SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Metolazone Tablets USP (METOZ 5 and METOZ 2.5)

2. Qualitative and quantitative composition

METOZ 5: Each uncoated tablet contains 5 mg metolazone.

METOZ 2.5: Each uncoated tablet contains 2.5 mg metolazone.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral tablets.

METOZ 5: Light blue coloured, round, flat-faced, beveled-edged, uncoated tablets with break line on one side and "5" embossed on the other side.

METOZ 2.5: Light pink coloured, round, flat-faced, beveled-edged, uncoated tablets with break line on one side and "2.5" embossed on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Metoz is indicated for the treatment of oedema accompanying congestive heart failure and renal diseases, including the nephritic syndrome and states of diminished renal function.

Metoz is also indicated for the treatment of mild and moderate hypertension, alone or in combination with other antihypertensive drugs of different classes.

4.2 Posology and method of administration

Posology

Dosage of Metoz should be individualised according to the indication and patient response.

Usual single daily dosage schedules:

- Oedema of cardiac failure: Metoz 5 mg to 20 mg once daily. Therapy should be initiated with a dose of 2.5 mg/day and adjusted according to the individual response of the patient. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose if possible.
- Oedema of renal disease: Metoz 5 mg to 20 mg once daily.
- Mild to moderate essential hypertension: Metoz 2.5 mg to 5 mg once daily. The recommended initial dose in mild and moderate hypertension is 2.5 mg/day and the dose must be adjusted according to the individual response of the patient. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose.

Renal impairment

Metolazone should be used with caution in patients with severely impaired renal function. If azotaemia and oliguria deteriorate during treatment of patients with severe renal disease, metolazone should be discontinued.

Hepatic impairment

Metolazone should be used with caution in patients with severely impaired hepatic function.

Patients with electrolyte disturbances

Metolazone should be used with caution in patients with pre-existing electrolyte disturbances. Careful monitoring of the fluid and electrolyte balance is required.

Elderly

Metolazone should be used with caution in elderly patients.

Method of administration

For oral use.

4.3 Contraindications

Anuria, hepatic coma or precoma, severe disturbances of the electrolyte balance, and known allergy or hypersensitivity to metolazone, sulfonamides, thiazides, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Renal impairment

Metolazone should be used with caution in patients with severe renal impairment. Renal function should be regularly monitored during thiazide therapy.

Hepatic impairment

In severe hepatic impairment, hypokalaemia caused by diuretics can precipitate encephalopathy.

Electrolyte imbalance

Fluid and electrolyte balance should be carefully monitored during treatment with metolazone, especially if the drug is used concurrently with medicines also affecting electrolyte balance, such as other diuretics (risk of hypokalaemia), corticosteroids, ACE inhibitors, angiotensin-II antagonists and aldosterone antagonists.

All patients receiving metolazone should have serum electrolytes measured at regular intervals and be observed for clinical signs of fluid and/or electrolyte imbalance, namely hypokalaemia, hyponatraemia and hypochloraemic alkalosis. Serum and urine electrolyte measurements are particularly important when the patient is vomiting excessively, has severe diarrhoea, or is receiving parenteral fluids.

Warning signs of electrolyte imbalance, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

The risk of hypokalaemia is increased when larger metolazone doses are used, when diuresis is rapid, when severe liver disease is present, when corticosteroids are given concomitantly, when oral intake is inadequate, or when excess potassium is being lost extrarenally, such as with vomiting or diarrhoea. Hypokalaemia should be corrected by the addition of potassium-sparing diuretics, potassium supplements, or potassium-containing salt substitutes to the regimen. Hyperkalaemia may also occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended.

Hyponatraemia may occur at any time during long-term therapy and, on rare occasions, may be life-threatening. Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Primary adrenal insufficiency

Diuretics should be avoided for the treatment of hypertension if the patient has primary adrenal insufficiency, known as Addison's disease.

Concurrent treatment with other drugs

Special care is advised, especially during initial therapy, when metolazone is used with other antihypertensive drugs of a different class to avoid hypotension. Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates and opioids.

Particular caution is also required when metolazone is used in combination with ACE inhibitors, angiotensin-II antagonists, aldosterone antagonists and/or NSAIDs, since there have been cases of renal failure, mostly due to enhanced dehydration. Dose adjustments may be required.

Concomitant use of metolazone and furosemide may lead to unusually large or prolonged losses of fluid and electrolytes.

Gout attacks

Azotaemia and hyperuricaemia may occur during the administration of thiazide therapy. Infrequently, attacks of gout have been reported in persons with a history of gout.

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.

Lupus erythematosus

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus.

Porphyria

Although not reported with metolazone, thiazides have been associated with acute attacks of porphyria. Caution is required when metolazone is used in porphyric patients.

Glucose metabolism

Metolazone has only a slight effect on glucose metabolism. Metolazone may increase the blood sugar level, which in patients with diabetes mellitus or latent diabetes

mellitus may lead to hyperglycaemia and glycosuria. Therefore, blood sugar levels should be checked on a regular basis. In diabetic patients, the antidiabetic treatment may have to be adjusted.

Laboratory values

Although not reported with metolazone, thiazides and thiazide-like diuretics have been reported to adversely affect the plasma lipid profile by increasing VLDL or LDL-cholesterol and triglycerides. The clinical relevance of these observations is unclear.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal product/class	Interaction/precaution
Diuretics	Furosemide and probably other loop diuretics given concomitantly with metolazone can cause unusually large or prolonged losses of fluid and electrolytes.
Other antihypertensives	When Metoz Tablets are used with other antihypertensive drugs, dosage adjustments of the latter may be necessary.
Alcohol, barbiturates and narcotics	The hypotensive effects of these drugs may be potentiated by the volume contraction associated with metolazone therapy.
Digital glycosides	Diuretic-induced hypokalaemia can increase the sensitivity of the myocardium to digitalis. Serious arrhythmias can result.
Corticosteroids or ACTH	May increase the risk of hypokalaemia and increase salt and water retention.
Salicylates and other non-steroidal anti-inflammatory drugs	May decrease the antihypertensive effects of Metoz Tablets.
Curariform drugs	Diuretic-induced hypokalaemia may enhance the neuromuscular blocking effects of curariform drugs, such as tubocurarine. The most serious effect would be respiratory depression, which could progress to apnoea. Accordingly, it is advisable to discontinue metolazone tablets three days before elective surgery.
Cyclosporine	Concurrent administration of metolazone and cyclosporine may lead to an increase in serum creatinine.
Antidiabetic medicinal products (oral agents and insulins)	Dosage adjustment of the antidiabetic medicinal product may be required.
Antiarrhythmic drugs (e.g., sotalol)	Hypokalaemia associated with thiazide therapy may increase the risk of sotalol-induced arrhythmia, including syncope and prolonged QT interval.
Sympathomimetics	May decrease the antihypertensive effect of metolazone. Metolazone may decrease arterial responsiveness to norepinephrine, but this effect is not sufficient to preclude the effectiveness of the pressor agent for therapeutic use.
Antigout medicinal products	Dosage adjustments of antigout medicinal products may be necessary, as thiazide diuretics may raise the level of serum uric acid. An increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to

	allopurinol.
Calcium salts	Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium-sparing medicinal products such as vitamin D therapy must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.
Lithium	Concurrent use of lithium and thiazides may reduce lithium clearance, leading to intoxication.
Cross-reactivity with other drugs	Cross-reactions may occur in patients who are allergic to sulfonamides or thiazides.
Anticoagulants	Metolazone, as well as other thiazide-like diuretics, may affect the hypoprothrombinaemic response to anticoagulants; dosage adjustments may be necessary.
Methenamine	Efficacy may be decreased due to the urinary alkalising effect of metolazone.

4.6 Pregnancy and lactation

Pregnancy category B

Reproduction studies performed in mice, rabbits and rats treated during gestation at doses up to 50 mg/kg/day have revealed no evidence of harm to the fetus due to metolazone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Metoz tablets should be used during pregnancy only if clearly needed.

Nursing mothers

Metolazone appears in breast milk. Because of the potential for serious adverse reactions in nursing infants from metolazone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on the ability to drive and use machines

Metolazone may cause adverse reactions affecting the ability to drive a vehicle and/or to operate machines, such as dizziness and fatigue.

4.8 Undesirable effects

Within each System Organ Class, adverse reactions are listed under headings of frequency, 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); not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Uncommon	Leukopenia
	Rare	Aplastic or hypoplastic anaemia, agranulocytosis, thrombocytopenia
Immune system disorders	Rare	Allergic reactions, including anaphylactic reactions
Metabolism and nutrition disorders	Common	Hypokalaemia, hyponatraemia, hypomagnesaemia, hypochloraemia, hypochloraemic alkalosis,

		hyperuricaemia, hyperglycaemia, azotaemia, glycosuria, increased serum urea (BUN), and serum creatinine
	Rare	Hypercalcaemia, hypophosphataemia
Psychiatric disorders	Rare	Psychotic depression, confusion
Nervous system disorders	Common	Headache, dizziness, fatigue
	Rare	Neuropathy, vertigo, paraesthesia, lethargy, drowsiness, weakness, restlessness (sometimes resulting in insomnia), apathy, seizures, hepatic encephalopathy
Eye disorders	Rare	Transient blurred vision
Cardiac disorders	Rare	Tachycardia, chest pain, palpitation
Vascular disorders	Common	Hypotension, orthostatic hypotension
	Rare	Syncope, dehydration, haemoconcentration, venous thrombosis
Gastrointestinal disorders	Common	Nausea, vomiting, constipation, diarrhoea
	Rare	Abdominal pain, anorexia, abdominal bloating
Hepatobiliary disorders	Rare	Hepatitis, intrahepatic cholestasis, pancreatitis
Skin and subcutaneous tissue disorders	Uncommon	Exanthema including urticaria, vasculitis
	Rare	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), purpura, dermatitis (photosensitivity)
Musculoskeletal and connective tissue disorders	Common	Muscle pain, muscle cramps
	Uncommon	Joint pain, gout
Renal and urinary disorders	Rare	Renal insufficiency, oliguria
Reproductive system and breast disorders	Rare	Erectile dysfunction
General disorders and administration site conditions	Rare	Chills
Investigations	Rare	Increased LDL cholesterol, increased triglycerides

Description of selected adverse reactions

Cases of choroidal effusion with visual field defect 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to the

National Regulatory Authority via the PPB reporting portal, PvERS: https://pv.pharmacyboardkenya.org/

4.9 Overdose

There is no specific antidote available, but immediate evacuation of stomach contents is advised. Care should be taken when evacuating the gastric contents to prevent aspiration, especially in the stuporous or comatose patients. Supportive measures should be initiated as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain, ATC code: C03BA08.

Metolazone is a quinazoline diuretic with properties generally similar to the thiazide diuretics. The action of metolazone results from interference with the renal tubular mechanism of electrolyte reabsorption. Metolazone acts primarily to inhibit sodium reabsorption at the cortical diluting site and to a lesser extent in the proximal convoluted tubule. Sodium and chloride ions are excreted in approximately equivalent amounts. The increased delivery of sodium to the distal tubular exchange site results in increased potassium excretion. Metolazone does not inhibit carbonic anhydrase. A proximal action of metolazone has been shown in humans by increased excretion of phosphate and magnesium ions and by a markedly increased fractional excretion of sodium in patients with severely compromised glomerular filtration. This action has been demonstrated in animals by micropuncture studies.

The antihypertensive mechanism of action of metolazone is not fully understood but is presumed to be related to its saluretic and diuretic properties.

5.2 Pharmacokinetic properties

Peak blood levels are obtained within 2 to 4 hours of oral administration of metolazone with an elimination half-life of approximately 14 hours. Metolazone tablets have been shown to produce blood levels that are dose proportional between 0.5 mg and 2 mg. Steady-state blood levels are usually reached in 4 to 5 days.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose (Chemicel pH 102), Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, and Colour Lake of Indigo Carmine (Metoz 5) / Colour Lake of Ponceau 4R (Metoz 2.5).

6.2 Incompatibilities

None.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C and protect from light. Keep in a dry place.

6.5 Nature and contents of container

Alu-Alu blister pack of 3 x 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Marketing Authorisation Holder:

M/s. Centaur Pharmaceuticals Pvt. Ltd., Centaur House, Near Grand Hyatt, Shanti Nagar, Vakola, Santacruz (E), Mumbai-400 055, India.

Manufactured by:

Centaur Pharmaceuticals Pvt. Ltd., Plant-I, Plot No. 3, 5B & 2C, Tivim Industrial Estate, Karaswada, Mapusa, Goa-403526, India.

8. Marketing authorisation number(s)

H2008/19477/487/R1

9. Date of first authorisation/renewal of the authorisation

04.07.2009

10. Date of revision of the text

March 2026