

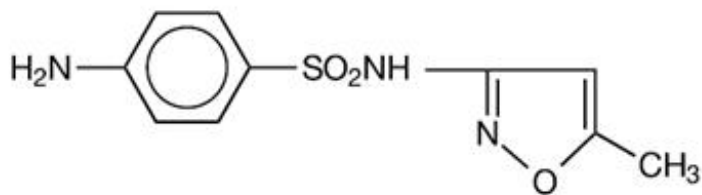
SULFAMETHOXAZOLE AND TRIMETHOPRIM- sulfamethoxazole and trimethoprim tablet
Amneal Pharmaceuticals of New York, LLC

Sulfamethoxazole and Trimethoprim Tablets and Double Strength Tablets, USP

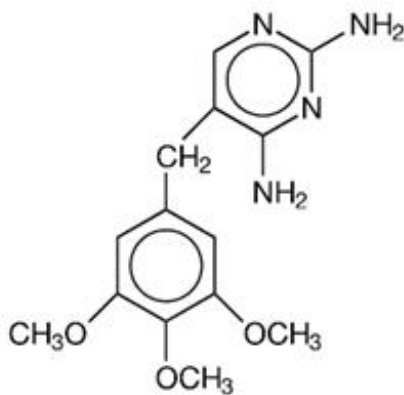
DESCRIPTION

Sulfamethoxazole and trimethoprim is a synthetic antibacterial combination product available in DS (double strength) tablets, each containing 800 mg sulfamethoxazole, USP and 160 mg trimethoprim, USP; in tablets, each containing 400 mg sulfamethoxazole, USP and 80 mg trimethoprim, USP for oral administration.

Sulfamethoxazole, USP is *N*¹-(5-methyl-3-isoxazolyl) sulfanilamide; the molecular formula is C₁₀H₁₁N₃O₃S. It is almost white, odorless, tasteless compound with a molecular weight of 253.28 and the following structural formula:



Trimethoprim, USP 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. It has the following structural formula:



Inactive Ingredients: Magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Sulfamethoxazole and trimethoprim 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 is metabolized in humans to at least 5 metabolites: the *N*₄-acetyl-, *N*₄-hydroxy-, 5-methylhydroxy-, *N*₄-acetyl-5-methylhydroxy-sulfamethoxazole metabolites and an *N*-glucuronide conjugate. The formulation of *N*₄-hydroxy

metabolite is mediated *via* CYP2C9.

Trimethoprim is metabolized *in vitro* to 11 different metabolites, of which, five are glutathione adducts and six are oxidative metabolites, including the major metabolites, 1- and 3-oxides and the 3- and 4-hydroxy derivatives.

The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms.

In vitro studies suggest that trimethoprim is a substrate of P-glycoprotein, OCT1 and OCT2, and that sulfamethoxazole is not a substrate of P-glycoprotein.

Approximately 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 does not influence the protein binding of sulfamethoxazole.

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 **DOSAGE AND ADMINISTRATION** section). Detectable amounts of sulfamethoxazole and trimethoprim are present in the blood 24 hours after drug administration. During administration of 800 mg sulfamethoxazole and 160 mg trimethoprim b.i.d., the mean steady-state plasma concentration of trimethoprim was 1.72 mcg/mL. The steady-state mean plasma levels of free and total sulfamethoxazole were 57.4 mcg/mL and 68 mcg/mL, respectively. These steady-state levels were achieved after three days of drug administration.¹ Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethoxazole and trimethoprim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N₄-acetylated metabolite.² When administered together as sulfamethoxazole and trimethoprim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both sulfamethoxazole and trimethoprim distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in human milk.

Geriatric Pharmacokinetics: The pharmacokinetics of sulfamethoxazole 800 mg and trimethoprim 160 mg were studied in 6 geriatric subjects (mean age: 78.6 years) and 6 young healthy subjects (mean age: 29.3 years) using a non-US approved formulation. Pharmacokinetic values for sulfamethoxazole in geriatric subjects were similar to those observed in young adult subjects. The mean renal clearance of trimethoprim was significantly lower in geriatric subjects compared with young adult subjects (19 mL/h/kg vs. 55 mL/h/kg). However, after normalizing by body weight, the apparent total body clearance of trimethoprim was on average 19% lower in geriatric subjects compared with young adult subjects.³

Microbiology

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

Sulfamethoxazole and trimethoprim have 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:

Streptococcus pneumoniae

Aerobic Gram-Negative Microorganisms:

Escherichia coli (including susceptible enterotoxigenic strains implicated in traveler's diarrhea)

Klebsiella species

Enterobacter species

Haemophilus influenzae

Morganella morganii

Proteus mirabilis

Proteus vulgaris

Shigella flexneri

Shigella sonnei

Other Organisms:

Pneumocystis jiroveci

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

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 test method (broth or agar)^{4,15}. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method^{14,15}. This procedure uses paper disks impregnated with 1.25/23.75 mcg of trimethoprim/sulfamethoxazole to test the susceptibility of microorganisms to trimethoprim/sulfamethoxazole. The disc diffusion interpretive criteria are provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Trimethoprim/Sulfamethoxazole

Bacteria	Minimal Inhibitory Concentration			Zone Diameter		
	(mcg/mL)			(mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤ 2/38	-	≥ 4/76	≥ 16	11 to 15	≤ 10
Haemophilus influenzae	≤ 0.5/9.5	1/19 to 2/38	≥ 4/76	≥ 16	11 to 15	≤ 10
Streptococcus pneumoniae	≤ 0.5/9.5	1/19 to 2/38	≥ 4/76	≥ 19	16 to 18	≤ 15

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the site of infection necessary to inhibit growth of the pathogen. 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 that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay and the techniques of the individuals performing the test^{4, 14, 15}. Standard trimethoprim/sulfamethoxazole powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 1.25/23.75 mcg trimethoprim/sulfamethoxazole disk the criteria in Table 2 should be achieved.

QC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)
<i>Escherichia coli</i> ATCC 25922	≤ 0.5/9.5	23 to 29
<i>Haemophilus influenzae</i> ATCC 49247	0.03/0.59 to 0.25/4.75	24 to 32
<i>Streptococcus pneumoniae</i> ATCC 49619	0.12/2.4 to 1/19	20 to 28

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfamethoxazole and trimethoprim tablets, USP and other antibacterial drugs, sulfamethoxazole and 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.

Urinary Tract Infections: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *Proteus mirabilis* and *Proteus vulgaris*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Acute Otitis Media: For the treatment of acute otitis media in pediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of sulfamethoxazole and trimethoprim in pediatric patients under two years of age. Sulfamethoxazole and trimethoprim is not indicated for prophylactic or prolonged administration in otitis media at any age.

Acute Exacerbations of Chronic Bronchitis in Adults: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when a physician deems that sulfamethoxazole and trimethoprim could offer some advantage over the use of a single antimicrobial agent.

Shigellosis: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Pneumocystis jiroveci Pneumonia: For the treatment of documented *Pneumocystis jiroveci* pneumonia and for prophylaxis against *P. jiroveci* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *P. jiroveci* pneumonia.

Traveler's Diarrhea in Adults: For the treatment of traveler's diarrhea due to susceptible strains of enterotoxigenic *E. coli*.

CONTRAINDICATIONS

Sulfamethoxazole and trimethoprim is contraindicated in patients with a known hypersensitivity to trimethoprim, USP or sulfonamides, in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim, USP and/or sulfonamides, and in patients with documented megaloblastic anemia due to folate deficiency.

Sulfamethoxazole and trimethoprim is contraindicated in pediatric patients less than 2 months of age. Sulfamethoxazole and trimethoprim is also contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

WARNINGS

WARNINGS

Embryofetal Toxicity

Some epidemiologic studies suggest that exposure to sulfamethoxazole/trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular malformations, urinary tract defects, oral clefts, and club foot. If sulfamethoxazole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the fetus.

Hypersensitivity and Other Fatal Reactions

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.

Sulfonamides, including sulfonamide-containing products such as sulfamethoxazole/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 blood disorders (see **PRECAUTIONS**). Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura or jaundice may be early indications of serious reactions.

Cough, shortness of breath and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

Thrombocytopenia

Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole and trimethoprim.

Streptococcal Infections and Rheumatic Fever

The sulfonamides should not be used for treatment of group A β -hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent

sequelae such as rheumatic fever.

***Clostridium difficile* associated diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including sulfamethoxazole and trimethoprim, 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 antibiotic 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.

Adjunctive treatment with Leucovorin for Pneumocystis jiroveci pneumonia

Treatment failure and excess mortality were observed when trimethoprim-sulfamethoxazole was used concomitantly with leucovorin for the treatment of HIV positive patients with *Pneumocystis jiroveci* pneumonia in a randomized placebo controlled trial.⁶ Co-administration of trimethoprim-sulfamethoxazole and leucovorin during treatment of *Pneumocystis jiroveci* pneumonia should be avoided.

PRECAUTIONS

Development of drug resistant bacteria

Prescribing sulfamethoxazole and trimethoprim tablets 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.

Folate deficiency

Sulfamethoxazole and trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome and patients in malnutrition states) and to those with severe allergies or bronchial asthma.

Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with preexisting folic acid deficiency or kidney failure. These effects are reversible by folic acid therapy.

Hemolysis

In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Hypoglycemia

Cases of hypoglycemia in non-diabetic patients treated with sulfamethoxazole and trimethoprim are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of sulfamethoxazole and trimethoprim are particularly at risk.

Phenylalanine metabolism

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

Porphyria and Hypothyroidism

As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

Use in the Treatment of and Prophylaxis for Pneumocystis jiroveci Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to sulfamethoxazole and trimethoprim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with sulfamethoxazole and trimethoprim therapy in AIDS patients who are being treated for *P. jiroveci* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole and trimethoprim in non-AIDS patients. Adverse effects are generally less severe in patients receiving sulfamethoxazole and trimethoprim for prophylaxis. A history of mild intolerance to sulfamethoxazole and trimethoprim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis.⁷ However, if a patient develops skin rash or any sign of adverse reaction, therapy with sulfamethoxazole and trimethoprim should be reevaluated (see **WARNINGS**).

Co-administration of sulfamethoxazole and trimethoprim and leucovorin should be avoided with *P. jiroveci* pneumonia (see **WARNINGS**).

Electrolyte Abnormalities

High dosage of trimethoprim, as used in patients with *P. jiroveci* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

Severe and symptomatic hyponatremia can occur in patients receiving sulfamethoxazole and trimethoprim, particularly for the treatment of *P. jiroveci* pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications.

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.

Information for Patients: Patients should be counseled that antibacterial drugs including sulfamethoxazole and trimethoprim tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When sulfamethoxazole and trimethoprim tablets 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 sulfamethoxazole and trimethoprim tablets or other antibacterial drugs in the future.

Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests: Complete blood counts should be done frequently in patients receiving sulfamethoxazole and trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole and trimethoprim should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions:

Potential for Sulfamethoxazole and Trimethoprim to Affect Other Drugs

Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when sulfamethoxazole and trimethoprim is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2.

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

It has been reported that sulfamethoxazole and trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin (a CYP2C9 substrate). 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.

Sulfamethoxazole and trimethoprim may inhibit the hepatic metabolism of phenytoin (a CYP2C9 substrate). Sulfamethoxazole and trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

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 and cyclosporine in renal transplant recipients.

Increased digoxin blood levels can occur with concomitant sulfamethoxazole and trimethoprim therapy, especially 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 may develop megaloblastic anemia if sulfamethoxazole and trimethoprim is prescribed.

The efficacy of tricyclic antidepressants can decrease when coadministered with sulfamethoxazole and trimethoprim.

Sulfamethoxazole and trimethoprim potentiates the effect of oral hypoglycemics that are metabolized by CYP2C8 (e.g., pioglitazone, repaglinide, and rosiglitazone) or CYP2C9 (e.g., glipizide and glyburide) or eliminated renally *via* OCT2 (e.g., metformin). Additional monitoring of blood glucose may be warranted.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin, have also been reported.

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.^{8,9}

Drug/Laboratory Test Interactions: Sulfamethoxazole and trimethoprim, specifically the trimethoprim component, 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 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Sulfamethoxazole was not carcinogenic when assessed in a 26-week tumorigenic mouse (Tg-rasH2) study at doses up to 400 mg/kg/day sulfamethoxazole; equivalent to 2.4-fold the

human systemic exposure (at a daily dose of 800 mg sulfamethoxazole *b.i.d.*).

Mutagenesis: *In vitro* reverse mutation bacterial tests according to the standard protocol have not been performed with sulfamethoxazole and trimethoprim in combination. An *in vitro* chromosomal aberration test in human lymphocytes with sulfamethoxazole/trimethoprim was negative. In *in vitro* and *in vivo* tests in animal species, sulfamethoxazole/trimethoprim did not damage chromosomes. *In vivo* micronucleus assays were positive following oral administration of sulfamethoxazole/trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethoxazole and trimethoprim revealed no chromosomal abnormalities.

Sulfamethoxazole alone was positive in an *in vitro* reverse mutation bacterial assay and in *in vitro* micronucleus assays using cultured human lymphocytes.

Trimethoprim alone was negative in *in vitro* reverse mutation bacterial assays and in *in vitro* chromosomal aberration assays with Chinese Hamster ovary or lung cells with or without S9 activation. In *in vitro* Comet, micronucleus and chromosomal damage assays using cultured human lymphocytes, trimethoprim was positive. In mice following oral administration of trimethoprim, no DNA damage in Comet assays of liver, kidney, lung, spleen, or bone marrow was recorded.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 350 mg/kg/day sulfamethoxazole plus 70 mg/kg/day trimethoprim doses roughly two times the recommended human daily dose on a body surface area basis.

Pregnancy:

While there are no large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, Brumfitt and Pursell, 10 in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or sulfamethoxazole and trimethoprim. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving sulfamethoxazole and trimethoprim. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter.

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

Teratogenic Effects: Pregnancy Category D.

Human Data:

While there are no large prospective, well controlled studies in pregnant women and their babies, some retrospective epidemiologic studies suggest an association between first trimester exposure to sulfamethoxazole/trimethoprim with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular abnormalities, urinary tract defects, oral clefts, and club foot. These studies, however, were limited by the small number of exposed cases and the lack of adjustment for multiple statistical comparisons and confounders. These studies are further limited by recall, selection, and information biases, and by limited generalizability of their findings. Lastly, outcome measures varied between studies, limiting cross-study comparisons. Alternatively, other epidemiologic studies did not detect statistically significant associations between sulfamethoxazole/trimethoprim exposure and specific malformations.

Animal Data:

In rats, oral doses of either 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palates. These doses are approximately 5 and 6 times the recommended human total daily dose on a body surface area basis. 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 some rabbit studies, an overall increase in fetal loss (dead and resorbed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose based on body surface area.

Nonteratogenic Effects: See **CONTRAINDICATIONS** section.

Nursing Mothers: Levels of trimethoprim/sulfamethoxazole in breast milk are approximately 2% to 5% of the recommended daily dose for infants over 2 months of age. Caution should be exercised when sulfamethoxazole and trimethoprim is administered to a nursing woman, especially when breastfeeding, jaundiced, ill, stressed, or premature infants because of the potential risk of bilirubin displacement and kernicterus.

Pediatric Use: Sulfamethoxazole and trimethoprim is contraindicated for infants younger than 2 months of age (see **INDICATIONS** and **CONTRAINDICATIONS** sections).

Geriatric Use: Clinical studies of sulfamethoxazole and trimethoprim 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, possible folate deficiency, or concomitant 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 certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels can occur with concomitant sulfamethoxazole and trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored. Hematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folic acid therapy. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimize risks of undesired reactions (see **DOSAGE AND ADMINISTRATION** section). The trimethoprim component of sulfamethoxazole and trimethoprim may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency or when given concomitantly with drugs known to induce hyperkalemia, such as angiotensin converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of sulfamethoxazole and trimethoprim treatment is recommended to help lower potassium serum levels. Sulfamethoxazole and Trimethoprim Tablets contain 1.8 mg sodium (0.08 mEq) of sodium per tablet. Sulfamethoxazole and Trimethoprim Double Strength Tablets contain 3.6 mg (0.16 mEq) of sodium per tablet.

Pharmacokinetics parameters for sulfamethoxazole were similar for geriatric subjects and younger adult subjects. The mean maximum serum trimethoprim concentration was higher and mean renal clearance of trimethoprim was lower in geriatric subjects compared with younger subjects (see **CLINICAL PHARMACOLOGY: Geriatric Pharmacokinetics**).

ADVERSE REACTIONS

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).**

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic

myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, 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.

Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.

Metabolic and Nutritional: Hyperkalemia, hyponatremia (see **PRECAUTIONS: Electrolyte Abnormalities**).

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with sulfamethoxazole and trimethoprim, mainly in AIDS patients.

Respiratory: Cough, shortness of breath and pulmonary infiltrates (see **WARNINGS**).

Miscellaneous: Weakness, fatigue, insomnia.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of trimethoprim-sulfamethoxazole. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Thrombotic thrombocytopenia purpura
- Idiopathic thrombocytopenic purpura
- QT prolongation resulting in ventricular tachycardia and *torsade de pointes*

OVERDOSAGE

Acute: The amount of a single dose of sulfamethoxazole and trimethoprim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating sulfamethoxazole and trimethoprim.

Chronic: Use of sulfamethoxazole and 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, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored.

DOSAGE AND ADMINISTRATION

Sulfamethoxazole and trimethoprim tablets, USP are contraindicated in pediatric patients less than 2 months of age.

Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients, and Acute Otitis Media in Children:

Adults: The usual adult dosage in the treatment of urinary tract infections is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet, USP or 2 sulfamethoxazole and trimethoprim tablets, USP every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 40 mg/kg sulfamethoxazole, USP and 8 mg/kg trimethoprim, USP per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage:

Children 2 months of age or older:

Weight		Dose – every 12 hours
lb	kg	Tablets
22	10	-
44	20	1
66	30	1 ½
88	40	2 or 1 DS tablet

For Patients with Impaired Renal Function: When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15 to 30	1/2 the usual regimen
Below 15	Use not recommended

Acute Exacerbations of Chronic Bronchitis in Adults:

The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is 1 sulfamethoxazole and trimethoprim double strength tablet, USP, or 2 sulfamethoxazole and trimethoprim single strength tablets, USP, every 12 hours for 14 days.

Pneumocystis Jiroveci Pneumonia

Treatment: Adults and Children:

The recommended dosage for treatment of patients with documented *Pneumocystis jiroveci* pneumonia is 75 to 100 mg/kg sulfamethoxazole, USP and 15 to 20 mg/kg trimethoprim, USP per 24 hours given in equally divided doses every 6 hours for 14 to 21 days.¹¹ The following table is a guideline for the upper limit of this dosage:

Weight		Dose – every 6 hours
lb	kg	Tablets
18	8	-
35	16	1
53	24	1 ½
70	32	2 or 1 DS tablet
88	40	2 ½
106	48	3 or 1 ½ DS tablets
141	64	4 or 2 DS tablets
176	80	5 or 2 ½ DS tablets

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

Prophylaxis

Adults:

The recommended dosage for prophylaxis in adults is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet, USP daily.¹²

Children:

For children, the recommended dose is 750 mg/m²/day sulfamethoxazole, USP with 150 mg/m²/day trimethoprim, USP given orally in equally divided doses twice a day, on 3 consecutive days per week.

The total daily dose should not exceed 1600 mg sulfamethoxazole, USP and 320 mg trimethoprim, USP.¹³ The following table is a guideline for the attainment of this dosage in children:

Body Surface Area	Dose – every 12 hours
(m ²)	Tablets
0.26	-
0.53	½
1.06	1

Traveler's Diarrhea in Adults:

For the treatment of traveler's diarrhea, the usual adult dosage is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet, USP or 2 sulfamethoxazole and trimethoprim single strength tablets, USP every 12 hours for 5 days.

HOW SUPPLIED

Sulfamethoxazole and Trimethoprim Tablets, USP are supplied as follows:

Sulfamethoxazole and Trimethoprim DS (double strength) Tablets, USP, **800 mg/160 mg**, are supplied as white, oval, bisected tablets debossed "IP" bisect "272" on one side.

They are available as follows:

Bottles of 10:	NDC 53746-272-11
Bottles of 24:	NDC 53746-272-24
Bottles of 100:	NDC 53746-272-01
Bottles of 250:	NDC 53746-272-02

Bottles of 500: NDC 53746-272-05

Sulfamethoxazole and Trimethoprim Tablets, USP, **400 mg/80 mg**, are supplied as white, round, bisected tablets debossed “IP” over “271” on one side.

They are available as follows:

Bottles of 50: NDC 53746-271-50

Bottles of 100: NDC 53746-271-01

Bottles of 500: NDC 53746-271-05

Bottles of 1000: NDC 53746-271-10

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

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

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14. **Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 11th ed. CLSI document M02–A11, CLSI, Wayne, PA, 2012.***
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Susceptibility Testing; Twenty-third Informational Supplement, CLSI document M100–S23. CLSI document M100–S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.


Distributed by:
Amneal Pharmaceuticals
Bridgewater, NJ 08807
Rev. 10-2015-00

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL


NDC 53746-271-01

**Sulfamethoxazole
and Trimethoprim
Tablets, USP**

400 mg/80 mg



Rx only
100 TABLETS



Each tablet contains:
Sulfamethoxazole, USP..... 400 mg
Trimethoprim, USP..... 80 mg


USUAL DOSAGE: See package insert.

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

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

Distributed by: **Amneal Pharmaceuticals**
Bridgewater, NJ 08807

Rev. 10-2015-00



400 mg/80 mg Label

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 53746-272-01

Sulfamethoxazole and Trimethoprim Tablets, USP

800 mg/160 mg

**DOUBLE
STRENGTH**



Rx only

100 TABLETS

Each tablet contains:

Sulfamethoxazole, USP 800 mg
Trimethoprim, USP 160 mg

USUAL DOSAGE: See package insert.

**DISPENSE IN TIGHT, LIGHT-RESISTANT
CONTAINER.**

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

Distributed by: **Amneal Pharmaceuticals**
Bridgewater, NJ 08807

Rev. 10-2015-00



800 mg/160 mg Label

SULFAMETHOXAZOLE AND TRIMETHOPRIM

sulfamethoxazole and trimethoprim tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:53746-271
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SULFAMETHOXAZOLE (UNII: JE4238 1TNV) (SULFAMETHOXAZOLE - UNII:JE4238 1TNV)	SULFAMETHOXAZOLE	400 mg
TRIMETHOPRIM (UNII: AN164J8 Y0 X) (TRIMETHOPRIM - UNII:AN164J8 Y0 X)	TRIMETHOPRIM	80 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6 I30)	
POVIDONE (UNII: FZ989 GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	WHITE	Score	2 pieces
Shape	OVAL	Size	13mm
Flavor		Imprint Code	IP;271

Contains**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53746-271-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/25/2010	
2	NDC:53746-271-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	02/25/2010	
3	NDC:53746-271-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	02/25/2010	
4	NDC:53746-271-50	50 in 1 BOTTLE; Type 0: Not a Combination Product	02/25/2010	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076899	02/25/2010	

SULFAMETHOXAZOLE AND TRIMETHOPRIM

sulfamethoxazole and trimethoprim tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:53746-272
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SULFAMETHOXAZOLE (UNII: JE42381TNV) (SULFAMETHOXAZOLE - UNII:JE42381TNV)	SULFAMETHOXAZOLE	800 mg
TRIMETHOPRIM (UNII: AN164J8Y0X) (TRIMETHOPRIM - UNII:AN164J8Y0X)	TRIMETHOPRIM	160 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE (UNII: FZ989GH94E)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	WHITE	Score	2 pieces
Shape	OVAL	Size	19mm
Flavor		Imprint Code	IP;272
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53746-272-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2010	
2	NDC:53746-272-02	250 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2010	
3	NDC:53746-272-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2010	
4	NDC:53746-272-11	10 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2010	
5	NDC:53746-272-24	24 in 1 BOTTLE; Type 0: Not a Combination Product	09/13/2010	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076899	09/13/2010	

Labeler - Amneal Pharmaceuticals of New York, LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals of New York, LLC		831227801	ANALYSIS(53746-271, 53746-272) , LABEL(53746-271, 53746-272) , MANUFACTURE(53746-271, 53746-272) , PACK(53746-271, 53746-272) , REPACK(53746-271, 53746-272)

Revised: 6/2016

Amneal Pharmaceuticals of New York, LLC