

PRODUCT MONOGRAPH

**ZAROXOLYN®
(Metolazone)**

2.5 mg Tablets

Diuretic/Antihypertensive

sanofi-aventis Canada Inc.
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NAME OF DRUG

ZAROXOLYN®
(Metolazone Tablets, USP)

2.5 mg tablets

THERAPEUTIC CLASSIFICATION

Diuretic/Antihypertensive

ACTIONS AND CLINICAL PHARMACOLOGY

ZAROXOLYN (metolazone) is a diuretic antihypertensive drug for the treatment of edema.

ZAROXOLYN is a quinazoline diuretic, with properties generally similar to the thiazide diuretics. The actions of ZAROXOLYN result from interference with the renal tubular mechanism of electrolyte reabsorption. ZAROXOLYN 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.

ZAROXOLYN does not inhibit carbonic anhydrase. A proximal action 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.

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

Pharmacokinetics: Metolazone is absorbed rapidly; however, rate and extent of absorption is dependent on the formulation. The table below shows that bioavailability of ZAROXOLYN is different from MYKROX (another product containing metolazone):

Pharmacokinetic Variables of Metolazone*

| Formulation | 0-48hr AUC ng.hr/mL | 0-∞ AUC ng.hr/mL | C _{MAX} ng/mL | T _{MAX} hr |
|------------------------|------------------------|---------------------|---------------------------|------------------------|
| Metolazone soln 2.5 mg | 230.59 (61.96) | 235.4 (61.50) | 37.50 (9.91) | 1.25 (0.44) |
| Mykrox 2.5 mg | 199.40 (36.38) | 209.4 (41.00) | 18.75 (2.58) | 3.17 (1.03) |
| Zaroxolyn 2.5 mg | 99.74 (28.97) | 127.0 (37.08) | 3.63 (0.87) | 7.67 (6.65) |

* Values presented are means (±SD)

Clinical studies have shown that ninety to nine-five percent of metolazone is bound to red blood cells and plasma protein. The prolonged duration of action of metolazone is attributed to its protein binding and allows for once a day dosing. Only a small amount of metolazone is metabolized. Most of the drug is excreted in the unconverted form in the urine.

When ZAROXOLYN (metolazone) is given, diuresis and saluresis usually begin within one hour and persist for 24 hours depending on the dose. The effect may be prolonged beyond 24 hours particularly at the higher recommended dosages.

INDICATIONS AND CLINICAL USE

ZAROXOLYN (metolazone) is indicated for the treatment of edema accompanying congestive heart failure and edema accompanying renal diseases including the nephrotic syndrome, and states of diminished renal function. ZAROXOLYN (2.5 mg) has also been used in the management of mild to moderate essential hypertension, alone or in combination with other antihypertensive drugs of a different class.

CONTRAINDICATIONS

ZAROXOLYN (metolazone) is contraindicated in anuria, in hepatic coma or pre-coma, and in cases of known allergy and hypersensitivity to metolazone.

WARNINGS

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, the drug should be discontinued and supportive measures should be initiated immediately. The appropriateness of therapy with this class of drug should be carefully re-evaluated.

Hypokalemia may occur, with consequent weakness, cramps, and cardiac arrhythmias. Hypokalemia is a particular hazard in digitalized patients or those who have had or have a ventricular arrhythmia; dangerous or fatal arrhythmias may be precipitated. Serum potassium should be determined at regular intervals, and dose reduction, potassium supplementation or addition of a potassium sparing diuretic instituted if indicated. Hypokalemia is dose related. (See PRECAUTIONS).

Azotemia and hyperuricemia may be noted or precipitated during the administration of ZAROXOLYN (metolazone). Infrequently, gouty attacks have been reported in persons with a history of gout. If azotemia and oliguria worsen during treatment of patients with severe renal disease, metolazone should be discontinued.

Unusually large or prolonged losses of fluid and electrolytes may result when metolazone is administered concomitantly to patients receiving furosemide.

Particular care must be taken, especially during initial therapy, when metolazone is used with other antihypertensive drugs of a different class to avoid excessive reduction in blood pressure. (See PRECAUTIONS, Drug Interactions).

PRECAUTIONS

All patients receiving metolazone should have serum electrolytes measured at appropriate intervals and be observed for clinical signs of fluid and/or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively, has severe diarrhea, or is receiving parenteral fluids.

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 of potassium is inadequate or when excess potassium is being lost extrarenally; such as with vomiting or diarrhea.

Hyponatremia may occur at any time during long term therapy and, on rare occasions, may be life threatening (See WARNINGS).

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.

Use of diuretics similar to metolazone have been associated, on rare occasions, with pathologic changes in the parathyroid glands. This possibility should be kept in mind with clinical use of metolazone. Hypercalcemia has been noted in a few patients.

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

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

Special caution should be used in treating patients with severe hepatic disease since metolazone may induce metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy. (See CONTRAINDICATIONS).

Caution should be observed when administering metolazone to patients with severely impaired renal function. As most of the drug is excreted by the renal route, cumulative effects may be seen. (See CONTRAINDICATIONS).

Metolazone may raise blood glucose concentrations, possibly causing hyperglycemia and glycosuria in patients with diabetes or latent diabetes.

Laboratory Tests: Periodic determination of serum electrolytes; blood urea nitrogen; uric acid, and glucose levels should be assessed at appropriate intervals during metolazone therapy. (See WARNINGS).

Drug Interactions:

Alcohol, barbiturates, or narcotics: See PRECAUTIONS.

Antihypertensives: See WARNINGS and PRECAUTIONS. When metolazone is used with other antihypertensive drugs, particular care must be taken, especially during initial therapy. Dosage of other antihypertensive agents, especially the ganglionic blockers and guanethidine, should be reduced. Hydralazine in therapeutic doses may interfere with the natriuretic action of metolazone.

Corticosteroids or ACTH Therapy: May increase the risk of hypokalemia and increase salt and water retention.

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.

Digitalis: See WARNINGS.

Drugs Used to Treat Gout: See WARNINGS. Dosage adjustment of the gout medication may be necessary to control hyperuricemia and gout.

Furosemide and Other Loop Diuretics: See WARNINGS. Unusually large or prolonged losses of fluids and electrolytes may result.

Insulin and Oral Antidiabetic Agents: Adjustment of dosage may be necessary. See PRECAUTIONS.

Lithium: See WARNINGS.

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

Salicylates and Other Nonsteroidal Anti-inflammatory Agents: May antagonize natriuretic, diuretic and antihypertensive effects of metolazone. Patients should be monitored carefully.

Sympathomimetics: May decrease the antihypertensive effect of metolazone. Metolazone may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Use in Pregnancy: Since metolazone crosses the placenta and appears in cord blood, its administration to women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. The potential effects on the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. However, teratogenic studies in mice, rats and rabbits, have not shown teratologic effects in these animals.

Nursing Mothers: Metolazone appears in breast milk. Thus, it is possible that the effects of metolazone may occur in the newborn under these circumstances. If the use of metolazone is deemed essential for a nursing mother, the patient should stop nursing.

Use in Children: Safety and effectiveness in children have not been established; therefore, metolazone is not recommended for use in the pediatric age group.

ADVERSE REACTIONS

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, paresthesias, psychotic depression, impotence, dizziness/lightheadedness, drowsiness, fatigue, weakness, restlessness, sometimes resulting in insomnia), headache.

Dermatologic/Hypersensitivity: Necrotizing angitis (cutaneous vasculitis), purpura, dermatitis (photosensitivity), urticaria and skin rashes.

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

Hematologic: Aplastic/hypolastic anemia, agranulocytosis, leukopenia.

Metabolic: Hypokalemia, hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia (See WARNINGS and PRECAUTIONS).

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

Other: Transient blurred vision, chills.

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms: Orthostatic hypotension, dizziness, drowsiness, syncope, diuresis with accompanying 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 appear and may progress to coma within a few hours. Also, GI irritation and hypermotility may occur. Temporary elevation of BUN has been reported, especially in patients with impairment of renal function.

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

Serum electrolyte change, and cardiovascular and renal functions, should be closely monitored.

DOSAGE AND ADMINISTRATION

Effective dosage of ZAROXOLYN (metolazone) should be individualized according to indications and patient response. A single daily dose is recommended. Therapy with ZAROXOLYN should be titrated to gain an initial therapeutic response and to determine the minimal dose possible to maintain the desired therapeutic response.

Usual Dosages:

Edema

Edema of cardiac failure: ZAROXOLYN 5-10 mg, once daily
Edema of renal disease: ZAROXOLYN 5-20 mg, once daily

Treatment of Edematous States: The time interval for the initial dosage to show effect may vary; diuresis and saluresis usually begin within one hour and persist for 12 to 24 hours, depending on dosage. When a desired therapeutic effect has been obtained, it may be advisable to reduce the dose, if possible. The daily dose depends on the severity of the patient's condition, sodium intake and responsiveness. A decision to change the daily dose should be based upon the results of thorough clinical and laboratory determinations. If antihypertensive drugs or diuretics are given concurrently with ZAROXOLYN, more careful dosage adjustment may be necessary. For patients with congestive cardiac failure who tend to experience paroxysmal nocturnal dyspnea, it is usually advisable to employ a dosage near the upper end of the range to ensure prolongation of diuresis and saluresis for a full 24-hour period.

Hypertension:

Mild to moderate essential hypertension: ZAROXOLYN 2.5 - 5 mg , once daily.

Treatment of Hypertension:

The time interval required for the initial dosage regimen of ZAROXOLYN to show effect may vary from three to four days, to three to six weeks, in the treatment of elevated blood pressure. Doses should be adjusted at appropriate intervals to achieve maximum therapeutic effect.

PHARMACEUTICAL INFORMATION

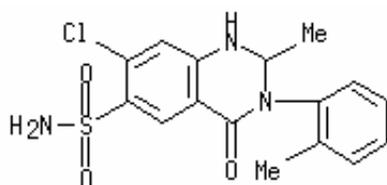
CHEMISTRY

Trade Name: ZAROXOLYN

Proper Name: metolazone

Chemical name: 7-chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide

Structural Formula:



Molecular Formula: C₁₆H₁₆ClN₃O₃S

Molecular Weight: 365.83

Description: white crystalline powder

Solubility:
in water (gm/mL): 2.4 x 10⁻⁵, 25 °C
in 95% ethanol (gm/mL): 9 x 10⁻³, 25 °C
in serum (gm/mL): 4.2 x 10⁻⁵, 37 °C

pKa: 9.7

Melting Point: 253 - 259 °C

Composition: ZAROXOLYN 2.5 mg tablets contain 2.5 mg of the active ingredient metolazone.

Stability and Storage Recommendations:

ZAROXOLYN (metolazone) should be stored at room temperature and protected from light. ZAROXOLYN should be dispensed in tight, light-resistant containers.

DOSAGE FORMS:

ZAROXOLYN (metolazone) 2.5 mg is available as a pink, slightly biconvex tablet, debossed with its numeric strength on one side and "ZAROXOLYN" on the other and contains 2.5 mg metolazone. The tablets are available in high density polyethylene bottles of 100 tablets.

Non-medicinal ingredients: D&C Red #33 aluminum lake, magnesium stearate and microcrystalline cellulose. Alcohol-, gluten-, lactose-, paraben-, sucrose- and tartrazine- free.

PHARMACOLOGY

Animal Pharmacodynamics:

The dominant pharmacologic actions of metolazone in animals are saluresis and diuresis. These effects have been demonstrated in rats and dogs and indicate an interference with the renal tubular mechanism of electrolyte reabsorption. The pattern of water and electrolyte excretion appears to be similar to that of some thiazides. Studies with desoxycorticosterone acetate saline-induced hypertension in rats have also demonstrated metolazone to be an effective antihypertensive agent; hypertension was reduced by metolazone, as well as inhibited by pretreatment with the drug.

Renal Effects:

Metolazone interferes with the renal tubular mechanism of electrolyte reabsorption and acts primarily to inhibit sodium reabsorption at the cortical diluting site of the distal segment and in the proximal convoluted tubule. Sodium and chloride ions are excreted in approximately equivalent amounts. Metolazone may also evoke a significant increase of potassium excretion in an amount sufficient to produce hypokalemia. With inhibition of sodium reabsorption, a higher concentration of this cation reaches the distal segment of the nephron and provides a more favorable milieu for the exchange process.

Metolazone produces a decrease in free water clearance in man and animals. Following intravenous administration of metolazone in doses up to 1 mg/kg, in hydrated dogs, free water clearance decreased, solute-free water reabsorption increased markedly, while the clearance of creatinine and PAH did not change significantly. Free water clearance is a function of sodium reabsorption in the cortical segment of the ascending Loop of Henle or early distal convoluted tubule. In most of the clinical studies, free water clearance diminished although urine flow increased, establishing a distal tubular site of action for metolazone.

In addition to this primary site of action in the cortical diluting segment, micropuncture and simultaneous clearance studies in dogs indicate a second site of action in the proximal tubule. In humans, a proximal site of action is inferred from measurements of excreted magnesium, phosphate and bicarbonate in the urine of hydrated and hydropenic subjects, from markedly increased fractional excretion of sodium and from increased excretion of phosphate and magnesium ions in patients with severely compromised glomerular filtration rate.

Metolazone possesses some carbonic anhydrase inhibitory action, and probably has a very slight action on bicarbonate transport by the kidney. The inhibition occurs *in vitro* only at high concentrations and, therefore, would appear to play little, if any, part in the diuretic action of the drug. The renal effects of the drug are virtually independent of alterations in acid-base balance. Dogs made acidotic or alkalotic by oral administration of ammonium chloride or sodium bicarbonate respectively, responded to intravenous administration of metolazone. Urinary sodium, potassium and chloride excretion are increased.

Metolazone does not significantly decrease the glomerular filtration rate in man, although in animals the effect is variable under different experimental conditions.

The drug exerted its natriuretic and diuretic effects on both normal and adrenalectomized rats. Its action, therefore, does not depend on aldosterone inhibition.

Pharmacokinetics:

Studies in several species of animals indicate that metolazone is readily absorbed with an onset of diuretic effect within one (1) hour. Absorption is dose related up to levels of 50 mg/kg orally; the maximum effect is attained within 3-6 hours of oral administration.

Within 48 hours of an oral dose, 95% of the administered dose of metolazone is eliminated in the urine and feces of rats, dogs and monkeys. An average of 50% is eliminated unchanged.

Rat studies have shown metolazone to be distributed mainly in the soft tissue with little, if any, in the nerves, brain, bones or eyes. Metolazone passes readily through the placental barrier to the fetus and is found in the milk of lactating animals.

TOXICOLOGY

Acute Toxicology:

A single oral dose of 10 gm/kg was not lethal in rats, and a single intraperitoneal dose of 5 gm/kg was not lethal in mice. Acute effects in susceptible animals include electrolyte imbalance.

Administration of single high doses (100 to 200 mg/kg) of metolazone intraperitoneally to rats caused a hyperglycemic effect, a decrease in liver glycogen, and an increase in plasma-free fatty acids. Adrenalectomy, nephrectomy, or pretreatment with α - and β -adrenergic blocking agents reduced this hyperglycemia significantly, suggesting that an adrenergic mechanism (possibly stress), as well as a renal mechanism, were involved.

Chronic Toxicity:

Daily doses up to 50 mg/kg given orally for one year did not produce noticeable toxic effects in rats, dogs, or monkeys. Mild hypokalemia and slight elevation of blood urea nitrogen occurred in some of the dogs. In the majority of these cases, the abnormal value returned to near normal before the study ended and while the animals were still under treatment.

Carcinogenicity:

Long-term animal studies with metolazone have not shown any evidence of carcinogenicity. Mice and rats given the drug for 18 months to 2 years at doses of 2, 10 and 50 mg/kg by stomach tube, showed no evidence that metolazone caused an increased number of tumors; however, the small number of animals examined histologically, and poor survival in the mice, limit conclusions that can be reached from these studies.

Mutagenicity:

A mutagenicity study using *Salmonella typhimurium* strains TA1535, TA97, TA98, TA100, and TA102 as indicator organisms and concentrations of 100 to 10,000 mcg/plate of metolazone showed no evidence of mutagenic potential.

Reproduction & Teratology:

Teratologic studies and studies of reproductive performance in mice, rats and rabbits (including a three-generation study with rats) treated with oral doses ranging from 0.2 to 50 mg/kg showed no evidence of teratologic effects. Reproductive studies in mice and rats have shown no evidence of altered reproductive capacity in mice; however, in a rat study in which males were treated orally with metolazone at doses of 2, 10 and 50 mg/kg for 127 days prior to mating with untreated females, an increased number of resorption sites were observed in dams mated with males from the 50 mg/kg group. In addition, the fetal weight was decreased and the pregnancy rate was reduced in dams mated with males from the 10 and 50 mg/kg group.

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