1. NAME OF THE MEDICINAL PRODUCT

GLEPID – 2
Glimepiride Tablets USP

2. COMPOSITION

Each uncoated tablet contains:
Glimepiride USP …… 2 mg
Excipients……q.s.
Colour: Red Oxide of Iron

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology

For the different dosage regimens, appropriate strengths are available.

The basis for successful treatment of diabetes is a good diet, regular physical activity, as well asroutine 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 of glimepiride per day. If good control is achieved, this dosage shouldalso be used for maintenance therapy.

If control is unsatisfactory, the dosage should be increased based on the glycaemic control, in astepwise 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, concomitantglimepiride therapy can be initiated.

While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and isthen 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, concomitantinsulin 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 duringthe 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 canbe 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 lifestyle of the patient, or other factors that increasethe 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 betaken into account. In some cases, especially in antidiabetics with a longer 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 toglimepiride may be indicated. The changeover should be undertaken under close medical supervision.

Use in renal or hepatic impairment

See section 4.3.

Paediatric population:

There are no data available on the use of glimepiride in patients under 8 years of age. For childrenaged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).

The available data on safety and efficacy are insufficient in the paediatric population andtherefore such use is not recommended.

Method of administration
For oral administration.

Tablets should be swallowed whole without chewing, with some liquid.

4.3. Contraindications

Glimepiride is contraindicated in patients with the following conditions:

- hypersensitivity to the active substance, other sulfonylureas or sulfonamides, or to any of theexcipients listed in section 6.1,
- insulin-dependent diabetes,
- diabetic coma,
- ketoacidosis,
- severe renal or hepatic function disorder.
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In case of severe renal or hepatic function disorders, a changeover to insulin is required.

4.4. Special warnings and precautions for use

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours, or, skipped altogether, glimepiride therapy may result in hypoglycaemia. Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, 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 up 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 can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect.

It is known from other sulfonylureas that, despite initially successful counter-measures hypoglycaemia may recur.

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

The following factors may favour hypoglycaemia:

unwillingness or (more commonly in older people) incapacity of the patient to co-operate,
under-nutrition, irregular mealtimes or missed meals, or periods of fasting, alterations in diet,
imbalance between physical exertion and intake of carbohydrates,
consumption of alcohol, especially in combination with skipped meals,
impaired renal function,
severe liver dysfunction,

- overdose with glimepiride,
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolismor counter-regulation of hypoglycaemia (e.g. in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency),
- concurrent use of certain other medicinal products (see section 4.5).

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

Regular hepatic and haematological monitoring (especially leukocytes and thrombocytes) arerequired during treatment with glimepiride.

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

Hepatic and/or renal impairment

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 orliver function change over to insulin is indicated.

G6PD-deficiency

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea

agents, caution should be used inpatients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance,total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially'sodium free'.

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

On concomitant administration of glimepiride and certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should be taken only with the knowledge (or at the prescription)of a doctor.

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

Results from an *in vivo* interaction study reported in literature show that glimepiride AUC isincreased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulfonylureas, the following interactionshave to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemiamay occur when one of the following medicinal products is taken, for example:
- phenylbutazone, azapropazone and oxyphenbutazone,
- insulin and oral antidiabetic medicinal products, such as metformin,
- salicylates and p-amino-salicylic acid,
- anabolic steroids and male sex hormones,
- chloramphenicol,
- certain long-acting sulfonamides,
- tetracyclines,

quinolone antibiotics,

- clarithromycin,
- coumarin anticoagulants,
- fenfluramine,
- disopyramide,
- fibrates,
- ACE inhibitors,
- fluoxetine,
- MAO inhibitors,
- allopurinol,
- probenecid,
- sulfinpyrazone,
- sympatholytics,

- cyclophosphamides, trophosphamides and iphosphamides,
- miconazole,
- fluconazole,
- pentoxifylline (high dose parenteral),
- tritoqualine.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occurwhen one of the following medicinal products is taken, for example:

- oestrogens and progestogens,
- saluretics, thiazide diuretics,
- thyroid stimulating agents, glucocorticoids,
- phenothiazine derivatives, chlorpromazine,
- adrenaline and sympathomimetics,
- nicotinic acid (high dosages) and nicotinic acid derivatives,
- laxatives (long-term use),
- phenytoin, diazoxide,
- glucagon, barbiturates and rifampicin,
- acetazolamide.

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

Under the influence of sympatholytic medicinal products such as beta blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may bereduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic effect of glimepiride in anunpredictable way.

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

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least for 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.6. Fertility, 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 haveshown 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 isdiscovered, the treatment should be switched as soon as possible to insulin therapy.

Breast-feeding

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.

Fertility

No data on fertility is available.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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 insituations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia while 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 itis advisable to drive or operate machinery in these circumstances.

4.8. Undesirable effects

The following adverse reactions from clinical investigations were based on experience with glimepiride and other sulfonylureas, are listed below by system organ class and in order of decreasing incidence:

	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not Known (cannot be estimated fromthe available data)
Blood and lymphatic systemdisorders	Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia andpancytopenia. These are in general reversible upondiscontinuation of medication.		Severe thrombocytopenia with a platelet count less than 10,000/µl, thrombocytopenic purpura

Immune system disorders		Leukocytoclasti cvasculitis. Mild hypersensitivity reactions that may developinto serious reactions withdyspnoea, fall in blood pressure and sometimes shock.	Cross allergy to sulfonylureas, sulfonamides or relatedsubstances is possible
Metabolism andnutrition disorders	Hypoglycaemia. These hypoglycaemic reactions mostly occur immediately, may be severe and are not always easy to correct. As with other hypoglycaemictherapies, the occurrence of such reactions depends on individual factors such as dietary habits anddosage (see section 4.4).		
Eye disorders			Transient visual disturbances, especially oninitiation of treatment due to changes in blood glucose levels.
Gastrointestina ldisorders	Dysgeusia,	Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominalpain. These disorders seldom lead to discontinuation of therapy.	
Hepatobiliar ydisorders		Hepatic function abnormal(e.g. with cholestasis and jaundice), hepatitis, hepatic failure.	Hepatic enzymes increased.
Skin and subcutaneous tissue disorders	Alopecia.		Hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria andphotosensitivity.
Investigations	Weight gain.	Decrease in blood sodium concentration.	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. Itallows continued monitoring of the risk/benefit balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via <to be completed nationally>.

4.9 Overdose

Symptoms

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and mayrecur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. Ingeneral 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.

Management

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulfate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulfate. 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 withstrict monitoring of blood glucose. Further treatment should be symptomatic.

Paediatric population

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins: Sulfonylureas.ATC Code: A10B B12.

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

Mechanism of action

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreaticbeta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

Insulin release

Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in thebeta cell membrane. Closing the potassium channel induces depolarisation of the beta cell andresults - 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 associatedwith the ATP-sensitive potassium channel but which is different from the usual sulfonylurea binding site.

Extrapancreatic activity

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheraltissue 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 instimulated glucose uptake.

Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase Cwhich 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.

Pharmacodynamic effects

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 medicinal product was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serumglucose 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 inpatients not adequately controlled with the maximum dosage of metformin has been shown in onestudy.

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.

Special populations

Paediatric population:
An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2000 mgdaily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.

Both glimepiride and metformin exhibited a significant decrease from baseline in HbA_{1c} (glimepiride -0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of non-inferiority to metformin in mean change from baseline of HbA_{1c}. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the95% confidence interval for the difference was not below the 0.3% non-inferiority margin.

Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are availablein paediatric patients.

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 (Cmax) 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} andAUC (area under the time/concentration curve).

Distribution

Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to thealbumin 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 ofthe 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 werenoted.

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.

Special populations

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.

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

Paediatric population

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose ofglimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean $AUC_{(0\text{-last})}$, Cmax and $t_{1/2}$ similar to that previously observed in adults.

5.3. Preclinical safety data

Preclinical effects observed occurred at exposures significantly in excess of the maximum humanexposure as to indicate little relevance to clinical use or were due to pharmacodynamic action (hypoglycaemia) of the compound. The finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity) adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Anhydrous Lactose

Maize starch
Colour :Iron oxide
Isopropyl Alcohol
Colloidal Anhydrous silica
Purified Talc
Magnesium Stearate

6.1. Incompatibilities

Not applicable.

6.2. Shelf life

2 years

Store in the original package.

6.3. **Special precautions for storage**

Store below 30 ° C. Keep out of reach of children.

6.4. Nature and contents of container

A box of 3 strips containing 10 tablets in each strip with pack insert.

6.5. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

N/A

8. MARKETING AUTHORISATION NUMBER

N/A

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

N/A

10. DATE OF REVISION OF THE TEXT

N/A