SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glimepiride 2 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glimepiride 2 mg.

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Tablet

The tablet is green, flat, oblong tablet with bevelled edges and a score on one side and marked with “G” on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Glimepiride Tablet 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 can not 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 may be initiated.

While maintaining the metformin dose, 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 Tablet, 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. Tablets should be swallowed whole with some liquid.

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 Tablet
A switch over from other oral hypoglycaemic agents to to Glimepiride Tablet can generally be done. For the switch over to to Glimepiride Tablet 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 Tablet
In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to to Glimepiride Tablet 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

Glimepiride Tablet 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 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

Glimepiride Tablet must be taken shortly before or during a meal.

When meals are taken at irregular hours and especially if meals are omitted, treatment with Glimepiride Tablet may lead to hypoglycaemia. Symptoms of possible hypoglycaemia include e.g. headache, ravenous hunger, nausea, vomiting, fatigue, sleepiness, 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 amounting to 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. Symptoms are usually promptly controlled after immediate intake of carbohydrates. Artificial sweeteners have no effect.

It is known from other sulphonylureas that hypoglycaemia may recur despite

initially successful countermeasures.

Severe hypoglycaemia or prolonged hypoglycaemia, 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 incapacity of the patient to cooperate.
- undernutrition, 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 of Glimepiride Tablet
- Certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (e.g. certain disorders of thyroid function and anterior pituitary or adrenocortical insufficiency),
- Other concurrent administration of certain other medicines (see Interactions").

Treatment with Glimepiride Tablet 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 Glimepiride Tablet.

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

Experience with use of Glimepiride Tablet in patients with severe hepatic impairment and dialysis patients is missing. In patients with severe renal and hepatic impairment, switch to insulin is indicated.

This medicinal product contains lactose-monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant administration of Glimepiride Tablet and other medicines may result in undesired increases or decrease in the hypoglycaemic effect of glimepiride. For this reason, other medicines should only be taken with the

knowledge or at the prescription of 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. fluconazol).

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

Based on the experience with Glimepiride Tablet and with other sulphonylureas the following interactions have to be mentioned.

Hypoglycaemic actions as a result of the enhanced hypoglycaemic effect may occur upon concomitant administration of Glimepiride Tablet and e.g.

phenylbutazone, azapropazon 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 resulting in a reduced metabolic control if Glimepiride Tablet is administered concurrently with other medicines containing the following active ingredients:

– estrogens 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
- acetoxolamide

H_2 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 counterregulation to hypoglycaemia may be reduced or even be absent.

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

Glimepiride may either potentate 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 from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride (see section 5.3).

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.

Lactation

The excretion in human milk is unknown. 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, breast-feeding is advised against during treatment with glimepiride.

4.7. Effects on ability to drive and use machines

The patients ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or e.g. 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 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 Glimepiride Tablet 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 the 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 sulfunyl ureas, 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. The incidence of hypoglycaemic reactions depends on individual parameters such as food habits and dosage as with any other diabetic medication (se 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 Glimepiride Tablet. 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 prevention of absorption of glimepiride by inducing vomiting and subsequently let the patient drink 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. Initiate 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 or a 10% solution with strict monitoring of blood glucose. Further, symptomatic treatment.

Glucose must be administered with great caution during concomitant monitoring of blood glucose due to the possible risk of producing dangerous hyperglycaemia.
This applies particularly when treating accidental intake of Glimepiride Tablet in infants and young children.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulphonamides, urea derivatives.
ATC Code: A 10 BB 12

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in 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.

<u>Insulin release :</u>
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 increase 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 effect is e.g. 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 take place via special transport proteins located in the cell membrane. The transportation of glucose into these tissues is the rate limiting step in the glucose metabolism. 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 inhibits the gluconeogenesis.

Generally:
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 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 daily dosage of metformin has been shown in a clinical trial.

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 reached approximately 2.5 hours after oral intake (mean 0.3 μg/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%), low clearance (approximately 48 ml/min).
In animals, glimepiride is excreted in milk. Glimepiride passes 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 seen.
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, most probably resulting 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, preclinically effects were found which are regarded as having little clinical relevance or were due to the pharmacodynamic action (hypoglycaemia) of the product. These findings are based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), adverse reaction 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 excipients

Lactose monohydrate
Sodium starch glycolate (type A)
Magnesium stearate
Microcrystalline cellulose
Povidone K 29-32
Yellow iron oxide (E172)
Sunset yellow FCF aluminium lake (E110)
Tartrazin aluminium lake (E102)
Brilliant blue FCF aluminium lake (E133)

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4. Special precautions for storage

Do not store above 30^{o} 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. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 15764/0026

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