

Septra Tablets (trimethoprim and sulfamethoxazole tablets) Tablet
Septra Ds Tablets (trimethoprim and sulfamethoxazole ds tablets) Tablet
Septra Suspension (trimethoprim and sulfamethoxazole suspension) Suspension
Septra Grape Suspension (trimethoprim and sulfamethoxazole grape suspension) Suspension

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

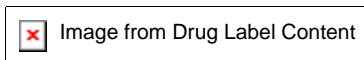
DESCRIPTION

SEPTRA (trimethoprim and sulfamethoxazole) is a synthetic antibacterial combination product. Each SEPTRA Tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole and the inactive ingredients docusate sodium (0.4 mg per tablet), FD&C Red No. 40, magnesium stearate, povidone, and sodium starch glycolate.

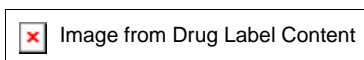
Each SEPTRA DS (double strength) Tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole and the inactive ingredients docusate sodium (0.8 mg per tablet), FD&C Red No. 40, magnesium stearate, povidone, and sodium starch glycolate.

Each teaspoonful (5 mL) of SEPTRA Suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole and the inactive ingredients alcohol 0.26%, methylparaben 0.1% and sodium benzoate 0.1% (added as preservatives), carboxymethylcellulose sodium, citric acid, FD&C Red No. 40 and Yellow No. 6, flavor, glycerin, microcrystalline cellulose, polysorbate 80, saccharin sodium, and sorbitol. Each teaspoonful (5 mL) of SEPTRA Grape Suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole and the inactive ingredients alcohol 0.26%, methylparaben 0.1%, and sodium benzoate 0.1% (added as preservatives), carboxymethylcellulose sodium, citric acid, FD&C Red No. 40 and Blue No. 1, flavor, glycerin, microcrystalline cellulose, polysorbate 80, saccharin sodium, and sorbitol. Both tablet and suspension forms are for oral administration.

Trimethoprim is 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.32, and the molecular formula $C_{14}H_{18}N_4O_3$. The structural formula is:



Sulfamethoxazole is 4-amino-N-(5-methyl-3-isoxazolyl)benzenesulfonamide. It is an almost white, odorless, tasteless compound with a molecular weight of 253.28, and the molecular formula $C_{10}H_{11}N_3O_3S$. The structural formula is:



CLINICAL PHARMACOLOGY

SEPTRA 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. The metabolism of sulfamethoxazole occurs predominately by N_4 -acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are

the 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. Approximately 44% of trimethoprim and 70% of sulfamethoxazole 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**). Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. During administration of 160 mg trimethoprim and 800 mg sulfamethoxazole b.i.d., the mean steady-state plasma concentration of trimethoprim was 1.72 mcg/mL. The steady-state minimal plasma levels of free and total sulfamethoxazole were 57.4 mcg/mL and 68.0 mcg/mL, respectively. These steady-state levels were achieved after 3 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 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 SEPTRA, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both trimethoprim and sulfamethoxazole distribute to sputum, vaginal fluid, and middle ear fluid; trimethoprim also distributes to bronchial secretions, 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 an 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, SEPTRA 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 SEPTRA than with either trimethoprim or sulfamethoxazole alone.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of SEPTRA includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli*, *Klebsiella species*, *Enterobacter species*, *Morganella morganii*, *Proteus mirabilis*, and indole-positive *Proteus species* including *Proteus vulgaris*.

The usual spectrum of antimicrobial activity of SEPTRA includes bacterial pathogens isolated from

middle ear exudate and from bronchial secretions (*Haemophilus influenzae*, including ampicillin-resistant strains, and *Streptococcus pneumoniae*), and enterotoxigenic strains of *Escherichia coli* (EPEC) causing bacterial gastroenteritis. *Shigella flexneri* and *Shigella sonnei* are also usually susceptible.

REPRESENTATIVE MINIMUM INHIBITORY CONCENTRATION VALUES FOR ORGANISMS SUSCEPTIBLE TO SEPTRA (MIC μ g/mL)

			TMP/SMX (1:19)	
	TMP	SMX		
Bacteria	Alone	Alone	TMP	SMX
<i>Escherichia coli</i>	0.05-1.5	1.0-245	0.05-0.5	0.95-9.5
<i>Escherichia coli</i> (enterotoxigenic strains)	0.015-0.15	0.285->950	0.005-0.15	0.095-2.85
<i>Proteus species</i> (indole positive)	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
			TMP/SMX (1:19)	
	TMP	SMX		
Bacteria	Alone	Alone	TMP	SMX
<i>Morganella morganii</i>	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
<i>Proteus mirabilis</i>	0.5-1.5	7.35-30	0.05-0.15	0.95-2.85
<i>Klebsiella species</i>	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
<i>Enterobacter species</i>	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
<i>Haemophilus influenzae</i>	0.15-1.5	2.85-95	0.015-0.15	0.285-2.85
			TMP/SMX (1:19)	
	TMP	SMX		
Bacteria	Alone	Alone	TMP	SMX
<i>Streptococcus pneumoniae</i>	0.15-1.5	7.35-24.5	0.05-0.15	0.95-2.85
<i>Shigella flexneri</i> *	<0.01-0.04	<0.16->320	<0.002-0.03	0.04-0.625
<i>Shigella sonnei</i> *	0.02-0.08	0.625->320	0.004-0.06	0.08-1.25

TMP=trimethoprim

SMX=sulfamethoxazole

*Rudoy RC, Nelson JD, Haltalin KC. *Antimicrobial Agents and Chemotherapy*. 1974;5:439-443.

Susceptibility Testing:

The recommended quantitative disc susceptibility method may be used for estimating the susceptibility of bacteria to SEPTRA.^{4,5} With this procedure, a report from the laboratory of “Susceptible to trimethoprim and sulfamethoxazole” indicates that the infection is likely to respond to therapy with SEPTRA. If the infection is confined to the urine, a report of “Intermediate susceptibility to trimethoprim and sulfamethoxazole” also indicates that the infection is likely to respond. A report of “Resistant to trimethoprim and sulfamethoxazole” indicates that the infection is unlikely to respond to therapy with SEPTRA.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of SEPTRA and other antibacterial drugs, SEPTRA 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, SEPTRA offers some advantage over the use of other antimicrobial agents. To date, there is limited data on the safety of repeated use of SEPTRA in pediatric patients under two years of age. SEPTRA 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, in the judgment of the physician, SEPTRA offers some advantage over the use of a single antimicrobial agent.

Travelers' Diarrhea in Adults:

For the treatment of travelers' diarrhea due to susceptible strains of enterotoxigenic *E. coli*.

Shigellosis:

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

Pneumocystis Carinii Pneumonia:

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

CONTRAINDICATIONS

SEPTRA is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. SEPTRA is also contraindicated in pregnant patients at term and in nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. SEPTRA is contraindicated in pediatric patients less than 2 months of age.

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 NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS.

SULFONAMIDES, INCLUDING SULFONAMIDE-CONTAINING PRODUCTS SUCH AS TRIMETHOPRIM/SULFAMETHOXAZOLE, 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 disorder (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.

The sulfonamides should not be used for the treatment of group A beta-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 (CDAD) has been reported with use of nearly all antibacterial agents, including SEPTRA, 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.

PRECAUTIONS

General

Prescribing SEPTRA 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.

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

Use in the Elderly:

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, or concomitant use of other drugs. Severe skin reactions, or generalized bone marrow suppression (see **WARNINGS** and **ADVERSE REACTIONS**), or a specific decrease in platelets (with or without purpura) 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. Appropriate dosage adjustments should be made for patients with impaired kidney function (see **DOSAGE AND ADMINISTRATION**).

Use in the Treatment of and Prophylaxis for *Pneumocystis carinii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS):

The incidence of side effects, particularly rash, fever, leukopenia, and elevated aminotransferase (transaminase) values in AIDS patients who are being treated with SEPTRA for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of SEPTRA in non-AIDS patients. The incidence of hyperkalemia and hyponatremia appears to be increased in AIDS patients receiving SEPTRA. Adverse effects are generally less severe in patients receiving SEPTRA for prophylaxis. A history of mild intolerance to SEPTRA in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis. However, if a patient develops skin rash or any sign of adverse reaction, therapy with SEPTRA should be re-evaluated (see **WARNINGS**).

The concomitant use of leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of *Pneumocystis carinii* pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

Information for Patients:

Patients should be counseled that antibacterial drugs including SEPTRA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When SEPTRA is 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 with SEPTRA 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 SEPTRA; if a significant reduction in the count of any formed blood element is noted, SEPTRA 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:

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. In the literature, two cases of hyperkalemia in elderly patients have been reported after concomitant intake of trimethoprim/sulfamethoxazole and an angiotensin converting enzyme inhibitor.

It has been reported that SEPTRA may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when SEPTRA is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

SEPTRA may inhibit the hepatic metabolism of phenytoin. SEPTRA, 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, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions:

SEPTRA, 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 trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with SEPTRA.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories, no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1,000 times human plasma levels in these same cells, a low level of chromosomal damage was induced at one of the laboratories. No chromosomal abnormalities were observed in cultured human leukocytes at concentrations of trimethoprim up to 20 times human steady-state plasma levels. No chromosomal effects were detected in peripheral lymphocytes of human subjects receiving 320 mg of trimethoprim in combination with up to 1,600 mg of sulfamethoxazole per day for as long as 112 weeks.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy

Teratogenic Effects:

Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause

cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratogenicity was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of nine when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim six times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursell,⁶ in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. 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 trimethoprim and sulfamethoxazole. 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 trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, SEPTRA 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:

SEPTRA is not recommended for pediatric patients younger than 2 months of age (see **INDICATIONS AND USAGE** and **CONTRAINDICATIONS**).

Geriatric Use:

Clinical studies of SEPTRA 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 Septra 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 folinic 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 Septra 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 Septra treatment is recommended to help lower potassium serum levels. Septra Tablets contain 1.8 mg (0.08 mEq) of sodium per tablet. Septra DS 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 subjects³ (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, OTHER BLOOD DYSCRASIAS, AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT (SEE WARNINGS).**

Hematologic:

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

Allergic:

Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch- Schönlein 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, pseudo-membranous 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, and crystalluria.

Metabolic:

Hyperkalemia, hyponatremia.

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.

Respiratory System:

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

Miscellaneous:

Weakness, fatigue, insomnia.

OVERDOSAGE

Acute:

The amount of a single dose of SEPTRA that is either associated with symptoms of overdose or is likely to be life-threatening has not been reported. Signs and symptoms of overdose 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 overdose. Signs of acute overdose 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 trimethoprim and sulfamethoxazole.

Chronic:

Use of SEPTRA 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 leucovorin daily has been recommended by some investigators.

DOSAGE AND ADMINISTRATION

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 Pediatric Patients:

Adults: The usual adult dosage in the treatment of urinary tract infections is one SEPTRA DS (double strength) tablet, two SEPTRA tablets, or four teaspoonfuls (20 mL) SEPTRA Suspension every 12 hours

for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Pediatric Patients: The recommended dose for pediatric patients with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole 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:

Pediatric Patients: Two Months of Age or Older

Weight		Dose – Every 12 Hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 mL)	
44	20	2 (10 mL)	1
66	30	3 (15 mL)	1 1/2
88	40	4 (20 mL)	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	Use Standard Regimen
15-30	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 one SEPTRA DS (double strength) tablet, two SEPTRA tablets, or four teaspoonfuls (20 mL) SEPTRA Suspension every 12 hours for 14 days.

Travelers' Diarrhea in Adults:

For the treatment of travelers' diarrhea, the usual adult dosage is one SEPTRA DS (double strength) tablet, two SEPTRA tablets, or four teaspoonfuls (20 mL) of SEPTRA Suspension every 12 hours for 5 days.

Pneumocystis Carinii Pneumonia:

Treatment:

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

Weight		Dose – Every 6 Hours	
lb	kg	Teaspoonfuls	Tablets

18	8	1 (5 mL)	
35	16	2 (10 mL)	1
53	24	3 (15 mL)	1 1/2
70	32	4 (20 mL)	2 (or 1 DS Tablet)
88	40	5 (25 mL)	2 1/2
106	48	6 (30 mL)	3 (or 1 1/2 DS Tablets)
141	64	8 (40 mL)	4 (or 2 DS Tablets)
176	80	10 (50 mL)	5 (or 2 1/2 DS Tablets)

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

Prophylaxis:

Adults: The recommended dosage for prophylaxis in adults is one SEPTRA DS (double strength) tablet daily.

Pediatric Patients: For pediatric patients, the recommended dose is 150 mg/m²/day trimethoprim with 750 mg/m²/day sulfamethoxazole given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 320 mg trimethoprim and 1,600 mg sulfamethoxazole. The following table is a guideline for the attainment of this dosage in pediatric patients:

Body Surface Area	Dose—every 12 hours	
(m ²)	Teaspoonfuls	Tablets
0.26	1/2 (2.5 mL)	
0.53	1 (5 mL)	1/2
1.06	2 (10 mL)	1

HOW SUPPLIED

TABLETS (pink, scored, round-shaped) containing 80 mg trimethoprim and 400 mg sulfamethoxazole: Bottles of 100 (NDC 61570-052-01). Imprint on tablets “M052”.

DS (DOUBLE STRENGTH) TABLETS (pink, scored, oval-shaped) containing 160 mg trimethoprim and 800 mg sulfamethoxazole: Bottles of 20 (NDC 61570-053-20), 100 (NDC 61570-053-01), 250 (NDC 61570-053-52) and 500 (NDC 61570- 053-05). Imprint on tablets “M053”.

ORAL SUSPENSIONS (pink, cherry-flavored) containing 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 mL): Bottle of 1 pint (473 mL) (NDC 61570-050-16) and 100 mL—package of 6 (NDC 61570-050-11); and (purple, grape-flavored) containing 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 mL): Bottle of 1 pint (473 mL) (NDC 61570-051-16).

Tablets should be stored at 15° to 25°C (59° to 77°F) in a dry place and protected from light.

Suspensions should be stored at 15° to 25°C (59° to 77°F) and protected from light.

REFERENCES

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2. Kaplan SA, Weinfeld RE, Abruzzo CW, McFaden K, Jack ML, Weissman L. Pharmacokinetic profile of trimethoprim- sulfamethoxazole in man. *J Infect Dis.* 1973;128(suppl):S547-S555.
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4. Antibiotic susceptibility discs; certification procedure. *Federal Register.* 1972;37:20527-20529.
5. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by standardized single disk method. *Am J Clin Pathol.* 1966;45:493-496.
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7. Marinella MA. Trimethoprim – induced hyperkalemia: An analysis of reported cases. *Gerontology* 45: 209-212, 1999.

Rx Only.

Prescribing Information as of March 2007.

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620

(A wholly owned subsidiary of King Pharmaceuticals, Inc.)

Manufactured by: King Pharmaceuticals, Inc., Bristol, TN 37620

Septra Tablets (trimethoprim and sulfamethoxazole tablets)

PRODUCT INFO

Product Code	61570-052	Dosage Form	TABLET
Route Of Administration	ORAL	DEA Schedule	

INGREDIENTS

Name (Active Moiety)	Type	Strength
trimethoprim (trimethoprim)	Active	80 MILLIGRAM In 1 TABLET
sulfamethoxazole (sulfamethoxazole)	Active	400 MILLIGRAM In 1 TABLET
docusate sodium	Inactive	
FD&C Red No. 40	Inactive	
magnesium stearate	Inactive	
povidone	Inactive	
sodium starch glycolate	Inactive	

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color	PINK	Score	2
Shape	ROUND	Symbol	false
Imprint Code	SEPTRA; M052	Coating	false
Size	11mm		

PACKAGING		
# NDC	Package Description	Multilevel Packaging
1 61570-052-01	100 TABLET In 1 BOTTLE (1 BOTTLE)	None

Septra DS Tablets (trimethoprim and sulfamethoxazole ds tablets)			
PRODUCT INFO			
Product Code	61570-053	Dosage Form	TABLET
Route Of Administration	ORAL	DEA Schedule	
INGREDIENTS			
Name (Active Moiety)	Type	Strength	
trimethoprim (trimethoprim)	Active	160 MILLIGRAM In 1 TABLET	
sulfamethoxazole (sulfamethoxazole)	Active	800 MILLIGRAM In 1 TABLET	
docusate sodium	Inactive		
FD&C Red No. 40	Inactive		
magnesium stearate	Inactive		
povidone	Inactive		
sodium starch glycolate	Inactive		
IMPRINT INFORMATION			
Characteristic	Appearance	Characteristic	Appearance
Color	PINK	Score	2
Shape	OVAL	Symbol	false
Imprint Code	SEPTRA DS; M053	Coating	false
Size	20mm		
PACKAGING			
# NDC	Package Description	Multilevel Packaging	
1 61570-053-01	100 TABLET In 1 BOTTLE (1 BOTTLE)	None	
2 61570-053-20	20 TABLET In 1 BOTTLE (1 BOTTLE)	None	
3 61570-053-52	250 TABLET In 1 BOTTLE (1 BOTTLE)	None	
4 61570-053-05	500 TABLET In 1 BOTTLE (1 BOTTLE)	None	

Septra Suspension (trimethoprim and sulfamethoxazole suspension)			
PRODUCT INFO			
Product Code	61570-050	Dosage Form	SUSPENSION

Route Of Administration	ORAL	DEA Schedule	
INGREDIENTS			
Name (Active Moiety)	Type	Strength	
trimethoprim (trimethoprim)	Active	40 MILLIGRAM In 5 MILLILITER	
sulfamethoxazole (sulfamethoxazole)	Active	200 MILLIGRAM In 5 MILLILITER	
alcohol	Inactive		
methylparaben	Inactive		
sodium benzoate	Inactive		
carboxymethylcellulose sodium	Inactive		
citric acid	Inactive		
FD&C Red No. 40	Inactive		
Yellow No. 6	Inactive		
flavor	Inactive		
glycerin	Inactive		
microcrystalline cellulose	Inactive		
polysorbate 80	Inactive		
saccharin sodium	Inactive		
sorbitol	Inactive		
IMPRINT INFORMATION			
Characteristic	Appearance	Characteristic	Appearance
Color	PINK (cherry flavored)	Score	_____
Shape	_____	Symbol	_____
Imprint Code	_____	Coating	_____
Size			
PACKAGING			
#	NDC	Package Description	Multilevel Packaging
1	61570-050-16	16 OUNCE In 1 BOTTLE (1 BOTTLE)	None
2	61570-050-11	100 MILLILITER In 1 BOTTLE (6 BOTTLE)	None

Septra Grape Suspension (trimethoprim and sulfamethoxazole grape suspension)

PRODUCT INFO			
Product Code	61570-051	Dosage Form	SUSPENSION
Route Of Administration	ORAL	DEA Schedule	
INGREDIENTS			

Name (Active Moiety)	Type	Strength
trimethoprim (trimethoprim)	Active	40 MILLIGRAM In 5 MILLILITER
sulfamethoxazole (sulfamethoxazole)	Active	200 MILLIGRAM In 5 MILLILITER
alcohol	Inactive	
methylparaben	Inactive	
sodium benzoate	Inactive	
carboxymethylcellulose sodium	Inactive	
citric acid	Inactive	
FD&C Red No. 40	Inactive	
Blue No. 1	Inactive	
flavor	Inactive	
glycerin	Inactive	
microcrystalline cellulose	Inactive	
polysorbate 80	Inactive	
saccharin sodium	Inactive	
sorbitol	Inactive	

IMPRINT INFORMATION			
Characteristic	Appearance	Characteristic	Appearance
Color	PURPLE (grape flavored)	Score	_____
Shape	_____	Symbol	_____
Imprint Code	_____	Coating	_____
Size			

PACKAGING		
# NDC	Package Description	Multilevel Packaging
1 61570-051-16	16 OUNCE In 1 BOTTLE (1 BOTTLE)	None