Professional Information for TORASEMIDE BIOTECH 5 / 10 / 20

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

TORASEMIDE BIOTECH 5 tablets

TORASEMIDE BIOTECH 10 tablets

TORASEMIDE BIOTECH 20 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TORASEMIDE BIOTECH 5: Each tablet contains 5 mg torasemide.

TORASEMIDE BIOTECH 10: Each tablet contains 10 mg torasemide.

TORASEMIDE BIOTECH 20: Each tablet contains 20 mg torasemide.

Excipients with known effect

Contains sugar (lactose monohydrate).

The 5 mg tablet contains 79 mg, the 10 mg tablet contains 158 mg and the 20 mg tablet contains 316 mg lactose monohydrate, respectively.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

TORASEMIDE BIOTECH 5: White to off white, oval shaped, scored tablets, debossed with '5' on plain side and scored on the other side.

TORASEMIDE BIOTECH 10: White to off white, oval shaped, scored tablets, debossed with ‘10’ on plain side and scored on the other side.

TORASEMIDE BIOTECH 20: White to off white, oval shaped, scored tablets, debossed with '20' on plain side and scored on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.

Oedema of cardiac and hepatic origin.

Pulmonary oedema due to acute cardiac insufficiency.

4.2 Posology and method of administration

Posology

Essential hypertension:

Treatment is initiated with 2,5 mg torasemide per day. The usual maintenance dose is 2,5 mg per day. If this is insufficiently effective, the dose can be doubled to 5,0 mg per day. Higher doses will not lead to a further reduction of blood pressure.

Oedema of cardiac, hepatic and renal origin:

Treatment is initiated with 5 mg per day. The usual maintenance dose is 5 mg per day. If this is insufficiently effective, the dose can be increased up to 20 mg per day depending on the severity of the disease. In individual cases as much as 40 mg per day has been administered.

Method of administration

For oral administration.

Oral TORASEMIDE BIOTECH may be taken with some liquid on an empty stomach or at any time in relation to a meal, as convenient.

4.3 Contraindications

- Hypersensitivity to torasemide or any of the other ingredients of TORASEMIDE BIOTECH

(see section 6.1).

- Renal failure with absence of urine production (anuria).
- Hepatic pre-coma and coma.
- Pregnancy and lactation (see section 4.6).
- Patients with known hypersensitivity to sulfonylureas.
- Hypovolaemia.
- Hyponatraemia, hypokalaemia.
- Severe disorders of micturition (e.g. prostate hypertrophy).

TORASEMIDE BIOTECH should not be used in children of 12 years or younger.

4.4 Special warnings and precautions for use

TORASEMIDE BIOTECH should not be given in pre-comatose states associated with hepatic cirrhosis.

Hypokalaemia, hyponatraemia, hypovolaemia disorders of micturition must be corrected before treatment.

TORASEMIDE BIOTECH should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

Careful monitoring of the carbohydrate metabolism is recommended in patients with latent or manifest diabetes mellitus, since a rise in blood glucose may occur.

Long term treatment with TORASEMIDE BIOTECH requires regular monitoring of the electrolyte balance, glucose, uric acid, creatinine and lipid levels.

Careful monitoring is required in patients with a tendency to hyperuricaemia and gout.

Patients with rare hereditary problems of lactose- or glucose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take TORASEMIDE BIOTECH.

4.5 Interaction with other medicines and other forms of interaction

The effect of antihypertensive medicines may be potentiated when used in combination with TORASEMIDE BIOTECH.

Consecutive treatment or start of a new co-medication with an ACE (angiotensin-converting enzyme) inhibitor may result in an excessive fall in blood pressure.

The action of antidiabetic medicines may be reduced by TORASEMIDE BIOTECH. Dosage adjustment of hypoglycaemic medications may be necessary.

Concurrent and/ or sequential administration with TORASEMIDE BIOTECH and amphotericin B parenteral should be avoided, since the potential for nephrotoxicity may be increased, especially in the presence of renal function impairment.

Anti-inflammatory medicines, nonsteroidal anti-inflammatory drugs (NSAIDs), especially indomethacin may reduce the natriuretic action of TORASEMIDE BIOTECH.

When using TORASEMIDE BIOTECH simultaneously with digoxin, a potassium and/ or magnesium deficiency may increase the sensitivity of the cardiac muscle to digoxin.

Concurrent use of lithium with TORASEMIDE BIOTECH may promote lithium toxicity because of reduced renal clearance.

Probenecid may reduce the diuretic and hypotensive effect of TORASEMIDE BIOTECH.

The risk of hypokalaemia may be increased by TORASEMIDE BIOTECH.

The kalidiuretic effect of mineralo- and glucocorticosteroids and laxatives may be increased.

TORASEMIDE BIOTECH may potentiate the damaging effects of aminoglycocide antibiotics, cisplatin preparations and cephalosporins on the ear and kidney and the cardio-and neurotoxic effect of lithium, especially at high dose therapy.

The action of curare containing muscle relaxants and of theophylline can be potentiated by TORASEMIDE BIOTECH. TORASEMIDE BIOTECH may decrease arterial responsiveness to pressor medicines, e.g. epinephrine (adrenaline) and norepinephrine (noradrenaline).

In patients receiving high doses of salicylates, salicylate-toxicity may be increased by TORASEMIDE BIOTECH. On concomitant treatment with colestyramine, bioavailability and thus the efficacy of TORASEMIDE BIOTECH may be reduced.

The anticoagulant effects of warfarin or heparin may be decreased when these medicines are used concurrently with TORASEMIDE BIOTECH.

The concurrent use of sympathomimetics with TORASEMIDE BIOTECH may reduce the antihypertensive effects of TORASEMIDE BIOTECH.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnant women have not been established. TORASEMIDE BIOTECH is contraindicated during pregnancy (see section 4.3).

Breastfeeding

It is not known whether TORASEMIDE BIOTECH is distributed into breast milk. TORASEMIDE BIOTECH is contraindicated during lactation (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Individually varying reactions can impair alertness (e.g. patient's ability to drive vehicles or to operate machinery). This applies particularly when beginning treatment, switching from another medicine or starting a new co-medication and in conjunction with alcohol.

Patients taking TORASEMIDE BIOTECH should be warned to take special caution when performing tasks requiring their attention, if they experience dizziness or related symptoms.

4.8 Undesirable effects

Blood and the lymphatic system disorders

Less frequent: Thrombocytopenia, leukopenia, anaemia.

Immune system disorders

Less frequent: Acute hypersensitivity reactions (which may be life-threatening).

Metabolism and nutrition disorders

Frequent: Metabolic alkalosis, fluid and electrolyte imbalance (e.g. hypovolaemia, hyponatraemia).

Less frequent: Lowered potassium levels.

Nervous system disorders

Frequent: Headache, dizziness.

Frequency unknown: Feelings of weakness, loss of appetite and cramps, confusional states,

paraesthesia, cerebral ischaemia.

Eye disorders

Frequency unknown: Visual disturbances.

Ear and labyrinth disorders

Less frequent: Ototoxicity (ringing or buzzing in ears or loss of hearing).

Cardiac disorders

Frequency unknown: Thromboembolic complications and cardiac ischaemia or myocardial infarction, angina pectoris, syncope.

Vascular disorders

Less frequent: Hypotension.

Frequency unknown: Embolism.

Gastrointestinal disorders

Frequent: Gastrointestinal symptoms (loss of appetite, upper abdominal pain, nausea, vomiting, diarrhoea, constipation).

Frequency unknown: Dry mouth, pancreatitis.

Hepato-biliary disorders

Less frequent: Hepatic enzyme increase (e.g. Gamma-glutamyl transferase increase).

Skin and subcutaneous tissue disorders

Less frequent: Allergic skin reactions, e.g. pruritus and exanthema or photosensitisation.

Frequency unknown: Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic

epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Frequent: Muscle spasm.

Renal and urinary disorders

Less frequent: Urinary retention, bladder dilation, increased blood urea, increased blood creatinine.

Frequency unknown: In patients with urinary obstructions, e.g. prostate hypertrophy, increased urine production can lead to urine retention resulting in distension of the bladder.

General disorders and administration site conditions

Frequent: Fatigue, asthenia.

Investigations

Less frequent: Increased blood uric acid, increased blood glucose, increased lipids (e.g. increased blood triglycerides, increased blood cholesterol.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TORASEMIDE BIOTECH is important. It allows continued monitoring of the benefit/ risk balance of TORESAMIDE BIOTECH. Healthcare providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In the event of overdosage there may be a marked diuresis with the danger of loss of liquids

and electrolytes which may lead to somnolence and confusion, hypotension, circulatory collapse and gastrointestinal symptoms. No specific antidote is known. Symptoms of overdosage generally disappear on reduction of the dose or withdrawal of the medicine and simultaneous replacement of fluid and electrolytes (to be monitored). Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 18.1 Diuretics.

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

5.1 Pharmacodynamic properties

Torasemide 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, torasemide induces a brisk diuresis in a dose dependant manner with a high ceiling of effect.

It inhibits activity of the Na^+-K^+-$2Cl^-$ symporter in the thick ascending limb of the loop of Henle, thereby inhibiting reabsorption of renal sodium and chloride. Owing to the blockade of the Na^+-K^+-$2Cl^-$ symporter, torasemide increases urinary Na^+ and Cl^- excretion profoundly. After oral administration the onset of diuresis is within the 1st hour with a peak action within 2 to 3 hours. The action may last up to 12 hours.

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, eg 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 torasemide dose has to be adequately increased in order to achieve effective amounts of medicine at the site of action.

Torasemide lowers blood pressure initially by reducing plasma and extracellular fluid volume; cardiac output also decreases. Eventually, cardiac output returns to normal with an accompanying decrease in peripheral resistance.

After oral administration the blood pressure lowering effect of torasemide starts within the first week of treatment, the maximum effect being achieved after about 12 weeks. The exact mechanism of action of antihypertensive treatment with diuretics has not been established.

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

5.2 Pharmacokinetic properties

Absorption

Torasemide is well absorbed following oral administration; not affected by food.
The onset of the diuretic action of torasemide is within 1 hour after oral administration. Time to peak concentration is 1 to 2 hours. Duration of the diuretic action is 6 to 8 hours.
The bio-availability is approximately 80 %.

Distribution

The volume of distribution (VolD) is 0,14 to 0,19 L per kg Torasemide has high protein binding properties ranging from 97 % to greater than 99 %.

Biotransformation

Torasemide is metabolised to three metabolites: M1, M3 and M5 by stepwise oxidation, hydroxylation or ring hydroxylation. Further metabolites (M2 and M4) have been found in animal experiments, but not in humans.

Torasemide is metabolised via the hepatic cytochrome P450 system to 5 metabolites. The major metabolite, M5, is pharmacologically inactive. Overall, torasemide appears to account for 80 % of the total diuretic activity, while metabolites M1 and M3 account for 9 % and 11 % respectively.

Elimination

The elimination half-life of torasemide is 2,2 to 3,8 hours; not affected by moderate renal failure.

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 %.

Torasemide is not significantly removed by haemodialysis.

In patients with congestive heart failure and disorders of liver function, the elimination half-lives of torasemide and metabolite M5 are only slightly increased compared with those in healthy volunteers. The amounts of torasemide and metabolites excreted in the urine are similar to those in healthy subjects; therefore, no accumulation is to be expected.

In the presence of renal failure, elimination half-life of torasemide is unchanged. Pharmacodynamic behaviour is not affected and the duration of action is not influenced by the severity of renal failure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

- Store at or below 25 ºC.
- Keep tablets in container until required for use.
- Keep container well closed.

6.5 Nature and contents of container

TORASEMIDE BIOTECH 5 & 10 :

30 and 100 tablets are packed in white HDPE container with white ribbed child resistant HDPE cap with a pulp liner in between the heat seal liner and inner cap.

TORASEMIDE BIOTECH 20:

100 tablets are packed in white HDPE container with white ribbed child resistant HDPE cap with a pulp liner in between the heat seal liner and inner cap, placed in outer cardboard carton

All pack size and strengths may not necessarily be marketed at one time.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand, 1685

South Africa

8. REGISTRATION NUMBERS

TORASEMIDE BIOTECH 5: 45/18.1/1185

TORASEMIDE BIOTECH 10: 45/18.1/1186

TORASEMIDE BIOTECH 20: 45/18.1/1187

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 November 2015

10. DATE OF REVISION OF THE TEXT

05 February 2024