

**SUMMARY OF PRODUCT CHARACTERISTICS
for**

Glimeryl tablets

1. NAME OF THE MEDICINAL PRODUCT

Glimeryl 1 mg tablets
Glimeryl 2 mg tablets
Glimeryl 3 mg tablets
Glimeryl 4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Glimeryl 1 mg]:
Each tablet contains 1 mg glimepiride
[Glimeryl 2 mg]:
Each tablet contains 2 mg glimepiride
[Glimeryl 3 mg]:
Each tablet contains 3 mg glimepiride
[Glimeryl 4 mg]:
Each tablet contains 4 mg glimepiride

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

[Glimeryl 1 mg]:
The tablet is pink, flat and oblong with bevelled edges and a score on one side and marked with “G” on the other side.
[Glimeryl 2 mg]:
The tablet is green, flat and oblong with bevelled edges and a score on one side and marked with “G” on the other side
[Glimeryl 3 mg]:
The tablet is yellow, flat and oblong with bevelled edges and a score on one side and marked with “G” on the other side
[Glimeryl 4 mg]:
The tablet is blue, flat and oblong with bevelled edges and a score on one side and marked with “G” on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimeryl 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 use.

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 2mg, 3mg or 4 mg glimepiride per day.

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

Concomitant glimepiride therapy may be initiated in patients not adequately controlled with the maximum daily dose of metformin, While maintaining the metformin dose, glimepiride therapy is started with a low dose, and is then titrated up to the maximum daily dose depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of Glimeryl, concomitant insulin therapy may 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. If no breakfast taken, the dose should be taken shortly before or during the first main meal.

If a dose is forgotten, this should not be corrected by increasing the next dose. Tablets should be swallowed whole with some liquid.

A hypoglycaemic reaction with a dose of 1 mg glimepiride daily indicates that the patient can be controlled by diet alone.

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

▪ Switch over from other oral hypoglycaemic agents to Glimeryl

A switch over from other oral hypoglycaemic agents to Glimeryl can generally be done. For a switch to Glimeryl, 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 Glimeryl

In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to Glimeryl may be indicated. The changeover should be undertaken under close medical supervision.

- Use in renal or hepatic impairment

See section 4.3 Contraindications.

4.3 Contraindications

Glimeryl must not be administered in the following cases:

- Insulin dependent diabetes
- diabetic coma
- ketoacidosis
- severe renal and hepatic disease
- known hypersensitivity to glimepiride, other sulphonylureas or other sulphonamides or hypersensitivity to any of the excipients in the tablet.

In case of severe renal or hepatic disease, a switch to insulin therapy is required.

4.4 Special warnings and precautions for use

Glimeryl must be taken shortly before or during a meal.

When meals are taken at irregular hours and especially if meals are omitted, treatment with Glimeryl may lead to hypoglycaemia. Symptoms of possible hypoglycaemia include e.g. headache, ravenous hunger, nausea, vomiting, fatigue, sleep disorders, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self control, delirium, cerebral convulsions, somnolence and loss of consciousness resulting in 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. Symptoms are usually promptly controlled after immediate intake of carbohydrates. Artificial sweeteners have no effect.

It has been shown following administration of other sulphonylureas that hypoglycaemia may recur despite initially successful countermeasures.

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

Factors favouring hypoglycaemia include:

- Unwillingness (more commonly in elderly patients) or failure of the patient to cooperate.
- Undernourishment, irregular meal times, skipped meals or periods of fasting.
- Changes in diet.
- Imbalance between physical activity and carbohydrate intake.
- Consumption of alcohol, especially in combination with skipped meals.
- Impaired renal function.
- Severe hepatic impairment.
- Overdosage with Glimeryl
- Disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (e.g. thyroid function disorders and anterior pituitary or adrenocortical insufficiency),
- Concurrent administration of certain other medicines (see "Interactions").

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

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

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

There is no Experience with the use of Glimeryl in patients with severe hepatic impairment and in dialysis patients. A switch to insulin is indicated in patients with severe renal and hepatic impairment.

This medicinal product contains lactose monohydrate.

Patients with rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Glimeryl 2 mg tablets

The colouring agents included Glimeryl, Sunset Yellow FCF (E 110) and Tartrazine (E102), may cause allergic reactions’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of Glimeryl with other medicines may result in an undesired increase or decrease in the hypoglycaemic effect of glimepiride. For this reason, other medicines should only be taken with the knowledge of and upon prescription by the physician.

Glimepiride is metabolised by cytochrome P450 2C9 (CYP2C9). The metabolism is known to be affected by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

Results from *in vivo* interaction studies reported in the literature show that the AUC of glimepiride is **approximately** doubled by fluconazole – one of the most potent CYP2C9 inhibitors.

Based on the experience with Glimeryl and with other sulphonylureas, concomitant administration of the following medicines may enhance the hypoglycaemic effect of glimepiride:

phenylbutazone, azapropazone and oxyfenbutazone	sulphinpyrazone
insulin and oral antidiabetics	certain long acting sulphonamides
metformin	tetracyclines
salicylates and p - amino- salicylic acid	MAO – inhibitors
anabolic steroids and male sex hormones	quinolones
chloramphenicol	probenecid
coumarin anticoagulants	miconazole
phenfluramine	pentoxifylline (high parenteral doses)
fibrates	tritoqualine
ACE inhibitors	fluconazole
fluoxetine	
allopurinol	
sympatholytics	
cyclo-, tro- and iphosphamides.	

The hypoglycaemic effect of glimepiride is reduced thereby resulting in a reduced metabolic control if Glimeryl is administered concurrently with other medicines containing the following active ingredients:

oestrogens and progestagens
saluretics, thiazide diuretics
thyroid stimulating agents, glucocorticoids
phenothiazine derivatives, chlorpromazine
adrenaline and sympathicomimetics
nicotinic acid (high doses) and nicotinic acid derivatives
laxatives (long term use)
phenytoin, diazoxide
glucagon, barbiturates and rifampicin
acetazolamide

H₂ antagonists, beta-blockers, clonidine and reserpine may either enhance or weaken the blood

glucose- lowering effect.

During treatment with sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter regulation to hypoglycaemia may be reduced or absent.

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

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

4.6 Pregnancy and lactation

Pregnancy

Risk related to the diabetes

Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

Risk related to glimepiride

There are no adequate data detailing the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which was probably related to the pharmacologic action (hypoglycaemia) of glimepiride (see section 5.3).

Consequently, glimepiride should not be used throughout pregnancy.

If a patient plans to become pregnant or if a pregnancy is detected during treatment with glimepiride, the treatment should be switched as soon as possible to insulin therapy.

Lactation

It is unknown whether the drug is excreted in human milk. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, it is inadvisable to breast-feed during treatment with glimepiride.

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 as a result of side effects such as 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 patients who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. In such situations, it should be considered whether it is advisable to drive or operate machinery.

4.8 Undesirable effects

Based on experience with Glimeryl 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.		Photosensitivity
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 (see also “Special warnings and precaution for use”).

*** 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 12-72 hours, and may recur after an initial recovery of blood glucose. Symptoms may not be present for up to 24 hours after ingestion of Glimeryl. In general hospitalisation is therefore recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia is in general accompanied by neurological symptoms such as agitation, tremor, visual disturbances, co-ordination problems, sleepiness, coma, and convulsions.

Treatment primarily consists of preventing the absorption of glimepiride by inducing vomiting and subsequently 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 substantial overdosage, hospitalisation in an intensive care department is indicated. The administration of glucose should be initiated as soon as possible, if necessary via a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion or a 10% solution with strict monitoring of blood glucose. Further treatment is symptomatic.

Glucose must be administered with great caution with concomitant monitoring of blood glucose due to the possible risk of inducing dangerous hyperglycaemia.

This particularly applies when treating accidental intake of Glimeryl in infants and young children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulphonamides, urea derivatives.
ATC Code: A10B B12

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in the treatment of 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 extra-pancreatic 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 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 binding and 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.

Extra-pancreatic effect:

The extra-pancreatic effects include an improvement of the sensitivity of the peripheral tissue for insulin and a decrease in the hepatic insulin uptake.

The uptake of glucose from blood into peripheral muscle and fat tissues takes place via special transport proteins located in the cell membrane. The transportation of glucose into these tissues is the

rate limiting step in glucose metabolism. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in enhanced 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 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 i.e. reduction of insulin secretion, continues during treatment with glimepiride.

There was no significant difference in effect regardless of whether the drug was given 30 minutes before 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 causes 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

In a clinical trial, patients not adequately controlled with the maximum daily dosage of metformin improved metabolic control with concomitant glimepiride and metformin therapy was attained, when compared to metformin alone.

Combination therapy with insulin

Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dose of glimepiride, concomitant insulin therapy can be initiated. In two clinical trials, 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 influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are attained approximately 2.5 hours after oral intake (mean 0.3 $\mu\text{g/ml}$ after multiple dosing of 4 mg daily) and there is a linear relationship between dose and C_{max} and dose and AUC (area under the time/concentration curve).

Distribution

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

In animals, glimepiride is excreted in milk and crosses the placenta. Glimepiride passes the blood brain barrier to a minor extent.

Biotransformation and elimination

Serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is 5-8 hours. After higher doses, slightly longer half-lives were observed.

After a single dose of radio-labelled glimepiride, 58% of the radioactivity was recovered in urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – hydroxy derivative and carboxy derivative - most probably resulting from hepatic metabolism - were identified both in urine and faeces. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3-6 and 5-6 hours, respectively.

Comparison of single and multiple once-daily dosing revealed no significant difference in pharmacokinetics, and the intra-individual variability was very low.

There was no relevant accumulation.

Pharmacokinetics were similar in males and females, as well as in the 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. This most probably resulted from a more rapid elimination due to lower protein binding. Renal elimination of the two metabolites was impaired. There is no further risk of accumulation in patients with renal impairment.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

5.3 Preclinical safety data

At doses that by far exceed the human therapeutic doses, preclinical effects were found and were regarded as having little clinical relevance or were attributed to the pharmacodynamic action (hypoglycaemia) of the product. These findings were based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter tests (i.e. those covering embryotoxicity, teratogenicity and developmental toxicity), the adverse reactions observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Lactose monohydrate
Sodium starch glycolate (type A)
Magnesium stearate
Microcrystalline cellulose
Povidone K 29-32

[Glimeryl 1 mg] also contains iron oxide red (E172)

[Glimeryl 2 mg] also contains iron oxide yellow (E172), Sunset yellow FCF (E110), tartrazine (E102), brilliant blue FCF (E133)

[Glimeryl 3 mg] also contains iron oxide yellow (E172)

[Glimeryl 4 mg] also contains indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

18 months.

6.4 Special precautions for storage

Do not store above 30° C.

6.5 Nature and contents of container

Clear PVC/Aluminium blisters.

Pack sizes: 10, 20, 30, 50, 60, 90 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis Ltd.
B16, Bulebel Industrial Estate
Zejtun ZTN 08
Malta

8. MARKETING AUTHORISATION NUMBER(S)

1 mg: MA245/00501
2 mg: MA245/00502
3 mg: MA245/00503
4 mg: MA245/00504

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT