

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Toraseamide 5 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains toraseamide 5 mg.

Each tablet contains 83.30 mg of lactose monohydrate

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablets.

White to off white, round tablets, with the imprint "T 5" and scoreline on one side and plain on other side.

Tablet dimension:  $6.50 \pm 0.20$  mm (6.30 to 6.70 mm)

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

### 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 toraseamide 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 toraseamide/day has been administered.

##### *Elderly*

No special dosage adjustments are necessary.

##### *Children*

There is no experience of torasemide in children.

### **4.3 Contraindications**

Renal failure with anuria; hepatic coma and pre-coma; hypotension; pre-existing hypovolaemia; pregnancy and lactation; hypersensitivity to torasemide and sulphonylureas; cardiac arrhythmias, simultaneous therapy with aminoglycosides or cephalosporins, or renal dysfunction due to drugs which cause renal damage.

### **4.4 Special warnings and precautions for use**

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

On long-term treatment with torasemide, regular monitoring of the electrolyte balance, glucose, uric acid, creatinine and lipids in the blood, is recommended.

Careful monitoring of patients with a tendency to hyperuricaemia and gout is recommended. Carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.

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

Patients with rare hereditary problems of glucose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medication.

#### ***Difficulty with micturition***

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

### **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 kaliuretic effect of mineralo- and glucocorticoids and laxatives may be increased.

As with other diuretics, the effect of antihypertensive drugs given concomitantly may be potentiated.

Torasemide, especially at high doses, may potentiate the toxicity of aminoglycoside antibiotics, cisplatin preparations, the nephrotoxic effects of cephalosporins, and the cardio- and neurotoxic effect of lithium. The action of curare-containing muscle relaxants and of theophylline can be potentiated. In patients receiving high doses of salicylates, salicylate toxicity may be increased. The action of anti-diabetic drugs may be reduced.

Sequential or combined treatment, or starting a new co-medication with an ACE inhibitor may result in transient hypotension. This may be minimised by lowering the starting dose of the ACE inhibitor and/or reducing or stopping temporarily the dose of torasemide. Torasemide may decrease arterial responsiveness to pressor agents e.g. adrenaline, noradrenaline.

Non-steroidal anti-inflammatory drugs (eg. Indometacin) and probenecid may reduce the diuretic and hypotensive effect of torasemide.

Concomitant use of torasemide and cholestyramine has not been studied in humans, but in an animal study co-administration of cholestyramine decreased absorption of oral torasemide.

#### **4.6 Fertility, pregnancy and lactation**

There are no data from experience in humans of the effect of torasemide on the embryo and foetus. Whilst studies in the rat have shown no teratogenic effect, malformed foetuses have been observed after high doses in pregnant rabbits. No studies have been conducted on excretion in breast milk. Consequently, torasemide is contra-indicated in pregnancy and lactation.

#### **4.7 Effects on ability to drive and use machines**

As for other drugs which produce changes in blood pressure, patients taking torasemide 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 ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$   $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from available data)

The following undesirable effects were observed whereas the frequency of undesirable effect is not known:

##### ***Blood and lymphatic system disorders***

Frequency not known: Thrombocytopenia, Leukopenia, Anaemia

##### ***Immune system disorders***

Very rare: Allergic skin reactions (eg Pruritus, Exanthema), Photosensitivity reaction

Frequency not known: Serious skin reactions (eg Stevens-Johnson syndrome, Toxic epidermal necrolysis)

##### ***Metabolism and nutrition disorders***

Common: Metabolic alkalosis, Fluid and electrolyte imbalance (eg 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

Frequency not 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***

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine..

## 4.9 Overdose

### *Symptoms and signs*

No typical picture of intoxication is known. 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. Symptoms and signs of overdosage require the reduction of the dose or withdrawal of torasemide, and simultaneous replacement of fluid and electrolytes.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

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.

Torasemide 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 1<sup>st</sup> 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, 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 drug at the site of action.

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 end-stage chronic renal failure there is a reduction of atrial blood pressure in addition to removal of edema and maintenance of residual diuresis.

### 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.

#### *Serum protein binding*

More than 99% of torasemide is bound to plasma proteins.

### ***Distribution***

The apparent distribution volume is 16 litres.

### ***Metabolism***

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.

### ***Elimination***

The terminal half-life of torasemide and its metabolites is three to four hours in healthy subjects. Total clearance of torasemide is 40ml/min and renal clearance about 10ml/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 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.

## **5.3 Preclinical safety data**

### ***Acute toxicity***

Very low toxicity.

### ***Chronic toxicity***

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.

### ***Teratogenicity***

Reproduction toxicology studies in the rat have shown no teratogenic effect, but malformed foetuses have been observed after high doses in pregnant rabbits. No effects on fertility have been seen.

Torasemide showed no mutagenic potential. Carcinogenicity studies in rats and mice showed no tumorigenic potential.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose monohydrate

Pregelatinised starch

Colloidal anhydrous silica

Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

30 months

**6.4 Special precautions for storage**

This medicinal product does not require any special storage condition.

**6.5 Nature and contents of container**

PVC/PVDC Clear Alu-blister pack, containing 10, 14, 28 and 100 tablets

PVC Clear Alu-Blister pack, containing 10, 14, 28 and 100 tablets

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Not applicable

**7 MARKETING AUTHORISATION HOLDER**

Medreich plc

Warwick House,

Plane Tree Crescent,

Feltham, TW13 7HF

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 21880/0303

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

19/12/2022

**10 DATE OF REVISION OF THE TEXT**

19/12/2022