NDA 17-943/S-010, S-015

Monarch Pharmaceuticals, Inc.
Attention: Joseph R. Gregory
President and Chief Operating Officer
335 Beecham Street
Bristol, TN 37620

AUG 6 1999

Dear Mr. Gregory:

Please refer to your supplemental new drug applications dated June 22, 1988, received June 22, 1988, for NDA 17-943/S-010 [amended November 15, 1989 and April 22, 1997] and November 11, 1997, received November 13, 1997, for NDA 17-943/S-015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proloprim® (trimethoprim) Tablets.

We also refer to the Agency's approvable letters dated March 1, 1989 and November 28, 1990 for supplement 010.

Supplement 010 provides for revisions to the **CLINICAL PHARMACOLOGY- Microbiology** subsection, **PRECAUTIONS- Pediatric Use** subsection, and **REFERENCES** section of the label.

Supplement 015 was submitted in response to the Agency's letter dated May 20, 1997, acknowledging your final printed labeling submitted February 26, 1997 for NDA 17-943/S-014, and provides for revisions to the **CLINICAL PHARMACOLOGY- Microbiology** subsection and the **DOSAGE AND ADMINISTRATION** section of the label.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling submitted November 11, 1997. Accordingly, these supplemental applications are approved effective on the date of this letter. Please note that supplement S-015 supercedes supplement S-010.

Additionally, we acknowledge that the labeling submitted complies with the requests made by the Division regarding the Microbiology subsection of the labeling in the approvable letter of November 28, 1990 [Supplement 010] and the letter dated May 20, 1997 acknowledging your final printed labeling submitted February 26, 1997 [Supplement 014]. However, on January 23, 1993, the Center for Drug Evaluation and Research issued an "NDA Holders Letter" which describes the content and format that is to be used in writing the Microbiology subsection of the package insert. Thus, the content and format of the Proloprim label is outdated and not written to reflect the NDA Holders Letter. Therefore, it is requested that a labeling supplement be submitted which revises the Microbiology subsection of the package insert as follows:

Microbiology: Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. This binding is much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of trimethoprim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa.*

The dominant non-*Enterobacteriaceae* fecal organisms, *Bacteroides* spp. and *Lactobacillus* spp., are not susceptible to trimethoprim concentrations obtained with the recommended dosage.

Trimethoprim has been shown to be active against most strains of the following microorganisms, **both** *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Staphylococcus species (coagulase-negative strains, including *S. saprophyticus)*

Aerobic gram-negative microorganisms

Enterobacter species
Escherichia coli
Kiebsiella pneumoniae
Proteus mirabilis

Susceptibility Testing Methods

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* spp.:

MIC (Fg/mL)	Interpretation
#8	Susceptible (S)
$16	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim[a] powder should provide the following MIC values:

Microorganism		MIC (Fg/mL)
Escherichia coli	ATCC 25922	0.5- 2.0
Staphylococcus aureus	ATCC 29213	1.0 - 4.0

[a]Very medium-dependent.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-Fg trimethoprim to test the susceptibility of microorganisms to trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-Fg trimethoprim disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* spp.:

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)
11-15	Intermediate (I)
#10	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC of trimethoprim.

As with standardized dilution techniques, diffusion methods require the use of the laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-Fg trimethoprimb disk should provide the following zone diamters in these laboratory test quality control stains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	21-28
Staphylococcus aureus	ATCC 25923	19-26

[b.] Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/ sulfamethoxazole disks. A zone of inhibition **3** 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997.

2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.

3. Brumfitt W, Pursell R. Trimethoprim-sulfamethoxazole in the treatment of bacteriuria in women. *J Infect Dis.* 1973;128(suppl): S657-S663.

The final printed labeling (FPL) must be identical to the labeling submitted November 11, 1997 [#RL 305. Revised November 1997].

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 17-943/S-010 & S-015." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely,

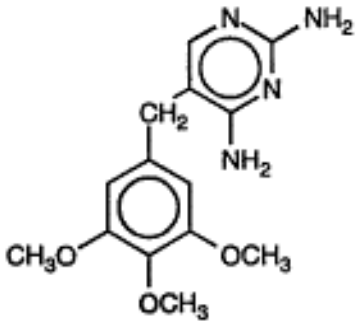
Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

PROLOPRIM® (trimethoprim) AUG 6 1999

100-mg and 200-mg Scored Tablets

DESCRIPTION: PROLOPRIM (trimethoprim) is a synthetic antibacterial available in tablet form for oral administration. Each scored white tablet contains 100 mg trimethoprim and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium starch glycolate. Each scored yellow tablet contains 200 mg trimethoprim and the inactive ingredients corn starch, D & C Yellow No. 10, magnesium stearate and sodium starch glycolate.

Trimethoprim is 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine. It is a white to light yellow odorless, bitter compound with a molecular weight of 290.32 and the molecular formula $C_{14}H_{18}N_4O_3$. The structural formula is:



CLINICAL PHARMACOLOGY: Trimethoprim is rapidly absorbed following oral administration. It exists in the blood as unbound, protein-bound, and metabolized forms. Ten to twenty percent of trimethoprim is metabolized, primarily in the liver; the remainder is excreted unchanged in the urine. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free form is considered to be the therapeutically active form. Approximately 44% of trimethoprim is bound to plasma proteins.

Mean peak serum concentrations of approximately 1.0 mcg/mL occur 1 to 4 hours after oral administration of a single 100-mg dose. A single 200-mg dose will result in serum levels approximately twice as high. The half-life of trimethoprim ranges from 8 to 10 hours. However, patients with severely impaired renal function exhibit an increase in the half-life of trimethoprim, which requires either dosage regimen adjustment or not using the drug in such patients (see DOSAGE AND ADMINISTRATION). During a 13-week study of trimethoprim administered at a daily dosage of 200 mg (50 mg q.i.d.), the mean minimum steady-state concentration of the drug was 1.1 mcg/mL. Steady-state concentrations were achieved within 2 to 3 days of chronic administration, and were maintained throughout the experimental period.

Excretion of trimethoprim is primarily by the kidneys through glomerular filtration and tubular secretion. Urine concentrations of trimethoprim are considerably higher than are the concentrations in the blood. After a single oral dose of 100 mg, urine concentrations in trimethoprim ranged from 30 to 160 mcg/mL during the 0- to 4-hour period and declined to approximately 18 to 91 mcg/mL during the 8- to 24-hour period. A 200-mg single oral dose will result in trimethoprim urine levels approximately twice as high. After oral administration, 50% to 60% of trimethoprim is excreted in the urine within 24 hours, approximately 80% of this being unmetabolized trimethoprim.

Since normal vaginal and fecal flora are the source of most pathogens causing urinary tract infections, it is relevant to consider the distribution of trimethoprim into these sites. Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentrations of simultaneously obtained serum samples. Sufficient trimethoprim is excreted in the feces to markedly reduce or eliminate trimethoprim-susceptible organisms from the fecal flora.

Trimethoprim also passes the placental barrier and is excreted in human milk.

Microbiology: PROLOPRIM blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. This binding is much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, PROLOPRIM selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of PROLOPRIM includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*.

The dominant non-*Enterobacteriaceae* fecal organisms, *Bacteroides* spp. and *Lactobacillus* spp., are not susceptible to trimethoprim concentrations obtained with the recommended dosage.

REPRESENTATIVE MINIMUM INHIBITORY CONCENTRATIONS FOR TRIMETHOPRIM-SUSCEPTIBLE ORGANISMS	
Bacteria	**Trimethoprim MIC mcg/mL (Range)**
Escherichia coli	0.05 — 1.5
Proteus mirabilis	0.5 — 1.5
Klebsiella pneumoniae	0.5—5.0
Enterobacter species	0.5—5.0
Staphylococcus species, coagulase-negative	0.15—5.0

Susceptibility Tests: *Dilution Techniques:* Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim powder. The MIC values should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
#8	Susceptible (S)
≥16	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim powder should provide the following MIC values:

Microorganism	MIC(mcg/mL)
S. aureus ATCC 29213	1 - 4
E. faecalis ATCC 29212	#1
E. coli ATCC 25922	0.5 - 2
P. aeruginosa ATCC 27853	>64

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg trimethoprim to test the susceptibility of microorganisms to trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-mcg trimethoprim disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
11-15	Intermediate (I)
#10	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trimethoprim.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-mcg trimethoprim disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	21 - 28 mm
S. aureus ATCC 25923	19 - 26 mm

INDICATIONS AND USAGE: For the treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter* species, and coagulase-negative *Staphylococcus* species, including *S. saprophyticus.*

Cultures and susceptibility tests should be performed to determine the susceptibility of the bacteria to trimethoprim. Therapy may be initiated prior to obtaining the results of these tests.

CONTRAINDICATIONS: PROLOPRIM is contraindicated in individuals hypersensitive to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS: Serious hypersensitivity reactions have been reported rarely in patients on trimethoprim therapy. Trimethoprim has been reported rarely to interfere with hematopoiesis, especially when administered in large doses and/or for prolonged periods.

The presence of clinical signs such as sore throat, fever, pallor, or purpura may be early indications of serious blood disorders (see OVERDOSAGE: Chronic).

Complete blood counts should be obtained if any of these signs are noted in a patient receiving trimethoprim and the drug discontinued if a significant reduction in the count of any formed blood element is found.

PRECAUTIONS: General: Trimethoprim should be given with caution to patients with possible folate deficiency. Folates may be administered concomitantly without interfering with the antibacterial action of trimethoprim. Trimethoprim should also be given with caution to patients with impaired renal or hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Drug Interactions: PROLOPRIM may inhibit the hepatic metabolism of phenytoin. Trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 51% and decreased the phenytoin metabolic clearance rate by 30%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Drug/Laboratory Test Interactions: Trimethoprim can interfere with a serum methotrexate assay as determined by the Competitive Binding Protein Technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in over estimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with trimethoprim.

Mutagenesis: Trimethoprim was demonstrated to be nonmutagenic in the Ames assay. In studies at two laboratories, no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1000 times human plasma levels in these same cells, a low level of chromosomal damage was induced at one of the laboratories. No chromosomal abnormalities were observed in cultured human leukocytes at concentrations of trimethoprim up to 20 times human steady-state plasma levels. No chromosomal effects were detected in peripheral lymphocytes of human subjects receiving 320 mg of trimethoprim in combination with up to 1600 mg of sulfamethoxazole per day for as long as 112 weeks.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Trimethoprim has been shown to be teratogenic in the rat when given in doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses six times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and

Pursell,[4] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, PROLOPRIM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival.

Nursing Mothers: Trimethoprim is excreted in human milk. Because trimethoprim may interfere with folic acid metabolism, caution should be exercised when PROLOPRIM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 months have not been established. The effectiveness of trimethoprim as a single agent has not been established in pediatric patients under 12 years of age.

ADVERSE REACTIONS: The adverse effects encountered most often with trimethoprim were rash and pruritus.

Dermatologic: Rash, pruritus, and phototoxic skin eruptions. At the recommended dosage regimens of 100 mg b.i.d. or 200 mg q.d. each for 10 days, the incidence of rash is 2.9% to 6.7%. In clinical studies which employed high doses of PROLOPRIM, an elevated incidence of rash was noted. These rashes were maculopapular, morbilliform, pruritic, and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

Hypersensitivity: Rare reports of exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell Syndrome), and anaphylaxis have been received.

Gastrointestinal: Epigastric distress, nausea, vomiting, and glossitis. Elevation of serum transaminase and bilirubin has been noted, but the significance of this finding is unknown. Cholestatic jaundice has been rarely reported.

Hematologic: Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia, and methemoglobinemia.

Metabolic: Hyperkalemia, hyponatremia.

Neurologic: Aseptic meningitis has been rarely reported.

Miscellaneous: Fever, and increases in BUN and serum creatinine levels.

OVERDOSAGE: Acute: Signs of acute overdosage with trimethoprim may appear following ingestion of 1 gram or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion, and bone marrow depression (see Chronic subsection).

Treatment consists of gastric lavage and general supportive measures. Acidification of the urine will increase renal elimination of trimethoprim. Peritoneal dialysis is not effective and hemodialysis only moderately effective in eliminating the drug.

Chronic: Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given leucovorin; 5 to 15 mg leucovorin daily has been recommended by some investigators.

DOSAGE AND ADMINISTRATION: The usual oral adult dosage is 100 mg of PROLOPRIM every 12 hours or 200 mg PROLOPRIM every 24 hours, each for 10 days. The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/min is not recommended. For patients with a creatinine clearance of 15 to 30 mL/min, the dose should be 50 mg every 12 hours.

HOW SUPPLIED: 100-mg Tablets (white, scored, round-shaped), containing 100 mg trimethoprim—bottle of 100 (NDC 0173-0820-55). Imprint on tablets “PROLOPRIM 09A.”

Store at 15° to 25°C (59° to 77°F) in a dry place.

200-mg Tablets (yellow, scored, round-shaped), containing 200 mg trimethoprim—bottle of 100 (NDC 0173-0825-55). Imprint on tablets “PROLOPRIM 200.”

Store at 15° to 25°C (59° to 77°F) In a dry place and protect from light.

REFERENCES:

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*. 3rd ed.: Approved Standard. NCCLS Document M7-A3. Vol. 13. No. 25. Villanova. Pa: NCCLS: 1993.
2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests.* 5th ed.: Approved Standard. NCCLS Document M2-A5. Vol. 13. No. 24. Villanova. Pa: NCCLS: 1993.
3. Brumfitt W, Pursell R. Trimethoprim-sulfamethoxazole in the treatment of bacteriuria in women. *J Infect Dis*. 1 973;128(suppl):5657-5663.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709