SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metolazon Abcur 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg metolazone.

Excipients with known effect
Each tablet contains 53 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Round, biplanar, white to off-white tablet with bevelled edges and single break notch, tablet size 7 x 2.6 mm.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oedema of kidney diseases resistant to other therapy.

4.2 Posology and method of administration

Posology
Important note: Different metolazone products have different bioavailability. Therefore, the dose in mg can differ between products. Once the appropriate dose has been identified for a patient with a certain product (brand), the product cannot readily be exchanged with another product (see 5.2).

Adults
Metolazone should generally be administered once a day.

The tablet should always be taken at the same time in relation to food.

The following dosages should serve as guidelines: 2.5-10 mg/day.

The therapy should be commenced with an initial dose of 2.5 mg/day, and the dose must be adjusted according to the individual reaction of the patient. Once the desired therapeutic effect has been achieved, the dose of metolazone as maintenance treatment may be decreased.

Elderly
Metolazon Abcur should be used with caution in elderly patients, in patients with impaired renal or hepatic function and in patients with electrolyte disturbances.

Paediatric population
There is currently no experience from use of metolazone in patients under 16 years of age.

Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substance, sulfonamides, thiazides or to any of the excipients listed in section 6.1.
Anuria, hepatic coma or precomatose conditions.
Serious disturbances of the electrolyte balance.

4.4 Special warnings and precautions for use

Fluid and electrolyte balance should be carefully monitored during treatment with Metolazon Abcur, especially if the drug is used concurrently with other diuretics (risk of hypokalaemia), corticosteroids, ACE-inhibitors, angiotensin-II-antagonists and aldosteron-antagonists.

The risk of electrolyte disturbances increases at administration of high metolazone doses.

Hyponatraemia or hypochloraemia may occur. Hyponatraemia is accompanied by neurological symptoms (nausea, debility progressive disorientation, apathy). Cases of hypomagnesia have also been observed.

In rare cases (as may be the case also for other diuretics) serious hyponatraemia/hypokalaemia may occur immediately after the beginning of treatment.

An individually adjusted dosage of a concurrently administered oral potassium salt (e.g. potassium chloride) may be considered for patients receiving digitalis or showing signs of coronary heart disease, provided that they are not concurrently receiving an ACE inhibitor. An individually adjusted dosage may also be considered for patients who are being treated with a high dose beta adrenergic agonist, and in all cases when the potassium concentration in the serum is below 3.0 mmol/l.

In all cases of combined treatment, the maintenance or normalization of the potassium balance should be monitored closely. If hypokalaemia is accompanied by clinical signs of potassium shortage (for instance muscular weakness, paresis or ECG-alterations) the administration of Metolazon Abcur should be discontinued.

Monitoring of serum electrolytes is particularly advisable in the elderly, in patients with ascites due to liver cirrhosis, or in patients with oedema as a consequence of a nephrotic syndrome. For the latter condition, Metolazon Abcur should be used only under severe control in normokalaemic patients who show no signs of volume depletion or severe hypoalbuminaemia.

There have been cases with renal failure mostly in the context of dehydration, aggrevated by concomitant medication such as ACE-inhibitors, angiotension-II-antagonists, aldosterone-antagonists and/or NSAIDs, see section 4.5.

Concurrent treatment with lithium should be avoided.

Cross reactions may occur in patients who are allergic to sulfonamides or thiazides.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms

include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

Metabolic effects
Like other diuretics Metolazon Abcur may raise the serum uric acid level, which in rare instances may lead to acute attacks of gout.

In case the condition of a patient with kidney insufficiency, oliguria or azotaemia deteriorates, the treatment should be discontinued.

Metolazon Abcur has only a slight effect on the glucose exchange. In patients suffering from diabetes the anti diabetes treatment may have to be readjusted. In cases with latent diabetes, glycosuria and hyperglycemia may occur. The blood sugar level should therefore be checked on a regular basis. Although no corresponding observations have been made for Metolazon Abcur, related diuretics have been reported to cause an increase in the response to norepinephrine.

Insignificant and partly reversible increases in the plasma concentration of total cholesterol, triglycerides or LDL-cholesterol were observed during long term treatment with thiazide or thiazide-like diuretics. The clinical relevance of these observations is debatable.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free’.

Paediatric population
There is currently no experience from use of metolazone in patients under 16 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

It is unknown whether metolazone might affect the plasma concentrations of concomitantly administered medicinal products by inhibition or induction of metabolising enzymes such as cytochrome (CYP) P450. Therefore, caution is advised at concomitant administration of CYP450 substrates with narrow therapeutic index.

Although no corresponding observations have been made for metolazone, related diuretics have been reported to cause increased responsiveness to tubocurarin and decreased arterial responsiveness to norepinephrine. The dosage of Metolazon Abcur should therefore be carefully adjusted in patients who are to undergo surgery.

Due to the risk of hypotension, especially in the initial phase, at concurrent administration of metolazone and antihypertensives caution in the treatment is paramount. If necessary the dosage must be adjusted.

Orthostatic hypotension may occur during treatment with metolazone. It is enhanced by alcohol, barbiturates and narcotics.

Concurrent use of furosemide and presumably also of other loop diuretics may enhance the effect of metolazone considerably and lead to serious disturbances of the electrolyte balance.

In case of concurrent administration of digitalis drugs the dosage must be adjusted (see section 4.4.).

Hypokalaemia associated with thiazide therapy is believed to increase the risk of arrhythmia (syncope, prolonged QT interval) provoked by sotalol.

Corticosteroids and ACTH may increase the risk of hypokalaemia and may intensify the electrolyte and fluid retention.

NSAIDs may impair the effect of metolazone.

There are reports on deterioration of the kidney function in connection with concurrent administration of ACE inhibitors, angiotension-II-antagonists, aldosterone-antagonists and NSAIDs.

Metolazone may increase the level of lithium in serum (see section 4.4).

Metolazone may increase the blood sugar level, which in patients with diabetes mellitus or latent diabetes mellitus may lead to hyperglycaemia and glycosuria.

Concurrent administration of metolazone and cyclosporine may lead to an increase in serum creatinine.

It has been reported that concurrent use of metolazone and warfarin may lead to prolonged bleeding time.

The effect on concomitant food intake has not been studied (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
Thiazide diuretics and related diuretics may pass over to the foetus and cause electrolyte imbalance. Cases of neonatal thrombocytopenia have been reported. Therefore, metolazone must not be administered during the last trimester of pregnancy unless absolutely necessary, and then with the lowest recommended dose.

Breastfeeding
Metolazon passes over to the breast milk in such an amount that there is a risk for the child even at therapeutic doses. Inhibition of lactation has been observed in treatment with diuretics.

Fertility
There is currently no data available.

4.7 Effects on ability to drive and use machines

No studies have been performed.
However treatment with Metazolane Abcur may cause adverse reactions affecting the ability to drive a vehicle and/or to operate machines, such as tiredness and dizziness.

4.8 Undesirable effects

Within the system organ class, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: 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).

System organ class	Adverse reactions
Blood and lymphatic system disorders	
Uncommon:	Leukopenia
Rare:	Aplastic or hypoplastic anaemia, agranulocytosis, thrombocytopenia

Metabolism and nutrition disorders	
Common:	Hypokalaemia, hyponatraemia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glukosuria, increased S-urea and S-creatinin
Rare:	Hyperkalcemia, hypomagnesemia
Gastrointestinal disorders	
Common:	Nausea, vomiting, congestion, diarrhoea
Hepatobiliary disorders	
Rare:	Hepatitis, intrahepatic cholestasis
Skin and subcutaneous tissue disorders	
Uncommon:	Exanthema incl. urticaria, vasculitis
Rare:	Toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Common:	Muscle cramps
Uncommon:	Gout
Renal and urinary disorders	
Rare:	Renal insufficiency (due to dehydration)
General disorders and administration site conditions	
Common:	Headache, dizziness, fatigue

Patients with known allergy to sulfonamides and its derivatives may show allergic reactions.

Description of selected adverse reactions:
Cases of choroidal effusion with visual field defect, acute myopia and acute angle-closure glaucoma have been reported after the use of thiazide and thiazide-like diuretics.

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 professinals are asked to report any suspected adverse reactions via the national reporting system linsted in Appendix V*.

4.9 Overdose

Symptoms
Overdosing may lead to dehydration and electrolyte disturbances (primarily hyponatraemia, but also loss of potassium and magnesium), and as a consequence the patient may experience thirst, nausea, vomiting, disorientation, somnolence, headache, muscle cramps, arterial hypotension, and in severe cases dysrhythmia (hypokalaemia).

Treatment
Within the first hour of ingestion the absorption may be reduced by administration of medicinal charchoal (1 g/kg body weight). Thereafter priority should be given to establish adequate hydration and re-establishment of the electrolyte balance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain, ATC code: C03BA08

Mechanism of action
Metolazone obstructs the re-absorption of sodium in the ascending branch of the loop of Henle and in the proximal tubules, which leads to excretion of approximately equivalent amounts of sodium and chloride.

At the optimal therapeutic dosage metolazone leads to approximately the same diuretic activity as diuretics of the thiazide-type. However, it may also stimulate the diuresis in patients with a very low glomerular filtration rate (less than 20 ml/min).

The diuresis starts within the first hour after administration and will continue for 12-24 hours depending on the dose. The maximum effect will be achieved after approximately 2 hours.

5.2 Pharmacokinetic properties

Comparative bioavailability studies have shown that the bioavailability (AUC) might differ up to about 2-fold between different metolazone products. Therefore, once the appropriate dose has been identified for a patient with a certain product, this product cannot readily be exchanged with another product.

Absorption
Metolazone is rapidly absorbed in the digestive tract. The maximal plasma concentration is on average reached after 2 hours. The effect of concomitant food on metolazone bioavailability has not been evaluated. Therefore, to minimise variability for the individual patient, the tablet should always be taken at the same time in relation to food, e.g. always with breakfast.

Distribution
The apparent volume of distribution amounts to 113 litres; 95% of the substance will be bound to plasma proteins. Metolazone crosses the placental barrier and do also pass over to the breast milk.

Biotransformation
Metolazone is virtually not metabolized. The formed metabolites have proven to be non-toxic.

Elimination
70% of the absorbed dose is renally excreted as unchanged metolazone at a half life of 8-10 hours. Another 20% of the absorbed dose appears in urine as other drug-related material and the remaining amount appears in the faeces. In case of impaired kidney function the excretion is delayed, as the clearance of metolazone is directly related to renal function (creatinine clearance).

5.3 Preclinical safety data

No data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Microcrystalline cellulose
Lactose monohydrate
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister of PVC/PVDC/Al with 20, 28, 30, 50, 56, 60, 98 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special 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

To be completed nationally

10. DATE OF REVISION OF THE TEXT

2021-08-17