SULFAMETHOXAZOLE is a dihydrofolate reductase inhibitor. It is a white to light yellow, odorless, bitter compound. It has the following structural formula:

\[
\text{H}_2\text{N}-\text{C}-(5-\text{CH}_3-\text{ISOXAZOLYL})-\text{SO}_2\text{NH}_2
\]

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

**DESCRIPTION**

Sulfamethoxazole and trimethoprim oral suspension USP is in a synthetic antibiotic combination product. Sulfamethoxazole is \(\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_3\text{S}\), M.W. 250.32. Each teaspoonful (5 mL) of the oral suspension contains 200 mg sulfamethoxazole and 40 mg trimethoprim as the following inactive ingredients: 0.04% (w/v), carboxymethylcellulose sodium, cherry flavoring, citric acid, color red FD&C #40, dyes, gluten, gelatin, praspur, propylene glycol 80, purified water, saccharin sodium, sodium benzoate, and sorbitol solution.

**CLINICAL PHARMACOLOGY**

Sulfamethoxazole and trimethoprim oral suspension is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form (sulfamethoxazole glucuronide) that is present predominately as N-acetyl conjugate, although the glucuronide conjugate has been identified. The principal metabolites of sulfamethoxazole are the 1- and 3-oxides and the 1- and 4-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms, although 70% of sulfamethoxazole and 44% of trimethoprim are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim concentrations are considerably higher than are the concentrations in the blood.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. Absorption of sulfamethoxazole and trimethoprim is complete and unchanged by the presence or absence of food. The percent of dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethoxazole and trimethoprim is 74 to 78% for sulfamethoxazole, 16 to 18% for trimethoprim, 77 to 81% for total sulfamethoxazole and 16 to 18% for total trimethoprim. The steady-state mean plasma levels of free and total sulfamethoxazole were 64.7 mcg/mL and 68.0 mcg/mL, respectively. These steady-state levels were achieved after three days of drug administration. Excretion of sulfamethoxazole and trimethoprim is by the kidneys through both the glomerular filtrate and the tubular secretion. Concentrations of both sulfamethoxazole and trimethoprim are higher in the more concentrated urine of patients with renal failure. Patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage adjustments.

Sulfamethoxazole and trimethoprim oral suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**INDICATIONS AND USAGE**

Aerobic gram-positive microorganisms:

- *Streptococcus pneumoniae*
- *Staphylococcus aureus*

**Aerobic gram-negative microorganisms:**

- *Escherichia coli*
- *Shigella flexneri*

**Other Organisms:**

- *Pneumocystis carinii Pneumonia*

**Sensitivity Testing Methods**

**DIFFERENTIAL TREATMENT**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs) that are interpreted according to the following criteria: and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents is often complicated by the presence of noninfectious causes of diarrhea. Although sulfamethoxazole and trimethoprim are effective against *Shigella* infections, they are not effective against noroviruses, astroviruses, adenoviruses or rotaviruses. The finding of a pathogen that is susceptible to sulfamethoxazole and trimethoprim should not be taken as evidence that it is the cause of the patient's diarrhea. In the absence of contradictory evidence, the finding of a sulfa-susceptible *Shigella* strain indicates that the patient's diarrhea is caused by *Shigella*. The finding of a sulfa-resistant *Shigella* strain indicates that the patient's diarrhea is not caused by *Shigella* and probably indicates a nonbacterial cause for the diarrhea. However, the presence of sulfa-susceptible or sulfa-resistant *Shigella* strains does not prove the causal role of *Shigella* in the patient's diarrhea.

**Acute Exacerbations of Chronic Bronchitis in Adults**

For the treatment of acute exacerbations of chronic bronchitis due to streptococcal or pneumococcal etiologies, the following dilution techniques may be used. The zone diameter interpretative standards procedure require the use of laboratory control microorganisms to correct the technical aspects of the laboratory procedures. Standardized procedures are based on a dilution method4 (broth or peptone water, saccharin sodium, sodium benzoate, and sorbitol solution.

Each teaspoonful (5 mL) of the oral suspension contains 200 mg sulfamethoxazole and 40 mg trimethoprim as the following inactive ingredients: 0.04% (w/v), carboxymethylcellulose sodium, cherry flavoring, citric acid, color red FD&C #40, dyes, gluten, gelatin, praspur, propylene glycol 80, purified water, saccharin sodium, sodium benzoate, and sorbitol solution.

This quality control range is applicable only to tests performed by the broth dilution method only interpretation involves correlation of the diameter obtained in the disk test with the MIC for sulfamethoxazole and trimethoprim oral suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**WARNINGS**

**FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES.**

Although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic failure, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamides, including sulfamethoxazole and trimethoprim, should be discontinued at the first appearance of skin rash or any sign of adverse reaction. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious bowel disorders (see PRECAUTIONS). C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertrophic producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD is considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over three to seven days after the administration of the agent. The quality of CDAD-producing strains of *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic therapy of *C. difficile* is available. Each teaspoonful (5 mL) of the oral suspension contains 200 mg sulfamethoxazole and 40 mg trimethoprim as the following inactive ingredients: 0.04% (w/v), carboxymethylcellulose sodium, cherry flavoring, citric acid, color red FD&C #40, dyes, gluten, gelatin, praspur, propylene glycol 80, purified water, saccharin sodium, sodium benzoate, and sorbitol solution.

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In some rabbit studies, an overall increase in fetal loss (dead and resorbed and two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In the highest dose which did not cause cleft palates in rats was 512 mg/kg.

Sulfamethoxazole and trimethoprim. Observations of leukocytes obtained from patients concentrations used exceeded blood levels of these compounds following therapy with Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim. Specific hereditary factors, such as excess levels of folate derived from bacterial synthesis, may predispose an individual to the development of toxicity.

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé potentiates the effect of oral hypoglycemics. Increased digoxin blood levels can occur with concomitant sulfamethoxazole and trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

There have been reports of marked but reversible nephrotoxicity with coadministration of sulfamethoxazole and trimethoprim in renal transplant recipients. Increased digoxin blood levels may occur in patients who are also receiving indomethacin.

Occasional reports suggest that patients receiving gynecomastia in males as a result of prolonged treatment with methotrexate. The efficacy of tricyclic antidepressants may decrease when coadministered with sulfamethoxazole and trimethoprim. Like other sulfonamide-containing drugs, sulfamethoxazole and trimethoprim potentiate the effect of oral hypoglycemics.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine. In three patients, the drug has been reported after concomitant intake of sulfamethoxazole/trimethoprim and an antiplatelet causing enzyme inhibitor.

Drug/Laboratory Test Interactions Sulfamethoxazole and trimethoprim. Specifically, the trimethoprim component, can interfere with the measurement of 17-ketosteroids using the competitive binding technique (CBP) when a bacterial dihydropyrimidinase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé 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 sulfamethoxazole and trimethoprim. Mutagenicity Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim. The results of the in vitro mammalian somatic cell mutagenicity tests conducted with sulfamethoxazole and trimethoprim were negative.

Carcinogenicity in animals has not been tested in humans in any long-term study. The use of sulfamethoxazole and trimethoprim in combination has the potential to alter the normal flora of the gut. The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé test. In a study of leukocyte cultures in vitro with sulfamethoxazole and trimethoprim alone or in combination, the combination inhibited DNA synthesis at all protein concentrations tested. The presence of sulfamethoxazole and trimethoprim revealed no chromosomal abnormalities. Impairment of fertility. No adverse effects on fertility or general reproductive performance were observed in rats and dogs after 6 months as high as 350 mg/kg/day sulfamethoxazole plus 70 mg/kg/day trimethoprim.

Pregnancy Teratogenic Effects Pregnancy category C In rats, oral doses of 533 mg/kg or 200 mg/kg produced teratogenic effects manifested mainly as cleft palate. The highest dose which did not cause cleft palate in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palate was observed in one litter out of 9 when 355 mg/kg sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, there was an overall increase in fetal loss (dead and resorbed and malformed fetuses) associated with doses of trimethoprim 6 times the human therapeutic dose.

While very few, large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, Brumfit and Purcell in a retrospective study, reported the outcome of 106 pregnancies during which the mother received either placebo or sulfamethoxazole or trimethoprim. In 82 women, no congenital abnormalities were found. In 14 cases (3.5% of 396) in those who received placebo and 3.3% (12 of 360) in those receiving sulfamethoxazole or trimethoprim. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfit and Purcell did not find congenital abnormalities in 35 children whose mothers received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter.

Because sulfamethoxazole and trimethoprim may interfere with folate metabolism, sulfamethoxazole and trimethoprim oral suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects See CONTRAINDICATIONS section.

Nursing Mothers See CONTRAINDICATIONS section.

Pediatric Use Clinical studies of sulfamethoxazole and trimethoprim oral suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Geriatric Use Clinical studies of sulfamethoxazole and trimethoprim oral suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, concurrent use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS sections), a specific decrease in platelets (with or without purpura), and hyperkalemia are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving these drugs, particularly those patients in whom the use of one drug is being stopped and the other drug is being started, the possibility of an additive effect should be considered.

For Patients With Impaired Renal Function A decrease in creatinine clearance, a reduced dosage should be employed using the following table.

Acute Exacerbations of Chronic Bronchitis in Adults The recommended dosage for treatment of acute exacerbations of chronic bronchitis is 400 mg sulfamethoxazole and trimethoprim oral suspension every 12 hours for 14 days.

For the lower limit dose (15 mg/kg sulfamethoxazole and 15 mg trimethoprim per 24 hours) administer 75% of the dose in the above table.

Prophylaxis Adults The recommended dosage for prophylaxis in adults is four doses (20 mL) of the oral suspension daily.

Children For children, the recommended dose is 750 mg/m²/day sulfamethoxazole with 750 mg/m²/day trimethoprim given orally once daily for 3 consecutive days per week. The total daily dose should not exceed 1600 mg sulfamethoxazole and 320 mg trimethoprim. The following table is a guideline for the attainment of this dosage in children:

For the overweight child (75 mg/kg sulfamethoxazole and 15 mg trimethoprim per 24 hours) administer 75% of the dose in the above table.

Traveler’s Diarrhea in Adults For the treatment of traveler’s diarrhea, the usual adult dosage is 40 mL of sulfamethoxazole and trimethoprim oral suspension every 12 hours for 3 days.

Now Supplied Sulfamethoxazole and trimethoprim oral suspension USP contains 200 mg sulfamethoxazole and 40 mg trimethoprim in each teaspoonful (5 mL). Available as a pink, cherry-flavored syrup suspension in one 5 (473 mL) bottle.

Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature) and protect from light. SHAKE WELL BEFORE USING. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant cap. 0.5 mg/mL

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-800-438-2727, M3X1 and drug.safety@tevapharmam.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.


44 16 2 (10 mL) 66 30 3 (15 mL) 88 40 4 (20 mL)

lb kg Teaspoonfuls

18 8 1 (5 mL) 36 16 2 (10 mL) 54 24 3 (15 mL) 72 32 4 (20 mL) 88 40 5 (25 mL) 114 56 6 (30 mL) 141 64 8 (40 mL) 168 80 10 (50 mL)

TEVA PHARMACEUTICALS USA

Sulfamethoxazole and trimethoprim oral suspension is not recommended for infants 2 months of age or younger. The recommended dosage for children with urinary tract infections or acute otitis media is 15 to 30 1/2 the Usual Regimen.

Reference ID: 3172378

Sulfamethoxazole and trimethoprim oral suspension is not recommended for infants 2 months of age or older.

For the younger child (75 mg/kg sulfamethoxazole and 15 mg trimethoprim per 24 hours) administer 75% of the dose in the above table.

Chronic renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis, including kidney failure, may occur with concomitant sulfamethoxazole and trimethoprim therapy, especially in elderly patients. Serum creatinine levels should be monitored.

Sulfamethoxazole and trimethoprim oral suspension is not recommended for infants 2 months of age or younger. The recommended dosage for children with urinary tract infections or acute otitis media is 15 to 30 1/2 the Usual Regimen.

For the older child (75 mg/kg sulfamethoxazole and 15 mg trimethoprim per 24 hours) administer 75% of the dose in the above table.