Metoz®

Tablets

Composition:

Each tablet contain

Metolazone 2.5/5mg

Pharmacokinetic properties:

Metolazone is slowly and incompletely absorbed from the gastrointestinal tract. An average of about 65% of a dose has been reported to be absorbed after oral doses in healthy subjects, and an average of about 40% in patients with cardiac disease. In some countries a formulation with enhanced bioavailability is available. About 95% of the drug is bound in the circulation: about 50 to 70% to the red blood cells and between 15 and 33% to plasma proteins. The half-life has been reported to be 8 to 10 hours in whole blood, and 4 to 5 hours in plasma, but the diuretic effect persists for up to 24 hours or more. About 70 to 80% of the amount of Metolazone absorbed is excreted in the urine, of which 80 to 95% is excreted unchanged. The remainder is excreted in the bile and some enterohepatic circulation has been reported. Metolazone crosses the placenta and is distributed into breast milk.

Mechanism of Action:

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

Other pharmacodynamic properties:

Metolazone is a quinazoline diuretic, with properties generally similar to the thiazide diuretics. 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.

Indication:

- Meltor is indicated for the treatment of edema associated with congestive heart failure and renal disease.
- Meltor is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents

Contraindication:

The use of Metoz is contraindicated in patients with:

- Known hypersensitivity or allergy to Metolazone.
- Anuria, hepatic coma or pre coma.

Drug Interaction:

- 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, care must be taken, especially during initial therapy. Dosage adjustments of other antihypertensives may be necessary.
- Alcohol, Barbiturates, and Narcotics: The hypotensive effects of these drugs may be potentiated by the volume contraction that may be associated with metolazone therapy.
- Digitalis Glycosides: Diuretic-induced hypokalemia can increase the sensitivity of the myocardium to digitalis. Serious arrhythmias can result.
- Corticosteroids or ACTH: Nay increase the risk of hypokalemia and increase salt and water retention.
- Lithium: Serum lithium levels may increase.
- 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 may be advisable to discontinue metolazone tablets three days before elective surgery.
- Salicylates and Other Non-Steroidal Anti-Inflammatory Drugs: Nay decrease the antihypertensive effects of METOZ Tablets.
- Sympathomimetics: Metolazone may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

- Methenamine: Efficacy may be decreased due to urinary alkalizing effect of metolazone.
- Anticoagulants: Metolazone, as well as other thiazide-like diuretics, may affect the hypoprothrombinaemia response to anticoagulants; dosage adjustments may be necessary.

Adverse effects:

Metolazone is usually well tolerated, and most reported adverse reactions have been mild and transient. Many related adverse reactions represent extensions of its expected pharmacologic activity and can be attributed to either its antihypertensive action or its renal/metabolic actions. The following adverse reactions have been reported. Several are single or comparably rare occurrences. Adverse reactions are listed in decreasing order of severity within body systems.

Cardiovascular: Chest pain/discomfort, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitations.

Central and Peripheral Nervous System: Syncope, neuropathy, vertigo, paraesthesia, psychotic depression, impotence, dizziness/light headedness, drowsiness, fatigue, weakness, restlessness (sometimes resulting in insomnia), and headache.

Dermatologic/Hypersensitivity: Toxic epidermal necrolysis (TEN), Steven-Johnson Syndrome necrotizing angiitis (cutaneous vasculitis), purpurea, dermatitis (photosensitivity), urticaria, skin rashes.

Gastrointestinal: Hepatitis, intrahepatic cholestatic jaundice, pancreatitis, vomiting, nausea, epigastric distress, diarrhea, constipation, anorexia, abdominal bloating.

Hematologic: Aplastic/hypoplastic anemia, agranulocytosis, leukopenia, thrombocytopenia.

Metabolic: Hypokalemia, hyponatremia, hyperuricemia, hypochloraemia, hypochloraemia alkalosis, hyperglycaemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia, hypomagnesaemia, hypercalcemia.

Musculoskeletal: Joint pain, acute gouty attacks, muscle cramps or spasm.

Other: Transient blurred vision, chills, and dries mouth.

In addition, adverse reactions reported with similar antihypertensive-diuretics, but which have not been reported to date for metolazone include: bitter taste, sialaadenitis, xanthopsia, respiratory distress (including pneumonitis), and anaphylactic reactions. These reactions should be considered as possible occurrences with clinical usage of METOZ.

Whenever adverse reactions are moderate or severe, NETOZ dosage should be reduced or therapy withdrawn.

Overdosage

Intentional overdosage has been reported rarely with metolazone and similar diuretic drugs.

Signs and Symptoms: Orthostatic hypotension, dizziness, drowsiness, syncope, electrolyte abnormalities, hemoconcentration and hemodynamic changes due to plasma volume depletion may occur. In some instances depressed respiration may be observed. At high doses, lethargy of varying degree may progress to coma within a few hours. The mechanism of CNS depression with thiazide overdosage is unknown. Also, GI irritation and hypermotility may occur. Temporary elevation of BUN has been reported, especially in patients with impairment of renal function. Serum electrolyte changes and cardiovascular and renal function should be closely monitored.

Treatment: There is no specific antidote available but immediate evacuation of stomach contents is advised. Dialysis is not likely to be effective. Care should be taken when evacuating the gastric contents to prevent aspiration, especially in the stuporous or comatose patient. Supportive measures should be initiated as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

Warnings and Precautions:

- Rapid Onset Hyponatremia and/or Hypokalemia: Rarely, the rapid onset of severe hyponatremia and/or hypokalemia has been reported following initial doses of thiazide and non-thiazide diuretics. When symptoms consistent with severe electrolyte imbalance appear rapidly, drug should be discontinued and supportive measures should be initiated immediately. Parenteral electrolytes may be required. Appropriateness of therapy with this class of drugs should be carefully re-evaluated.
- Hypokalemia: Hypokalemia may occur with consequent weakness, cramps, and cardiac dysrhythmias. Serum potassium should be determined at regular and appropriate intervals, and dose reduction, potassium supplementation or addition of a potassium-sparing diuretic instituted whenever indicated. Hypokalemia is a particular hazard in patients who are digitalized or who have or have had a ventricular arrhythmia; dangerous or fatal arrhythmias may be precipitated. Hypokalemia is dose related.
- Concomitant Therapy:

Lithium: In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity.

Furosemide: Unusually large or prolonged losses of fluids and electrolytes may result when METOZ is administered concomitantly to patients receiving furosemide.

Other Antihypertensive Drugs: When METOZ is used with other antihypertensive drugs, particular care must be taken to avoid excessive reduction of blood pressure, especially during initial therapy.

Cross-Allergy: Cross-allergy, while not reported to date, theoretically may occur when METOZ is given to patients Known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

Sensitivity Reactions: Sensitivity reactions (e.g., angioedema, bronchospasm) may occur with or without a history of allergy or bronchial asthma and may occur with the first dose of METOZ.

- Precautions

General: Fluid and Electrolytes: All patients receiving therapy with METOZ Tablets should have serum electrolyte measurements done at appropriate intervals and be observed for clinical signs of fluid and/or electrolyte imbalance: namely, hyponatremia, hypochloraemia alkalosis, and hypokalemia. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced, especially with hot weather and a low-salt diet.

Serum and urine electrolyte determinations are particularly important when the patient has protracted vomiting, severe diarrhea, or is receiving parenteral fluids.

Warning signs of imbalance are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyponatremia may occur at any time during long-term therapy and, on rare occasions, may be life threatening.

The risk of hypokalemia is increased when larger 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 diarrhea.

Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesaemia

Glucose Tolerance: Metolazone may raise blood glucose concentrations possibly causing hyperglycaemia and glycosuria in patients with diabetes or latent diabetes.

Hyperuricemia: Metolazone regularly causes an increase in serum uric acid and can occasionally precipitate gouty attacks even in patients without a prior history of them.

Azotemia: Azotemia, presumably prerenal azotemia, may be precipitated during the administration of metolazone. If azotemia and oliguria worsen during treatment of patients with severe renal disease, METOZ should be discontinued.

Renal Impairment: Use caution when administering metolazone to patients with severely impaired renal function. As most of the drug is excreted by the renal route, accumulation may occur.

Orthostatic Hypotension: Orthostatic hypotension may occur; this may be potentiated by alcohol, barbiturates, narcotics, or concurrent therapy with other antihypertensive drugs.

Hypercalcemia: Hypercalcemia may infrequently occur with metolazone, especially in patients taking high doses of vitamin D or with high bone turnover states, and may signify hidden hyperparathyroidism. metolazone should be discontinued before tests for parathyroid function are performed.

Systemic Lupus Erythematosus: Thiazide diuretics have exacerbated or activated systemic lupus erythematosus and this possibility should be considered with NETOZ Tablets.

Information for Patients: Patients should be informed of possible adverse effects, advised to take the medication as directed, and promptly report any possible adverse reactions to the treating physician

Use in special population:

1. **Pediatric:** Safety and effectiveness in pediatric patients have not been established in controlled clinical trials.
2. **Geriatric:** Appropriate studies performed to date have not demonstrated geriatrics-specific problems that would limit the usefulness of metolazone in the elderly. However, elderly patients are more likely to have age-related kidney, liver, or heart problems, which may require an adjustment in the dose for patients receiving metolazone .
3. **Liver impairment:** Use with caution.
4. **Renal failure:** Use with caution.
5. **Pregnancy and lactation:** Pregnancy Category B. NETOZ Tablets should be used during pregnancy only if clearly needed. Metolazone crosses the placental barrier and appears in cord blood. 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.

Dosage:

As directed by physician.

Presentation:

METOZ Tablets (metolazone tablets, USP) are available in two strengths: 2.5 mg and 5 mg in a strip of 10 tablets.

Storage and handling:

Store at 25°C. Protect from light. Keep out of the reach of children.