SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Toras-Denk 5

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains;
Torasemide .....5 mg

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Toras-Denk 5
White to off-white, round tablet imprinted with "5" on one side and a score line on the other side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of recurrent cardiac oedema and/or effusion in cardiac failure.

4.2 Posology and method of administration

Posology

Cardiac oedema and/or effusion in cardiac failure
Treatment is initiated with 5 mg torasemide daily. This dose is normally also the maintenance dose.

Treatment with 5 mg torasemide is indicated when the normal dose of 5 mg torasemide daily has insufficient effect.

In these cases, 5 mg torasemide is taken daily; depending on the severity of the condition, the dose may be increased up to 20 mg torasemide.

Paediatric population
The safety and efficacy of torasemide in children under the age of 12 years has not yet been established.

Patients with renal insufficiency
While clearance is reduced in patients with renal failure, there is no significant impact on the total plasma level.

Patients with hepatic impairment
Dosage does not have to be adjusted in patients with mild to moderate hepatic impairment because the elimination half-live of torasemide and its metabolites is only slightly increased in these patients.
Torasemide is contraindicated in patients with hepatic coma (see section 4.3). Special caution is required in patients with hepatic cirrhosis and ascites (see section 4.4). Extreme caution is required if torasemide is administered to patients with a history of hepatic encephalopathy.

Elderly patients
The recommended dosage does not differ in elderly patients. However, there are no adequate studies comparing the elderly and paediatric population.

Method of administration

The tablets should be swallowed whole in the morning

with some liquid. The bioavailability of torasemide does

not depend on food intake.

4.3 Contraindications

- Hypersensitivity to the active substance, to sulfonylureas or to any of the excipients listed in section 6.1
- Renal failure with anuria
- Hepatic coma until this condition improves or resolves
- Hypotension
- Hypovolaemia
- Hyponatraemia
- Hypokalaemia
- Marked micturition disorder (e.g. in prostatic hypertrophy)
- Breast-feeding
- Gout
- Cardiac arrhythmia (e.g. SA block, second or third degree AV block)
- Concomitant treatment with aminoglycoside or cephalosporin
- Renal insufficiency as sequela of nephrotoxic substances

4.4 Special warnings and precautions for use

As there is insufficient treatment experience to date, torasemide should not be administered in:
- pathological changes in the acid-base balance
- pathological changes in the blood count (e.g. thrombocytopenia or anaemia in patients without renal insufficiency)

Micturition disorders must be corrected prior to the start of torasemide treatment.

Note:
In prolonged treatment with torasemide the electrolyte balance, particularly serum potassium, must be monitored regularly.

Blood glucose, uric acid, creatinine and lipids must also be monitored at regular intervals. Due to the possible elevation in blood glucose level, careful monitoring of carbohydrate metabolism is recommended in patients with latent or manifest diabetes mellitus.

The blood count (red blood cells, white blood cells, platelets) should also be monitored at regular intervals.

Attention should be paid to signs of electrolyte loss and haemoconcentration, particularly at the start of treatment and in elderly patients.
The administration of loop diuretics can trigger a potentially life-threatening risk in patients with arrhythmia due to changes in the electrolyte levels (potassium, sodium, calcium, and magnesium). The blood electrolyte levels should be monitored at regular intervals.

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

The use of torasemide may return positive results in antidoping tests. The use of torasemide as a doping agent may be harmful to health.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions of this medicinal product must be heeded:

Torasemide potentiates the effect of other blood pressure-lowering medicinal products, particularly that of ACE inhibitors. The administration of ACE inhibitors in addition to or immediately after treatment with torasemide may result in an excessive fall in blood pressure. The risk of ACE-induced renal insufficiency may be increased.

A torasemide-induced potassium deficiency may increase and potentiate the side effects of concomitantly administered digitalis products.

Torasemide may attenuate the effect of antidiabetic agents.

Probenecid and non-steroidal anti-inflammatory drugs (e.g. indometacin, acetylsalicylic acid) may attenuate the diuretic and hypotensive effect of torasemide. Diuretics may increase the risk of NSAID-induced renal failure. During high-dose salicylate therapy, torasemide may potentiate the toxic effect of the salicylate on the central nervous system. In addition, the risk of recurrent gout attacks is increased in patients taking salicylates.

Torasemide may potentiate the following side effects, particularly during high-dose therapy: Ototoxic and nephrotoxic effects of aminoglycoside antibiotics (e.g. kanamycin, gentamicin, tobramycin) and cytostatic platinum derivatives, as well as nephrotoxic effects of cephalosporins.

Torasemide may influence (potentiate or attenuate) the effects of theophylline as well as the muscle-relaxant effect of medicinal products containing curare. Monitoring of the serum theophylline level is recommended.

Laxatives as well as mineralocorticoids and glucocorticoids may potentiate torasemide-induced potassium loss.

Concomitant treatment with torasemide and lithium may elevate the serum lithium level and thus potentiate effects and side effects of lithium.

Torasemide may attenuate the vasoconstrictive effect of catecholamines (e.g. epinephrine, norepinephrine).

Concomitant cholestyramine therapy may decrease the absorption of oral torasemide and thus its effect.

Torasemide is a substrate of cytochrome P450 CYP2C8 and CYP2C9. There may be an interaction between ligands for the same enzyme. Therefore, concomitant administration of medicinal products also catalysed by these cytochrome isoforms should be monitored closely to avoid unwanted serum levels of these medicinal products. This interaction has been demonstrated for coumarin derivatives. The possibility of a drug-drug interaction may be critical in substances with a small therapeutic index.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no adequate clinical experience concerning the effect of torasemide on the human embryo or foetus. Studies in animals have shown reproductive toxicity. Animal studies have demonstrated placental transfer of torasemide (see section 5.3).

Until further data are available, torasemide administration during pregnancy must be reserved for compelling indications. In such cases only the lowest effective dose may be administered.

Diuretics are not suitable for routine treatment of hypertension and oedema in pregnancy because they may interfere with placental perfusion and thus impair intrauterine growth. If torasemide has to be administered in pregnancy with cardiac or renal failure, electrolytes and haematocrit, as well as foetal growth, must be monitored closely.

Breast-feeding

There is insufficient information on the excretion of torasemide in human milk. A risk to the newborn/infant cannot be excluded. Loop diuretics may reduce milk production. Therefore, the use of torasemide during breast-feeding is contraindicated (see section 4.3). A decision must be made whether to discontinue breast-feeding or to abstain from torasemide therapy

taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Even when used as directed, torasemide may alter the reactions to such an extent that the ability to drive, use machines or work without a secure hold is impaired. This applies in particular at the beginning of treatment, following an increase in dosage, following a change of brand or when starting add-on medication and in combination with alcohol.

4.8 Undesirable effects

The following adverse reactions may occur during treatment with torasemide.

The frequencies of adverse reactions are ranked according to the following convention: Very common: ≥ 1/10
Common: ≥ 1/100 - < 1/10 Uncommon: ≥ 1/1,000 - < 1/100 Rare: ≥ 1/10,000 - < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

Blood and lymphatic system disorders
Very rare: decrease in the platelet, red blood cell and/or white blood cell count

Immune system disorders
Very rare: allergic reactions such as itching (pruritus), rash (exanthema), photosensitivity, severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis)

Metabolism and nutrition disorders
Common: exacerbation of metabolic alkalosis, hypokalaemia on a concomitant low-potassium diet, vomiting, diarrhoea, after excessive use of laxatives, and in patients with chronic hepatic dysfunction.

Depending on dosage and duration of treatment, water and electrolyte imbalances, e.g. hypovolaemia, hypokalaemia and/or hyponatraemia, may occur.

Nervous system disorders
Common: headache, dizziness Uncommon: paraesthesia
Not known: cerebral ischaemia, confusion

Eye disorders
Very rare: visual impairment

Ear and labyrinth disorders
Very rare: tinnitus, deafness

Cardiac disorders
Very rare: Due to haemoconcentration, hypotension as well as cardiac and central circulation disorders (incl. cardiac ischaemia) may occur. These may result, for example, in arrhythmia, angina pectoris, acute myocardial infarction or syncope.

Vascular disorders
Very rare: thromboembolic complications due to haemoconcentration

Gastrointestinal disorders
Common: gastrointestinal disorders (e.g. loss of appetite, gastric pain, nausea, vomiting, diarrhoea, constipation), particularly at the start of treatment
Uncommon:
xerosto
mia Very rare:
pancreat
itis

Hepatobiliary disorders
Common: elevated blood levels of certain liver enzymes (gamma-glutamyl transferase)

Skin and subcutaneous tissue disorders
Very rare: allergic skin reactions (e.g. pruritus, exanthema), photosensitivity reactions, severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis)

Musculoskeletal and connective tissue disorders
Common: muscle cramps (particularly at the start of treatment)

Renal and urinary disorders
Uncommon: elevated blood levels of creatinine and urea
In patients with micturition disorders (e.g. due to prostatic hypertrophy), increased urine production may lead to urinary retention and bladder dilatation.

General disorders and administration site conditions
Common: tiredness, weakness (particularly at the start of treatment)

Investigations
Common: elevated blood levels of uric acid, glucose and lipids (triglycerides, cholesterol)

Effect on laboratory parameters
<u>Potassium</u>
After administration of 2.5 mg and 5 mg torasemide over 12 to 14 weeks, the mean reduction in serum level was between 0.2 and 0.3 mM/l. The maximum mean reduction after administration of 10 mg torasemide over a period of 6 weeks was 0.39 mM/l, and after the administration of 40 mg torasemide it was 0.42 mM/l (see section 4.4)

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms of intoxication
There is no known typical poisoning profile. Overdose may lead to severe diuresis with a risk of fluid and electrolyte loss and potential somnolence, confusion, symptomatic hypotension, circulatory collapse and gastrointestinal symptoms.

Treatment of intoxication
A specific antidote is not known. The symptoms of intoxication generally resolve following a dose reduction or discontinuation of the medicinal product and concomitant fluid and electrolyte replacement (monitoring). Torasemide is not dialysable and therefore haemodialysis will not accelerate elimination.

Treatment in hypovolaemia: volume replacement.

Treatment in hypokalaemia: potassium replacement.

Treatment in circulatory collapse: shock position, treatment for shock if necessary.

Immediate measures in anaphylactic shock:
At the first signs (e.g. cutaneous reactions such as urticaria or flushing, restlessness, headache, sweating, nausea, cyanosis):
- establish a venous access
- besides taking the other usual emergency measures, place the patient in the Trendelenburg position, maintain clear airways, administer oxygen.
- if necessary, also initiate further intensive care procedures (including administration of epinephrine, volume replacement, glucocorticoids), where appropriate.

5.1 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: high-ceiling diuretics, sulfonamides, pure ATC code: C03C A04

Torasemide has a saluretic effect due to inhibition of renal sodium and chloride reabsorption in the ascending limb of the loop of Henle.

In humans, the onset of the diuretic effect is rapid following IV and PO administration with a peak effect within the first hour and after 2 to 3 hours, respectively, and persists for up to 12 hours. An increase in diuresis ("high-ceiling activity") proportional to the logarithm of the dose has been observed in the dose range 5 - 100 mg in healthy subjects. Diuresis may also increase if other diuretics (e.g. distally acting thiazides) are not sufficiently effective, e.g. in renal dysfunction.

Due to these properties, torasemide washes out oedema. In cardiac failure, torasemide improves symptoms and, by reducing preload and afterload, also myocardial workload.

In oral administration, the onset of the hypotensive effect of torasemide occurs slowly during the first week of treatment, with the peak hypotensive effect after about 12 weeks at the latest. Torasemide lowers blood pressure by reducing peripheral resistance. This effect is attributed to the normalisation of an electrolyte imbalance and chiefly to a reduction of the free Ca^{2+} ion activity that in hypertensive patients is increased in arterial vascular muscle cells. As a result, this presumably increases the contractility and responsiveness of the vessels to endogenous pressor substances, e.g. catecholamines.

5.2 Pharmacokinetic properties

Absorption and distribution
Torasemide is rapidly and almost completely absorbed after oral administration, and peak serum levels are reached after 1 to 2 hours.

Bioavailability is approx. 80% - 90 %; with a maximum first-pass effect of 10% - 20%, assuming complete absorption.

The data from two studies consistently show that, although the total (time-dependent) absorption rate of torasemide decreases after food intake (lower C_{max} and higher t_{max} values), total torasemide absorption is not, however, impaired by food intake.

Torasemide is more than 99% plasma protein-bound, and the metabolites M1, M3 and M5 are 86%, 95% and 97% plasma protein-bound, respectively. The apparent volume of distribution (Vz) is 16 L.

Biotransformation
In humans, torasemide is metabolised to the three metabolites M1, M3 and M5. There is no evidence of the occurrence of other metabolites. The

metabolites M1 and M5 are produced by stepwise oxidation of the methyl group at the phenyl ring to carboxylic acid, and the metabolite M3 by ring hydroxylation.

The metabolites M2 and M4, found in animal studies, could not be detected in humans.
Torasemide and its metabolites are characterised by dose-linear kinetics, i.e. the peak serum level and the areas under the serum level curves are proportionate to the dose.

Elimination
In healthy subjects the terminal half-life ($t_{1/2}$) of torasemide and its metabolites is 3 to 4 hours. Total torasemide clearance is 40 mL/min and renal clearance is approx. 10 mL/min.
Torasemide is metabolised in the liver and the unchanged substance and its metabolites are excreted via the kidneys.

In healthy subjects approx. 80% of the dose administered is recovered in the urine as torasemide and metabolites, with the following mean percentage distribution: torasemide approx. 24%, metabolite M1 approx. 12%, metabolite M3 approx. 3%, metabolite M5 approx. 41%. The main metabolite, M5, has no diuretic effect; while approx. 10% of the pharmacodynamic effect is attributable to the active metabolites M1 and M3.

In the presence of renal insufficiency, total clearance and the elimination half-life of torasemide remain unchanged, while the half-life of M3 and M5 is lengthened. However, the pharmacodynamic behaviour remains unchanged and the duration of action is not influenced by the severity of the renal insufficiency. Haemodialysis and haemofiltration do not eliminate torasemide and its metabolites to a significant extent.

The elimination half-live of torasemide and the metabolite M5 is lengthened slightly in patients with hepatic dysfunction or cardiac failure; and the quantity of substances excreted in the urine is largely consistent with that in healthy subjects.

Therefore, accumulation of torasemide and torasemide metabolites is not expected.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development, mutagenicity and carcinogenic potential.

There were no teratogenic effects in reproduction toxicity studies in rats, but foetal and maternal toxicity was observed at high doses in pregnant rabbits and rats. Torasemide placental transfer has been demonstrated in rats. No effects on fertility have been observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose-monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), magnesium stearate [vegetable], colloidal anhydrous silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PE/PCTFE (PVC/PE/Aclar®)-

Aluminium blisters Pack size: 30 tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS IN GERMANY

H2009/20301/162/R1

9. DATE OF FIRST AUTHORISATION IN GERMANY

02.03.2005

10. DATE OF REVISION OF THE TEXT

09/2019, 18th August 2026