urticaria.		
Investigations			Drop in serum sodium

*These alterations are usually reversible upon discontinuation of treatment.

** These reactions which often occur immediately may be serious and are not always easy to correct. As with any other diabetic medication, the incidence of hypoglycaemic reactions depends on individual parameters such as food habits and dosage.

*** These disorders are transient and are especially seen at the beginning of the treatment, due to changes in blood glucose levels.

**** These reactions rarely cause discontinuation of treatment.

***** Hepatitis may progress to hepatic failure.

4.9 Overdose

After ingestion of an overdosage hypoglycaemia 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 hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

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. In case of (severe) overdosage hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary 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.

In particular when treating hypoglycaemia due to accidental intake of glimepiride in young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent diabetes mellitus.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas 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 extrapancreatic effects also postulated for other sulphonylureas.

Insulin release

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation 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.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulphonylurea binding site.

Extrapancreatic activity

The extrapancreatic 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.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.

Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in its turn inhibits the gluconeogenesis.

General

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether the drug was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total drug effect.

Combination therapy with metformin

Improved metabolic control for concomitant glimepiride therapy compared to metformin alone in patients not adequately controlled with the maximum dosage of metformin has been shown in one study.

Combination therapy with insulin

Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dosage of glimepiride, concomitant insulin therapy can be initiated. In two studies, the combination achieved the same improvement in

metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.

5.2 Pharmacokinetic properties

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 (C_{max}) are reached approx. 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 C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min). In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and 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 were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. 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 faeces: 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 revealed no significant differences in pharmacokinetics, and the intraindividual variability was very low. There was no relevant accumulation.

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

5.3 Preclinical safety data

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Purified Talc
Magnesium Stearate
Colour Red Oxide of Iron

6.2 Incompatibilities

None

6.3 Shelf life

36 months from the date of manufacture

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

10 Tablets packed in a PVC Blister packs which are packed in a unit carton

6.6 Instructions for use and handling

No special requirement

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT