SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Torsemide 5 mg Tablets

2 Qualitative and quantitative composition

Each tablet contains Torsemide USP 5 mg.

Excipient with known effects: Each tablet contains lactose.

For a full list of excipients, see section 6.1

3 Pharmaceutical form

Tablet.
A white to off-white, round shaped, biconvex, uncoated tablets, having break-line on one side and plain on other side.

4 Clinical particulars

4.1 Therapeutic indications

Essential hypertension; oedema due to congestive heart failure; hepatic, pulmonary or renal oedema.

4.2 Posology and method of administration

Adults

Essential hypertension: A dose of 2.5mg Torsemide once daily is recommended. If necessary, the dose may be increased to 5mg once daily. Studies suggest that doses above 5mg daily will not lead to further reduction in blood pressure. The maximum effect is exhibited after approximately twelve weeks of continuous treatment.

Oedema: The usual dose is 5mg once daily. If necessary, the dose can be increased stepwise up to 20mg once daily. In individual cases, as much as 40mg Torsemide/day has been administered.

Special populations

Elderly

No special dosage adjustments are necessary.

Children

There is no experience of Torsemide in children.

Patients with hepatic impairment

As elimination half-lives of Torsemide and its metabolites in patients with mild to moderate hepatic impairment are only slightly increased, dose adjustment in these patients is not required. Special caution is required for patients with hepatic cirrhosis and ascites (see 4.4). Extreme caution is required when Torsemide is administered in patients with a history of hepatic encephalopathy.

Method of administration

Torsemide tablets are intended to be administered by oral route. Tablets must be swallowed with some fluid without chewing. For convenience, the tablets should be taken in the morning.

4.3 Contraindications

- Anuria with renal failure
- Hepatic coma until the condition is improved or corrected
- Hypotension
- Pre-existing hypovolaemia
- Hypersensitivity to the active substances, sulphonamides ("sulfa drugs") or to any of the excipients listed in section 6.1.
- Cardiac arrhythmias
- Simultaneous therapy with aminoglycosides or cephalosporins
- Renal dysfunction due to drugs which cause renal damage

4.4 Special warnings and precautions for use

Torsemide may lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose schedules have to be adjusted to the individual patient's needs. Especially at the start of the treatment and in elderly, patients must be carefully monitored.

Regular blood monitoring of the electrolyte balance, potassium values and the parameters glucose, uric acid, and creatinine should be carried out especially during long-term treatment with Torsemide for signs of electrolyte and volume deficiency and haemoconcentration.

Urine retention must be corrected before or during treatment with Torsemide. Extreme caution is required when Torsemide is administered in patients suffering from severe urine retention. Patients with partial occlusion of the urinary tract must be closely monitored.

There is an increased risk of gout attacks with patients

taking diuretics. Caution is required when Torsemide is administered in patients with gout.
Carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.
In nephrotic syndrome, treatment of the primary disease should take precedence.

In patients with hepatic cirrhosis and ascites, it is recommended that diuresis with any drug be initiated in the hospital. Too rapid diuresis in such patients can precipitate severe electrolyte disturbances and hepatic coma. Extreme caution is required when Torsemide is administered in patients with a history of hepatic encephalopathy. The concomitant use of an aldosterone antagonist or a potassium-sparing drug is recommended to prevent hypokalemia and metabolic alkalosis.

As for other drugs which produce changes in blood pressure, patients taking Torsemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

Torsemide might cause hypokalaemia that has prominent effects on cardiac, skeletal, and intestinal muscle cells. In particular, it is a major risk factor for both ventricular and atrial arrhythmias. Therefore the potassium level of patients must be closely monitored during treatment with Torsemide. Existing hypokalemia or hypokalemia developing during Torsemide treatment has to be corrected.

Low levels of sodium must be corrected before or during treatment with Torsemide.

Hypovolemia must be corrected before or during treatment with Torsemide. Torsemide must only be given in exceptional cases to patients with hypovolemia under close monitoring.

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

4.5 Interaction with other medicinal products and other forms of interaction

When used simultaneously with cardiac glycosides, a potassium and/or magnesium deficiency may increase sensitivity of the cardiac muscle to such drugs. The potassium-depleting effect of mineralo- and glucocorticoids and laxatives may be increased.
As with other diuretics, the effect of antihypertensive drugs given concomitantly may be potentiated.
Combination of loop diuretics with ACE inhibitors or AT2 antagonists may cause severe hypotension.
The risk of ACE-induced renal impairment may be increased.

Torsemide, especially at high doses, may potentiate the totoxicity and nephrotoxic effects of aminoglycoside antibiotics, cytostatic platinum derivatives, the nephrotoxic effects of cephalosporins, and the cardio-and neurotoxic effect of lithium. In patients receiving high doses of salicylates, salicylate toxicity may be increased. The action of anti-diabetic drugs may be reduced. Additionally, the risk of recurrent gout attacks is increased in patients taking salicylates.
Torsemide is a substrate for Cytochrome P450 CYP2C8 and CYP2C9. A mutual interaction between ligands for the same enzyme might occur. Therefore, comedication that is also affected by these Cytochrome isoforms should be monitored closely to avoid unwanted plasma levels of these drugs. This interaction has been established for coumarin derivates. The possibility of Drug-Drug interaction may be crucial with drugs that have a narrow therapeutic range.

The antihypertensive and diuretic effects of loop diuretics appear to be reduced by NSAIDs. Diuretics may increase the risk of NSAID-induced acute renal failure.

Probenecid may reduce the diuretic effect of Torsemide.
The effect of some muscle relaxants and the plasma level of theophylline may be influenced (increase or decrease possible). Monitoring of theophylline plasma levels is recommended.
Concomitant use of Torsemide and cholestyramine has not been studied in humans, but in an animal study co-administration of cholestyramine decreased absorption of oral Torsemide.
Simultaneous use of alcohol and Torsemide may cause dizziness or other related symptoms.

4.6 Fertility, pregnancy, and lactation

Pregnancy
There is insufficient data from the use of Torsemide in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). Torsemide should not be used during pregnancy, unless the clinical condition of the woman requires treatment with Torsemide.

Breastfeeding
There is insufficient information on the excretion of Torsemide in human milk. A risk to the suckling child cannot be excluded. Loop diuretics may suppress lactation. A decision should be made whether to discontinue breast-feeding or to discontinue from Torsemide therapy taking into account the benefit of breast feeding for the child and the benefit of the therapy for the woman.

4.7 Effects on ability to drive and use machines

As for other drugs which produce changes in blood pressure, patients taking Torsemide, even when used at recommended doses, they should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

Very common (≥1/10)
Common (≥1/100 to
<1/10) Uncommon
(≥1/1,000 <1/100) Rare
(≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from available data). The

following undesirable effects were observed:

Blood and lymphatic system disorders
Frequency not known: Thrombocytopenia, Leukopenia, Anaemia

Immune system disorders
Very rare: Allergic skin reactions (e.g., Pruritus, Exanthema), Photosensitivity reaction
Frequencynot known: Serious skin reactions(e.g., Stevens-Johnson syndrome, Toxic epidermal necrolysis

Metabolism and nutrition disorders
Common: Metabolic alkalosis, Fluid and electrolyte imbalance (e.g., Hypovolaemia, Hyponatraemia)
Nervous system disorders
Common: Headache, Dizziness

Frequency not known: Cerebral ischaemia, Paraesthesia, confusional state

Eye disorders
Frequency not known: Visual impairment

Ear and labyrinth disorders
Frequency not known: Tinnitus, Deafness

Cardiac disorders
Frequency not known: Acute myocardial infarction, Myocardial ischaemia, Angina pectoris, Syncope, Hypotension

Vascular disorders
Frequency not known: Embolism

Gastrointestinal disorders

Common: Gastrointestinal disorder, (e.g., Loss of appetite, abdominal pain upper, Nausea, Vomiting, Diarrhoea, Constipation)
Frequency not known: Dry mouth, Pancreatitis

Hepatobiliary disorders
Uncommon: Hepatic enzyme increased (e.g., Gamma-glutamyltransferase increased)

Skin and subcutaneous tissue disorders
Very rare: Allergic skin reactions (e.g., Pruritus, Exanthema), Photosensitivity reaction
Frequencynot known: Serious skin reactions(e.g., Stevens-Johnson syndrome, Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Common: Muscle spasms

Renal and urinary disorders
Uncommon: Urinary retention, Bladder dilatation Rare: Blood urea increased, Blood creatinine increased

General disorders and administration site conditions
Common: Fatigue, Asthenia

Investigations
Uncommon: Blood uric acid increased, Blood glucose increased, Lipids increased (e.g., Blood triglycerides increased, Blood cholesterol increased)

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 and signs
Signs and symptoms of overdosage are those of excessive pharmacologic effects. If overdosage occurs, then there may be marked diuresis with the danger of loss of fluid and electrolytes which may lead to somnolence, confusion, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, hemoconcentration dehydration and circulatory collapse. Gastrointestinal disturbances may occur.

Treatment
No specific antidote is known. No data are available to suggest physiological manoeuvres (e.g., manoeuvers to change the pH of the urine) that might accelerate elimination of Torsemide and its

metabolites. Torsemide is not dialyzable, so haemodialysis will not accelerate elimination. Symptoms and signs of overdosage require the reduction of the dose or withdrawal of Torsemide, and simultaneous replacement of fluid and electrolytes.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High ceiling diuretics, sulphonamide monodrugs, ATC code: C03CA04

Torsemide is a loop diuretic. However, at low doses its pharmacodynamic profile resembles that of the thiazide class regarding the level and duration of diuresis. At higher doses, Torsemide induces a brisk diuresis in a dose dependent manner with a high ceiling of effect.

Torsemide acts as a salidiuretic by inhibition of renal sodium and chloride reabsorption in the ascending limb of the loop of Henle. After oral administration the onset of diuresis is within the 1st hour with a peak action within 2 to 3h. The action may last up to 12h.

In healthy subjects an increase in dose results in a linear increase in urine excretion corresponding to the logarithm of the dose (high-ceiling activity) within the 5 to 100 mg dose range. An increase in diuresis may also take place if other diuretics are no longer active, e.g., in the presence of impaired renal function.

In renal failure endogenous organic acids compete with loop diuretics for the acid secretion mechanism in the proximal tubule. Therefore, the Torsemide dose has to be adequately increased in order to achieve effective amounts of drug at the site of action.

Torsemide leads to a gentle removal of oedema and especially to an improvement of the working condition of the heart failure by reducing the preload and afterload. In patients with severe to end stage chronic renal failure there is a reduction of arterial blood pressure in addition to removal of oedema and maintenance of residual diuresis.

5.2 Pharmacokinetic properties

Absorption and distribution

Torsemide is absorbed rapidly and almost completely after oral administration, and peak serum levels are reached after one to two hours.

More than 99% of Torsemide is bound to plasma proteins, the metabolites M1, M3 and M5 are 86%, 95% and 97% bound.

The apparent distribution volume is 16 litres.

Metabolism

In humans, Torsemide is metabolised to two active (M1 and M3)

and one inactive metabolite (M5). Further metabolites (M2 and M4) have been found in animal experiments, but not in humans. Metabolites M1 and M5 are produced by stepwise oxidation. Hydroxylation of the methyl group on the phenyl ring leads to M1, which is further oxidized to the respective carboxylic acid M5. Metabolite M3 is formed by ring hydroxylation.
Torsemide and its metabolites are characterised by dose-linear kinetics, i.e. maximum serum concentration and areas under the serum level curves increase proportionately to the dose.

Elimination
The terminal half-life of Torsemide and its metabolites is three to four hours in healthy subjects. Total clearance of Torsemide is 40ml/min and renal clearance about 10ml/min. About 80% of the dose administered is excreted as Torsemide and metabolites into the renal tubule with the following mean percentage distribution– Torsemide about - Torsemide about 24% metabolitr, M1 about 12%, M3 about 3%, M5 about 41%.
Torsemide is eliminated by hepatic metabolism and renal excretion of the unchanged drug and its metabolites.
In patients with congestive heart failure and disorders of liver function, the elimination half-lives of Torsemide and metabolite M5 are only slightly increased compared with those in healthy volunteers. The amounts of Torsemide and metabolites excreted in the urine are similar to those in healthy subjects; therefore, no accumulation is to be expected.

In spite of decreased renal elimination, the total clearance and elimination half-life of Torsemide is unaffected in renal failure; the half-lives of M3 and M5 are prolonged, while the half-life of M1 is unchanged. The duration of action is not influenced by the severity of renal failure. Torsemide and its metabolites are not eliminated by hemodialysis or hemofiltration.

5.3 Preclinical safety data

Data from non-clinical studies do not show special risks for humans according to conventional safety pharmacology studies, repeated dose toxicology, genotoxicity, and carcinogenic potential.
The changes observed in toxicity studies in dogs and rats at high doses are attributable to an excess pharmacodynamic action (diuresis). Changes observed were weight reduction, increases in creatinine and urea and renal alterations such as tubular dilatation and interstitial nephritis. All drug induced changes were shown to be reversible.
In mice Torsemide showed no evidence of tumorigenic potential. In rats a statistically significant increase in renal adenomas and carcinomas was observed in the high-dose female group. This seems related to excessive diuresis (which is not relevant for therapeutic doses in humans).

In studies in pregnant rats and rabbits toresamide showed no

teratogenic effects but dose related embryofetal loss and retarded fetal development coincident with maternal toxicity. A study in rats of perinatal effects showed dose-related reductions in body weight of mothers and fetuses and higher pup mortality. In rats no effects on fertility were observed

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline Cellulose (PH 101)
Povidone
Crospovidone (Kollidon CL-M)
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture. Keep the Medicine out of reach of children.

6.5 Nature and contents of container

Blister pack.

6.6 Special precautions for disposal

Not applicable.

7 Marketing authorisation holder

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