

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.

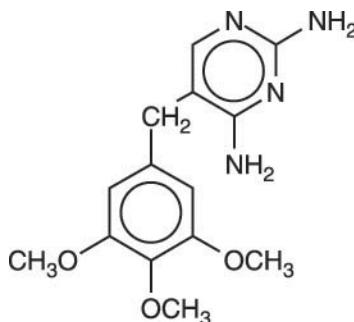
DESCRIPTION

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.

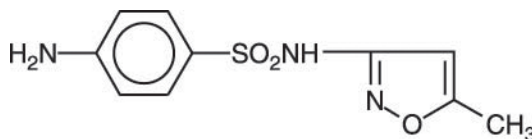
Each SEPTRA DS (double strength) Tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole and the inactive ingredients docusate sodium (0.8 mg per tablet), FD&C Red No. 40, magnesium stearate, povidone, and sodium starch glycolate.

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-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 C₁₄H₁₈N₄O₃. 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 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:

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, SEPTRA blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

Mechanism of Resistance

In vitro studies have shown that bacterial resistance develops more slowly with SEPTRA than with either trimethoprim or sulfamethoxazole alone.

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

SEPTRA 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

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)^{4,5}. 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^{5,6}. This procedure uses paper disks impregnated with 1.25/23.75 µg of trimethoprim/sulfamethoxazole to test the susceptibility of microorganisms to SEPTRA. The disc diffusion interpretive criteria are provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Trimethoprim/Sulfamethoxazole

| Bacteria | Minimal Inhibitory Concentration (mcg/mL) | | | Zone Diameter (mm) | | |
|---------------------------------|---|-------------|--------|--------------------|---------|------|
| | S | I | R | S | I | R |
| <i>Enterobacteriaceae</i> | ≤ 2/38 | - | ≥ 4/76 | ≥ 16 | 11 – 15 | ≤ 10 |
| <i>Haemophilus influenzae</i> | ≤ 0.5/9.5 | 1/19 – 2/38 | ≥ 4/76 | ≥ 16 | 11 – 15 | ≤ 10 |
| <i>Streptococcus pneumoniae</i> | ≤ 0.5/9.5 | 1/19 – 2/38 | ≥ 4/76 | ≥ 19 | 16 – 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 test⁴⁻⁶.

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 µg trimethoprim/sulfamethoxazole disk the criteria in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Trimethoprim/Sulfamethoxazole

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

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 jiroveci* Pneumonia:**

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

CONTRAINDICATIONS

SEPTRA is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides, in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides, and in patients with documented megaloblastic anemia due to folate deficiency. SEPTRA is contraindicated in pediatric patients less than 2 months of age.

SEPTRA is also contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

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/trimethoprim.

Streptococcal Infections and Rheumatic Fever:

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:

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.

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.⁷ Co-administration of trimethoprim-sulfamethoxazole and leucovorin during treatment of *Pneumocystis jiroveci* 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 jiroveci* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS):

AIDS patients may not tolerate or respond to SEPTRA in 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. jiroveci* 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 or any sign of adverse reaction, therapy with SEPTRA should be re-evaluated (see [WARNINGS](#)).

Co-administration of SEPTRA 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/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 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.

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.⁸

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.

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.

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 co-administration of SEPTRA and cyclosporine in renal transplant recipients.

Increased digoxin blood levels can occur with concomitant SEPTRA therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.

Reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if SEPTRA is prescribed.

The efficacy of tricyclic antidepressants can decrease when co-administered with SEPTRA.

SEPTRA 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

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,⁹ 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 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 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.⁸ 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, 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:

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, 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 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

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) |

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 jiroveci* Pneumonia:**

Treatment:

Adults and Pediatric Patients: The recommended dosage for treatment of patients with documented *P jiroveci* 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 (m ²) | Dose—every 12 hours 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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