CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19532

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF LABELING SUPPLEMENTS

JUN - 4 1987

NDA 17368[86], Zaroxolyn (metolozone) Tablets
NDA 19532, Microx (metolozone) Tablets

SUBMISSION DATE: 29 MAY 1987

SPONSOR: Pennwalt Corporation

COMMENTS: A review of the PRECAUTIONS sections of the submitted revised labeling for the two Pennwalt metolozone products has identified the following common inadequacies:

A. Chronic studies conducted in rats and mice were too deficicient in terms of dosing regimen, survival and numbers of animals microscopically examined, to support a conclusion of lack of evidence of oncogenic effect in these species. (See review by R. Harris of S/015 to NDA 17386.)

B. Under Pregnancy, the indicated multiples of the daily human dose of metolozone need to be accompanied by the dosage and patient weight assumptions underlying their calculation.

/S/

Charles A. Resnick, Ph.D.
04 June 1987

cc: Orig.
HFN/110
HFN/110/CSO
HFN/110/CResnick/6/4/87

REVIEW AND EVALUATION OF NONCLINCIAL BIOLOGIC DATA

NDA 19532

SPONSOR: Pennwalt Corporation
Rochester, New York

ORIGINAL SUBMISSION
CD&B Receipt:
10/08/85

DRUG: Microx (metolazone-PSF) 1/2 mg Tablet

INDICATION: hypertension

DOSAGE: Recommended dose is 1/2 mg once daily. Although a 1 mg dose might provide additional efficacy, labeling notes that "this increase may result in the loss of some of the benefits of Microx tablets 1/2 mg, such as the minimal effects on K, Na, Cl, Mg, cholesterol and uric acid".

IND UNDER WHICH CLINICAL INVESTIGATIONS CONDUCTED:

RELATED NDA: 17-386 (Zaroxolyn)

NONCLINICAL BIOLOGIC DATA: Sponsor references their approved NDA 17386 for Zaroxolyn (metolozone) tablets. Nonclinical study reports limited to carcinogenicity and reproductive toxicity experiments and these were submitted (at our request) May 15, 1986 as an amendment to the NDA (original receipt date was 10/4/85).

LABELING: Differs substantially from current labeling for Zaroxolyn. PRECAUTIONS subsections describing results of animal experiments will need to be reviewed. The preclinical reports needed for such review were only recently submitted by Pennwalt.

EVALUATION: Although revision of labeling may be required this should not affect approvability of the application. Microx is simply a more bioavailable form of the marketed diuretic Zaroxolyn (metolazone, Pennwalt) and there are no animal study requirements beyond what was provided for Zaroxolyn at time of its approval. We would not, therefore, object to approval of this application with the understanding that any statements regarding carcinogenicity or reproductive toxicity experiments that are not included in present labeling for Zaroxolyn, will not be included in labeling for Microx till such time that we are in a position to certify that they have been adequately documented.

/S/

Charles A. Resnick, Ph.D.
5/30/86

cc:
Orig. NDA
HFN-110
HFN-110/CResnick
HFN-110/CSO

SEP 12

SUPPLEMENTAL REVIEW AND EVALUATION OF NONCLINICAL BIOLOGIC DATA

NDA 17-386 S/015

SPONSOR: PENNWALT CORPORATION
ROCHESTER, NY

SUBMISSION DATE: 4/30/86

DRUG: ZAROXOLYN

INDICATION: HYPERTENSION

Review 8/12/86
Concurred

RELATED INDs/NDAs: IND - METOLAZONE
NDA 19-532 - MICROX

RELATED CORRESPONDENCE:
P: LABELING SUPPLEMENT S/015 (4/4/83)
F: REQUEST (1/3/85)
P: RESPONSE (6/4/85)
F: APPROVAL w CONTINGENCIES (8/12/85)

History : Supplement S/015 has requested approval of labeling for Zaroxolyn revised and updated in accordance with CFR 201.57 and 201.59. Previous correspondence to the sponsor dated January 3, 1985 requested additional changes to the proposed draft labeling submitted on April 4, 1983. These included a reordering of the statements in the "Pregnancy - Teratogenic Effects" subsection and inclusion of the appropriate regulatory statement in the "Nursing Mothers" subsection. The changes were incorporated in a submission of a draft labeling on June 4, 1985. The supplement was approved in correspondence dated August 12, 1985. Final printed labeling was requested in the latter letter and was provided in the subject submission. In addition the sponsor provided full reports of all animal carcinogenicity and reproductive studies for Microx under NDA 19-532 on May 15, 1986. Microx is a sustained released dosage form of metolazone pending approval under NDA 19-532.

The preclinical studies submitted to NDA 17-386 have been reviewed prior to approval. The studies and dates of their original submission are appended. All reproduction studies, which support the labeling for metolazone, were reviewed by Dr. E. Fefer (2/6/73). The carcinogenicity studies with metolazone were submitted to IND and subsequently to the NDA prior to approval. Although the carcinogenicity studies were reviewed on March 13, 1973 [referenced in the review of Dr. E. Fefer (10/26/73)], the review itself is not contained in the correspondence files for either IND on NDA 17-386. It must be presumed that the review of these studies was favorable based on the summary basis for approval of NDA 17-386 signed by Dr. E. Belton on October 29, 1973.

Review: Dr. Fefer has adequately reviewed the reproduction studies of metolazone supplied by the sponsor. Upon reviewing the full reports, I concur with Dr. Fefer's conclusions. The studies are adequate for the assessment of reproductive performance, teratogenicity, and peri- and post-natal drug effects. Although a formal segment III study was not conducted the information obtained from the three generation rat study provides sufficient data to assess the impact of metolazone on the important parameters of such a study.

The carcinogenicity studies in mice and rats are inadequate for the assessment of the carcinogenic potential of the drug. The rat study in particular suffers from several design and technical flaws and an insufficient number of animals at risk to make an assessment of toxicity.

Rats of the Sprague-Dawley strain (15/sex/dose) were initiated on treatment with metolazone (2, 10, or 50 mg/kg) or vehicle at the sponsor's laboratories on 1/26/70. Drug was administered by gavage; hematology studies were done during the first 18 weeks on treatment and clinical chemistry during the second year. The design problems which rendered this study inadequate included :

1) Pretreatment of animals for one year under a pharmacology protocol which did not include close monitoring of the outcome of individual animals.

2) A significant number of animals died on study due to intubation errors and respiratory disease.

3) Rats were treated for 5 days per week throughout the course of the study.

4) Many of those animals which died on study seemed not to have been necropsied for whatever reasons.

5) Only 12-14 rats per treatment group (5-8 rats/sex/dose) were entered into the second year of the study and of these only 2-7 rats/sex/dose had histopathological exams at death, sacrifice or termination.

Among the few number of animals available for histopathologic examination, pituitary adenomas occurred more frequently in mid (4/6) and high dose (5/6) females than in the controls (1/6). Given the low number of animals at risk and the high prevalence rate for this type of tumor in aging female rats, no conclusions can be reached about its relationship to treatment. In an 18-month chronic rat study no increase in pituitary adenomas was observed in the treatment groups, but this study also inadequate for the assessment of tumorigenic potential of the drug for many of the same reasons mentioned above.

Fibroadenomas of the mammary gland also appeared to be slightly increased in the high dose females (3/6) relative to the controls (1/6). But again no conclusions can be reached about this finding in the carcinogenicity study.

The carcinogenicity study in albino mice (strain unspecified) was more acceptable from a design standpoint but still suffered from numerous deficiencies. Fifty animals/sex/dose were initiated on treatment with metolazone (2,10, or 50 mg/kg) but again dosing was conducted only 5 days/week. The study was conducted at the sponsor's laboratories and began on 1/21/70. Drug was administered by gavage.

Many animals died on study apparently from intubation errors and intercurrent illness although the details as to how many were not available. However, as many as 28 females in the low dose group had died by the third month of treatment. The number of animals available for histopathological examination ranged from 10 - 24 for the different groups which was insufficient in most cases to make an assessment of tumorigenic potential. From the available data on these limited number of animals there was no evidence of tumorigenicity with metolazone.

Evaluation: The reproduction studies conducted with metolazone are adequate for a presentation of results in the labeling, the carcinogenicity studies are not.

Specifically, the following changes should be made in the final printed labeling prior to approval.

Carcinogenesis, Mutagenesis, Impairment of Fertility

1) The first paragraph of this section should be replaced with the following statement: "Studies to adequately assess the carcinogenic potential of metolazone have not been conducted."

2) In the second paragraph of this section, references to studies of reproductive performance in rabbits should be deleted from the first and last sentences since no formal studies of this kind were conducted in this species

3) In the second paragraph, the second sentence should be modified to read: "In a rat study, in which males were treated orally with metolazone at doses of 2, 10 and 50 mg/kg (equivalent to 5, 25 and 125 times the maximum recommended human dose respectively based on 50 kg body weight for man) 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."

Pregnancy

1) The first sentence under subsection 'Teratogenic effects' should be modified to read: "Reproductive studies performed in mice, rabbits, and rats treated during the appropriate periods of gestation with doses up to 50mg/kg/day have revealed no evidence of harm to the fetus due to metolazone."

Recommendations

The sponsor should incorporate the above changes in the labeling prior to final approval. Comparable or identical statements should be recommended for the labeling of Microx (NDA 19-532).

The sponsor should be informed that the carcinogenicity studies conducted with metolazone were inadequate for the purpose of making an unequivocal assessment of the tumorigenic potential of the drug. Further, the sponsor should be informed that an additional study or studies will be necessary to modify this section of the labeling for metolazone.

/S/

CAR
8/22/86

cc
Orig.
HFN/110
HFN/110/CSO
HFN/110/RHarris/8/12/86
R/D init: CResnick/8/22/86

Table 20

NEOPLASMS OBSERVED IN RATS MEDICATED
WITH METOLAZONE FOR TWO YEARS AND IN CONTROL RATS

Dose of Metolazone (mg/kg)	2.0		10.0		50.0		Control	
	M	F	M	F	M	F	M	F
ENDOCRINE ORGANS								
Adrenal Gland Adenoma								1
Pituitary Adenoma				4	1	5		1
Pancreas - Acinar Adenoma		1	1					
Thyroid - Light Cell Adenoma		1						
MAMMARY GLAND								
Fibroadenoma		1		1		3		1
Carcinosarcoma		1*						
Reticulum Cell Sarcoma		1						
UTERINE HORN								
Leiomyoma		1						
Polyp		1						1
ACOUSTIC NEURINOMA				1				
ASTROCYTOMA					1			
TRANSITIONAL CELL CARCINOMA							1	
MALIGNANT LYMPHOMA		1*						
OVARIAN TUMOR						1		
TOTAL TUMORS		8	1	6	2	9	1	4
SINGLE TYPE TUMOR - CASES		1	1	4	2	2	1	2
MULTIPLE NEOPLASIA - CASES	0	3	0	1	0	3	0	1
TOTAL ANIMALS	5	7	2	6	4	6	3	6

*Metastatic to Lungs

Table 21

NEOPLASMS OBSERVED IN MICE MEDICATED WITH METOLAZONE FOR EIGHTEEN MONTHS AND IN CONTROL MICE

Dose of Metolazone (mg/kg)	2.0		10.0		50.0		Control	
Sex	M	F	M	F	M	F	M	F
Lungs - Bronchogenic			2	1		2		1
Liver - Hepatoma	2							
Hemangioma							1	
Reticulum Cell Sarcoma - Generalized		2	1			2	1	2
Total Neoplasms	2	2	3	1		4	2	3
Number of Mice Examined	24	24	22	16	21	19	14	10
Neoplasm Incidence Percent	8.3	8.3	13.6	6.3	0	21.1	14.3	30.0

Supplement: APR 30 1986

Labeling: Final
NDA No: 17-386 Rec'd. 5-5-86
Reviewed by: _____

R-197A
Rev. 3/86

PENNWALT

ZAROXOLYN®

(metolazone)

Each ZAROXOLYN Tablet contains
2½, 5 or 10 mg of metolazone.

R-197A
Rev. 3/86

PENNWALT

ZAROXOLYN®

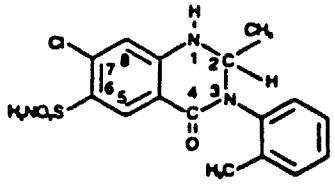
(metolazone)

Each ZAROXOLYN Tablet contains
2½, 5 or 10 mg of metolazone.

DESCRIPTION

ZAROXOLYN Tablets for oral administration contain 2½, 5, or 10 mg of metolazone, a diuretic/saluretic/antihypertensive drug of the quinazoline class. ZAROXOLYN Tablets also contain magnesium stearate, microcrystalline cellulose and dye. 2½ mg—D&C Red No. 33, 5 mg—FD&C Blue No. 2, 10 mg—D&C Yellow No. 10 and FD&C Yellow No. 6.

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.

CLINICAL PHARMACOLOGY

The diuretic and/or antihypertensive action of metolazone results in an interference with the renal tubular mechanism of electrolyte reabsorption. The mechanism of the action is unknown. Metolazone acts primarily to inhibit sodium reabsorption at the cortical diluting site and 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 may result in increased potassium excretion. In clinical usage, metolazone does not inhibit carbonic anhydrase. Its proximal action has been evidenced in humans by increased excretion of phosphate and magnesium ions, by markedly increased fractional excretion of sodium in patients with severely compromised glomerular filtration, and in animals by the results of micropuncture studies. Decrease in calcium ion excretion has not been noted.

When ZAROXOLYN Tablets are given, diuresis and saluresis usually begin within one hour and persist for 12 to 24 hours depending on the dosage. Maximum effect occurs about two hours after administration. At the higher recommended dosages, effect may be prolonged beyond 24 hours. For most patients, the duration of effect can be varied by adjusting the daily dose. A single daily dose is recommended. When an initially-desired therapeutic effect has been obtained, it is ordinarily advisable to reduce dosage to a lower maintenance level.

The diuretic potency of ZAROXOLYN at maximum therapeutic dosage is approximately equal to thiazide diuretics. However, unlike thiazides, ZAROXOLYN may produce diuresis in patients with glomerular filtration rates below 20 ml/min.

ZAROXOLYN (metolazone) and furosemide, administered concurrently, have produced marked diuresis in some patients where edema or ascites was refractory to treatment with maximum recommended doses of these or other diuretics administered alone. The mechanism of this interaction is unknown (see Drug Interactions).

The mechanism whereby diuretics function in the control of hypertension is unknown. Both renal and extra-renal actions may be involved. An antihypertensive effect may be seen as early as three to four days after therapy with ZAROXOLYN has been started. Administration for three to four weeks, however, is usually required for optimum antihypertensive effect.

Metolazone is absorbed rapidly. Maximum blood levels are found between 4 and 10 hours after dosing. The prolonged duration of action of metolazone is attributed to protein-binding. A small amount of metolazone is metabolized and the fraction so changed is nontoxic. Most of the drug is excreted in the unconverted form in the urine.

Drug Interaction Studies. In animals pretreated with metolazone, the drug did not alter the characteristic effect of heparin on clotting time nor protamine antagonism, dicumarol on prothrombin time nor Vitamin K antagonism; the response of guanethidine, reserpine and hydralazine to cardiovascular parameters nor the pressor response of the subsequent dose of norepinephrine.

roxolyn® (metolazone)
DA 17-386/S-015
ew Format Labeling
inal Printed Copy (page 2 of 4)

Supplement: APR 30 1996

INDICATIONS AND USAGE

ZAROXOLYN is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

ZAROXOLYN is indicated for the treatment of salt and water retention including

—edema accompanying congestive heart failure

—edema accompanying renal diseases, including the nephrotic syndrome, and states of diminished renal function.

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 satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. ZAROXOLYN is indicated in pregnancy when edema is due to pathologic causes, just as it is in the absence of pregnancy (however, see Precautions). 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 provide relief and may be appropriate.

CONTRAINDICATIONS

Anuria.

Hepatic coma or pre-coma; known allergy or hypersensitivity to metolazone.

WARNINGS

Rarely, the rapid onset of severe hyponatremia and/or hypokalemia has been reported following initial doses of thiazide or non-thiazide diuretics. When symptoms consistent with severe electrolyte imbalance appear rapidly, drug should be discontinued and supportive means should be initiated immediately. Appropriateness of diuretic therapy should be carefully re-evaluated.

Hypokalemia may occur, with consequent weakness, cramps, and cardiac arrhythmias. Hypokalemia is a particular hazard in digitalized patients, dangerous or fatal arrhythmias may be precipitated.

Azotemia and hyperuricemia may be raised or precipitated during the administration of ZAROXOLYN. Infrequently, gouty attacks have been reported in persons with history of gout.

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

Particular care must be taken, especially during initial therapy, when ZAROXOLYN is used with other antihypertensive drugs. Dosage of other antihypertensive agents, especially the ganglionic blockers, should be reduced.

While not reported to date, cross-allergy theoretically may occur when ZAROXOLYN is given to patients known to be allergic to sulfonamide-derived drugs, (eg., thiazides, furosemide)

PRECAUTIONS

General

Caution should be observed when administering ZAROXOLYN (metolazone) to patients with severely impaired renal function. Since most of the drug is excreted by the renal route, cumulative effects may be seen in this circumstance.

Caution should be observed when administering ZAROXOLYN to hyperuricemic or gouty patients. Infrequently, gouty attacks have been reported in persons with history of gout.

Hyperglycemia and glycosuria may occur in patients with latent diabetes although ZAROXOLYN exerts minimal effects on glucose metabolism.

Chloride deficit and hypochloremic alkalosis may occur. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced. Hot weather and a low-salt diet will contribute.

All patients receiving therapy with a diuretic should be observed for clinical signs of fluid and/or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis and hypokalemia. Hypokalemia will be more common in association with intensive or prolonged diuretic therapy, with concomitant steroid or ACTH therapy, and with inadequate electrolyte intake. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively, has severe diarrhea, or is receiving parenteral fluids. Warning signs 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.

While not reported for metolazone, use of other diuretics has been associated on rare occasions with pathologic changes in the parathyroid glands and with hypercalcemia. This possibility should be kept in mind with use of ZAROXOLYN.

Information for Patients

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

Laboratory Tests

The serum potassium should be determined at regular intervals and potassium supplementation instituted whenever indicated. Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Blood urea nitrogen, uric acid, and glucose levels should be assessed at intervals during diuretic therapy.

Drug

Supplement: APR 30 1986

Drug Interactions

Furosemide: Unusually large or prolonged effects on volume and electrolytes may result when ZAROXOLYN (metolazone) and furosemide are administered concurrently. It is recommended that concurrent administration of these diuretics for treatment of resistant edema be started under hospital conditions in order to provide for adequate monitoring.

Potassium-sparing diuretics: In concomitant use with metolazone, diuresis may be potentiated and dosages should be reduced. Potassium retention and hyperkalemia may result; the serum potassium should be determined frequently. Potassium supplementation is ordinarily not given when a potassium-sparing diuretic is used.

Digitalis: Metolazone may cause hypokalemia which is a condition that predisposes to digitalis toxicity.

Lithium: Diuretics may cause increased serum levels of lithium with the risk of lithium toxicity.

Insulin: Insulin requirements may be affected in diabetics taking metolazone.

Alcohol, barbiturates, narcotics, or antihypertensive drugs: Patients taking metolazone may develop orthostatic hypotension when any of these drugs are taken concomitantly.

Tubocurarine and norepinephrine: While not reported to date for metolazone, related diuretics have increased responsiveness to tubocurarine and decreased arterial responsiveness to norepinephrine. Accordingly, it may be advisable to discontinue ZAROXOLYN three days before elective surgery.

Steroid or ACTH therapy: Hypokalemia will be more common in association with concomitant steroid or ACTH therapy.

Animal studies concerning drug interactions with metolazone are discussed in the Pharmacology section.

Drug/Laboratory Interactions

There are no known instances of interference by the drug with laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies with metolazone have not shown any evidence of carcinogenicity. Mice and rats given the drug for 1½ to 2 years at doses of 2, 10 and 50 mg/kg (13, 67 and 333 times respectively, the usual daily human dose of 0.15 mg/kg) showed no evidence that metolazone caused an increased number of tumors.

Reproductive performance has been evaluated in mice, rats and rabbits. 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 and a decreased pregnancy rate occurred in dams mated with males from the 10 and 50 mg/kg groups. There is no evidence that metolazone possesses the potential for altering reproductive capacity in mice and rabbits.

Pregnancy

Teratogenic effects: Category B. Reproductive studies have been performed in mice, rabbits and rats at doses up to 333 times the human dose and 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, ZAROXOLYN should be used during pregnancy only if clearly needed.

Nonteratogenic effects: Metolazone crosses the placental barrier and appears in cord blood. The use of ZAROXOLYN 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.

Labor and Delivery

Based on clinical studies in which women received metolazone in late pregnancy up until the time of delivery, there is no evidence that the drug has any adverse effect on the duration or 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 in children have not been established.

ADVERSE REACTIONS

ZAROXOLYN is usually well tolerated, and most reported adverse reactions have been mild and transient. Many ZAROXOLYN 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 observed, but there is not enough systematic collection of data to support an estimate of their true incidence in the absence of such frequency data. Adverse reactions are listed in decreasing order of severity within body systems.

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

Central and peripheral nervous system: Syncope, neuropathy, vertigo, paresthesias, dizziness/light-headedness, drowsiness, fatigue, weakness, restlessness sometimes resulting in insomnia, headache.

Dermatologic/hypersensitivity: Necrotizing angiitis (cutaneous vasculitis), purpura, dermatitis (photosensitivity), urticaria and other skin rashes.

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

Hematologic: Aplastic/hypoplastic anemia, agranulocytosis, leukopenia.

Metabolic: Symptomatic and asymptomatic hyponatremia, hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hyponatremia.

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

Other: Transient blurred vision, chills, dryness of the mouth.

In addition, adverse reactions reported with other antihypertensive/diuretics, but which have not been reported to date for metolazone, include sialadenitis, xanthopsia, respiratory distress (including pneumonitis), pancreatitis, 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.

Zaroxolyn® (metol. ne)
NDA 17-386/S-015
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OVERDOSAGE

Signs and symptoms: Orthostatic hypotension, dizziness, drowsiness, syncope, electrolyte abnormalities, hemo-concentration and hemodynamic changes due to plasma volume depletion may occur. In some instances depressed respiration may be observed. In 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. Serum electrolyte changes and cardiovascular and renal function should be closely monitored. Supportive measures should be initiated as required to maintain hydration, electrolyte balance, respiration and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION

Effective dosage of ZAROXOLYN (metolazone) should be individualized according to indication 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 therapeutic response.

USUAL SINGLE DAILY DOSAGE SCHEDULES

Suitable initial dosages will usually fall in the ranges given:

Mild to moderate essential hypertension:
ZAROXOLYN 2½-5mg, once daily

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

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

Treatment of hypertension: The time interval required for the initial dosage regimen to show effect may vary from three or four days to three to six weeks in the treatment of elevated blood pressure. Doses should be adjusted at appropriate intervals to allow for a full manifestation of dose effect.

Treatment of edematous states: The time interval required 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 an initially-desired therapeutic effect has been obtained, it may be advisable to reduce the dosage. The daily dosage depends on the severity of the patient's condition, sodium intake, and responsiveness. A decision to change the daily dosage should be based on the results of thorough clinical and laboratory evaluations. If antihypertensive drugs or diuretics are given concurrently with ZAROXOLYN, more careful dosage adjustment may be necessary. For patients 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.

HOW SUPPLIED

ZAROXOLYN (metolazone) is provided as: pink 2½ mg tablets (NDC 0018-0875), blue 5 mg tablets (NDC 0018-0850) and yellow 10 mg tablets (NDC 0018-0835). The tablets are round and debossed on opposite sides with the tablet strength and ZAROXOLYN. Packages for all strengths are stock bottles of 100, 500 and 1000 and a unit-dose strip pack of 100.

Store at room temperature.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without a prescription.

RJS™

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

R-187A
Rev. 3/86

Litho in U.S.A.

MEMO REC	AVOID ERRORS PUT IT IN WRITING	DATE 10/14/87
FROM: Director, Division CR Drug Products		OFFICE ODRR
TO: Director ODRR		DIVISION HFN-110
SUBJECT: Safety Update NDA 19,532 Micrex Penwest		

SUMMARY

There are 2 safety updates (7/29/86 and 8/11/87) that have been submitted and have been reviewed. The safety update consist of reports of adverse reactions observed in 5 controlled clinical trials which are ongoing or are completed but not completely analyzed. There are no findings of note. Interesting is one study comparing 0.5 mg micrex with 2 Dyazide a day. Micrex caused fewer side effects than Dyazide.

All requirements are fullfilled and labelling is acceptable. The Division recomends completion of the approval process.

SIGNATURE /S/

DOCUMENT NUMBER

FD FORM 2034 (2/72)