SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Torasemid Zentiva 2.5 mg tablets
Torasemid Zentiva 5 mg tablets
Torasemid Zentiva 10 mg tablets
Torasemid Zentiva 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<[Invented name]> 2.5 mg tablets
Each tablet contains 2.5 mg of torasemide.
Excipient with known effect: Each tablet contains 48 mg of lactose (as monohydrate).

<[Invented name]> 5 mg tablets
Each tablet contains 5 mg of torasemide.
Excipient with known effect: Each tablet contains 97 mg of lactose (as monohydrate).

<[Invented name]> 10 mg tablets
Each tablet contains 10 mg of torasemide.
Excipient with known effect: Each tablet contains 193 mg of lactose (as monohydrate).

<[Invented name]> 20 mg tablets
Each tablet contains 20 mg of torasemide.
Excipient with known effect: Each tablet contains 386 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

<[Invented name]> 2.5 mg tablets
White to off-white round tablet of approx. 5 mm diameter.

<[Invented name]> 5 mg tablets
White to off-white oblong tablet of dimensions approx. 9 × 4 mm with score line on one side.
The tablet can be divided into equal doses.

<[Invented name]> 10 mg tablets
White to off-white round tablet of approx. 9 mm diameter with a debossed “e“ in the middle of one side.

<[Invented name]> 20 mg tablets
White to off-white oblong tablet of dimensions approx. 14 × 7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oedema due to congestive heart failure; hepatic or renal oedema.

In addition, <[Invented name]> 2.5 mg and 5 mg tablets are indicated for treatment of essential hypertension.

<[Invented name]> is indicated in adults and adolescents over 12 years of age.

4.2 Posology and method of administration

Posology
Adults and adolescents over 12 years of age
Oedema in heart and liver failure
Individual dosage. The usual dose is 5-10 mg daily, preferably with breakfast. If necessary, the dose can be increased to 20 mg per day. In rare cases, 40 mg torasemide per day has been used.

Hypertension
The usual dose is 2.5 mg daily, preferably with breakfast. The dose should not be increased until after 2 months and the maximum dose is 5 mg once daily.

Oedema in renal insufficiency
Individual dosage depending on the degree of renal impairment. If the normal dose of 20 mg per day does not give sufficient effect, the dose can be increased to 50 mg daily and then, if necessary, gradually increased up to 200 mg once daily, preferably with breakfast. The 200 mg dose should only be used in patients with creatinine clearance <30 ml/min. The maximum daily dose used for a long time is 200 mg.

Torasemide can be combined with beta-receptor blockers or ACE inhibitors, for more information see section 4.5.

Paediatric population
No data are available for children below 12 years of age.

Method of administration
<[Invented name]> tablets are for oral use. The tablets should be swallowed with a little liquid without chewing. The tablets should preferably be taken in the morning.

4.3 Contraindications

- Hypersensitivity to torasemide, sulphonylurea or to any of the excipients listed in section 6.1.
- Threatening or manifest hepatic coma.
- Anuria in renal failure.
- Hypovolaemia.
- Hypotension.

4.4 Special warnings and precautions for use

Torasemide can lead to extensive diuresis with salt and fluid deficiency as a result. Patients must be closely monitored, especially at the beginning of treatment and in elderly patients.

Hypokalaemia, hyponatremia and hypovolaemia must be corrected before treatment.

Problems with urination (e.g. benign prostatic hyperplasia) must be corrected before treatment as there is an increased risk of acute urinary retention.

Cardiac arrhythmias (e.g. sinoatrial block, second or third degree atrioventricular block).

During long-term treatment with torasemide, regular check-ups of the electrolyte balance in the blood, especially potassium (especially in patients treated concomitantly with digitalis glycosides, glucocorticoids, mineralocorticoids or laxatives), glucose, uric acid, creatinine and blood lipids.

In patients with liver cirrhosis and ascites, it is recommended that diuretic therapy be initiated in a hospital. Excessive diuresis in these patients can trigger severe electrolyte disturbances and hepatic coma. Caution should be exercised when administering torasemide to patients who have had hepatic encephalopathy. Concomitant use of an aldosterone antagonist or potassium-sparing drug is recommended to prevent hypokalaemia and metabolic alkalosis.

Close monitoring of patients with a tendency to hyperuricaemia and gout problems is recommended. Carbohydrate metabolism in patients with latent or manifest diabetes mellitus should be monitored. Especially at the start of treatment and in elderly patients, signs of electrolyte and volume deficiency and hemoconcentration should be carefully monitored.

Due to insufficient experience with torasemide therapy, caution should be exercised in:
- Pathological changes in the acid-base balance.
- Concomitant treatment with lithium, aminoglycosides or cephalosporins.
- Renal insufficiency due to nephrotoxic substances.
- Children under 12 years.

Lactose
<[Invented name]> tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on torasemide
Probenecid may reduce the effect of torasemide by inhibiting tubular secretion.

Concomitant treatment with cholestyramine may impair the efficacy and bioavailability of torasemide.

Non-steroidal anti-inflammatory/anti-rheumatic agents, NSAIDs (e.g. indomethacin) may reduce the diuretic and antihypertensive effect of torasemide, probably via inhibition of prostaglandin synthesis.

Effect of torasemide on other medicinal products
In patients with high salicylate intake, torasemide may cause salicylate poisoning by inhibiting renal salicylate excretion.

There are case reports of increased efficacy of warfarin and other coumarin-type anticoagulants during concomitant treatment with torasemide. Patients concomitantly treated with anticoagulants and torasemide should be closely monitored.

The effect of antihypertensive drugs, especially ACE inhibitors, can be potentiated with concomitant treatment. Subsequent or combination therapy, or initiation of new concomitant therapy with an ACE inhibitor, may cause severe hypotension. This can be minimized by lowering the starting dose of the ACE inhibitor and/or reducing or temporarily stopping the torasemide dose 2 or 3 days before treatment with the ACE inhibitor.

The effect of antidiabetic drugs may be reduced.

The ototoxic and nephrotoxic effects of aminoglycosides (e.g. gentamicin and tobramycin), cisplatin and cephalosporins may be potentiated by high dose torasemide therapy.

During concomitant cardiac glycoside therapy, hypokalaemia and/or magnesium deficiency may cause increased cardiac muscle sensitivity to these drugs.

Potassium excretion in the urine may increase during treatment with mineralocorticoids, glucocorticoids and laxatives.

Serum lithium concentrations and cardiac and neurotoxic effects of lithium may be increased.

The mechanisms of action of curare-containing muscle relaxants and theophylline can be potentiated.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no or limited amount of data from the use of torasemide in pregnant women. Thiazides, thiazide-related diuretics and loop diuretics can pass to the fetus and cause electrolyte disturbances. Cases of neonatal thrombocytopenia have been reported with thiazides and thiazide-related diuretics. This risk may also be present when using loop diuretics such as furosemide, torasemide and bumetanide.

During pregnancy, until further experience is available, torasemide should be given only after special consideration and in the lowest adequate dose.

Breast-feeding
There is no information on whether torasemide passes into breast milk. The risk to the breast-fed child cannot be ruled out. Loop diuretics may reduce lactation. Torasemide should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Individually varying reactions can impair the ability to react (e.g. patients' ability to drive and use machines). This happens especially at the beginning of the treatment or when the treatment is changed.

4.8 Undesirable effects

Summary of the safety profile
The overall frequency of side effects is about 8%. The most common adverse reactions are headaches, fatigue and dizziness.

Tabulated list of adverse reactions
Adverse reactions are listed below by system organ class and frequency. The frequencies are defined as:
common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
Immune system disorders	Not known	Severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis)
Metabolism and nutrition disorders	Uncommon	Hyperglycaemia, hypokalaemia, cholesterol increased, blood triglycerides increased
	Rare	Hyponatremia
Nervous system disorders	Common	Dizziness
	Rare	Paraesthesia of the extremities
	Not known	Cerebral ischemia, confusion
Ear and labyrinth disorders	Rare	Hearing loss, tinnitus
Cardiac disorders	Rare	Myocardial infarction, hypovolaemia, cardiac arrhythmia, angina pectoris

Vascular disorders	Not known	Embolism
Gastrointestinal disorders	Uncommon	Appetite lost, abdominal pain, vomiting, diarrhoea, constipation, nausea
Hepatobiliary disorders	Uncommon	Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Rare	Exanthema, photosensitivity, itching, urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps, muscle pain
Renal and urinary disorders	Uncommon	Urinary retention, bladder dilatation, hyperuricaemia
	Rare	Blood urea increased, blood creatinine increased
General disorders and administration site conditions	Common	Headache, fatigue
	Uncommon	Asthenia
	Rare	Dry mouth

Depending on the dose and duration of treatment, fluid and electrolyte imbalances may occur.

Metabolic alkalosis may be exacerbated.

Isolated cases of complications with thrombosis and circulatory disorders in the heart and central nervous system due to haemoconcentration (including cardiac and cerebral ischaemia) can occur and lead to, e.g. arrhythmia, angina, myocardial infarction or syncope.

Isolated cases of pancreatitis, erythropaenia and visual disturbances have been reported.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience with torasemide overdose.

Symptoms
Fluid and electrolyte disturbances, thirst, dehydration, metabolic alkalosis. Initial polyuria, in case of large fluid loss oliguria, anuria. Secondary to fluid and electrolyte losses are headaches, confusion, dizziness, paresthesias, muscle weakness, possible seizures and coma, orthostatic hypotension, syncope, ECG changes, arrhythmias. Nausea, vomiting, abdominal pain.

Management
If justified gastric lavage, activated charcoal. Rehydration, adjustment of electrolyte and acid balance. Continuous ECG monitoring in case of severe dehydration/electrolyte disturbance. Other symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diuretics; sulfonamides, plain.
ATC code: C03CA04

Mechanism of action
Torasemide, a sulphonylurea derivative, acts by inhibiting the absorption of sodium and chloride in the ascending part of the Henle loop. With diuresis, the excretion of potassium and magnesium increases. The diuretic effect occurs within 1 hour with maximum effect after 2-3 hours and lasts up to 12 hours. Maximum blood pressure lowering effect with repeated dosing is seen after up to 10-12 weeks.

Torasemide is a loop diuretic and with the dosage that is relevant for hypertension treatment has a weak diuretic and saluretic effect. The antihypertensive effect is not correlated with diuresis or electrolyte secretion.

The diuresis increases linearly with the dose.

5.2 Pharmacokinetic properties

Absorption
The bioavailability is 80-90%. Maximum serum concentration is reached after 1-2 hours.

Distribution
The volume of distribution is about 16 l.

Biotransformation
Torasemide is metabolised to three metabolites, of which the two hydroxymetabolites are diuretically active in humans. Torasemide itself accounts for about 80% of the diuretic effect.

Elimination
Total clearance is about 40 ml/min of which renal clearance is about 25%. Torasemide is approximately 99% bound to plasma proteins. The half-life is about 3 hours for oral administration.

About 80% of the dose is excreted as torasemide and metabolites by the kidneys by tubular secretion. In patients with heart failure or hepatic impairment, increased plasma concentrations have been noted, probably due to decreased metabolism in the liver. However, no accumulation occurs.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2.5 mg
18 months

5 mg, 10 mg, 20 mg

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu foil blisters.

Pack size
<[Invented name]> 10 mg tablets
14, 30 tablets

<[Invented name]> 2.5 mg, 5 mg, 20 mg tablets
14, 28, 30, 56, 60, 84, 90, 98, 112, 120, 150, 168, 180 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}
<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2023-09-12