TRIMETHOPRIM TABLETS, USP

℞ only

2158
2159

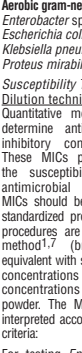
Rev. I 1/2012

To reduce the development of drug-resistant bacteria and maintain the effectiveness of trimethoprim tablets, USP and other antibacterial drugs, trimethoprim tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Trimethoprim is a synthetic antibacterial available in tablet form for oral administration. Each scored white tablet contains 100 mg trimethoprim or 200 mg trimethoprim.

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:



Inactive Ingredients

Colloidal silicon dioxide, dibasic calcium phosphate dihydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate.

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 of 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

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
Klebsiella 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[1,7] (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 (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[a] powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	0.5 to 2
Staphylococcus aureus ATCC 29213	1 to 4

[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[2,7] 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:

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

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥ 16	Susceptible (S)	≤ 4
11 to 15	Intermediate (I)	-
≤ 10	Resistant (R)	≥ 16

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 mcg trimethoprim[b] disk should provide the following zone diameters in these laboratory test quality control stains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	21 to 28
Staphylococcus aureus ATCC 25923	19 to 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 ≥ 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of trimethoprim tablets, USP and other antibacterial drugs, trimethoprim tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

Trimethoprim 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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including trimethoprim tablets, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antiobiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Prescribing trimethoprim tablets, USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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**).

Information for Patients

Patients should be counseled that antibacterial drugs including trimethoprim tablets, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When trimethoprim tablets, USP are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by trimethoprim tablets, USP or other antibacterial drugs in the future.

Reference ID: 3:

Rev. 1 /2012

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured in Canada By:
TEVA CANADA LIMITED
Toronto, Canada M1B 2K9

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure (as required).

REFERENCES

1. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Ninth Edition; CLSI Document M07-A9, Vol. 32, No. 2, CLSI, Wayne, PA, January, 2012.

2. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard-Eleventh Edition. CLSI Document M02-A11, Vol. 32, No. 1, CLSI, Wayne, PA, January, 2012.

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4. Lacey RW, Simpson MHC, Fawcett RS. Comparison of single-dose trimethoprim with a five-day course of the treatment of urinary tract infections in the elderly. Age and Ageing 10: 179-185, 1981.

5. Ewer TC, Bailey RR, Gilchrist NL, et al. Comparative study of norfloxacin and trimethoprim for the treatment of elderly patients with urinary tract infection. NZ Med J 101: 537-539, 1988.

6. Marinella MA. Trimethoprim-induced hyperkalemia: An analysis of reported cases. Geronotology 45: 209-212, 1999.

7. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. CLSI Document M100-S22 Vol. 32 No. 3, CLSI, Wayne, PA, January 2012.

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Dermatologic
Rash, pruritus, and parotoxic skin eruptions. At the recommended dosage regimens of 100 and 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 macropapular, 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 is 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. Folic acid should be given concurrently with trimethoprim to 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 and every 12 hours.

HOW SUPPLIED

Trimethoprim tablets, USP, 100 mg: White, round, convex tablet, debossed "9", scored, "3" on one side and debossed "2158" on the other, in bottle of 100.

Trimethoprim tablets, USP, 200 mg: white, round, scored, convex tablet, debossed "93" above the score and debossed "2159" below the score on one side and plain on the other, in bottles of 100.

The presence of trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations 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 shown mutagenic 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 aberrations were observed in cultured human leukocytes at trimethoprim concentrations 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 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[3] in a retrospective study, reported the outcome of 186 pregnancies in either placebo or trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 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. Purcell 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, trimethoprim 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 from conception through parturition and continuing through gestation 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 trimethoprim 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.

Geriatric Use

Clinical studies of trimethoprim tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience[4,5] has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Case reports of hyperkalemia in elderly patients receiving trimethoprim-sulfamethoxazole have been published.[6] Trimethoprim is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor possessium concentrations and to monitor renal function by calculating creatinine clearance.

ADVERSE REACTIONS

Most adverse effects encountered with trimethoprim were rash and pruritus.

Dermatologic
Rash, pruritus, and parotoxic skin eruptions. At the recommended dosage regimens of 100 and 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 macropapular, morbilliform, pruritic, and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

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