SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION, USP
200 mg / 40 mg per 5 mL

Each teaspoonful (5 mL) contains:
Sulfamethoxazole .................................. 200 mg
Trimethoprim ..................................... 40 mg
Alcohol .............................................. 0.26%

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP. Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Protect from light.

SHAKE WELL BEFORE USING.

16 fl oz (473 mL)

Hi-Tech Pharmacal Co., Inc.
Amityville, NY 11701

Rx only

16 oz. Sulfamethoxazole and Trimethoprim OS, USP
Cherry Flavor

Hi-Tech Pharmacal Co., Inc.
920 Avenue R Bldg. #200
Grand Prairie, TX 75050 (469)733-1506

Healthcare Packaging

Base Label

Hi-Tech PHARMACAL

SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION, USP
200 mg / 40 mg per 5 mL

Cherry Flavor

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16 fl oz (473 mL)

CHERRY FLAVOR

Hi-Tech Pharmacal Co., Inc.
Amityville, NY 11701

Hi-Tech PHARMACAL

NDC 50383-823-16

SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION, USP
200 mg / 40 mg per 5 mL

Cherry Flavor

Rx only

16 fl oz (473 mL)

Rev. 823:07 7/11

Hi-Tech PHARMACAL CO., INC.
Amityville, NY 11701

This proof is not intended for color representation. Please review for copy and positioning of graphics and text.

Reference ID: 3057440
Complete blood counts should be done frequently in patients receiving sulfamethoxazole and trimethoprim; if a significant... renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

It has been reported that sulfamethoxazole and trimethoprim may prolong the prothrombin time in patients who are... metabolism of phenytoin. Sulfamethoxazole and trimethoprim, when administered concurrently, have been reported to... rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfamethoxazole and trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole and trimethoprim, when administered concurrently, may... in elderly patients. Serum digoxin levels should be monitored.

Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin. Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly...

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for... antibacterial activity of sulfamethoxazole and trimethoprim.

Carcinogenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in... sulfamethoxazole and trimethoprim are not genotoxic in vivo or in vitro. Studies have been performed using the... in rats, oral doses of 533 mg/kg or 200 mg/kg produced teratologic effects... in a retrospective study, reported the outcome of 186 pregnancies during which the mother received sulfamethoxazole and trimethoprim.

CONTRAINDICATIONS

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions... or bone marrow depression. Severe skin reactions, generalized bone marrow suppression (see... of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal... in children: • Use of sulfamethoxazole and trimethoprim in children and infants is not recommended.

REVIEW FOR COPY AND POSITIONING

11

#4

APPROVED

REVIEW AND RE-PROOF

APPROVAL SIGNED AND DATED

Reference ID: 3057440
1-(5-methyl-3-isoxazolyl)sulfanilamide; the molecular formula is C10H11N3O3S. It is an almost white, odourless, bitter compound with a molecular weight of 245.22 g/mol and the following structural formula:

\[
\text{CH}_3
\]

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine; the molecular formula is C14H18N4O3. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3 g/mol and the following structural formula:

\[
\text{CH}_3
\]

Sulfamethoxazole and trimethoprim is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bile. These drugs are rapidly metabolized by acetylation. The acetylated metabolites of sulfamethoxazole and trimethoprim are eliminated in urine. The 4-acetylated metabolite is the major metabolite of both drugs. When administered together as sulfamethoxazole and trimethoprim, neither sulfamethoxazole nor trimethoprim are significantly excreted unchanged in urine or bile.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment.

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria. These are the dihydropteroate synthetase (DHPS) and dihydrofolate reductase (DHFR) steps. Sulfamethoxazole and trimethoprim inhibit these enzymes in a sequence of two sites.

Escherichia coli, Klebsiella species, Haemophilus influenzae, and Enterobacter species are susceptible to sulfamethoxazole and trimethoprim.

Susceptibility Testing Methods:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the drug concentrations likely to inhibit 90% (MIC90) or 99% (MIC99) of test organisms that may be encountered in clinical infections. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method using standardized inoculum concentrations and standardized concentrations of sulfamethoxazole/trimethoprim powder. The MIC values should be interpreted according to the following criteria:

- Susceptible (S): MIC ≤ 1 μg/mL for sulfamethoxazole and ≤ 1/19 μg/mL for trimethoprim
- Intermediate (I): 1 < MIC ≤ 4 μg/mL for sulfamethoxazole and 1/19 < MIC ≤ 2/38 μg/mL for trimethoprim
- Resistant (R): MIC > 4 μg/mL for sulfamethoxazole and MIC > 2/38 μg/mL for 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 sulfamethoxazole/trimethoprim.

In rare instances of significant local antimicrobial resistance in the patient's population, the MICs of all isolated bacteria may need to be considered.

Sulfamethoxazole and trimethoprim is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides. It is also contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

Side effects may include:

- Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with preexisting folic acid deficiency.
- Thrombocytopenia, which is reversible, may occur in patients receiving sulfamethoxazole and trimethoprim.
- High dosage of trimethoprim, as used in patients with impaired renal function, may be more prone to idiosyncratic reactions to sulfonamides.
- Patients who are "slow acetylators" may be more prone to reactions to sulfonamides.
- Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of secondary infection, and symptomatic and supportive treatment of CDAD may be required.

During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are prone to develop crystalluria (e.g., elderly patients, seriously ill patients, patients on diuretics, and patients with impaired renal function) should receive fluids to maintain urine output at least 1 mL/kg/day.

In patients with renal impairment, sulfamethoxazole and trimethoprim should be administered with caution. If renal function is substantially impaired, dose adjustments may be necessary. In patients with severe renal insufficiency, dosage adjustments should be made to ensure adequate drug concentrations are achieved.

Use in the Treatment of and Prophylaxis for Pneumocystis carinii pneumonia in individuals who are immunosuppressed and considered to be at an increased risk for pulmonary complications of Pneumocystis carinii pneumonia.
Hi-Tech Pharmacal Co., Inc.
16oz. Sulfamethoxazole and Trimethoprim OS, USP
Grape Flavor

SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION, USP 200 mg / 40 mg per 5 mL

Each teaspoonful (5 mL) contains:
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Trimethoprim ...................................... 40 mg
Alcohol ............................................... 0.26%

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP. Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Protect from light.

SHAKE WELL BEFORE USING.

16 fl oz (473 mL)

HI-TECH PHARMACAL Co., INC.
Amityville, NY 11701

Ref. 824:07 7/11

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APPROVAL SIGNATURE/DATE: ____________________________

Ref. ID: 3057440
Complete blood counts should be done frequently in patients receiving sulfamethoxazole and trimethoprim; if a significant decrease in platelets (with or without purpura), and hyperkalemia are the most frequently reported severe adverse reactions. In elderly patients, concurrent administration of thiazide diuretics may increase the incidence of thrombocytopenia with purpura. An increased incidence of thrombocytopenia with purpura has been reported in elderly patients concurrently receiving the anticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole and trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

There have been reports of marked but reversible nephrotoxicity with coadministration of sulfamethoxazole and trimethoprim in elderly patients. Serum digoxin levels should be monitored. In the literature, three cases of hyperkalemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and an angiotensin converting enzyme inhibitor.

The presence of sulfamethoxazole and 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. While there are no large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, the incidence of congenital abnormalities was 4.5% (3 of 66) in infants whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter. Sulfamethoxazole and trimethoprim is not recommended for infants younger than 2 months of age (see INDICATIONS).

Precautions:

Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and metabolic and nutritional disorders may occur among patients receiving sulfamethoxazole and trimethoprim. Hyperkalemia (see ADVERSE REACTIONS).

In patients with underlying disorders of potassium metabolism, with renal insufficiency or when given with potassium-sparing diuretics, the potassium levels should be monitored, and the dosage of potassium-sparing diuretics should be reduced or sulfamethoxazole and trimethoprim treatment discontinued if hyperkalemia occurs. Discontinuation of sulfamethoxazole and trimethoprim treatment is recommended to help lower potassium serum levels.

Known allergy to sulfonamides or trimethoprim is a contraindication for sulfamethoxazole and trimethoprim.

CONTRAINDICATIONS:

Sulfamethoxazole and trimethoprim is not recommended for infants younger than 2 months of age (see INDICATIONS).

Adverse Reactions:

The most frequent adverse reactions experienced during sulfamethoxazole and trimethoprim therapy were nausea, vomiting, diarrhea, abdominal pain, and flatulence. The frequency of these reactions was no greater than that observed with placebo. Other reactions reported are:

- Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia,
- Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.
- Metabolic and Nutritional: Hyperkalemia (see PRECAUTIONS: ADVERSE REACTIONS).
- Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. Hallucinations, depression, apathy, nervousness.
- Miscellaneous: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with sulfamethoxazole and trimethoprim.

OVERDOSAGE:

Acute: Upon signs of severe toxicity occurring, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored. Not recommended for use in pediatric patients less than 2 months of age.

Treatment:

- Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients, and Acute Otitis Media in Children:
  - Treatment of shigellosis.

Drug/Laboratory Test Interactions:

In vitro studies have shown that sulfamethoxazole and trimethoprim interfere with the azo-dye absorption test.

In patients with chronic renal insufficiency, sulphonamides have been shown to cause a false positive Jaffé reaction and to interfere with the glucose oxidase test for glucose in urine.

In the presence of sulfamethoxazole and trimethoprim, serum creatinine determinations may be spuriously elevated. The mechanism of this interference is not yet known.

Sulfamethoxazole and 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.

When administered to patients with underlying disorders of potassium metabolism, with renal insufficiency or when given with potassium-sparing diuretics, the potassium levels should be monitored, and the dosage of potassium-sparing diuretics should be reduced or sulfamethoxazole and trimethoprim treatment discontinued if hyperkalemia occurs. Discontinuation of sulfamethoxazole and trimethoprim treatment is recommended to help lower potassium serum levels.

Sulfamethoxazole and 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.


color representation. Please revise and re-proof.
**DESCRIPTION**

Sulfamethoxazole and trimethoprim is a synthetic antibacterial combination product containing 200 mg sulfamethoxazole and 40 mg trimethoprim per 5 mL for oral administration.

**Healthcare Packaging**

![Chemical structure](attachment:image.png)

Light yellow, odorless, bitter compound with a molecular weight of 290.3 and the following structural formula:

\[
\text{CH}_2\text{OCH}_3
\]

4-acetylation, although the glucuronide

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see section).

Detectable amounts of sulfamethoxazole and trimethoprim are present in the blood 24 hours after the dose.

**Glomerular filtration and tubular secretion.** Urine concentrations of both sulfamethoxazole and trimethoprim are reduced in patients with renal impairment. The free sulfamethoxazole is almost entirely excreted unchanged by the kidneys, whereas the free trimethoprim is extensively transformed to conjugated forms in the liver. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N-sulfates and glucuronides.

**Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA).** Trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

**in vitro (including susceptible enterotoxigenic strains implicated in traveler's diarrhea)**

**Species**

- **Enterobacter**
- **Haemophilus influenzae**
- **Streptococcus pneumoniae**

**Dilution Techniques:**

**GRAPHICS**

![Zone Diameter Ranges](attachment:image.png)

**Microorganism  Zone Diameter Ranges (mm)**

- **Escherichia coli**
  - ATCC 25922: 23–29
- **Haemophilus influenzae**
  - ATCC 49247: 0.03/0.59 – 0.25/4.75
- **Streptococcus pneumoniae**
  - ATCC 33186: may be tested with sulfamethoxazole/trimethoprim disks. A zone of inhibition ≥ 16 mm indicates susceptibility; a zone of inhibition of ≥ 10 mm suggests possible susceptibility. For testing either species, ATCC 49247 tested by broth microdilution (HTM).

**Interpretative Standards**

- **a.** These interpretative standards are applicable only to broth microdilution susceptibility tests with a 1.25/23.75 μg/mL sulfamethoxazole/trimethoprim disk.

**Test Medium (HTM).4**

- **c.** This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5 % defibrinated sheep blood.

**Urinary Tract Infections:**

For the treatment of urinary tract infections due to susceptible strains of the following organisms:

- **Escherichia coli**
- **Enterococcus faecalis**
- **Klebsiella pneumoniae**
- **Proteus mirabilis**

**Agent rather than the combination.**

**Acute Otitis Media:**

For the treatment of enteritis caused by susceptible strains of

- **Escherichia coli**
- **Streptococcus pneumoniae**
- **Staphylococcus aureus**

**Shigella flexneri**

**Shigella sonnei**

**Streptococcus:***

**Pneumonia:**

For the treatment of pneumonia (including Legionella pneumophila, Mycoplasma pneumoniae, and Pneumocystis carinii) caused by susceptible strains of the following organisms:

- **Legionella pneumophila**
- **Mycoplasma pneumoniae**
- **Pneumocystis carinii**

**WARNINGS**

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING FULMINANT HEPATIC NECROSIS, SEPTIC SHOCK, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

In rare cases, fever, arthralgia, pallor, purpura or jaundice may be early indications of serious reactions. These reactions have been reported in association with sulfonamide treatment.

**PRECAUTIONS**

Sulfamethoxazole and trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with glucose-6-phosphate dehydrogenase deficiency or kidney failure. These effects are reversible by folinic acid therapy.

Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

Antibacterial agents may alter the normal flora of the colon leading to overgrowth of toxigenic **Clostridium difficile**, which can cause pseudomembranous colitis. The clinical spectrum of **Clostridium difficile**-associated diarrhea includes mild, moderate and severe disease. For severe disease, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of the underlying infection and if indicated, administration of **vancomycin** or **metronidazole** is recommended. **Clostridium difficile** infection may need to be discontinued.

Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of the underlying infection and if indicated, administration of vancomycin or metronidazole is recommended.

**Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS):**

During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.