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Zenomite 5mg Tablet

(M e t o l a z o n e)

زینومائٹ ۵ ملی گرام ٹیبلٹ

(میٹولازون)

COMPOSITION

Each film coated tablet contains:
Metolazone…….5mg
(USP Specifications)

DESCRIPTION

Zenomite tablet contains Metolazone as an active component. Metolazone is a quinazoline-sulfonamide that is considered a thiazide-like diuretic which is long-acting so useful in chronic renal failure. It also tends to lower blood pressure and increase potassium loss.

INDICATIONS

Metolazone is indicated for the treatment of

- Edema related to kidney diseases, including the nephrotic syndrome and states of impaired renal function.
- Oedema related to congestive heart failure.
- It is also indicated for the treatment of mild and moderate hypertension, alone or in combination with other antihypertensive medicines of a different class.

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 diuretic 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.

DOSAGE & ADMINISTRATION

Adults

Treatment of edema

Metolazone should generally be administered once daily. The tablet should always be taken at the same time in relation to food.
The following dosages should serve as guidelines:
edema related to congestive heart failure and kidney disease: 2.5-5 mg/day.
The therapy should be initiated with a 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, it may be advisable to reduce the maintenance dose if possible.

Hypertension

Mild and moderate hypertension: 2.5mg-5mg/day
The recommended initial dose in mild and moderate hypertension is 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, it may be advisable to reduce the maintenance dose.

Renal impairment

Metolazone should be used with caution in patients with severe impaired renal function. If azotemia 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 severe impaired hepatic
Function.

Patient with electrolyte disturbances

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

Elderly

Metolazone should be used with caution in elderly patients.

Pediatric population

The safety and efficacy of Metolazone in children aged under 18 years has not yet been established.

PHARMACOKINETICS

Absorption

Metolazone is rapidly absorbed in the digestive tract. The maximal plasma concentration is on average reached after 2 hours. The rate and extent of absorption are formulation dependent. The effect of concomitant food on the bioavailability of Metolazone has not been evaluated. In order, to minimize variability for the individual patient, the tablet should always be taken at the same time in relation to food.

Distribution

The apparent volume of distribution is estimated

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approximately 113 liters; 95 % of the substance is bound to red blood cells and to plasma proteins. Metolazone crosses the placenta and pass into breast milk.

Metabolism and Elimination

Metabolism of metolazone appears to be minimal. Most of the absorbed drug is excreted in urine, mainly unchanged. The elimination half-life of metolazone is reported to be 8-10 hours. In case of impaired kidney function, the excretion is delayed, as the clearance of metolazone is directly related to renal function (creatinine clearance).

WARNINGS & PRECAUTIONS

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, hyponatremia, hyperchloremic alkalosis. Serum and urine electrolyte measurements are particularly important when the patient is vomiting excessively, has severe diarrhea, 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 extra-renally such as with vomiting or diarrhea. Hypokalaemia should be corrected by the addition of potassium-sparing diuretics, potassium supplements or potassium containing salts substitutes to the regimen. Hyperkalemia 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.

Hyponatremia 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 hypercalcemia 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

Azotemia and hyperuricemia 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 ahistory of sulfonamide or penicillin allergy.

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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 the glucose metabolism. Metolazone may increase the blood sugar level, which in patients with diabetes mellitus or latent diabetes mellitus may lead to hyperglycemia 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 effect the plasma lipid profile by increasing VLDL or LDL-cholesterol and triglycerides. The clinical relevance of these observations is unclear.

Pregnancy
Thiazide diuretics and related diuretics may pass over to the fetus 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.

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

SIDE EFFECTS
Cardiovascular
Chest pain/discomfort, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitations.
Central And Peripheral Nervous System
Syncope, neuropathy, vertigo, paresthesias, psychotic depression, impotence, dizziness/lightheadedness, drowsiness, fatigue, weakness, restlessness (sometimes resulting in insomnia), headache.
Dermatologic/Hypersensitivity
Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome, necrotizing angiitis (cutaneous vasculitis), skin necrosis, purpura, petechiae, dermatitis (photosensitivity), urticaria, pruritus, skin rashes.
Gastrointestinal
Hepatitis, intrahepatic cholestatic jaundice, pancreatitis, vomiting, nausea, epigastric distress, diarrhea, constipation, anorexia, abdominal bloating, abdominal pain.
Hematologic
Aplastic/hypoplastic anemia, agranulocytosis, leukopenia, thrombocytopenia
Metabolic
Hypokalemia, hyponatremia, hyperuricemia, hypochloremia, hypochloremia alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia, hypomagnesemia, hypercalcemia.
Musculoskeletal
Joint pain, acute gouty attacks, muscle cramps or spasm.
Other
Transient blurred vision, chills, dry mouth.

DRUG INTERACTIONS
No formal interaction studies have been performed with Metolazone.
Loop Diuretics (e.g. furosemide)
Concurrent use of furosemide and presumably also of other loop diuretics may potentiate the effect of metolazone considerably and lead to serious disturbances of the electrolyte balance.
Curariform Drugs
Diuretic-induced hypokalemia may enhance neuromuscular blocking effects of curariform drugs (such as tubocurarine). The most serious effect would be respiratory depression which could proceed to apnea. 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.
Alcohol, barbiturates and narcotics
Alcohol, barbiturates and narcotics may potentiate orthostatic hypotension which may occur during treatment with metolazone.
Antidiabetic medicinal products (oral agents and insulins)
Dosage adjustment of the antidiabetic medicinal product may be required.
Corticosteroids and ACTH
Corticosteroids and ACTH may increase the risk of hypokalaemia and increase salt and water retention.
Cardiac Glycosides
Hypokalaemia may increase the risk of digitalis toxicity with higher risk of severe arrhythmias. In case of concurrent administration with digitalis drugs the dosage may need to be adjusted. Antiarrhythmic Drugs (e.g. Sotalol) Hypokalaemia associated with thiazide therapy may increase the

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risk of sotalol induced arrhythmia (syncope, prolonged QT interval).

Non-steroidal anti-inflammatory drugs (NSAIDs)
The administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics. As with other diuretics, metolazone may increase the risk of nephrotoxicity of NSAIDs and lead to deterioration of renal function.

Sympathomimetics
May decrease the antihypertensive effect of metolazone. Metolazone may decrease arterial responsiveness to norepinephrine, but this effect is not sufficient to preclude 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. 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 (e.g. 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.

Other antihypertensive drugs
Concomitant administration of Metolazone and other antihypertensive drugs may result in hypotension. Particular caution is required in the initial phase. Dosage adjustments of other antihypertensives may be necessary.

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 hypoprothrombinemic response to anticoagulants; dosage adjustments may be necessary.

Methenamine
Efficacy may be decreased due to urinary alkalizing effect of metolazone.

CONTRAINDICATIONS

- Hypersensitivity to the active substance, sulfonamides, thiazides or to any of the excipients.
- Anuria.
- Hepatic coma or pre comatose conditions.
- Severe disturbances of the electrolyte balance.

OVER DOSAGE

Symptoms: Overdosing may lead to dehydration and electrolyte disturbances (primarily hyponatremia, 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 (hypokalemia).

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

STORAGE & INSTRUCTIONS

Store below 30°C
Protect from heat, sunlight and moisture.
Keep away from the reach of the children.
To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

50 Tablets

خوراک وطریقہ استعمال:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت میں رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

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