SEPTRA® Tablets
SEPTRA® DS (Double Strength) Tablets
(trimethoprim and sulfamethoxazole)

PRODUCT OVERVIEW:

SEPTRA TABLET

SEPTRA DS TABLET

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.

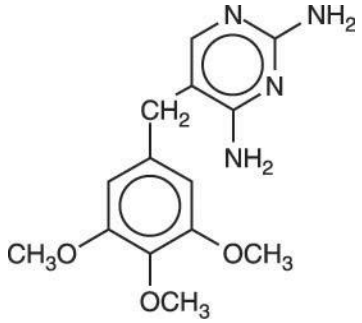
DESCRIPTION

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.

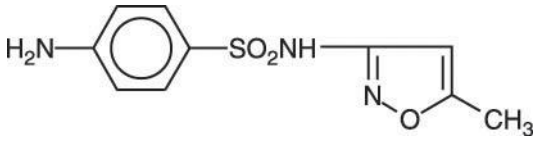
Each SEPTRA DS (double strength) Tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole and the inactive ingredients docusate sodium (0.8 mg per tablet), FD&C Red No. 40, magnesium stearate, povidone, and sodium starch glycolate.

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-trimeth-oxyphenyl)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. Sulfamethoxazole is metabolized in humans to at least 5 metabolites: the N4-acetyl-, N4-hydroxy-, 5-methylhydroxy-, N4-acetyl-5-methylhydroxy- sulfamethoxazole metabolites, and an N-glucuronide conjugate. The formation of N4-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 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 N_4-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.

Pharmacokinetics in Pediatric Patients

A simulation conducted with data from a pharmacokinetic study in 153 infants and children demonstrated that mean steady state AUC and maximum plasma concentrations of trimethoprim and sulfamethoxazole would be comparable between pediatric patients 2 months to 18 years receiving 8/40 (trimethoprim/sulfamethoxazole) mg/kg/day divided every 12 hours and adult patients receiving 320/1600 (trimethoprim/sulfamethoxazole) mg/day.

Pharmacokinetics in Geriatric Patients

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

Mechanism of Action
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.

Resistance
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.

Antimicrobial Activity
SEPTRA has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive bacteria:
Streptococcus pneumoniae

Aerobic gram-negative bacteria:
Escherichia coli
Klebsiella species
Enterobacter species
Haemophilus influenzae
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Shigella flexneri
Shigella sonnei

Other Organisms:
Pneumocystis jirovecii

Susceptibility Testing
For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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, a physician deems that, SEPTRA could offer 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 jirovecii* Pneumonia**

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

CONTRAINDICATIONS

SEPTRA is contraindicated in patients with the following:

- known hypersensitivity to trimethoprim or sulfonamides
- history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides
- documented megaloblastic anemia due to folate deficiency
- pediatric patients less than 2 months of age
- marked hepatic damage
- severe renal insufficiency when renal function status cannot be monitored
- concomitant administration with dofetilide (see PRECAUTIONS)

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 Serious or Fatal Reactions
Fatalities and serious adverse reactions, including severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and acute

febrile neutrophilic dermatosis (AFND), fulminant hepatic necrosis, agranulocytosis, aplastic anemia, other blood dyscrasias, acute and delayed lung injury, anaphylaxis, and circulatory shock have occurred with the administration of trimethoprim-sulfamethoxazole including SEPTRA (see PRECAUTIONS and ADVERSE REACTIONS).

Cough, shortness of breath, and pulmonary infiltrates potentially representing hypersensitivity reactions of the respiratory tract have been reported in association with trimethoprim-sulfamethoxazole treatment.

Other severe pulmonary adverse reactions occurring within days to week of SEPTRA initiation and resulting in prolonged respiratory failure requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), lung transplantation or death have also been reported in patients and otherwise healthy individuals treated with trimethoprim-sulfamethoxazole products.

Circulatory shock with fever, severe hypotension, and confusion requiring intravenous fluid resuscitation and vasopressors has occurred within minutes to hours of re-challenge with trimethoprim-sulfamethoxazole in patients with history of recent (days to weeks) exposure to sulfamethoxazole-trimethoprim.

SEPTRA should be discontinued at the first appearance of skin rash or any sign of a serious adverse reaction. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, AGEP, or AFND, hepatic necrosis, and serious blood disorders (see PRECAUTIONS and ADVERSE REACTIONS). Clinical signs, such as rash, pharyngitis, fever, cough, arthralgia, chest pain, dyspnea, pallor, purpura or jaundice may be early indications of serious reactions.

Thrombocytopenia
Trimethoprim-sulfamethoxazole-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 trimethoprim-sulfamethoxazole.

Streptococcal Infections and Rheumatic Fever
SEPTRA should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, SEPTRA will not eradicate the *Streptococcus* and, therefore, will not prevent sequelae such as rheumatic fever.

***Clostridioides difficile* Associated Diarrhea**
Clostridioides 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.

Risk of Failure and Excess Mortality with Leucovorin Use for *Pneumocystis jirovecii* Pneumonia Treatment
Treatment failure and excess mortality were observed when trimethoprim-sulfamethoxazole was used concomitantly with leucovorin for the treatment of HIV positive patients with *Pneumocystis jirovecii* pneumonia in a randomized placebo controlled trial.[4] Co-administration of trimethoprim-sulfamethoxazole and leucovorin during treatment of *Pneumocystis jirovecii* pneumonia should be avoided.

PRECAUTIONS

Development of drug resistant bacteria

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.

Folate deficiency

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.

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/trimethoprim have been reported, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of SEPTRA 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 jirovecii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS)

AIDS patients may not tolerate or respond to SEPTRA it the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia, and elevated aminotransferase (transaminase) values in AIDS patients who are being treated with SEPTRA for *P. jirovecii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of SEPTRA in non-AIDS patients. 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, fever, leukopenia, or any other sign of adverse reaction, therapy or re-challenge with SEPTRA should be re-evaluated (see WARNINGS).

Co-administration of SEPTRA and leucovorin should be avoided with *P. jirovecii* pneumonia (see WARNINGS).

Electrolyte Abnormalities

Hyperkalemia
High dosage of trimethoprim, as used in patients with *P. jirovecii* 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.

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

Crystalluria
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 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

Potential for SEPTRA 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 SEPTRA is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2.

Drug Interactions with SEPTRA

Drug(s)	Recommendation	Comments
Diuretics	Avoid concurrent use	In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.
Warfarin	Monitor prothrombin time and INR	It has been reported that SEPTRA may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin (a CYP2C9 substrate). This interaction should be kept in mind when SEPTRA is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.
Phenytoin	Monitor serum phenytoin levels	SEPTRA may inhibit the hepatic metabolism of phenytoin (a CYP2C9 substrate). 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.
Methotrexate	Avoid concurrent use	Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

Cyclosporine	Avoid concurrent use	There have been reports of marked but reversible nephrotoxicity with co-administration of SEPTRA and cyclosporine in renal transplant recipients.
Digoxin	Monitor serum digoxin levels	Increased digoxin blood levels can occur with concomitant SEPTRA therapy, especially in elderly patients.
Indomethacin	Avoid concurrent use	Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.
Pyrimethamine	Avoid concurrent use	Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if SEPTRA is prescribed.
Tricyclic Antidepressants (TCAs)	Monitor therapeutic response and adjust dose of TCA accordingly	The efficacy of tricyclic antidepressants can decrease when co-administered with SEPTRA.
Oral hypoglycemics	Monitor blood glucose more frequently	Like other sulfonamide-containing drugs, SEPTRA potentiates the effect of oral hypoglycemic 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.
Amantadine	Avoid concurrent use	In the literature, a single case of toxic delirium has been reported after concomitant intake of SEPTRA and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin, have also been reported.
Angiotensin Converting Enzyme Inhibitors	Avoid concurrent use	In the literature, three cases of hyperkalemia in elderly patients have been reported after concomitant intake of SEPTRA and an angiotensin converting enzyme inhibitor.[5,6]
Zidovudine	Monitor for hematologic toxicity	Zidovudine and SEPTRA are known to induce hematological abnormalities. Hence, there is potential for an additive myelotoxicity when co-administered.[7]
Dofetilide	Concurrent administration is contraindicated	Elevated plasma concentrations of dofetilide have been reported following concurrent administration of trimethoprim and dofetilide. Increased plasma concentrations of dofetilide may cause serious ventricular arrhythmias associated with QT interval prolongation, including *torsade de pointes*.[8,9]
Procainamide	Closely monitor for clinical and ECG signs of procainamide toxicity and/or procainamide plasma concentration if available	Trimethoprim increases the plasma concentrations of procainamide and its active *N*-acetyl metabolite (NAPA) when trimethoprim and procainamide are co-administered. The increased procainamide and NAPA plasma concentrations that resulted from the pharmacokinetic interaction with trimethoprim are associated with further prolongation of the QT_c interval.[10]

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
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 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole, 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 trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursell,[11] 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 (see WARNINGS).

Teratogenic Effects

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 2-5% of the recommended daily dose for infants over 2 months of age. Caution should be exercised when SEPTRA 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

SEPTRA is contraindicated 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.[5] 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 trimpethoprim was lower in geriatric subjects compared with younger subjects[3] (see CLINICAL PHARMACOLOGY: Geriatric Pharmacokinetics).

ADVERSE REACTIONS

The following adverse reactions associated with the use of SEPTRA or trimethoprim-sulfamethoxazole were identified in clinical studies, postmarketing or published reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 have occurred due to severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS), fulminant hepatic necrosis, agranulocytosis, aplastic anemia, other blood dyscrasias, acute and delayed lung injury, anaphylaxis, and circulatory shock (see WARNINGS).**

Hematologic
Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura.

Allergic
Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, acute generalized exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis (AFND), 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 transaminases and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary
Renal failure, interstitial nephritis, BUN and serum creatinine elevation, renal insufficiency, anuria, crystalluria, and nephrotoxicity in association with cyclosporine.

Metabolic
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. Cases of rhabdomyolysis have been reported with SEPTRA, mainly in AIDS patients.

Respiratory System
Cough, shortness of breath, pulmonary infiltrates, acute eosinophilic pneumonia, acute and delayed lung injury, interstitial lung disease, and acute respiratory failure (see WARNINGS).

Cardiovascular System
QT prolongation resulting in ventricular tachycardia and *torsade de pointes,* circulatory shock.

Miscellaneous
Weakness, fatigue, insomnia.

OVERDOSAGE

Acute

The amount of a single dose of SEPTRA 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 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

SEPTRA is 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)

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 jirovecii* Pneumonia**

Treatment

Adults and Pediatric Patients: The recommended dosage for treatment of patients with documented *P jirovecii* 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/m^2/day trimethoprim with 750 mg/m^2/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.

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