CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19532

FINAL PRINTED LABELING

Front

SEP 0 1 1987

Systemic Lupus Erythematosus
Thiazide diuretics have exacerbated or activated systemic lupus erythematosus and this possibility should be considered with MICROX (metolazone) Tablets.

B. INFORMATION FOR PATIENTS: Patients should be informed of [illegible]

PENNWALT

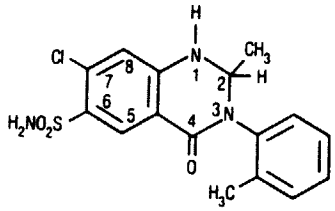
MICROX® TABLETS
(metolazone)

DO NOT INTERCHANGE

MICROX® TABLETS ARE A RAPIDLY AVAILABLE FORMULATION OF METOLAZONE FOR ORAL ADMINISTRATION. MICROX 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 MICROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.

DESCRIPTION

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.

Other ingredients in MICROX Tablets: dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate.

CLINICAL PHARMACOLOGY

MICROX is a quinazoline diuretic, with properties generally similar to the thiazide diuretics. The actions of MICROX (metolazone) result from interference with the renal tubular mechanism of electrolyte reabsorption. MICROX 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. MICROX 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. 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 MICROX 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 1/2 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 1/2 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/

of increase in BUN at increasing doses.
The rate and extent of absorption of metolazone from MICROX 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. MICROX Tablets have been shown to produce blood levels that are dose proportional between 1/2-2 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

MICROX Tablets are indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs of a different class.
MICROX 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, MICROX 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. MICROX 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 pre-coma, known allergy or hypersensitivity to metolazone.

WARNINGS

Rapid Onset Hyponatremia

Rarely, the rapid onset of severe hyponatremia and/or hypokalemia has been reported following initial doses of thiazide and nonthiazide diuretics. When symptoms consistent with 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 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.

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.

Concomitant Therapy

Furosemide: Unusually large or prolonged losses of fluids and electrolytes may result when metolazone is administered concomitantly to patients receiving furosemide (see DRUG INTERACTIONS).

Other Antihypertensive Drugs: When MICROX 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, while not reported to date, theoretically may occur when MICROX Tablets are given to patients known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

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A. GENERAL:

Fluid and Electrolytes

All patients receiving therapy with MICROX 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

PENWALT CORP.
PRESCRIPTION DIVISION
ROCHESTER, N.Y. 14623

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fects, advised to take the medication as directed and promptly report any possible adverse reactions to the treating physician.

C. 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 MICROX 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 MICROX Tablets three days before elective surgery.

Salicylates and Other Non-Steroidal Anti-Inflammatory Drugs

May decrease the antihypertensive effects of MICROX 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 **GENERAL PRECAUTIONS**.

Methenamine

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

D. DRUG/LABORATORY TEST INTERACTIONS: None reported.

E. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Mice and rats given metolazone for 1½ to 2 years at daily doses of 2, 10 and 50 mg/kg (approximately 100, 500, and 2,500 times the recommended maximum daily dose of MICROX 1 mg given to a 50 kg person) showed no evidence that metolazone caused an increased number of tumors. The small number of animals examined histologically and poor survival in the mice limit the conclusions that can be reached from these studies.

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 fetal weight of offspring was decreased and the pregnancy rate was reduced in dams mated with males from the 10 and 50 mg/kg groups.

F. PREGNANCY:

Teratogenic Effects–Pregnancy Category B. Reproduction studies performed in mice, rabbits and rats treated during the appropriate periods of gestation at doses up to 50 mg/kg/day (2,500 times the recommended maximum daily human dose of MICROX) have revealed no evidence of impaired fertility or 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, MICROX 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 MICROX 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.

G. 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.

H. NURSING MOTHERS: Metolazone appears in breast milk. Because of the potential for serious adverse reactions in nursing in-

established, and such use is not recommended.

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 MICROX from which incidences can be calculated.

In controlled clinical trials with MICROX, adverse experiences resulted in discontinuation of therapy in 6.7-6.8% of patients given 1/2 to 1 mg of MICROX.

Adverse experiences occurring in controlled clinical trials with MICROX 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)*

	MICROX 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 (1/2, 1 and 2 mg).

Some of the adverse effects reported in association with MICROX 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 MICROX 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: Pruritis, 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—necrotizing angiitis (cutaneous vasculitis), purpura, dermatitis, photosensitivity, urticaria.
Gastrointestinal—hepatitis, intrahepatic cholestatic jaundice, pancreatitis, anorexia.
Hematologic—aplastic (hypoplastic) anemia, agranulocytosis, leukopenia.
Metabolic—hypokalemia, hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia.
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), thrombocytopenia 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 appear and 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 the 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.

For initial treatment of mild to moderate hypertension, the recommended dose is one MICROX Tablet (1/2 mg) once daily, usually in the morning. If patients are inadequately controlled with one 1/2 mg tablet, the dose can be increased to two MICROX Tablets (1 mg) once a day. An increase in hypokalemia may occur. Doses larger than one mg do not give increased effectiveness.

The same dose titration is necessary if MICROX 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 MICROX Tablets alone, the dose should not be increased; rather, another antihypertensive agent with a different mechanism of action should be added to therapy with MICROX Tablets.

HOW SUPPLIED

MICROX (metolazone) Tablets, 1/2 mg: White, flat-faced, round tablets embossed, MICROX on one side and, 1/2, on reverse side.

Bottles of 100 NDC 0018-0847-71
Bottles of 500 NDC 0018-0847-85
Bottles of 1000 NDC 0018-0847-90

Store at room temperature. Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

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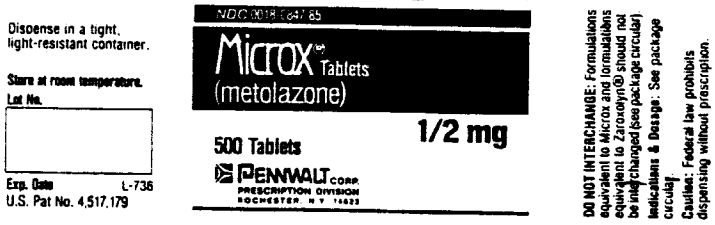
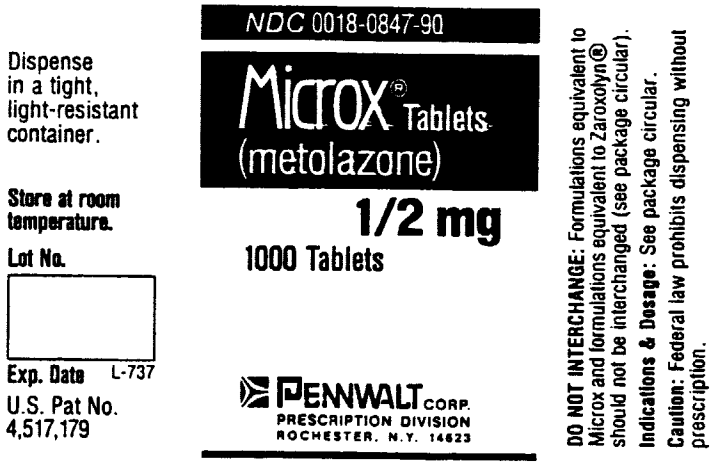
Labeling: Dup

FDA No: 19532 Rec'd. 9-2-

Reviewed by:





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PROFESSIONAL SAMPLE

Microx® Tablets
(metolazone)
1/2 mg 6 Tablets