Summary of Product Characteristics
TORSENONE
(Torsemide 10 mg and eplerenone 25 mg film-coated tablets)

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1. Name of the medicinal product

TORSENONE (Torsemide 10 mg and Eplerenone 25 mg Tablets)

2. Qualitative and quantitative composition

Each film-coated tablet contains torsemide USP 10 mg and eplerenone BP 25 mg.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

A reddish-brown, diamond-shaped, biconvex film-coated tablet, plain on one side and with a break-line on the other.

4. Clinical particulars

4.1 Therapeutic indications

TORSENONE is indicated for the treatment of hypertension and of heart failure, including left ventricular systolic dysfunction, where combined treatment with a loop diuretic (torsemide) and an aldosterone antagonist (eplerenone) is appropriate.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet once daily, or as directed by the physician. Serum potassium and renal function should be checked before initiation, within the first week and at one month after the start of treatment or dose adjustment, and periodically thereafter (see section 4.4).

Paediatric population

The safety and efficacy of TORSENONE in children and adolescents aged 0 to less than 18 years have not been established.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to torsemide, eplerenone, sulphonamides, or to any of the excipients listed in section 6.1.
- Anuria, renal failure with anuria, and hepatic coma or pre-coma.
- Hypotension, hypovolaemia, and clinically significant hyponatraemia or hypokalaemia.
- Serum potassium above 5.0 mmol/L at initiation.
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Severe hepatic impairment (Child-Pugh class C).

- Concomitant treatment with potassium-sparing diuretics or potassium supplements.
- Concomitant treatment with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin, nefazodone).

4.4 Special warnings and precautions for use

Hyperkalaemia (eplerenone)

In view of the mechanism of action of eplerenone, hyperkalaemia may occur. Serum potassium should be monitored in all patients at initiation and at dose changes; regular monitoring is particularly important in patients at risk of hyperkalaemia, such as the elderly, those with renal impairment or diabetes. The use of potassium supplements or potassium-sparing diuretics after initiation is not recommended. If serum potassium rises, the dose should be reduced or treatment stopped.

Renal function

Renal function should be monitored periodically. Eplerenone is not removed by haemodialysis. Eplerenone should not be used in patients with severe renal impairment, and should be used with caution in moderate renal impairment with close monitoring of serum potassium.

Electrolyte and metabolic monitoring (torsemide)

Hypokalaemia, hyponatraemia, hypovolaemia and disorders of micturition must be corrected before treatment. On long-term treatment with torsemide, regular monitoring of the electrolyte balance, glucose, uric acid, creatinine and lipids in the blood is recommended. Careful monitoring is required in patients with a tendency to hyperuricaemia and gout, and carbohydrate metabolism should be monitored in latent or manifest diabetes mellitus.

Difficulty with micturition

Particular caution is required in patients with difficulty in micturition, including prostatic hypertrophy, as they have an increased risk of acute urinary retention and require careful monitoring.

Hepatic impairment

Eplerenone exposure is increased in patients with hepatic impairment; TORSENONE should not be used in severe hepatic impairment and used with caution in mild to moderate impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Torsemide

With cardiac glycosides, potassium and/or magnesium deficiency may increase the sensitivity of the cardiac muscle. The potassium-depleting effect of mineralo- and glucocorticoids and of laxatives may be increased. The effect of concomitant antihypertensive drugs may be potentiated, and the combination of loop diuretics with ACE inhibitors or angiotensin-II antagonists may cause severe hypotension and increase the risk of renal impairment. Torsemide may potentiate the nephrotoxicity of aminoglycosides, platinum cytostatics and cephalosporins, and the cardio- and neurotoxicity of lithium; salicylate toxicity may be increased at high salicylate doses. The action of antidiabetic drugs may be reduced. Torsemide is a substrate of CYP2C8 and CYP2C9 (an interaction is established for coumarin derivatives). NSAIDs may reduce its antihypertensive and diuretic effects and increase the risk of acute renal failure. Probenecid may reduce the diuretic effect.

Eplerenone

Eplerenone must not be given with potassium-sparing diuretics or potassium supplements. The risk of hyperkalaemia is increased with ACE inhibitors, angiotensin-II antagonists, trimethoprim, and ciclosporin or tacrolimus (which may also impair renal function); these combinations require close monitoring or should be avoided. Co-administration of eplerenone and lithium should be avoided. Alpha-1-blockers, tricyclic antidepressants, neuroleptics, amifostine and baclofen may increase the antihypertensive effect and the risk of postural hypotension; glucocorticoids and

tetracosactide may decrease it. Eplerenone increases digoxin exposure by about 16%. Concomitant use with strong CYP3A4 inhibitors is contraindicated; with mild to moderate CYP3A4 inhibitors (e.g. erythromycin, saquinavir, amiodarone, diltiazem, verapamil, fluconazole), the eplerenone dose should not exceed 25 mg daily. The concomitant use of strong CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort) is not recommended, owing to reduced eplerenone efficacy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of torsemide or eplerenone in pregnant women. Loop diuretics are not recommended during pregnancy, as they are not indicated for gestational hypertension or oedema and may reduce placental perfusion. Animal studies with eplerenone did not indicate direct harmful effects, but human data are limited. TORSENONE should not be used during pregnancy unless clearly necessary, and only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether torsemide or eplerenone is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of the combination on human fertility.

4.7 Effects on ability to drive and use machines

As with other medicines that produce changes in blood pressure, patients should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

4.8 Undesirable effects

The adverse reactions are listed below by System Organ Class and frequency, defined as: 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) and not known (cannot be estimated from the available data). Reactions attributed specifically to torsemide are tagged (T) and those to eplerenone (E).

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known	Thrombocytopenia, leucopenia, anaemia (T)
Immune system disorders	Not known	Hypersensitivity reactions (T/E)
Metabolism and nutrition disorders	Common	Metabolic alkalosis, fluid and electrolyte imbalance (e.g. hypovolaemia, hyponatraemia), hyperkalaemia (E), hypercholesterolaemia
Nervous system disorders	Common	Headache, dizziness, syncope
	Not known	Cerebral ischaemia, paraesthesia, confusional state
Eye disorders	Not known	Visual impairment
Ear and labyrinth disorders	Not known	Tinnitus, deafness
Cardiac disorders	Common	Left ventricular failure, atrial fibrillation
	Not known	Myocardial infarction, myocardial ischaemia, angina pectoris
Vascular disorders	Common	Hypotension
	Not known	Embolism
Gastrointestinal disorders	Common	Decreased appetite, upper abdominal pain, nausea, vomiting, diarrhoea, constipation
	Not known	Dry mouth, pancreatitis
Hepatobiliary disorders	Uncommon	Hepatic enzymes increased (e.g. gamma-glutamyltransferase increased)
Skin and subcutaneous	Very rare	Allergic skin reactions (e.g. pruritus, exanthema),

System Organ Class	Frequency	Adverse reaction
tissue disorders		photosensitivity reaction
	Not known	Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis)
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, back pain
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 and cholesterol increased)

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 to the National Regulatory Authority.

4.9 Overdose

Torsemide: signs and symptoms of overdose are those of excessive pharmacological effect — marked diuresis with the danger of fluid and electrolyte loss, which may lead to somnolence, confusion, hypotension, hyponatraemia, hypokalaemia, hypochloraemic alkalosis, haemoconcentration and circulatory collapse. There is no specific antidote; torsemide is not dialysable. Treatment consists of dose reduction or withdrawal and replacement of fluid and electrolytes.

Eplerenone: the most likely manifestations of overdose would be hypotension or hyperkalaemia. Eplerenone cannot be removed by haemodialysis but binds extensively to charcoal. Symptomatic hypotension and hyperkalaemia should be managed with standard supportive treatment.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-ceiling diuretics, sulphonamides (torsemide, ATC code C03CA04) in combination with aldosterone antagonists (eplerenone, ATC code C03DA04).

Torsemide

Torsemide is a loop diuretic that acts from within the lumen of the thick ascending limb of the loop of Henle, where it inhibits the Na+/K+/2Cl− carrier system. Compared with other loop diuretics, torsemide has a more prolonged diuretic effect.

Eplerenone

Eplerenone binds selectively to human mineralocorticoid receptors relative to glucocorticoid, progesterone and androgen receptors. It prevents the binding of aldosterone, a key hormone in the renin-angiotensin-aldosterone system involved in the regulation of blood pressure and the pathophysiology of cardiovascular disease. The combination provides complementary control of fluid overload and neurohormonal (aldosterone) activation.

5.2 Pharmacokinetic properties

Absorption

Torsemide has a high oral bioavailability (generally above 80%), with maximum serum concentrations reached about 1 hour after dosing; absorption is not affected by food. The absolute bioavailability of eplerenone is not established.

Distribution

The volume of distribution of torsemide is about 0.2 L/kg; that of eplerenone is 43 to 90 L.

Biotransformation

Torsemide is extensively metabolised in the liver, mainly by CYP2C8 and CYP2C9, to five metabolites; only about 20% is excreted unchanged. The major metabolite (M5) is pharmacologically inactive, while M3 is equal in activity to torsemide and M1 has about one-tenth the activity. Eplerenone is metabolised primarily by CYP3A4, and no active metabolites have been identified in human plasma.

Elimination

The terminal half-life of torsemide and its metabolites is three to four hours in healthy subjects; total clearance is about 40 mL/min. In renal failure, the total clearance and elimination half-life of torsemide are unaffected. Torsemide and its metabolites are not removed by haemodialysis. For eplerenone, less than 5% is recovered as unchanged drug; approximately 67% of a dose is excreted in the urine and 32% in the faeces, and the elimination half-life is approximately 4 to 6 hours.

5.3 Preclinical safety data

Torsemide and eplerenone are well-established active substances. Non-clinical data reveal no special hazard for humans beyond that reflected in other sections of this Summary of Product Characteristics; as expected for a loop diuretic and a mineralocorticoid-receptor antagonist, effects observed in animal studies were related to exaggerated pharmacology (fluid, electrolyte and endocrine changes).

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

- Microcrystalline cellulose
- Dibasic calcium phosphate
- Povidone (K-30)
- Magnesium stearate
- Purified talc
- Colloidal silicon dioxide

Film coat:

- Hypromellose
- Titanium dioxide
- Red iron oxide
- Macrogol 6000 (PEG-6000)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Protect from direct sunlight, heat and moisture. Keep out of the reach and sight of children.

6.5 Nature and contents of container

3 x 10 tablets in Alu-Alu blister packs, presented in a printed carton together with the package insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Krishna Chemists Ltd, P.O. Box 3328-00506, Nairobi, Kenya.

Manufacturer

HBC Healthcare Pvt. Ltd., Block/Survey No. 609paiki 002, Ambasan (Amipura), Nr. Shanku's Water Park, Ahmedabad-Mehsana Highway, Dist. Mehsana-384 435, Gujarat, India.

8. Marketing Authorisation Number

H2009/24469/501

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text