MYKROX TABLETS- metolazone tablets tablet
Celltech Pharmaceuticals, Inc.

Mykrox® Tablets

(metolazone tablets, USP)

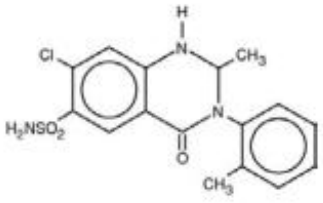
DO NOT INTERCHANGE:

MYKROX TABLETS ARE A RAPIDLY AVAILABLE FORMULATION OF METOLAZONE FOR ORAL ADMINISTRATION. MYKROX TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS MORE RAPID AND COMPLETE BIOAVAILABILITY ARE NOT THERAPEUTICALLY EQUIVALENT TO ZAROXOLYN® TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY. FORMULATIONS BIOEQUIVALENT TO MYKROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.

DESCRIPTION

MYKROX Tablets (metolazone tablets, USP) for oral administration contain ½ mg of metolazone, USP, a diuretic/saluretic/antihypertensive drug of the quinazoline class.

Metolazone has the molecular formula $C_{16}H_{16}ClN_3O_3S$, the chemical name 7-chloro-1, 2, 3, 4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide, and a molecular weight of 365.83. The structural formula is:



Metolazone is only sparingly soluble in water, but more soluble in plasma, blood, alkali, and organic solvents.

Inactive Ingredients: Dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate.

CLINICAL PHARMACOLOGY

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

In two double-blind, controlled clinical trials of MYKROX Tablets, the maximum effect on mean blood pressure was achieved within 2 weeks of treatment and showed some evidence of an increased response at 1 mg compared to ½ mg. There was no indication of an increased response with 2 mg.

After six weeks of treatment, the mean fall in serum potassium was 0.42 mEq/L at ½ mg, 0.66 mEq/L at 1 mg, and 0.7 mEq/L at 2 mg. Serum uric acid increased by 1.1 to 1.4 mg/dL at increasing doses. There were small falls in serum sodium and chloride and a 1.3-2.1 mg/dL increase in BUN at increasing doses.

The rate and extent of absorption of metolazone from MYKROX Tablets were equivalent to those from an oral solution of metolazone. Peak blood levels are obtained within 2 to 4 hours of oral administration with an elimination half-life of approximately 14 hours. MYKROX Tablets have been shown to produce blood levels that are dose proportional between ½ -2 mg. Steady state blood levels are usually reached in 4-5 days.

In contrast, other formulations of metolazone produce peak blood concentrations approximately 8 hours following oral administration; absorption continues for an additional 12 hours.

INDICATIONS AND USAGE

MYKROX Tablets are indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs of a different class.

MYKROX TABLETS HAVE NOT BEEN EVALUATED FOR THE TREATMENT OF CONGESTIVE HEART FAILURE OR FLUID RETENTION DUE TO RENAL OR HEPATIC DISEASE AND THE CORRECT DOSAGE FOR THESE CONDITIONS AND OTHER EDEMA STATES HAS NOT BEEN ESTABLISHED.

SINCE A SAFE AND EFFECTIVE DIURETIC DOSE HAS NOT BEEN ESTABLISHED, MYKROX TABLETS SHOULD NOT BE USED WHEN DIURESIS IS DESIRED.

Usage in Pregnancy

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no evidence that they are useful in the treatment of developed toxemia (see PRECAUTIONS).

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. MYKROX is not indicated for the treatment of edema in pregnancy. Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may be appropriate.

CONTRAINDICATIONS

Anuria, hepatic coma or precoma, known allergy or hypersensitivity to metolazone.

WARNINGS

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 reevaluated.

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.

In controlled clinical trials, 1.5% of patients taking ½ mg and 3.1% of patients taking 1 mg of MYKROX daily developed clinical hypokalemia (defined as hypokalemia accompanied by signs or symptoms); 21% of the patients taking ½ mg and 30% of the patients taking 1 mg of MYKROX daily developed hypokalemia (defined as a serum potassium concentration below 3.5 mEq/L); in another controlled clinical trial in which the patients started therapy with a serum potassium level greater than 4.0 mEq/L, 8% of patients taking ½ mg of MYKROX daily developed hypokalemia (defined as a serum potassium concentration below 3.5 mEq/L).

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. Read prescribing information for lithium preparations before use of such concomitant therapy.

Furosemide

Unusually large or prolonged losses of fluids and electrolytes may result when metolazone is administered concomitantly to patients receiving furosemide (see PRECAUTIONS, Drug Interactions).

Other Antihypertensive Drugs

When MYKROX Tablets are 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 may occur when MYKROX Tablets are 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 MYKROX.

PRECAUTIONS

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General

Fluid and Electrolytes

All patients receiving therapy with MYKROX Tablets should have serum electrolyte measurements done at appropriate intervals and be observed for clinical signs of fluid and/or electrolyte imbalance: namely, hyponatremia, hypochloremic 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 hypomagnesemia.

Glucose Tolerance

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

Hyperuricemia

MYKROX 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 MYKROX Tablets. If azotemia and oliguria worsen during treatment of patients with severe renal disease, MYKROX Tablets should be discontinued.

Renal Impairment

Use caution when administering MYKROX Tablets 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. In controlled clinical trials, 1.4% of patients treated with MYKROX Tablets (½ mg) had orthostatic hypotension; this effect was not reported in the placebo group.

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 MYKROX 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.

Drug Interactions

Diuretics

Furosemide and probably other loop diuretics given concomitantly with metolazone can cause unusually large or prolonged losses of fluid and electrolytes (see WARNINGS).

Other Antihypertensives

When MYKROX 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

May increase the risk of hypokalemia and increase salt and water retention.

Lithium

Serum lithium levels may increase (see WARNINGS).

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 MYKROX® Tablets (metolazone tablets, USP) three days before elective surgery.

Salicylates and Other Non-Steroidal Anti-Inflammatory Drugs

May decrease the antihypertensive effects of MYKROX 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.

Insulin and Oral Antidiabetic Agents

See Glucose Tolerance under PRECAUTIONS, General.

Methenamine

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

Anticoagulants

Metolazone, as well as other thiazide-like diuretics, may affect the hypoprothrombinemic response to anticoagulants; dosage adjustments may be necessary.

Drug/Laboratory Test Interactions

None reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mice and rats administered metolazone 5 days/week for up to 18 and 24 months, respectively, at daily doses of 2, 10, and 50 mg/kg, exhibited no evidence of a tumorigenic effect of the drug. The small number of animals examined histologically and poor survival in the mice limit the conclusions that can be reached from these studies.

Metolazone was not mutagenic *in vitro* in the Ames Test using Salmonella typhimurium strains TA-97, TA-98, TA-100, TA-102, and TA-1535.

Reproductive performance has been evaluated in mice and rats. There is no evidence that metolazone possesses the potential for altering reproductive capacity in mice. 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 was observed in dams mated with males from the 50 mg/kg group. In addition, the birth weight of offspring was decreased and the pregnancy rate was reduced in dams mated with males from the 10 and 50 mg/kg groups.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies performed in mice, rabbits, and rats treated during the appropriate period of 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, MYKROX Tablets should be used during pregnancy only if clearly needed. Metolazone crosses the placental barrier and appears in cord blood.

Non-Teratogenic Effects

The use of MYKROX Tablets in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. It is not known what effect the use of the drug during pregnancy has on the later growth, development, and functional maturation of the child. No such effects have been reported with metolazone.

Labor and Delivery

Based on clinical studies in which women received metolazone in late pregnancy until the time of delivery, there is no evidence that the drug has any adverse effects on the normal course of labor or delivery.

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.

Pediatric Use

Safety and effectiveness of MYKROX Tablets in pediatric patients have not been established, and such use is not recommended.

Geriatric Use

Clinical studies of MYKROX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Adverse experience information is available from more than 14 years of accumulated marketing experience with other formulations of metolazone for which reliable quantitative information is lacking and from controlled clinical trials with MYKROX from which incidences can be calculated.

In controlled clinical trials with MYKROX, adverse experiences resulted in discontinuation of therapy in 6.7-6.8% of patients given ½ to 1 mg of MYKROX.

Adverse experiences occurring in controlled clinical trials with MYKROX with an incidence of >2%, whether or not considered drug-related, are summarized in the following table.

Incidence of Adverse Experiences Volunteered or Elicited (by Patient in Percent)*

	MYKROX
	n = 226†
Dizziness (lightheadedness)	10.2
Headaches	9.3
Muscle Cramps	5.8
Fatigue (malaise, lethargy, lassitude)	4.4
Joint Pain, swelling	3.1
Chest Pain (precordial discomfort)	2.7

* Percent of patients reporting an adverse experience one or more times.

† All doses combined (½, 1, and 2 mg).

Some of the adverse effects reported in association with MYKROX also occur frequently in untreated hypertensive patients, such as headache and dizziness, which occurred in 14.8 and 7.4% of patients in a smaller parallel placebo group.

The following adverse effects were reported in less than 2% of the MYKROX treated patients.

Cardiovascular

Cold extremities, edema, orthostatic hypotension, palpitations.

Central and Peripheral Nervous System

Anxiety, depression, dry mouth, impotence, nervousness, neuropathy, weakness, “weird” feeling.

Dermatological

Pruritus, rash, skin dryness.

Eyes, Ears, Nose, Throat

Cough, epistaxis, eye itching, sinus congestion, sore throat, tinnitus.

Gastrointestinal

Abdominal discomfort (pain, bloating), bitter taste, constipation, diarrhea, nausea, vomiting.

Genitourinary

Nocturia.

Musculoskeletal

Back pain.

Other Adverse Experiences

Adverse experiences reported with other marketed metolazone formulations and most thiazide diuretics, for which quantitative data are not available, are listed in decreasing order of severity within body systems. Several are single or rare occurrences.

Cardiovascular

excessive volume depletion, hemoconcentration, venous thrombosis.

Central and Peripheral Nervous System

syncope, paresthesias, drowsiness, restlessness (sometimes resulting in insomnia).

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, anorexia, nausea, diarrhea, abdominal pain.

Hematologic

aplastic (hypoplastic) anemia, agranulocytosis, leukopenia, thrombocytopenia.

Metabolic

hypokalemia (see WARNINGS, Hypokalemia), hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia, hypomagnesemia, hypercalcemia.

Musculoskeletal

acute gouty attacks.

Other

transient blurred vision, chills.

In addition, rare adverse experiences reported in association with similar antihypertensive-diuretics but not reported to date for metolazone include: sialadenitis, xanthopsia, respiratory distress (including pneumonitis), and anaphylactic reactions. These experiences could occur with clinical use of metolazone.

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.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response.

For initial treatment of mild to moderate hypertension, the recommended dose is one MYKROX Tablet (½ mg) once daily, usually in the morning. If patients are inadequately controlled with one ½ mg tablet, the dose can be increased to two MYKROX Tablets (1 mg) once a day. An increase in hypokalemia may occur. Doses larger than 1 mg do not give increased effectiveness.

The same dose titration is necessary if MYKROX Tablets are to be substituted for other dosage forms of metolazone in the treatment of hypertension.

If blood pressure is not adequately controlled with two MYKROX Tablets alone, the dose should not be increased; rather, another antihypertensive agent with a different mechanism of action should be added to therapy with MYKROX Tablets.

HOW SUPPLIED

MYKROX Tablets (metolazone tablets, USP), ½ mg are white, flat-faced, round tablets, debossed “MYKROX” on one side, and “½” on reverse side.

NDC 53014-847-71 Bottle of 100’s

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect from light. Keep out of the reach of children.

Celltech Pharmaceuticals, Inc.

Rochester, NY 14623 USA

® Celltech Manufacturing, Inc.

Rev. 2/03

R528B

MYKROX TABLETS

metolazone tablets tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	53014-847
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
metolazone (UNII: TZ7V40X7VX) (metolazone - UNII:TZ7V40X7VX)		500 ug

Inactive Ingredients	
Ingredient Name	**Strength**
dibasic calcium phosphate ()	
magnesium stearate ()	
microcrystalline cellulose ()	
pregelatinized starch ()	
sodium starch glycolate ()	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	MYKROX;1/2
Contains			
Coating	false	**Symbol**	false

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:53014-847-71	100 in BOTTLE, PLASTIC		

Labeler - Celltech Pharmaceuticals, Inc.