

PRODUCT MONOGRAPH

TRIMETHOPRIM

**Trimethoprim Tablets USP
100 mg and 200 mg**

ANTIBACTERIAL AGENT

**AA PHARMA INC.
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THERAPEUTIC CLASSIFICATION

Antibacterial agent

ACTIONS AND CLINICAL PHARMACOLOGY

Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme; thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins by causing a deficiency of endogenously produced thymine. The effect is usually bactericidal in the absence of an adequate external supply by thymine or thymidine (see MICROBIOLOGY).

Trimethoprim is rapidly absorbed following oral administration. It exists in the blood as unbound, protein-bound and metabolized forms. Ten to 20% 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 µg/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 µg/mL. Steady-state concentrations were achieved within two to three 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 of trimethoprim ranged from 30 to 160 µg/mL during the 0 to 4 hour period and declined to approximately 18 to 91 µg/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 in 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.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of trimethoprim was measured and compared following oral administration of a single 200 mg dose of the test product, TRIMETHOPRIM Tablets, 200 mg, to the marketed reference product, Proloprim® Tablets, 200 mg. The results from the measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Trimethoprim (Dose: 1 x 200 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	TRIMETHOPRIM Tablets	Proloprim®† Tablets	
AUC _T (µg·hr/mL)	24.69 25.27 (21.7)	24.86 25.61 (24.3)	99.32%
AUC _I (µg·hr/mL)	27.20 27.80 (21.7)	27.73 28.54 (24.5)	98.09%
C _{max} (µg/mL)	1.862 1.900 (19.3)	2.004 2.055 (22.0)	92.91%
T _{max} (hr)*	1.954 (48.0)	1.428 (45.3)	--
t _{1/2} (hr)*	9.111 (16.9)	9.361 (18.4)	--

*Expressed as arithmetic means (CV%) only.

†Proloprim® is manufactured by Glaxo Wellcome Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

For the treatment of acute, uncomplicated urinary tract infections due to susceptible strains of *Escherichia coli* and *Klebsiella pneumoniae*. Limited clinical experience suggests the probability of therapeutic response in infections due to susceptible strains of *Proteus mirabilis* and *Enterobacter* species.

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.

For infections associated with urinary tract complications such as obstruction, or where tissue involvement is suspected, the combination of trimethoprim/sulfamethoxazole has been shown to be superior to trimethoprim alone.

CONTRAINDICATIONS

Trimethoprim is contraindicated in individuals hypersensitive to trimethoprim, during pregnancy, and during the nursing period (see "Reproduction Studies").

It is also contraindicated in individuals with documented megaloblastic anemia due to folate deficiency.

WARNINGS

Rare incidents of serious hypersensitivity reactions have been reported in patients on trimethoprim therapy.

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

Rare incidents of trimethoprim interfering with hematopoiesis have been reported, especially when administered in large doses and/or for prolonged periods.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be early indications of serious blood disorders (see SYMPTOMS AND TREATMENT OF

OVERDOSAGE). 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, except in *Enterococci* infections.

An increased incidence of skin rashes has been observed when double the recommended dosage was administered.

Use in Children

The safety and effectiveness of trimethoprim in infants under two months of age has not been demonstrated. The effectiveness of trimethoprim as a single agent has not been established in children under 12 years of age.

Use in 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.

Patients with Special Diseases and Conditions

Trimethoprim should also be given with caution to patients with impaired renal or hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Drug Interactions

Trimethoprim may inhibit the hepatic metabolism of phenytoin. When given at a common clinical dosage, trimethoprim 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.

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 assay for creatinine resulting, from overestimations of about 10% in the range of normal values.

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.

ADVERSE REACTIONS

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

The following adverse reactions are reported to have occurred in patients receiving trimethoprim:

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 trimethoprim, 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.

Hematologic

Leukopenia, neutropenia, megaloblastic anemia, thrombocytopenia and methemoglobinemia. **In rare cases, immune-mediated thrombocytopenia has been suspected with use of trimethoprim. Drug-induced immune thrombocytopenia is one type of hypersensitivity reaction.**

Hypersensitivity

Rare incidents of exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome and anaphylaxis have been reported.

Gastrointestinal

Nausea, vomiting, abdominal cramps, glossitis, stomatitis. Elevation of serum transaminase and bilirubin have been noted, but the significance of this finding is unknown. There have been rare reports of cholestatic jaundice.

Metabolic

Hyperkalemia, hyponatremia.

Neurologic

Aseptic meningitis has rarely been reported.

Miscellaneous

Headache, joint pain, apathy, fatigue, muscle weakness, nervousness, fever and increases in BUN and serum creatinine levels.

The following adverse reactions have not been reported in patients receiving trimethoprim; however, based upon clinical experience with chemically related drugs, the possibility of these reactions occurring should be recognized.

CNS

Convulsions, ataxia, tinnitus, and vertigo.

SYMPTOMS AND TREATMENT OF 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).

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 in 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 trimethoprim every 12 hours or 200 mg 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.

PHARMACEUTICAL INFORMATION

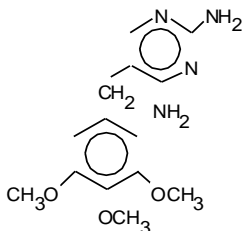
DRUG SUBSTANCE

Common Name: Trimethoprim

Chemical Names:

- 1) 2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]-;
- 2) 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine.

Structural Formula:



Molecular Formula: C₁₄H₁₈N₄O₃

Molecular Weight: 290.32

Description: Trimethoprim is a white, crystalline, odourless solid, with a very bitter taste. It is very slightly soluble in water.

COMPOSITION

In addition to trimethoprim, each tablet contains the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, methylcellulose, D&C Yellow No. 10 Aluminum Lake 16% (200 mg strength only).

STABILITY AND STORAGE RECOMMENDATIONS

TRIMETHOPRIM Tablets should be stored at room temperature (15-30°C). Preserve in tight, light-resistant containers.

AVAILABILITY OF DOSAGE FORM(S)

TRIMETHOPRIM Tablets, 100 mg: White, round, biconvex tablets, bisected and engraved "TRI" over "100" on one side. Available in bottles of 100 and 500 tablets, and unit-dose packages of 100 tablets.

TRIMETHOPRIM Tablets, 200 mg: Yellow, round, biconvex tablets, bisected and engraved "TRI" over "200" on one side. Available in bottles of 100 tablets and unit-dose packages of 100 tablets.

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, *Bacteroids* spp. and *Lactobacillus* spp. are not susceptible to trimethoprim concentrations obtained with the recommended dosage.

Susceptibility Tests

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such standard procedure which has been recommended for use with disks to test the susceptibility of organisms to trimethoprim uses the 5-mcg disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for trimethoprim.

Reports from the laboratory giving 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
11-15	Moderately susceptible
≤10	Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 5-mcg trimethoprim disk should give the following zone diameters:

Organism	Zone Diameter (mm)
<i>E. coli</i> ATCC 25922	21 - 28 mm
<i>S. aureus</i> ATCC 25923	19 - 26 mm

Dilution Techniques: Use a standardized dilution method (broth, agar, microdilution) or equivalent with trimethoprim powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 8	Susceptible
≥16	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard trimethoprim powder should provide the following MIC values:

Organism	MIC (µg/mL)
<i>S. aureus</i> ATCC 29213	1 - 4
<i>E. faecalis</i> ATCC 29212	≤ 1
<i>E. coli</i> ATCC 25922	0.5 - 2
<i>P. aeruginosa</i> ATCC 27853	>64

Representative Minimum Inhibitory Concentrations for Trimethoprim Susceptible Organisms (MIC - µg/mL)*			
Organisms (No. strains)	Dilution of Inoculum	TMP	
		Range	Median
<i>Streptococcus pyogenes</i> (35)	10 ⁻³	0.02 - 0.8	0.1
<i>Enterococcus</i> (25)	10 ⁻³	0.02 - 0.2	0.1
<i>Diplococcus pneumoniae</i> (33)	10 ⁻³	0.04 - 0.8	0.4
<i>Staphylococcus aureus</i> (36)	10 ⁰	0.8 - 6.3	1.6
<i>Staphylococcus epidermidis</i> (35)	10 ⁻³	0.4 - 1.6	0.8
	10 ⁰	0.8 - 12.5	1.6
<i>Neisseria gonorrhoeae</i> (35)	10 ⁻³	0.2 - 6.3	0.4
	10 ⁰	0.3 - 3.1	0.8
<i>Neisseria meningitidis</i> (11)	10 ⁰	6.3 - 50	25
	10 ⁻³	3.1 - 25	6.3
<i>Haemophilus influenzae</i> †(35)	10 ⁰	0.1 - 12.5	0.8
	10 ⁻³	0.2 - 0.4	0.4
<i>Escherichia coli</i> (36)	10 ⁰	0.4 - 12.5	0.8
	10 ⁻³	0.2 - 0.8	0.4
<i>Klebsiella pneumoniae</i> (33)	10 ⁻³	all 3.1	3.1
	10 ⁻³	0.2 - 1.6	0.8
<i>Enterobacter</i> (35)	10 ⁻³	0.8 - 25	6.3
	10 ⁰	0.4 - 3.1	0.8
<i>Serratia marcescens</i> (27)	10 ⁻³	1.6 - 50	3.1
	10 ⁻³	0.4 - 6.3	3.1
<i>Proteus</i> (35)	10 ⁻³	0.8 - 6.3	1.6
<i>Providencia</i> (35)	10 ⁻³	50 - 1000	1000
<i>Pseudomonas aeruginosa</i> (35)	10 ⁻³	0.1 - 0.2	0.1
<i>Salmonella</i> (34)	10 ⁻³	0.1 - 0.8	0.4
<i>Shigella</i> (31)	10 ⁻³	3.1 - 12.5	6.3
<i>Herellea vaginicola</i> (16)	10 ⁻³		

*On modified Mueller-Hinton agar except where otherwise indicated.

†With inoculum diluted 10⁻³, the medium used was trypticase-soy agar with 5% lysed horse blood.

‡Lysed horse blood was added to the modified Mueller-Hinton agar for these strains.

PHARMACOLOGY

Animals

Studies with anesthetized cats and dogs indicated that doses of 100 mg/kg had no influence on blood pressure (carotid), pulse rate, pressure in the right cardiac auricle, circulation in the femoral artery, oxygen content of the thigh muscles, respiration or electrocardiogram.

With excessively high doses, circulatory and respiratory depressive effects were evident and were protracted due to the slow resorption of large amounts of orally applied active ingredients.

Human

A single oral dose of 100 mg produced serum trimethoprim levels ranging from 0.42 to 1.68 $\mu\text{g/mL}$ at 2 hours and 0.32 to 1.55 $\mu\text{g/mL}$ at 4 hours after dosing. Single 200 mg doses of trimethoprim produced serum levels approximately twice as high: ranging from 1.87 to 3.11 $\mu\text{g/mL}$ at 2 hours and 1.57 to 2.58 $\mu\text{g/mL}$ at 4 hours after dosing. The following table gives the mean serum concentrations as a function of time for both of these doses.

Dose (mg)	No. of Volunteers	Mean Serum Concentration of Trimethoprim ($\mu\text{g/mL}$ at indicated times [h] after dosing)					
		0.5	1	2	4	8	24
100	18	0.68	1.06	1.11	0.96	0.68	0.20
200	6	1.50	2.29	2.12	2.03	1.58	0.43

Excretion of trimethoprim is chiefly by the kidneys through glomerular filtration and tubular secretion. Urine concentrations are considerably higher than blood concentrations. Urine levels of trimethoprim are time and dose related. After a single oral dose of 100 mg, urinary trimethoprim levels ranged from 30 to 160 $\mu\text{g/mL}$ for the 0 to 4 hour collection period and declined to 18 to 91 $\mu\text{g/mL}$ for the 8 to 24 hour collection period. In this study, 50% to 60% of the trimethoprim was excreted in the urine within 24 hours. Single doses of 200 mg produced urinary trimethoprim levels approximately twice as high. In one study, urinary concentrations ranged from 74 to 394 $\mu\text{g/mL}$ for the 0 to 4 hour collection period and in a second study from 71 to 91 $\mu\text{g/mL}$ for a 0 to 12 hour collection period. Approximately 85% of the excreted drug is in its unmetabolized form. These urinary levels are well above the MIC values of the majority of commonly encountered urinary pathogens (see table on page 9).

Concentrations of trimethoprim in prostatic and vaginal secretions are consistently greater than those found in the serum. Oral administration of 5.0 to 8.1 mg/kg for 1 to 2 days produced trimethoprim levels of 1.9 to 5.6 µg/mg in prostatic tissue, and levels of 2.5 to 5.6 µg/mL in prostatic secretions. Administration of 320 mg/day of trimethoprim in combination with sulfamethoxazole for 10 days produced levels of 2.5 to 10 µg/mL in vaginal secretions.

Sufficient trimethoprim is excreted in the feces to eliminate susceptible organisms from the fecal flora. The dominant fecal organisms, *Bacteroides* species and *Lactobacillus* species, are not susceptible to trimethoprim; trimethoprim does not cause intestinal upset due to imbalance in the normal colonic flora.

Emergence of resistant strains of fecal bacteria has not been a problem, thus preventing urogenital superinfection by such organisms from the gut.

Trimethoprim should be given with caution to patients with possible folate deficiency. Trimethoprim *in vivo* and *in vitro*, in concentrations achieved in plasma by standard dosages, caused no disturbances of folate metabolism in human bone marrow. Folates may be administered concomitantly without interfering with the antibacterial action of trimethoprim except in *Enterococci* infections.

TOXICOLOGY

Acute Toxicity

	Trimethoprim LD ₅₀ ± SE (mg/kg p.o.)
Mice	1460 ± 130
Rats	880 ± 120
Rabbits	540 ± 90
Neonatal Rats	195 ± 27

Death from respiratory depression is preceded by severe tremors and convulsions.

Subacute Toxicity

Daily dosages of 100 and 300 mg of trimethoprim were given to freshly weaned 21-day-old Wistar rats orally. No deaths occurred and there was no effect on weight gain.

Juvenile Rhesus monkeys received 33, 100 or 300 mg/kg orally for one month. Three of four animals on 300 mg/kg daily died. No abnormalities were seen in a group of Rhesus monkeys

fed 120 mg/kg/day of trimethoprim for 13 weeks. A group of 16 rats were fed 113 mg/kg of trimethoprim for 90 days. All rats survived the study. No signs of overt excitation or depression were noted and general physical appearance was normal. Some growth depression was noted in the females of the group, but no other abnormal findings.

Chronic Toxicity

Trimethoprim was given orally to young rats at doses of 33, 100 and 300 mg/kg for 6 months and did not produce any significant change in weight gain in males or in females. Deaths occurred at high and medium dosages, but were not significant.

Changes occurred in hemopoiesis which were consistent with trimethoprim's action in interfering with dihydrofolate reductase activity. The peripheral blood changes were slight.

Twelve-month toxicity studies in monkeys using dosages of 10 - 60 mg/kg of trimethoprim per day showed no signs of abnormal effects. A 60-week study in rats using dosages of 5 to 120 mg/kg/day was carried out, again with negative adverse results.

Reproduction Studies

Daily doses of 14 to 70 mg/kg of trimethoprim administered by intubation to rats on days 6 through 14 of gestation produced no teratogenic effects. In another study a daily dose of 133 mg/kg, administered to the rat on days 8 through 16 of gestation, did not produce teratogenic effects; however, a dose of 200 mg/kg or greater, given daily, was found to be teratogenic. Single doses of trimethoprim administered to rats on any single day between the 8th and 16th day of gestation had no effect on the fetus and dam up to and including a dose of 500 mg/kg. A single dose of 2000 mg/kg was lethal to most fetuses when given on the 8th or 9th day, and produced a high incidence of fetal malformations when given on day 10, 11 or 12.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

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