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Rebate**



PRIMSOL[®] solution

trimethoprim hydrochloride
oral solution 50 mg/5 mL

Please mail in the completed rebate form, along with the pharmacy receipt to the address provided to receive the rebate.

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*Please note: The pharmacy receipt comes with your prescription and differs from the cash register receipt in that it identifies the product purchased.

Send to: FSC Laboratories, Inc.
Attn: Primsol Rebate Program
6000 Fairview Road, Suite 600
Charlotte, NC 28210

Receive: \$20 refund check for prescription**.
**Not to exceed patient copay.

Rebates are not valid for prescriptions reimbursed under a federally funded health care program, including Medicare or Medicaid as well as similar state medical assistance programs. Offer void where prohibited by law, taxed, or restricted. Offer good only in USA. Void where and as prohibited by law, except for prescriptions that are NOT reimbursed by any third-party payer. FSC Laboratories reserves the right to rescind, revoke, or amend this offer without notice. Offer limited to one rebate per month.

By my signature below, I certify that I am not being reimbursed for this product by Medicare or Medicaid, any other federal or state program, including any state pharmaceutical assistance program or any other third-party payers. I also understand that I am responsible for any reporting or other requirements with respect to receipt of this rebate.

Name: _____

Address: _____

City: _____ State: _____ ZIP _____

Physician Name: _____

I have complied with all the terms of this offer.

Signature (*must be signed in order to be valid*)

For more information about FSC Pediatrics and our products, please visit us at www.fscpediatrics.com.
Please refer to the attached U.S. Prescribing Information for important product safety and dosing information.

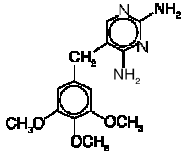
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Please allow 4-6 weeks for delivery.
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Primso[®] Solution
(trimethoprim hydrochloride oral solution)
Dye-free, alcohol-free, flavored solution,
50 mg trimethoprim per 5 mL

DESCRIPTION

PRIMSOL (trimethoprim hydrochloride oral solution) is a solution of the synthetic antibacterial trimethoprim in water prepared with the aid of hydrochloric acid. Each 5 mL for oral administration contains trimethoprim hydrochloride equivalent to 50 mg trimethoprim and the inactive ingredients bubble gum flavor, fructose, glycerin, methylparaben, monoammonium glycyrrhizinate, povidone, propylparaben, propylene glycol, saccharin sodium, sodium benzoate, sorbitol, water and hydrochloric acid and/or sodium hydroxide to adjust pH to a range of 3.0 - 5.0. Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. Trimethoprim is a white to cream-colored, odorless, bitter compound with a molecular formula of C₁₄H₁₈N₄O₃ and a molecular weight of 290.32 and the following structural formula:



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 plasma concentrations of approximately 1 mcg/mL occur 1 to 4 hours after oral administration of a single 100 mg dose. A single 200 mg dose will result in plasma concentrations approximately twice as high. The mean half-life of trimethoprim is approximately 9 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 section). During a 13-week study of trimethoprim tablets administered at a dosage of 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 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 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 concentrations 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.

Trimethoprim half-life, clearance, and volume of distribution vary with age. Excluding newborns, an apparent trend of increasing half-life, volume of distribution, and decreasing clearance is observed with increasing age until adulthood.

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

Trimethoprim also concentrates into middle ear fluid (MEF) very efficiently. In a study in children aged 1 to 12 years, administration of a single 4 mg/kg dose resulted in a mean peak MEF concentration of 2.0 mcg/mL.

Trimethoprim also passes the placental barrier and is excreted in breast 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 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.

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*)
Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic gram-negative microorganisms

Enterobacter species
Escherichia coli
Haemophilus influenzae (excluding beta-lactamase negative, ampicillin resistant strains)
Klebsiella pneumoniae
Proteus mirabilis

NOTE: Moraxella catarrhalis isolates were found consistently resistant to trimethoprim.

Susceptibility Tests

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method¹ (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 aerobic microorganisms isolated from urinary tract infections:

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

When testing Haemophilus influenzae^a

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1-2	Intermediate (I)
≥ 4	Resistant (R)

When testing Streptococcus pneumoniae^b

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
≥ 4	Resistant (R)

^a Interpretive criteria applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM).¹

^b Interpretive criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.¹

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	ATCC	MIC (mcg/mL)
Escherichia coli	ATCC 25922	0.5 - 2
Haemophilus influenzae ^b	ATCC 49247	0.06 - 0.5
Staphylococcus aureus	ATCC 29213	1 - 4
Streptococcus pneumoniae ^c	ATCC 49619	1 - 4

^a Trimethoprim very medium-dependent.

^b Range applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM).¹

^c Range applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.¹

Dilution techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² 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^a disk should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

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

For testing Haemophilus influenzae^b:

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

^a Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. 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.

^b Interpretive criteria applicable only to tests performed by disk diffusion method using Haemophilus Test Medium (HTM).²

Note:

Diffusion techniques are not recommended for determining susceptibility of Streptococcus pneumoniae to trimethoprim.

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^a disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism	ATCC	Zone Diameter (mm)
Escherichia coli	ATCC 25922	21 - 28
Haemophilus influenzae ^b	ATCC 49247	27 - 33
Staphylococcus aureus	ATCC 25923	19 - 26

^a Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. 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.

^b Range applicable only to tests performed by disk diffusion method using Haemophilus Test Medium (HTM).²

Note:

Diffusion techniques are not recommended for determining susceptibility of Streptococcus pneumoniae to trimethoprim.

INDICATIONS AND USAGE

PRIMSOL Solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Pediatric Patients:

Acute Otitis Media: For the treatment of acute otitis media due to susceptible strains of Streptococcus pneumoniae and Haemophilus influenzae.

NOTE: Moraxella catarrhalis isolates were found consistently resistant to trimethoprim in vitro. Therefore, when infection with Moraxella catarrhalis is suspected, the use of alternative antimicrobial agents should be considered. PRIMSOL is not indicated for prophylactic or prolonged administration in otitis media at any age.

Adults:

Urinary Tract Infections: 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.

CLINICAL STUDIES

The results of one multicenter, 30-day, comparative, randomized clinical trial without tympanocentesis in 262 pediatric patients with acute otitis media (AOM) are shown below. In this clinical trial, strict evaluability criteria were used to determine clinical response.

	PRIMSOL	SMX + TMP ^a
Enrolled	133	129
Evaluable	130	129
Clinical Cure	64/130 (49%)	63/129 (49%)
Clinical Improvement	30/130 (23%)	31/129 (24%)
Relapse/Recurrence	19/130 (15%)	18/129 (14%)
Outcome (based on 95% confidence interval)		PRIMSOL equivalent to TMP + SMX

^asulfamethoxazole + trimethoprim oral suspension