# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Glimepiride Denk 3

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: glimepiride
Each tablet contains 3 mg glimepiride.

Excipients with known effect:
Glimepiride Denk 3 contains lactose monohydrate and less than 1 mmol sodium (23 mg) per tablet.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet
Yellow coloured, oblong, flat, uncoated tablet with facet and with breakline on one side.
The tablets can be divided into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Glimepiride 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 suitable diet, regular physical activity as well as routine checks of blood and urine values. Antidiabetic agents or insulin cannot compensate if the patient does not keep to the recommended diet.

**Posology**
The dose is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg glimepiride a day. If sufficient metabolic control is achieved, this dose should be used for maintenance therapy.

For the different dose regimens appropriate strengths are available.

If metabolic control is unsatisfactory, the dose should be increased gradually, based on glycaemic situation, to 2, 3 or 4 mg glimepiride per day at intervals of about 1 to 2 weeks.

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

If patient's metabolism is not adequately controlled with the maximum daily dose of metformin alone, concomitant therapy with glimepiride 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. This combination therapy must be initiated under careful medical supervision.

In patients whose metabolism is not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be given if necessary. While maintaining the glimepiride dose, insulin treatment is started with a low dose, and is then titrated up depending on the desired level of metabolic control. This combination therapy should be initiated under careful 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 no breakfast 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 he/she can be controlled by diet alone.

In the course of treatment glimepiride requirements may fall, as an improvement in control of metabolism is associated with higher insulin sensitivity. In order to avoid hypoglycaemia, a timely dose reduction or cessation of therapy must therefore be considered. A dose adaption may also be necessary if there are changes in the weight or lifestyle of the patient or other factors that increase the risk of hypo- or hyperglycaemia.

Switch over from other oral antidiabetic agents to glimepiride
A switch over from other oral antidiabetic agents to glimepiride can generally be done. For the switch over to glimepiride the strength and half-life of the previous medicinal product must be taken into consideration. In some cases, especially in the case of 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 additive effect.

The recommended starting dose is 1 mg glimepiride per day. Based on the patient's response, the glimepiride dose may be gradually increased, as described above.

Switch over from insulin to glimepiride
In exceptional cases, where type 2 diabetic patients are treated with insulin, a changeover to glimepiride may be indicated. This changeover should be undertaken under close medical supervision.

Special populations

*Use in patients with 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 children aged 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 and therefore such use is not recommended.

**Method of administration**
The tablets are swallowed whole 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 the excipients listed in section 6.1.
- insulin dependent diabetes
- diabetic coma
- ketoacidosis
- severe renal or hepatic function disorders. In cases of severe renal or hepatic function disorders, a change over to insulin is required.

## 4.4 Special warnings and precautions for use

Glimepiride must be taken shortly before or during a meal.

If meals are taken irregularly or skipped altogether, treatment with glimepiride may lead to hypoglycaemia. Possible symptoms of hypoglycaemia include, for example: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction times, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, light-headedness and loss of consciousness up to and including coma, shallow breathing and bradycardia.

In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety and restlessness, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias.

The clinical picture of severe hypoglycaemia may resemble that of a stroke.

Symptoms can almost always be promptly controlled by immediate ingestion of carbohydrates (sugar). Artificial sweeteners have no effect.

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

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

The following factors may favour hypoglycaemia:

- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate
- 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
- severe liver dysfunction
- overdose 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 medicinal products (see section 4.5.).

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 of leukocytes and thrombocytes) is 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 liver impairment or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.

Treatment of patients with glucose-6-phosphate dehydrogenase deficiency (G6PD-deficiency) with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be exercised in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

**This medicine contains lactose**.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride may occur.
For this reason, other medicinal products should only be taken with the knowledge of (or when prescribed by) your doctor.

Glimepiride is metabolised by the 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 a published *in-vivo* drug interaction study show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on experience with glimepiride and with other sulfonylureas the following interactions have to be mentioned:

Potentiation of the blood-glucose-lowering effect and, thus in some instances hypoglycaemia may occur when one of the following medicinal products is taken, for example:
- phenylbutazone, azapropazone and oxyphenbutazone
- insulin and oral antidiabetic products, such as metformin
- salicylates and p-amino-salicylic acid
- anabolic steroids and male sex hormones
- chloramphenicol, certain long acting sulfonamides, tetracyclines, quinolone antibiotics and clarithromycin
- coumarin anticoagulants
- fenfluramine
- disopyramide
- fibrates
- ACE inhibitors
- fluoxetine, MAO inhibitors
- allopurinol, probenecid, sulfinpyrazone
- sympatholytics
- cyclophosphamide, trophosphamide and iphosphamide
- miconazole, fluconazole
- pentoxifylline (high parenteral dose)
- tritoqualine,

Weakening of the blood-glucose-lowering effect, and thus raised blood glucose levels may occur when 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 doses) and nicotinic acid derivatives
- laxatives (long term use)
- phenytoin, diazoxide
- glucagon, barbiturates and rifampicin
- acetazolamide.

$H_2$ antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening 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 be reduced or absent.

Alcohol consumption may potentiate or weaken the hypoglycaemic effect of glimepiride in an unpredictable fashion.

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 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Risks related to diabetes:
Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. The blood glucose level must therefore be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who are planning a pregnancy must inform their doctor.

Risks related to glimepiride:
There are no adequate data on the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemiac) of glimepiride (see section 5.3).

Consequently, glimepiride must not be taken at any time during pregnancy. If a patient plans to become pregnant or if a pregnancy is discovered during treatment with glimepiride, the treatment should be switched to insulin therapy as soon as possible.

Breast-feeding
It is not known whether or not glimepiride 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, breast-feeding is advised against during treatment with glimepiride.

Fertility
There are no fertility data available.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and operate machinery have been conducted.

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 suffer frequent episodes of hypoglycaemia or in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia. It should be considered whether it is 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, were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythrocytopenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication.
Not known: severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.

Immune system disorders
Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.
Not known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

Metabolism and nutrition disorders
Rare: hypoglycaemia
These reactions usually occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic therapies, on individual factors such as dietary habits and dose (see further under section 4.4).

Eye disorders
Not known: visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

Gastrointestinal disorders
Rare: dysgeusia
Very rare: nausea, vomiting, diarrhoea, abdominal distension, epigastric fullness and abdominal pain, which seldom lead to discontinuation of therapy.

Hepatobiliary disorders

Very rare: Abnormal hepatic function (e.g. with cholestasis and jaundice), hepatitis and hepatic failure
Not known: hepatic enzymes increased.

Skin and subcutaneous tissue disorders
Rare: alopecia
Not known: hypersensitivity reactions of the skin may occur as pruritis, rash, urticaria and photosensitivity

Investigations
Rare: weight increase
Very rare: Blood sodium decrease

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

### 4.9 Overdose

Symptoms
Hypoglycaemia may occur after an overdose, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be noticeable for up to 24 hours after ingestion. Inpatient observation is generally recommended. Nausea, vomiting and epigastric pain may occur. Hypoglycaemia may generally be accompanied by neurological symptoms such as 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 (absorbent) and sodium sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by administration of activated charcoal and sodium-sulphate. In the case of a (severe) overdosing hospitalisation in an intensive care department is indicated. The administration of glucose should be started 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 ingestion of glimepiride in toddlers and children, the dose of glucose administered must be carefully controlled in order to avoid the possibility of producing 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: A10BB12.

Glimepiride is an oral active hypoglycaemic substance belonging to the sulfonylurea 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 sulfonylureas, this effect is based on an increased 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 sulfonylureas.

Insulin release
Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channels in the beta cell membrane. Closing the potassium channels induces depolarisation of the beta cells and, by opening the calcium channels, results 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 sulfonylurea binding site.

Extra-pancreatic activity
The extra-pancreatic 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 in the cell membrane. The transport of glucose in this tissue is the limiting factor in the consumption of glucose. Glimepiride very rapidly increases the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose intake.

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
The minimal effective oral dose is approx. 0.6 mg in healthy subjects. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, a 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 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, this 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 dose of metformin alone 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 daily dose of glimepiride alone, 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 2,000 mg daily) 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 HbA1c (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 the 95% 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 available in 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 the 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 repeated 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 that of albumin, a high protein binding (>99 %) and a low clearance (approx. 48 ml/min.).
In animals, glimepiride is excreted in mother milk. Glimepiride is transferred to the placenta. It passes the blood brain barrier in small amounts.

Biotransformation and elimination
The mean serum half-life, which is of relevance for the serum concentration after repeated dose conditions, is about 5 to 8 hours. After intake of high doses, slightly longer half-lives were noted.

After a single dose of radioactive labelled glimepiride, 58% of the radioactivity was recovered in the urine and 35% in the faeces. No unchanged substance was detected in urine. Two metabolites – most probably resulting from hepatic metabolism (mainly CYP2C9) were identified both in urine and in 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 repeated once-daily dosing revealed no significant differences in pharmacokinetics, and the intra-individual 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 reduced. Overall no increased risk of accumulation is to be assumed in such patients.
Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

*Paediatric population*

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

### 5.3 Preclinical safety data

Preclinical effects observed occurred at exposures clearly in excess of the maximum human exposure and therefore are of little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the active ingredient. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and reproduction toxicity studies. In the latter (studies covering embryotoxicity, teratogenicity and developmental toxicity) adverse drug reactions were considered to be secondary to the hypoglycaemic effects induced by the substance in dams and offspring.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate
Maize starch
Sodium starch glycolate
Povidone
Polysorbate 80
Iron oxide yellow
Talc
Magnesium stearate [vegetable]

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

4 years

### 6.4 Special precautions for storage

Store in a dry place below 30 ℃.
Store in the original package in order to protect from moisture.

### 6.5 Nature and contents of container

PVC/PVDC/aluminium blisters

Pack size: 30 tablets

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

## 8. MARKETING AUTHORISATION NUMBER IN ETHIOPIA

04457/07014/REN/2019

09513/08318/VAR/2023

## 9. DATE OF FIRST AUTHORISATION IN ETHIOPIA

Apr 30, 2019

## 10. DATE OF REVISION OF THE TEXT

02/2020

## 11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription