SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Torasemide 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each torasemide tablet contains 5 mg torasemide.

Excipient(s) with known effect:
Lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Torasemide 5 mg Tablets are white to almost white, round, biconvex tablets with a score line on one side and embossing 915 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oedema due to congestive heart failure.

4.2 Posology and method of administration

Posology

Adults
The usual dose is 5 mg orally once daily. Usually this is the maintenance dose.

Treatment with 10 mg torasemide is indicated when the normal dose of 5 mg torasemide per day is insufficient. In these cases, 10 mg torasemide are taken

daily, depending on the severity of the clinical picture, the dose can be increased to up to 20 mg torasemide.

Elderly
There are no deviating dose recommendations for elderly. However there are insufficient comparative studies between elderly and younger patients.

Renal impairment
Clearance is reduced in patients with renal insufficiency, but total plasma concentration is not significantly affected.

Hepatic impairment
Patients with hepatic impairment should be treated with some caution since plasma concentrations might be increased (see section 5.2). Torasemide is contra-indicated in patients with coma hepaticum (see section 4.3). Special caution is required for patients with hepatic cirrhosis and ascites. Extreme caution is required when torasemide is administered in patients with a history of hepatic encephalopathy.

Paediatric population
There is no experience of use of torasemide in children below the age of 12 years.

Method of administration

Oral use.

The tablets should be taken in the morning, without chewing, with a small quantity of liquid.

Torasemide is usually given for long-term treatment or until disappearance of oedema.

4.3 Contraindications

- Hypersensitivity to the active substance, to sulphonylureas or to any of the excipients listed in section 6.1
- Renal failure with anuria
- Hepatic coma until improvement or removal of this condition
- Hypotension
- Hypovolaemia
- Hyponatraemia
- Hypokalaemia
- Severe micturition disorders (e.g. due to prostatic hyperplasia)
- Lactation
- Gout
- Cardiac arrhythmias (e.g. sino-atrial -block, atrioventricular-block second or third degree)
- Concomitant treatment with aminoglycosides or cephalosporins

- Renal impairment due to nephrotoxic agents

4.4 Special warnings and precautions for use

Due to insufficient experience with torasemide treatment, care should be exerted in the following conditions:

- Pathological changes of the acid-base balance
- Pathological changes of the blood cells (e.g. thrombocytopenia or anaemia in patients without renal insufficiency)

Micturition disorders must be corrected prior treatment start with torasemide.

Note
On long-term treatment with torasemide, regular monitoring of the electrolyte balance (particularly serum potassium and in particular in patients with concomitant therapy with digitalis glycosides, glucocorticoids, mineralocorticoids or laxatives), glucose, uric acid, creatinine and lipids in the blood and the blood cells (red and white blood cells and platelets), is recommended.

Since an increase in blood glucose can occur, carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.

The blood counts (erythrocytes, leukocytes, thrombocytes) are also to be monitored at regular intervals.

Be aware of signs of electrolyte loss and haemoconcentration, particularly at the beginning of treatment and in older patients.
In patients with arrhythmias, the administration of loop diuretics may be potentially life-threatening due to changes in electrolyte levels (potassium, sodium, calcium, and magnesium). There should be regular blood control of the electrolyte composition.

The use of torasemide can lead to positive results in doping controls. The use of torasemide as a doping agent can be harmful to health.

<u>Excipient(s)</u>

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

Sodium
This medicinal product 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

When used simultaneously with cardiac glycosides, a potassium and/or magnesium deficiency may increase sensitivity of the cardiac muscle to such

medicinal products. The kaliuretic effect of mineralo- and glucocorticoids and laxatives may be increased.

The effect of antihypertensive medicinal products, in particular ACE inhibitors, given concomitantly may be potentiated.

Sequential or combined treatment, or starting a new co-medication with an ACE inhibitor may result in severe hypotension. This may be minimised by lowering the starting dose of the ACE inhibitor and/ or reducing or stopping temporarily the dose of torasemide, 2 or 3 days before treatment with the ACE inhibitor.
The risk of ACE-induced renal insufficiency may be increased.

Torasemide may decrease arterial responsiveness to pressor agents e.g. adrenaline, noradrenaline.

Torasemide may reduce the effect of anti-diabetics.

Torasemide, especially at high doses, may potentiate the nephrotoxic and ototoxic effects of aminoglycoside antibiotics (e.g. kanamycin, gentamicin, tobramycin), cytotoxicity of platin derivatives and the nephrotoxic effects of cephalosporins.

The action of theophylline and curare-containing muscle relaxants can be influenced (potentiated or decreased) by torasemide. Monitoring of serum theophylline levels is recommended.

Non-steroidal anti-inflammatory drugs (eg. indomethacin, acetylsalicylic acid) may reduce the diuretic and hypotensive effect of torasemide possibly through an inhibition of prostaglandin synthesis. Diuretics may increase the risk of NSAID-induced renal failure.

Probenecid may reduce efficacy of torasemide by inhibition of tubular secretion.

Lithium serum-concentrations and cardio- and neurotoxic effects of lithium may be increased in concomitant use with torasemide.

Torasemide inhibits the renal excretion of salicylates, increasing the risk for neurotoxic effects of salicylate in patients receiving high doses of salicylates. In addition, the risk of recurrent gout attacks is increased in patients taking salicylates.

Concomitant use of torasemide and cholestyramine may reduce absorption and hence efficacy of oral torasemide.

Torasemide is a substrate for cytochrome P450 CYP2C8 and CYP2C9. There may be an interaction between the ligands for the same enzyme. Therefore, concomitant administration of medicinal products that are also catalysed by these cytochrome isoforms should be closely monitored to avoid undesirable

serum levels of these medicinal products. This interaction has been demonstrated for coumarin derivatives. The potential for drug-drug interaction may be critical for substances with a narrow therapeutic range.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient clinical experience in humans on the effect of torasemide on the embryo and foetus.

Whilst studies in the rat have shown no teratogenic effect, foetal and maternal toxicity have been observed after high doses in pregnant rabbits and rats.

Torasemide passes into the foetus and causes electrolyte disturbances. There is also a risk of neonatal thrombocytopenia.

Until further experience is available, torasemide should only be given during pregnancy after careful consideration of whether the benefits clearly outweigh the risks. The lowest possible dose should be used.

Diuretics are not suited for routine therapy of hypertension and oedema during pregnancy, since they can impair placental perfusion and thus intrauterine growth. If, in case of cardiac or renal insufficiency, torasemide must be administered to a pregnant woman, electrolytes and haematocrit as well as foetal growth must be thoroughly monitored.

Breast-feeding
There is insufficient information on whether torasemide passes into breast milk. A risk for the newborn/child cannot be excluded. Loop diuretics can reduce milk production. Therefore, torasemide should not be used during breast-feeding (see section 4.3). A decision must be made as to whether breast-feeding should be interrupted or whether treatment with torasemide should be discontinued. Both the benefits of breast-feeding for the child and the benefits of the therapy for the woman should be considered.

4.7 Effects on ability to drive and use machines

As for other medicinal products that produce changes in blood pressure, patients taking torasemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms. This applies in particular at the beginning of the therapy, when increasing the dosage, changing the preparation, initiating additional medication or when concomitantly ingesting alcohol.

4.8 Undesirable effects

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
Very rare: Red blood cell, white blood cell and platelet count decreased

Metabolism and nutrition disorders
Common: Aggravation of metabolic alkalosis
Hypokalaemia in cases of low potassium diet, vomiting, diarrhoea/excessive use of laxatives, or chronic hepatic dysfunction

Depending on the dosage and duration of treatment, disturbances of water and electrolyte balance can occur, particularly e.g. hypovolaemia, hypokalaemia and/or hyponatraemia. Symptoms and signs of electrolyte and volume depletion, such as headache, dizziness, hypotension, weakness, drowsiness, confusional states, loss of appetite and cramps, if diuresis is marked (especially at the start of treatment and in elderly patients) - dose adjustment may be necessary.

Nervous system disorders
Common: Headache, dizziness
Uncommon: Limb paraesthesia
Not known: Cerebral ischaemia, confusion

Eye disorders
Very rare: Visual disturbance

Ear and labyrinth disorders
Very rare: Tinnitus, hearing loss

Cardiac disorders
Very rare: On account of haemoconcentration, hypotension as well as cardiac and central circulatory disorders (including cardiac ischaemia) can occur. These can lead to e.g. arrhythmias, angina pectoris, acute myocardial infarction, or syncopes.

Vascular disorders
Very rare: Thromboembolic complications due to hemoconcentration

Gastrointestinal disorders

Common: Gastro-intestinal disorders (e.g. loss of appetite, abdominal pain upper, nausea, vomiting, diarrhoea, constipation), particularly at the beginning of treatment
Uncommon: Xerostomia
Very rare: Pancreatitis

Hepatobiliary disorders
Common: Increases in certain liver enzyme concentrations, eg. gamma-glutamyltransferase in the blood

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

Musculoskeletal and connective tissue disorders
Common: Muscle spasms (particularly at the beginning of therapy)

Renal and urinary disorders
Uncommon: Increase in the concentrations ofcreatinine and urea in the blood
In patients with impaired micturition (e.g. due to prostatic hyperplasia), increased urinary production can lead to urinary retention and overexpansion of the bladder.

General disorders and administrative site conditions
Common: Fatigue, asthenia (particularly at the beginning of therapy)

Investigations
Common: Increases in the concentration of uric acid and glucose in the blood as well as in blood lipids (triglycerides, cholesterol)

Effect on laboratory parameters
Potassium
Following administration of 2.5 mg and 5 mg torasemide over 12 to 14 weeks the mean decrease in serum concentration was 0.2 to 0.3 mM/l. The maximum average decrease was 0.39 mM/l after 6 weeks administration of 10 mg torasemide and 0.42 mM/l after 6 weeks administration of 40 mg torasemide (see section 4.4).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs
No typical picture of intoxication is known. If overdose occurs, then there may be marked diuresis with the danger of loss of fluid and electrolytes that may lead to somnolence and confusion, hypotension, circulatory collapse. Gastrointestinal disturbances may occur.

Treatment
No specific antidote is known. Symptoms and signs of overdose subside the reduction of the dose or withdrawal of torasemide, and simultaneous replacement of fluid and electrolytes (control).
Torasemide is not dialysable; haemodialysis does not accelerate its elimination.

Therapy in case of hypovolaemia: volume substitution
Therapy in case of hypokalaemia: potassium substitution
Therapy in case of circulatory collapse: shock positioning, if necessary, shock therapy

Immediate measures in case of anaphylactic shock:
At first signs (e.g. cutaneous reactions such as urticaria or flush, restlessness, headache, extensive perspiration, nausea, cyanosis):
- Create venous access
- Besides other usual emergency measures, head-chest down position, maintain patent airways, application of oxygen
- If necessary, further, even intensive care measures (including administration of adrenaline, volume substitutes, glucocorticoid) should be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-ceiling diuretics, sulfonamides, plain, ATC Code: C03 CA 04

Torasemide acts saluretic by inhibition of renal sodium and chloride reabsorption in the ascending limb of the loop of Henley. In humans, the onset of the diuretic effect is rapid after i.v. and oral administration, with a maximum effect within the first hour and after 2 to 3 hours, respectively, and may last for up to 12 hours.
In healthy volunteers, increased diuresis proportional to the logarithm of the dose (“high-ceiling activity”) was observed in the dose range 5-100 mg. Diuresis can also increase if other diuretics (e.g. distal thiazides) are no longer sufficiently effective, e.g. in case of impaired renal function.

Due to these properties, torasemide leads to a removal of oedema. In heart failure, torasemide causes an improvement of symptoms and an improvement of the working conditions of the myocardium by reducing the preload and afterload.

5.2 Pharmacokinetic properties

Absorption
Torasemide is absorbed rapidly and almost completely after oral administration, and peak serum levels are reached after one to two hours. Systemic bioavailability after oral administration is 80-90%. A first-pass effect is a maximum of 10-20% assuming complete absorption.

Data from two studies consistently show that although the (time-dependent) absorption rate of torasemide is reduced after food intake (lower Cmax as well as increased tmax values), the total absorption of torasemide is not affected by food intake.

Serum protein binding
More than 99% of torasemide is bound to plasma proteins**,** while metabolites M1, M3 and M5 are bound 86%, 95% and 97%, respectively.

Distribution
The apparent distribution volume is 16 litres (Vz: 16 l).

Biotransformation
Torasemide is metabolised to three metabolites, M1, M3 and M5 by stepwise oxidation, hydroxylation or ring hydroxylation. The hydroxyl-metabolites have diuretic activity. Metabolites M1 and M3 add to about 10% of the pharmacodynamic action, whereas M5 is inactive.

The metabolites M2 and M4 found in animal experiments could not be detected in humans.

Elimination
The terminal half-life of torasemide and its metabolites is three to four hours in healthy subjects. Torasemide is eliminated by hepatic metabolism and renal excretion of the unchanged substance and its metabolites. Total clearance of torasemide is 40 ml/min and renal clearance about 10 ml/min. About 80% of the dose administered is excreted as torasemide and metabolites into the renal tubule - torasemide 24%, M1 12%, M3 3%, M5 41%.

In the presence of renal failure, the elimination half-life of torasemide is unchanged but the half-lives of metabolites M3 and M5 are increased. However, the pharmacodynamic properties remain unchanged, the duration of effect is not influenced by the severity of renal insufficiency. Torasemide and its metabolites are not significantly removed by hemodialysis or hemofiltration.

In patients with hepatic impairment, increases in plasma concentrations of torasemide have been observed, likely due to decreased hepatic metabolism. In patients with cardiac or hepatic failure the half-lives of torasemide and metabolite M5 are slightly increased but the quantities of the substance

excreted in urine largely correspond to those in healthy persons. Accumulation of torasemide and torasemide metabolites is unlikely.

Linearity/non-linearity
Torasemide and its metabolites are characterised by dose-linear kinetics, i.e. maximum serum concentration and areas under the serum level curves increase proportionally to the dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on single dose toxicity, genotoxicity and carcinogenicity studies.

The changes observed in toxicity studies in dogs and rats at high doses are considered 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 medicinal product induced changes were shown to be reversible.

Reproduction toxicology: Studies in the rat have shown no teratogenic effects, but foetal and maternal toxicity have been observed after high doses in pregnant rabbits and rats. No effects on fertility have been seen. Torasemide passes into the foetus and causes electrolyte disturbances.

In mice torasemide 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 to have no relevance for therapeutic doses in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Sodium starch glycollate Type A
Silica colloidal anhydrous
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC /PVDC //Al blisters containing 14, 28, 30, 50, 100 or 112 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
United Kingdom

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