Product Monograph

Including Patient Medication Information

PrSEPTRA® Injection

sulfamethoxazole (80 mg/mL) + trimethoprim (16 mg/mL), BP
sterile solution for the preparation of intravenous infusions

Antibacterial Agent
ATC J01EE01

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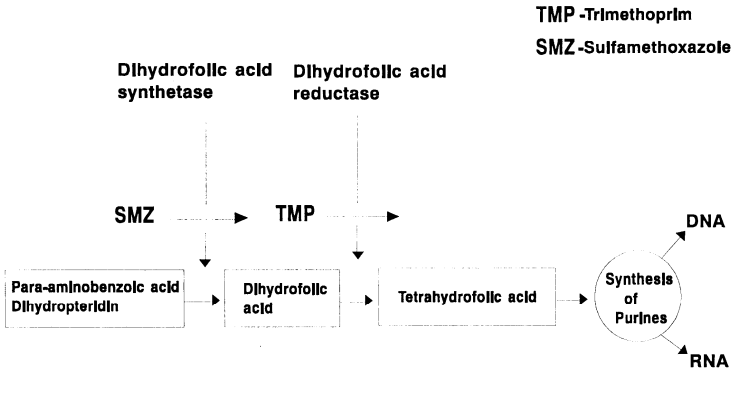
Clinical Pharmacology

SEPTRA® (sulfamethoxazole and trimethoprim) is an antibacterial agent with a wide spectrum of activity. It contains two active antibacterial components, sulfamethoxazole and trimethoprim, which act synergistically on many species of bacteria.

Figure 1



Sulfamethoxazole and trimethoprim act sequentially in two successive steps in the biosynthesis of nucleic acids. Trimethoprim is an inhibitor of dihydrofolate reductase, the enzyme which reduces dihydrofolic acid to its tetrahydro form. This biochemical step is essential in the production of the folate coenzymes which are involved in the biosynthesis of thymine, purine,

serine and methionine. Sulfamethoxazole exerts its antibacterial activity by competing with para-aminobenzoic acid.

Most pathogenic bacteria meet their need for dihydrofolic acid by synthesizing it from para-aminobenzoic acid, pteridine and glutamic acid. Animals, in contrast, depend on exogenous sources for their needs of folic acid and do not rely upon intracellular synthesis.

Under usual circumstances, sulfamethoxazole or trimethoprim acting alone do not produce complete block in this biosynthesis of nucleic acids. Instead, they cause sufficient reduction in the synthesis of folate coenzymes to produce bacteriostasis. When the two agents act together, the superimposition of their effects produces a complete block in the synthesis, leading to death of the organism. Thus the effect of the dual action is to reduce the minimum inhibitory concentrations (MIC) of each agent (synergism) and to convert a bacteriostatic action to a bactericidal action.

The activity of SEPTRA® therefore depends upon the ability of both sulfamethoxazole and trimethoprim to affect the folate metabolism of the bacterium; however, for SEPTRA® to be therapeutic it must not affect the folate metabolism of the host. Since sulfamethoxazole affects only the *de novo* synthesis of dihydrofolic acid by bacteria, it does not affect folate metabolism of animals. Since in animals, as in bacteria, the folates have to be recycled to the active form by dihydrofolate reductase, trimethoprim could be expected to affect mammalian folate metabolism. Trimethoprim, however, was especially selected from similar folate inhibitors because of its low toxicity for animals and high toxicity for bacteria. This difference has since been shown to be due to the fact that the affinity of trimethoprim for the dihydrofolate reductase of bacteria is some 40,000 times greater than for the corresponding mammalian enzyme.

Indications and Clinical Use

SEPTRA® (sulfamethoxazole and trimethoprim) has been effective in the treatment of infections associated with the following gram-positive and gram-negative organisms:

Gram-Negative Organisms
Haemophilus influenzae
Neisseria gonorrhoeae
Escherichia coli
Klebsiella species
Enterobacter (Aerobacter) aerogenes
Proteus mirabilis
Proteus vulgaris
Salmonella species
Shigella species
Vibrio cholerae

Gram-Positive Organisms
Streptococcus pyogenes
Streptococcus viridans
Staphylococcus albus
Staphylococcus aureus
Diplococcus pneumoniae

Other Organisms
Brucella melitensis
Nocardia asteroides
Nocardia brasiliensis
Paracoccidioides brasiliensis
Pneumocystis jiroveci
Streptomyces somaliensis

Sensitivity tests should be performed wherever possible to determine choice of therapy. These tests should be repeated if there is a failure to respond, relapse or early recurrence.

SEPTRA® may be indicated for the following infections when caused by susceptible strains of the above organisms.

Urinary Tract Infections:

Treatment of acute uncomplicated urinary tract infections*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Upper and Lower Respiratory Tract Infections:

Treatment of acute exacerbations of chronic bronchitis.

Treatment of *Pneumocystis jiroveci* pneumonia*. SEPTRA® is also indicated in the treatment of infants and children with a diagnosis of *Pneumocystis jiroveci* pneumonitis, especially if they are immunosuppressed.

Gastrointestinal Tract Infections:

Treatment of cholera, as an adjunct to fluid and electrolyte replacement, when the organism has been shown to be sensitive *in vitro*.

Treatment of bacilliary dysentry*.

Other Infections:

Treatment of nocardiosis*. Brucellosis (second line therapy), when used in combination with gentamicin or rifampicin.

SEPTRA® is not indicated in infections associated with Pseudomonas, Mycoplasma, nor when the infection is caused by a virus.

This drug has not yet been fully evaluated in streptococcal infections.

*SEPTRA® Injection has been investigated clinically in these indications.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of SEPTRA® Injection and other antibacterial drugs, SEPTRA® Injection should be used only to treat 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.

Contraindications

SEPTRA® (sulfamethoxazole and trimethoprim) is contraindicated in patients with a known hypersensitivity, **including a history of drug-induced immune thrombocytopenia, in association with** trimethoprim or sulfonamides, co-trimoxazole or any excipients of SEPTRA® and in patients with documented megaloblastic anemia due to folate deficiency, evidence of marked liver parenchymal damage, or blood dyscrasias.

SEPTRA® is contraindicated in patients with marked renal impairment where repeated serum assays cannot be carried out (see also PRECAUTIONS).

SEPTRA® is contraindicated in pregnant patients and in nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.

SEPTRA® is contraindicated in infants less than two months of age.

Warnings

Fatalities associated with the administration of sulfonamides and SEPTRA®, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), fulminant hepatic necrosis, agranulocytosis, aplastic anemia, other blood dyscrasias, and hypersensitivity of the respiratory tract.

Rare life-threatening and fatal cases of immune thrombocytopenia have been reported with the use of sulfamethoxazole-trimethoprim.

SEPTRA® (sulfamethoxazole and trimethoprim) should be discontinued at the first appearance of skin rash or any sign of adverse reaction. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura, or jaundice may be early indications of serious reactions. Cough, shortness of breath, and/or pulmonary infiltrates may be indicators of pulmonary hypersensitivity to sulfonamides which while rare, has been fatal. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, or serious blood disorder. Complete blood counts should be done frequently in patients receiving sulfonamides.

SEPTRA® should not be used in the treatment of streptococcal pharyngitis. Clinical studies have documented that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with SEPTRA® than to those patients treated with penicillin, as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

SEPTRA® Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing SEPTRA® Injection in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Precautions

General

SEPTRA® should only be used where, in the judgement of the physician, the benefit of treatment outweighs any possible risks; consideration should be given to the use of a single effective antibacterial agent.

Clinicians should be aware that first line therapy in the management of all patients with diarrheal disease in the maintenance of adequate hydration.

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, rheumatoid arthritics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states), and to those with severe allergy or bronchial asthma. Because of possible interference with folate metabolism, regular blood counts are advisable in these patients as well as patients who are on long term therapy. Changes indicative of folic acid impairment have, in certain specific situations, been reversed by folinic acid therapy.

A folate supplement should also be considered with prolonged high dosage of SEPTRA® (see Adverse Reactions).

In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

The administration of SEPTRA® to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulfonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Caution should be exercised in administering trimethoprim to patients at risk of hyperkalemia and hyponatremia. Serum potassium and sodium and renal function should be closely monitored, and dosage should be adjusted for renal function (see Precautions, Renal Impairment and Dosage and Administration).

The risk factors for hyperkalemia are high trimethoprim dosage (20 mg/kg/day), renal insufficiency (serum creatinine $\geq$ 1.2 mg/dl), hypoaldosteronism, older age, dietary potassium and other drugs that impair potassium excretion. The likely mechanism is via trimethoprim inhibition of sodium channels in the distal nephron, similar to that of the potassium-sparing diuretic amiloride.

Hyperkalemia is generally reversible on discontinuation of trimethoprim. In patients presented with hyperkalemia due to SEPTRA®, SEPTRA® can be discontinued and appropriate standard potassium-lowering therapy instituted.

Except under careful supervision trimethoprim-sulfamethoxazole should not be given to patients with serious hematological disorders (see Adverse Reactions).

Functional inhibition of the renal tubular secretion of creatinine may produce a spurious fall in the estimated rate of creatinine clearance.

SEPTRA® may affect the results of thyroid function tests but this is probably of little or no clinical significance.

The possibility of superinfection with a non-sensitive organism should be borne in mind.

Local irritation and inflammation due to extravascular infiltration of the infusion has been observed with SEPTRA® Injection. If these occur, the infusion should be discontinued and restarted at another site.

Fluid Overload is possible, especially when very high doses are being administered to patients with underlying cardio-pulmonary disease.

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulfonamide crystals have been noted in cooled urine from treated patients. In patients suffering from hypoalbuminaemia the risk may be increased.

Gastrointestinal

Clostridium difficile – Associated Disease (CDAD)

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including SEPTRA®. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *C. difficile. Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile.* In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see ADVERSE REACTIONS).

Renal Impairment

In patients with renal impairment, a reduced or less frequent dosage is recommended in order to avoid accumulation of trimethoprim in the blood (see Dosage and Administration). Non-ionic diffusion is the main factor in the renal handling of trimethoprim, and as renal failure advances, trimethoprim excretion decreases. For such patients, serum assays are necessary. SEPTRA® should not be used when the serum creatinine level is above 2 mg per 100 mL, in order to avoid possible permanent impairment of renal function.

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 or without purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see Dosage and Administration).

Close supervision is recommended when SEPTRA® is used in elderly patients or in patients taking high doses of SEPTRA® as these patients may be more susceptible to hyperkalemia and hyponatremia.

Special care should be exercised when treating the elderly or suspected folate-deficient patients; folate supplementation should be considered.

Use in Children

SEPTRA® is not recommended for pediatric patients younger than 2 months of age (see CONTRAINDICATIONS).

Use in Pregnancy

Trimethoprim and sulfamethoxazole cross the placenta and their safety in human pregnancy has not been established. Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause fetal abnormalities. At doses in excess of the recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other fetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, fetal loss was seen at doses of trimethoprim in excess of human therapeutic doses. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Therefore, SEPTRA® should be avoided in pregnancy, particularly in the first trimester, unless the potential benefit to the mother outweighs the potential risk to the fetus; folate supplementation should be considered if SEPTRA® is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significant maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when SEPTRA® is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

Use in Nursing Mothers

Trimethoprim and sulfamethoxazole are excreted in breast milk. Administration of SEPTRA® should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing hyperbilirubinaemia. Additionally, administration of SEPTRA® should be avoided in infants younger than eight weeks in view of predisposition of young infants to hyperbilirubinaemia.

Patients with Special Diseases and Conditions

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

The incidence of side effects, particularly rash, severe hypersensitivity reactions, fever, leukopenia, neutropenia, thrombocytopenia and elevated aminotransferase (transaminase) values in AIDS patients who are being treated with SEPTRA® for Pneumocystis jiroveci pneumonia (PJP) has been reported to be greatly increased compared with the incidence normally associated with the use of SEPTRA® in non-AIDS patients. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10 mg/day). 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). Rhabdomyolysis has been reported in HIV positive patients receiving trimethoprim-sulfamethoxazole for prophylaxis or treatment of PJP. In some cases, rhabdomyolysis led to acute renal failure requiring emergency dialysis.

Severe hypersensitivity reactions have also been reported in HIV-infected patients on re-exposure to SEPTRA®, sometimes after a dosage interval of a few days. Concomitant administration of intravenous diphenhydramine may permit continued infusion.

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

Phenylketonuric Patients

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

Drug-Food Interactions

Caution should be excercised in patients following potassium enriched dietary regimens.

Drug-Drug Interactions

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with or without purpura has been reported.

Occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anemia should SEPTRA® be prescribed concurrently.

In some situations, concomitant treatment with zidovudine may increase risk of hematological adverse reactions to SEPTRA®. If concomitant treatment is necessary, consideration should be given to monitoring of hematological parameters.

Administration of SEPTRA® 160 mg/800 mg causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

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. Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations. Folate supplementation should be considered. If SEPTRA® is considered appropriate therapy in patients receiving other anti-folate drugs, a folate supplementation should be considered.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Caution should be exercised in patients taking any other drugs that can cause hyperkalemia.

Reversible deterioration in renal function has been observed in patients treated with SEPTRA® and cyclosporin following renal transplantation.

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g., procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.

Interaction with sulphonylurea hypoglycemic agents is uncommon but potentiation has been reported.

Concurrent use of rifampicin and SEPTRA® results in a shortening of the plasma half life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

Trimethoprim is an inhibitor of cytochrome P450 2C8 enzyme and may interact with other drugs that are primarily metabolized by the 2C8 isoform. Sulfamethoxazole is an inhibitor of cytochrome P450 2C9 and may interact with other drugs that are primarily metabolized by the 2C9 isoform.

Laboratory Tests

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.

Information for Patients

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

Patients should tell their physician of all dietary regimens and supplements.

Adverse Reactions

The most common adverse effects are hyperkalemia, anorexia, monilial overgrowth, headache, local thrombophlebitis at the site of injection, gastrointestinal disturbances (nausea, vomiting, diarrhea) and allergic skin reactions (such as rash and urticaria). FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES AND SEPTRA® ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS (LYELL'S SYNDROME), FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, OTHER BLOOD DYSCRASIAS, AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT (SEE WARNINGS).

General

Weakness, fatigue, insomnia, vision troubles, alopecia, epistaxis, local thrombophlebitis at the site of injection, edema. Monilial overgrowth is common.

Allergic

Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), anaphylaxis, allergic myocarditis, erythema multiforme, toxicoderma, exfoliative dermatitis, angioedema, drug fever, chills, allergic vasculitis resembling Henoch-Schönlein purpura, serum sickness, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, fixed drug eruption, photosensitivity, conjunctival and scleral injection, pruritus, urticaria, and rash. In addition, periarteritis nodosa and systemic lupus erythematosus and anaphylactoid reactions (sweating and collapse) have been reported.

Cardiovascular

QT prolongation

Endocrine and Metabolism

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.

Anorexia, hyperkalemia, hyponatremia, hypoglycemia (see also PRECAUTIONS).

Gastrointestinal

Pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, dry mouth, nausea, vomiting, pyrosis, gastric intolerance, gastritis or gastroenteritis, dyspepsia emesis, abdominal pain, constipation, flatulence, diarrhea.

Genitourinary

Impaired renal function (sometimes reported as renal failure), interstitial nephritis, kidney changes (as indicated by abnormal elevations in blood urea nitrogen, blood non-protein nitrogen, serum creatinine and urine protein levels), toxic nephrosis with oliguria and anuria, crystalluria, hematuria, urgency, and dysuria.

Hematologic

Leukopenia, neutropenia, thrombocytopenia, megaloblastic anaemia,
aplastic and hemolytic anemia, methemoglobinemia, purpura, agranulocytosis,
hypoprothrombinemia, eosinophilia, haemolysis in certain susceptible G-6-PD deficient patients

and bone marrow depression.

Hepatic/Biliary/Pancreatic

Hepatitis, including cholestatic jaundice and hepatic necrosis, jaundice, elevation of serum transaminase, alkaline phosphatase and bilirubin.

Hepatic changes including fatalities have been recorded in at-risk patients. Cholestatic jaundice and hepatic necrosis may be fatal.

Musculoskeletal

Arthralgia, rhabdomyolysis and myalgia.

Neurologic

Aseptic meningitis, convulsions, peripheral neuritis, ataxia, tremor, vertigo, tinnitus, headache.

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either SEPTRA® or to trimethoprim alone.

Ophthalmologic

Uveitis

Psychiatric

Hallucinations, depression, apathy, nervousness, dizziness.

Respiratory

Pulmonary infiltrates, cough, shortness of breath, dyspnea.

Symptoms and Treatment of Overdosage

Acute

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

General principles of treatment include the 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. Inducing diuresis plus alkalinisation of urine will enhance the elimination of sulfamethoxazole. Alkalinisation will reduce the rate of 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.

There is no known antidote for sulfonamide poisoning; however, calcium folinate (leucovorin), 3 to 6 mg I.M. for 5 to 7 days, is an effective antidote for adverse effects in the hemopoietic system caused by trimethoprim.

Chronic

Use of SEPTRA® at high doses and/or for extended periods of time may cause confusion and 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Dosage and Administration

Intravenous Administration

SEPTRA® Injection may be used only in patients who are unable to take oral medication or where there is a need for rapid attainment of high serum concentrations. Oral treatment should be substituted as soon as possible.

Serious Systemic Infections

Adults

The intravenous dosage of SEPTRA® Injection depends on the severity of the infection. A dose of 160 to 240 mg trimethoprim + 800 to 1200 mg sulfamethoxazole may be given every 6, 8 or 12 hours. This dose must be properly diluted (see Pharmaceutical Information: Parenteral Products) and infused over a period of one-half to one hour.

Children:

The recommended daily dosage for children is 5 to 10 mg trimethoprim/kg body weight/day and 25 to 50 mg sulfamethoxazole/kg body weight/day. This daily dosage must be properly diluted and administered in equally divided doses by infusion over a period of one-half to one hour.

Volume of Undiluted SEPTRA® Injection per Body Weight* (conversion factor 0.31 to 0.63 mL/kg)				
Body Weight (kg)	**Volume of Undiluted SEPTRA® for Infusion (mL)**			
	Total DailyDose	**Dose Every**		
		12 Hours (b.i.d.)	**8 Hours (t.i.d.)**	**6 Hours (q.i.d.)**
5	1.6 - 3.2	0.8 - 1.6	0.5 - 1.1	0.4 - 0.8
10	3.1 - 6.3	1.6 - 3.2	1.0 - 2.1	0.8 - 1.6
20	6.2 - 12.6	3.1 - 6.3	2.1 - 4.2	1.6 - 3.2
40	12.4 - 25.2	6.2 -12.6	4.1- 8.4	3.1 - 6.3
60	18.6 - 37.8	9.3 -18.9	6.2 - 12.6	4.7 - 9.5

* SEPTRA® Injection must be properly diluted (see Pharmaceutical Information: Parenteral Products) and administered in equally divided doses.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least five days.

Other diseases, including certain tropical diseases rarely seen in Canada have also been successfully treated with SEPTRA®. The duration of treatment is as follows:

Disease	Duration
Cholera	7 days
Nocardiosis	12 weeks
Brucellosis	2 weeks to 3 months

Pneumocystis jiroveci Pneumonitis

Children and Adults

The recommended daily intravenous dosage is 20 mg trimethoprim/kg body weight + 100 mg sulfamethoxazole/kg body weight. This daily dosage is to be divided into four equal doses infused over a period of one-half to one hour, at six-hour intervals, until oral therapy can be instituted.

Volume of Undiluted SEPTRA® Injection per Body Weight* (conversion factor 1.25 mL/kg)		
Body Weight (kg)	**Volume of Undiluted SEPTRA® Injection (mL)**	
	Total Daily Dose	**Dose Every 6 Hours (q.i.d.)**
5	6.3	1.6
10	12.5	3.1
20	25.0	6.3
40	50.0	12.5
60	75.0	18.8
80	100.0	25.0

***** SEPTRA® Injection must be properly diluted (see Pharmaceutical Information: Parenteral Products) and administered at six-hour intervals.

Therapy should be continued for a total treatment period of at least two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of greater than or equal to 5 micrograms/mL (see Adverse Reactions)

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 Dose Regimen
Above 25	Usual standard regimen
15-25	Half the usual regimen
Below 15	Use not recommended

Pharmaceutical Information

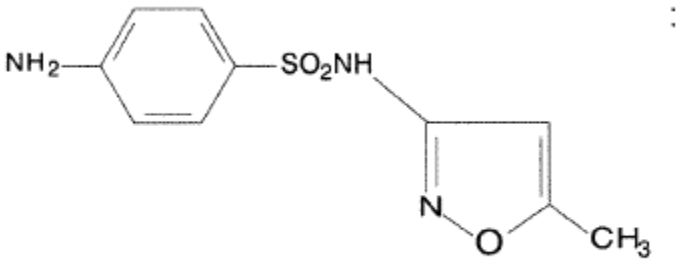
Drug Substance

The active ingredients of SEPTRA® are a combination of trimethoprim and sulfamethoxazole which has been established in a ratio of 1:5.

Proper Name: Sulfamethoxazole

Chemical Name: N^1-(5 - methyl - 3 - isoxazolyl) sulfanilamide

Structural Formula:



Molecular Formula: $C_{10}H_{11}N_3O_3S$

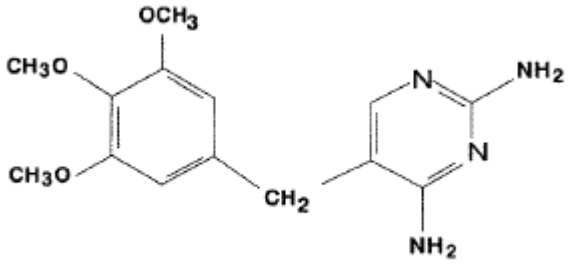
Molecular Weight: 253.31

Description: Sulfamethoxazole is a white to off-white, practically odourless, crystalline compound. It has a melting point of 167°C.

Proper Name: Trimethoprim

Chemical Name: 2,4 - diamino - 5 - (3,4,5 - trimethoxabenzyl) pimidine

Structural Formula:



Molecular Formula: $C_{14}H_{18}N_4O_3$

Molecular Weight: 290.32

Description: Trimethoprim is a white to cream, bitter crystalline powder. It has a melting point of 199-203°C and a solubility in water of 0.4 mg/mL.

Composition

Strong Sterile Co-Trimoxazole Solution: Each mL of SEPTRA® Injection contains 16 mg trimethoprim, 80 mg sulfamethoxazole and the following non-medicinal ingredients: propylene glycol (0.45 g), tromethamine (14.00 mg), sodium hydroxide (13.10 mg and for pH adjustment), sodium metabisulphite (1.00 mg), ethanol 96% (13.2% v/v), and water for injection.

Stability and Storage Recommendations

SEPTRA® Injection should be stored at room temperature between 15° and 30°C and protected from light.

Parenteral Products

CAUTION: Direct intravenous injection is not recommended. SEPTRA® Injection must be diluted in one of the following diluents:

a. Ringer's Solution
b. Sodium chloride 0.9% Solution
c. Sodium chloride 0.18% + Dextrose 4% Solution
d. Dextrose 5% Solution
e. Dextrose 10% Solution
f. 10% Dextran 40 in Sodium chloride 0.9% Solution
g. 10% Dextran 40 in Dextrose 5% Solution
h. 6% Dextran 70 in Sodium chloride 0.9% Solution
i. 6% Dextran 70 in Dextrose 5% Solution

	Volume of Diluent (mL)	Approx. Available Volume (mL)	Nominal Concentration (mg/mL)	
			Trimethoprim	Sulfamethoxazole
5 mL ampoule	125	130	0.62	3.1

The prepared solution must be kept at room temperature and administration started within five hours. Do not mix the prepared infusion solution with other drugs or solutions. If, upon visual inspection, there is cloudiness or evidence of precipitation after mixing, the solution should be discarded and a fresh solution prepared.

Availability of Dosage Forms

SEPTRA® Injection containing trimethoprim (16 mg/mL) and sulfamethoxazole (80 mg/mL).

Ampoules of 5 mL. Packages of 10.

Microbiology

SEPTRA® (sulfamethoxazole and trimethoprim) is bactericidal *in vitro* against the gram-negative and gram-positive organisms listed in Table 3.

In vitro Activity: Trimethoprim is, in general, more active than sulfamethoxazole against most bacterial species (see Table 1). Notable exceptions to this include *Neisseria gonorrhoeae* and *Pseudomonas aeruginosa* (which is, in general, insensitive to these drugs).

Table 1

COMPARISON OF ACTIVITY OF TRIMETHOPRIM AND SULFAMETHOXAZOLE *IN VITRO*

	MIC (µg/mL)	
	Trimethoprim	Sulfamethoxazole
Streptococcus pyogenes	0.4	100 (± 25)
Diplococcus pneumoniae Type II	1	32 (± 16)
Viridans streptococci	0.25	8
Streptococcus faecalis	0.5	100
Streptococcus agalactiae	4	50
Staphylococcus aureus	0.2	4
Erysipelothrix rhusiopathiae	8	>100
Corynebacterium pyogenes	0.4	>100
Corynebacterium diphtheriae	0.4	>100
Clostridium perfringens	50	16 (± 8)
Mycobacterium tuberculosis	250	>1000
Nocardia asteroides	10	5
Escherichia coli	0.2	8
Citrobacter freundii	0.1	3
Klebsiella pneumoniae	0.5	16
Klebsiella rhinoscleromatis	0.5	10
Enterobacter aerogenes	3	>100
Salmonella typhi	0.4	4
Salmonella typhimurium	0.3	10
Shigella spp.	0.4	4
Vibrio comma	0.8	32
Pasteurella septica	0.1	8
Haemophilus influenzae	0.12	>50
Bordetella pertussis	3	100
Moraxella lacunata	4	8 (± 2)
Proteus spp.	1	8
Providence B	1	30
Pseudomonas aeruginosa	>100	25
Pseudomonas pseudomallei	4	10
Neisseria gonorrhoeae	12	1.6
Neisseria meningitidis	8	1.5

The activities were compared in the Wellcome Nutrient Agar containing 5% lysed horse blood. For *Neisseria* and *Haemophilus* spp., the medium was heated at 80°C for 5 minutes and in the case of *Mycobacterium tuberculosis*, Peizer and Schacter medium was used.

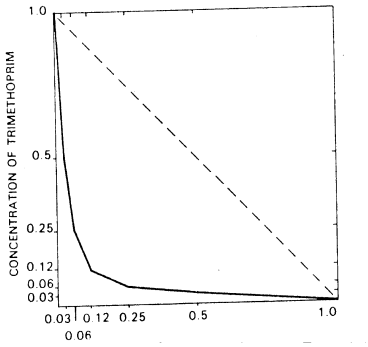
Demonstration of Synergy

By testing trimethoprim and sulfamethoxazole, both separately and in combination, synergy can be demonstrated *in vitro*. Synergy is indicated by one or all of the following:

1. by a reduction in the MIC of each drug when the drugs are used in combination
2. by an increase in the size of the zone of inhibition around the combination disc; and
3. by an increase in bactericidal activity when the drugs are used in combination

The reduction in the MIC varies with the ratio of the drugs present and it has been demonstrated that the optimum ratio, as measured by maximum reduction in the MIC's of both drugs, is that in which the drugs are present in proportions corresponding to their respective MIC when acting singly. It should be emphasized, however, that potentiation occurs over a wide range of ratios. With an excess of one of the drugs, the proportion of the other drug may be markedly reduced below that of the optimum ratio, yet still produce a synergistic effect.

Figure 2
CONCENTRATION OF SULFAMETHOXAZOLE



CONCENTRATION OF SULFAMETHOXAZOLE: Isobologram showing the synergy existing between trimethoprim and sulfamethoxazole. Concentrations required to produce 50% inhibition of bacterial growth.

Because of the wide variation in sensitivities of organisms to trimethoprim and sulfamethoxazole, the optimum ratio is also variable and could be different for each organism. Since, in general, trimethoprim is about 20 to 100 times more active than sulfamethoxazole, when examining strains for enhanced susceptibility to the combination investigators have generally preferred to use a fixed ratio, choosing one near the modal optimum. The 1:20 ratio is used most frequently, and examples of the increase in activity are shown in Table 2.

Table 2
EFFECT ON MIC OF COMBINING 1 PART OF TRIMETHOPRIM WITH 20 PARTS OF SULFAMETHOXAZOLE

Organism	MIC µg/mL			
	Sulfamethoxazole		Trimethoprim	
	Alone	Mixture	Alone	Mixture
Streptococcus pyogenes	>100	1.0	1.0	0.050
Diplococcus pneumoniae	30	2.0	2.0	0.100
Staphylococcus aureus	3	0.3	1.0	0.015
Haemophilus influenzae	10	0.3	1.0	0.015
Bordetella pertussis	50	4.0	3.0	0.200
Klebsiella pneumoniae	>100	4.0	1.0	0.200
Klebsiella aerogenes	>100	4.0	1.0	0.200
Escherichia coli	3	1.0	0.3	0.050
Salmonella typhimurium	10	1.0	0.3	0.050
Shigella sonnei	10	1.0	0.3	0.050
Proteus vulgaris	30	3.0	3.0	0.150
Neisseria gonorrhoeae	27	1.0	14.4	0.540

Table 3 shows the consolidated reported incidence of sensitivity of 49 165 strains of 40 species to trimethoprim plus sulfamethoxazole from 28 studies. A standard sensitivity disc containing 1.25 µg trimethoprim and 23.75 µg sulfamethoxazole was used in each study, but the medium varied.

Table 3

INCIDENCE OF SENSITIVITY TO TRIMETHOPRIM + SULFAMETHOXAZOLE

Species	Total No. of Strains	Sensitive Strains	
		Total	%
S. aureus	4 929	4 280	86.8
S. epidermidis	99	83	83.8
D. pneumoniae	140	140	100.0
St. Pyogenes	757	699	92.3
St. viridans	873	803	91.9
Streptococci	191	102	53.4
St. agalactiae	20	20	100.0
Enterococci	7 394	3 798	51.4
Escherichia coli	18 903	16 851	89.1
Klebsiella	1 365	1 109	81.2
K. pneumoniae	12	12	100.0
Proteus spp.	3 142	2 436	77.5
Pr. vulgaris	610	402	65.9
Pr. mirabilis	2 730	2 337	85.6
Pr. morganii	183	160	87.4
Pr. rettgeri	498	431	86.5
Providence A	133	104	78.2
Klebs.-Enterobacter	670	458	68.4
Kl. edwardsii	2	2	100.0
Enterobacter	1 344	1 169	86.9
Ent. cloacae	193	187	96.9
Salmonella	594	586	98.6
Hafnia	92	82	89.1
Shigella	226	222	98.2
Sh. dysenteriae	12	8	66.7
Ps. aeruginosa	3 081	600	19.5
Ps. pseudomallei	12	6	50.0
Citrobacter	202	184	91.1
Serratia	28	26	92.9
Paracolobactrum	84	59	70.2
Haemophilus influenzae	284	218	76.8
Flavobacterium	2	2	100.0
Achromobacter	160	124	77.5
Arizona sp.	18	10	55.6
Alcaligenes sp.	150	127	84.7
AD group	4	4	100.0
Cory. diphtheriae	2	2	100.0
Acinetobacter	16	15	93.7
Aeromonas	4	4	100.0
Neisseria Meningitidis	6	6	100.0
Neisseria gonorrhoeae	32	31	97.0

The resistance of *Bacteroides* spp. and *Lactobacilli* is of special interest, for they comprise the major portion of the flora of the gut. Trimethoprim plus sulfamethoxazole given daily for 10 days to 12 adult volunteers, eliminated all members of the *Enterobacteriaceae* family from the feces but did not affect either of the former bacterial groups. This lack of effect of these major groups probably accounts for the infrequent occurrence of intestinal upsets during therapy with SEPTRA®.

Trimethoprim and Sulfonamide-Resistant Strains

The theoretical basis for the synergistic effect of SEPTRA® is that sulfamethoxazole reduces the amount of dihydrofolate synthesized by the infecting organism (usually causing bacteriostasis), and an additional small amount of trimethoprim produces a complete block in the conversion of the folate to its active form (usually causing bacterial death).

When examined by conventional susceptibility methods, an organism is regarded as resistant to sulfonamides when its macroscopic growth is not affected. "Resistance" by this definition does not necessarily mean that the sulfonamide has not reduced the folate biosynthesis of the organism. There is indirect enzymatic evidence that the dihydrofolate content of such sulfonamide-resistant strains is, in fact, reduced in the presence of sulfonamides, although not to the same extent as that of sulfonamide-sensitive strains. Therefore, in the presence of sulfamethoxazole, the effect of trimethoprim on these sulfonamide-resistant strains should be increased because the amount of substrate against which the trimethoprim competes is reduced. *Streptococcus faecalis* is often regarded as being indifferent to the presence of sulfonamides, yet the susceptibility of this organism (and of sulfonamide-resistant strains of *Escherichia coli*) can be shown to be enhanced markedly with the addition of trimethoprim. Perhaps even more convincing evidence can be obtained by the diffusion method.

Although sulfonamide sensitivity discs produce no zones of inhibition with *Streptococcus faecalis*, discs containing 23.75 µg sulfamethoxazole plus 1.25 µg trimethoprim produce larger zones of inhibited growth of *Streptococcus faecalis* than do discs containing 1.25 µg trimethoprim. The difference in size is abolished when para-aminobenzoic acid is present.

Reversal of Trimethoprim Activity

Trimethoprim acts by interfering with the conversion of dihydrofolic acid to tetrahydrofolic acid. Therefore, the presence of an exogenous source of the latter should, theoretically, diminish or even abolish the antibacterial activity of SEPTRA® in the host.

In vitro, 1 µg/mL folinic acid affects only the sensitivities of *Streptococcus faecalis*, an organism known to utilize exogenous folates. *In vivo*, when administered subcutaneously to mice infected with *Diplococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Proteus vulgaris, Salmonella schottmuelleri* and *Salmonella typhimurium,* folinic acid does not affect the ability of trimethoprim to potentiate the antibacterial activity of sulfamethoxazole.

The *in vitro* interference with the action of trimethoprim and the sulfonamides by thymidine also raises the question of whether thymidine could affect *in vivo* activity. Experimental studies in the hamster indicate that thymidine is degraded rapidly *in vivo*. In experiments in mice where large doses of the nucleoside were given intraperitoneally, it did not interfere with the protection afforded by trimethoprim and sulfamethoxazole against *Proteus vulgaris*.

Resistance Development

During the serial passage in the presence of trimethoprim, little change in sensitivity occurs with light inocula; however, resistance develops rapidly with heavy inocula. With sulfonamide-sensitive strains, the emergence of these mutants is markedly delayed by the presence of sulfamethoxazole. The delaying effect of the sulfonamide depends, however, on the degree of sulfonamide resistance and is minimal with highly resistant strains.

Recently, R factors conferring high degrees of trimethoprim resistance have been identified in members of the *Enterobacteriaceae* family isolated from man and animals. A factor conferring high trimethoprim and sulfonamide resistance was detected in a strain of *Escherichia coli* and in a strain of *Klebsiella aerogenes*. Both strains were isolated from infected urine of human patients.

Pharmacology

Pharmacokinetics

Peak plasma levels of trimethoprim and sulfamethoxazole are higher and achieved more rapidly after one hour of intravenous infusion of SEPTRA® for infusion than after oral administration of an equivalent dose of a trimethoprim-sulfamethoxazole oral presentation. Plasma concentration, elimination half-life and urinary excretion rates show no significant differences following either the oral or intravenous route of administration.

Absorption

Both trimethoprim and sulfamethoxazole are rapidly absorbed following oral administration. Detectable levels of both drugs appear in the blood in about five minutes with significant levels being reached within an hour. Peak blood levels for both compounds are attained usually in two to four hours, are maintained for about seven hours, and detectable amounts are still present after 24 hours. When the two drugs are administered together, the individual blood levels are similar to those achieved when the drugs are administered separately, thus indicating no effect in absorption of one drug by the other.

Distribution

The ratio of one part trimethoprim to five parts sulfamethoxazole achieves drug concentrations in the blood in the ratio of approximately 1:20, a ratio considered to be optimal against a wide range of bacteria. Unlike sulfamethoxazole, trimethoprim concentrates in tissues; biopsy material from a small number of patients taking trimethoprim preoperatively indicated that the

concentration of trimethoprim in the tissues exceeded that of the plasma sampled at the same time - most significant in the lung (by 10 times). A similar pattern occurs in animals. Levels of trimethoprim in the sputum were also found to be higher than in the plasma following oral administration of trimethoprim-sulfamethoxazole. The concentrations of both drugs have also been found to be well-maintained in lymph and tissue fluids.

In serum, the degree of protein-binding by trimethoprim varies with the concentration, but it normally is about 44% bound to plasma protein. Sulfamethoxazole was found to be about 70% bound to plasma protein. Addition of sulfamethoxazole reduced the binding of trimethoprim by 3 to 4%, but there was no change in the protein-binding of sulfamethoxazole (about 66%) at therapeutically attainable concentrations of the two drugs.

Metabolism and Excretion

Studies conducted on the individual components administered separately, indicate that in the presence of a high fluid intake, approximately 50%, and in the presence of a low fluid intake, approximately 40% of the orally ingested trimethoprim is excreted unchanged in the urine within 24 hours. Approximately 10% of the excreted drug is in the form of metabolites with little or no antibacterial activity. Some trimethoprim is excreted in the bile, where concentrations twice those of plasma are obtained, but as it is almost completely reabsorbed; very little appears in the feces. Studies with radio-labelled trimethoprim indicated that it is almost completely absorbed following oral administration in man; less than 4% of the radioactivity appeared in the feces over a period of six days. Radioactivity was eliminated from the plasma and urine at almost identical rates; almost all of an oral dose being excreted in the urine within 48 hours. The biological half-life of trimethoprim was calculated to be 10 hours (range of 6.2 to 12 hours in four patients), which corresponds well to the half-life of 9 to 11 hours determined in man for sulfamethoxazole.

About 60% of the orally ingested sulfamethoxazole is excreted in the urine within 48 hours. Of the excreted drug, approximately half is the N^4 acetylated derivative, a fifth is the N^4 conjugate, a sixth is the unchanged parent compound, and about a tenth is another N^4 free compound.

Although the amount of each drug excreted is similar when given separately or in combination, the method of excretion by the kidney is quite different. Sharpstone demonstrated that there is net tubular reabsorption of filtered sulfamethoxazole, at least in patients with normal renal function, whereas with trimethoprim there is a tubular secretory mechanism of excretion in patients with normal or impaired renal function.

Renal clearance of sulfamethoxazole increased with rising urine flow-rate, was independent of urine pH when this was less than 7, but increased with alkalinization of the urine above a pH of 7. The clearance of trimethoprim was unaffected by alteration in urine flow-rate but increased sharply with falling urine pH.

In patients with impaired renal function, sulfamethoxazole excretion was only slightly decreased, whereas trimethoprim excretion decreased markedly in severe renal impairment.

Toxicology

Acute Studies

Acute toxicity studies in rats of the separate components and of trimethoprim and sulfamethoxazole combined in a ratio of 1:5 demonstrated the following LD_{50} values:

	Sulfamethoxazole	Trimethoprim	1:5
Rats (Adult) oral	2000 mg/kg	1500 mg/kg	6500 mg/kg
Rats (Neonates) oral	1360 mg/kg	195 mg/kg	1160 mg/kg

Subacute Studies

Daily dosages of 33, 100, and 300 mg/kg of trimethoprim and 133, 400, and 1200 mg/kg of sulfamethoxazole were given to young, sexually immature rhesus monkeys for one month. The

compounds were also given in combination; the lower doses of each being combined, and similarly the higher ones. Effects on weight gain were seen. Loss in weight was noted with high and medium dosage groups with the combined drugs. Changes were induced in hemopoiesis which were consistent with trimethoprim action in interfering with dihydrofolate reductase activity. Also high doses of the sulfonamide produce hypoplastic hemopoietic changes. Half the animals on high dose levels showed increased blood urea concentrations.

A similar study in rats produced similar results. In addition, some changes associated with the sulfonamide were noted in the thyroid and in the pituitary, such as increased weight and epithelial changes. Fatty changes were also seen in the liver of monkeys and rats on the medium and high dose levels.

Chronic Studies

Six Months

Toxicity studies of six months duration were conducted in rats and monkeys with a combination of trimethoprim and sulfamethoxazole (1:2 ratio) with total daily oral doses ranging between 99 and 900 mg/kg.

Doses of 99 mg/kg daily for six months were well-tolerated in both species with minimal signs of toxicity; 300 mg/kg was well-tolerated by monkeys, but in rats impaired growth was seen and 2 of the 10 animals in this dosage group died. With 900 mg/kg, marked effects on growth and on survival occurred in both species.

Histopathological examinations were made on more than 20 different tissues from each species; these showed depression of hematopoiesis in both species in the 300 and 900 mg/kg dosage groups and minor changes with 99 mg/kg. These bone marrow changes were related to trimethoprim's interference with dihydrofolate reductase activity. Other tissue changes

attributed to drug action seen in the rat, but not in the monkey, were thyroid hyperplasia and pituitary cytological effects, both associated with the sulfonamide moiety.

12-14 Months

Oral toxicity studies with trimethoprim and sulfamethoxazole, singly or in a 1:5 combination, were conducted in the monkey and in the rat. For the monkey, dose levels ranging from 10 + 50 to 60 + 300 mg/kg six days per week were employed for a period of 52 weeks; for the rat, dose levels ranging from 5 + 25 to 120 + 600 mg/kg per day were employed for a duration of 60 weeks.

In the monkey, the 1:5 combination did not produce any significant compound-related effects, except for a slight reduction in weight gain in the 60 + 300 mg/kg dose group.

In the rat study, thyroid hyperplasia of a dose-related severity was seen after 13 weeks in all animals receiving sulfamethoxazole. This hyperplasia progressed to nodularity or adenoma formation in some rats after 52 weeks at doses as low as 50 mg/kg per day, and to local vascular invasion and lung metastases after 60 weeks at doses as low as 150 mg/kg per day. Pituitary changes (large pale cells, often vacuolated), considered to be secondary to the thyroid change, were found in a few rats in all the sulfamethoxazole treated groups.

The phenomenon of thyroid hyperplasia in rats has been produced in this species by a number of sulfonamides and antithyroid drugs. The thyroid hyperplasia which occurs under the influence of these drugs is considered to be compensatory to the failure of thyroid hormone synthesis; it has been stated that this hyperplasia can be prevented or reversed by thyroid hormone. The progression of thyroid hyperplasia to nodule or adenoma formation is an observation in rats which has been reported previously in the literature on the antithyroid drugs, thiouracil and thiourea. It is considered that in these studies the production of thyroid tumours

was due, not to any direct carcinogenic action of the drugs, but rather to the excessive and prolonged stimulation of the thyroid epithelium by the thyrotropic secretion of the pituitary.

Other changes associated with sulfamethoxazole treatment in our animal studies were: a dose-related increased alkaline phosphatase, a dose-related reduction in mean body weight gain, slight depression of hematopoiesis, testicular atrophy, focal renal calcification, and slightly increased fat vacuolation of the liver and kidney.

Human Tolerance Studies

Chronic Tolerance and Toxicity Study

A double-blind, placebo-controlled trial designed to study human tolerance and possible toxic effects of an orally administered 1:5 trimethoprim/sulfamethoxazole combination, was completed in 36 normal healthy men for 13 weeks. At the two dose levels investigated (80 + 400 and 160 + 800 mg/kg three times daily) the drug appeared to be well-tolerated, with only a few minor, easily reversible side-effects occurring. The trial had to be stopped in two subjects due to recurrent black tongue.

Thyroid Function Study

Thyroid function tests (protein-bound iodine and serum cholesterol determinations) were conducted in 25 patients who received two to four SEPTRA® Tablets daily for a duration of 35 to 760 days. In none of these patients was there evidence of depression of thyroid function. One patient showed a diffused stroma of the thyroid and an increased ^{131}I uptake, and another patient had a small diffused goiter after 120 days of treatment.

Reproduction and Teratology

A three-phase investigation, comprised of a fertility and general reproductive performance study and a perinatal and postnatal study in the rat, and teratology studies in the rat and rabbit, were

conducted with an orally administered 1:5 combination of trimethoprim to sulfamethoxazole. The dose levels investigated, singly or combined, were 70 + 350, 30 + 150, 15 + 75, 0 + 350, 0 + 150, 0 + 75, and 14 + 0 or 70 + 0 mg/kg.

Some drug-related effects noted in the investigation were: a reduced body weight gain by eight weeks in males in the Fertility and General Reproductive Performance Study at dose levels of 150 or 350 mg/kg of sulfamethoxazole, alone or in combination, and an increased incidence of maternal mortality in the rabbit teratology study at the same dose levels. In one of the 18 litters of the high combination group, four of the eight pups were abnormal. Two had bone malformations and two had curled tails, missing or small kidneys, absence of eyelid and one also had misshapen lateral ventricles of the brain. The instances of small, underdeveloped kidneys were such as to raise a question of dose relationships. In the teratogenicity study in rats, instances of small, underdeveloped kidneys were seen: in control group - 0; in combination groups (420 mg/kg dose) - 6 (8.5%), (180 mg/kg dose) - 3 (4.7%), (90 mg/kg dose) - 2 (3.2%). Other malformations noted in a group receiving 420 mg/kg, were one instance of incomplete nasal septum and two fetuses with abnormally large openings in the lateral ventricles. Fertility and general reproductive performance, and early and late fetal development were not affected by the dose regimen employed.

Fertility

In these studies, the animals were dosed per os with a 1:5 mixture of trimethoprim to sulfamethoxazole daily from 60 days before mating until the end of weaning.

In the rat, at 600 mg/kg there was a slight, non-significant lowering of the pregnancy rate when compared with controls. The number of live progeny per litter at birth and at weaning was less than in controls. A slight treatment-related disturbance of estrus and of sperm count was also noted.

With 200 mg/kg the pregnancy rate was slightly lower than in controls, but the other effects seen with the higher dose were not noted.

In the rabbit, daily oral doses of 600 mg/kg produced vomiting, even with divided doses, and was therefore abandoned. Two hundred mg/kg did not have a significant effect on the pregnancy rate, on the number of live births per litter, or on the mean weight of progeny at birth or at weaning.

Teratogenicity

In these studies, rats and rabbits were dosed by stomach tube daily from days 8 to 16 of pregnancy, or on a single day of pregnancy (rat only). Trimethoprim and sulfamethoxazole were used alone, in a 1:4 combination, and in a 1:2 combination.

For the rat, dosing with 500 mg/kg of trimethoprim on any single day of gestation between days 8 to 16 had no effect on the dams or their fetuses. A single dose of 2000 mg/kg of trimethoprim was lethal to most fetuses when given on the eighth or ninth day, and it produced a very high incidence of malformations when given on days 10, 11 or 12. However, the incidence of these malformations dropped off precipitately when dosing was on the 13th day or later.

The most common abnormality seen with either compound in the rat, when dosing was daily on days 8 to 16 of pregnancy, was cleft palate which occurred with 200 mg/kg of trimethoprim alone and with 640 mg/kg of sulfamethoxazole alone. Higher doses of trimethoprim produced bony defects and exencephaly, related to its action in interfering with dihydrofolate reductase activity. The abnormalities could be prevented by the administration of folinic acid subcutaneously. No fetal abnormalities were found at daily doses of 160 mg/kg or less of trimethoprim, or 512 mg/kg or less of sulfamethoxazole. Using compounds in a 1:4 trimethoprim/sulfamethoxazole combination, fetal malformations appeared at between 128

mg/kg and 160 mg/kg of trimethoprim and 512 mg/kg and 640 mg/kg of sulfamethoxazole. There appeared to be a distinct synergism with the 1 to 2 mixture.

In rabbits given the drug daily during organogenesis (days 8 to 16), no teratogenic effect was revealed with the 1:4 mixture or its components. While no important effect on the incidence of dead fetuses was noted with daily doses of 125 mg/kg of trimethoprim, 500 mg/kg or less of sulfamethoxazole, or with 312.5 mg/kg of the combination, the incidence of fetuses dying before full term was higher than for controls in the groups given trimethoprim except at the 62.5 mg/kg dose. Pregnant does tolerated the combination better than sulfamethoxazole alone.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrSEPTRA® Injection
sulfamethoxazole + trimethoprim, BP
sterile solution for the preparation of intravenous infusions

Read this carefully before you start taking SEPTRA® Injection and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about SEPTRA® Injection.

Serious Warnings and Precautions

- SEPTRA® Injection can cause severe skin reactions that may be life threatening. These include Steven-Johnson syndrome and toxic epidermal necrolysis. Symptoms include: flat red rash, blisters, peeling skin, fever, body aches. You may also have blisters and sores or ulcers on your mucous membranes like your mouth, nose and genitals. Your eyes may get red and swollen. If you get any of these symptoms, stop taking SEPTRA® Injection and get immediate medical help.
- SEPTRA® Injection can cause a liver disease called fulminant hepatic necrosis that may be life-threatening. Symptoms include yellowing of the skin and whites of the eyes (jaundice), pain in your upper right abdomen, swelling of the abdomen, nausea (feeling sick) and vomiting (being sick). If you get any of these symptoms, stop taking SEPTRA® Injection and get immediate medical help.
- SEPTRA® Injection can cause a blood condition called agranulocytosis, where the number of white cells in the blood becomes dangerously low. Symptoms of this can include sudden fever, chills, a sore throat, feeling weak. You might also have a fast heart rate or fast breathing. If you get any of these symptoms, stop taking SEPTRA® Injection and get immediate medical help.
- SEPTRA® Injection can cause a blood disease called aplastic anemia, where the bone marrow is unable to make enough blood cells from being damaged. Symptoms of this can include feeling tired, feeling short of breath, pale skin, unexplained or easy bruising, fever, chills, sore throat, and a general feeling of being unwell. If you get any of these symptoms, stop taking SEPTRA® Injection and get immediate medical help.
- Another blood disease that can be caused by SEPTRA® Injection is a disease known as immune thrombocytopenia, which can be life-threatening. Symptoms of this include being easily bruised, a rash on the skin that appears tiny pinpoint-sized reddish or purple spots, usually on the lower legs, bleeding from the gums or nose, and blood in the urine or stool. If you get any of these symptoms, stop taking SEPTRA® Injection and get immediate medical help.
- SEPTRA® Injection can cause an allergic reaction in the lungs and in the airways, where the airways can close up and make breathing difficult, and can be life-threatening if the person does not get medical help. Symptoms include difficulty breathing, coughing, wheezing, and a feeling of tightness in the chest. If you get any of these symptoms, stop taking SEPTRA® Injection and get immediate medical help.

What is SEPTRA® Injection used for?

SEPTRA® Injection is used to treat:

- urinary tract infections;
- lung infections such as bronchitis or pneumocystis jiroveci pneumonia pneumocystis jiroveci pneumonitis in infants and children;
- gastrointestinal infections such as cholera or dysentery;
- nocardiosis, an infection of the lungs or other parts of the body;
- brucellosis which is a disease spread from animals to humans. When used to treat brucellosis it is used along with another medicine, gentamicin or rifampicin.

Antibacterial drugs like SEPTRA® Injection treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, SEPTRA® Injection should be used exactly as directed. Misuse or overuse of SEPTRA® Injection could lead to the growth of bacteria that will not be killed by SEPTRA® Injection (resistance). This means that SEPTRA® Injection may not work for you in the future.

How does SEPTRA® Injection work?

SEPTRA® Injection contains two different antibiotics called sulfamethoxazole and trimethoprim. These two antibiotics work together to kill or to slow or stop the growth of micro-organisms (bacteria, fungi) that cause disease. This means that SEPTRA® can be given to prevent or to treat certain kinds of infectious diseases.

What are the ingredients in SEPTRA® Injection?
Medicinal ingredients: trimethoprim and sulfamethoxazole
Non-medicinal ingredients: propylene glycol, tromethamine, sodium hydroxide, sodium metabisulphite, ethanol 96% and water for injection.

SEPTRA® Injection comes in the following dosage forms:
Solution for the preparation of intravenous infusions: sulfamethoxazole (80 mg / mL) + trimethoprim (16 mg / mL).

Do not use SEPTRA® Injection if:

- you are allergic to sulfamethoxazole, trimethoprim or any of the other ingredients, including sodium metabisulfite, in SEPTRA® Injection;
- you are allergic to sulphonamide medicines. Examples include sulphonylureas (such as gliclazide and glibenclamide). Talk to your doctor if you are allergic to a medicine and you are not sure if it is a sulphonamide medicine;
- you have liver problems;
- you have kidney problems;
- you have a blood disorder;
- you are pregnant;
- you are breastfeeding.

Children
If it is for your child, SEPTRA® Injection should not be given if they are less than 2 months old.

If you are not sure if any of the above apply to you, talk to your healthcare professional before

being given SEPTRA® Injection.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SEPTRA® Injection. Talk about any health conditions or problems you may have, including if you:

- have severe allergies or asthma;
- you don't have enough folic acid (a vitamin) in your body called folate deficiency;
- you are taking medications for epilepsy or seizures;
- you are underweight or malnourished;
- you have a disease called glucose-6-phosphate dehydrogenase deficiency;
- you have a rare blood disorder called porphyria, which can affect your skin or nervous system;
- you have been told by your doctor that you have a high level of potassium in your blood;
- you have been told by your doctor that you have a low level of sodium or albumin in your blood;
- you have been told by your doctor that you have any serious disorder of the blood or blood forming tissues such as low blood cell counts;
- you have existing heart or lung disease, which may lead to a build-up of fluid in your body;
- you have hereditary disorder called phenylketonuria and are not on a special diet to help your condition;
- you are human immunodeficiency virus (HIV) positive or have a condition called Acquired Immunodeficiency Syndrome (AIDS).

Other warnings you should know about:

Use in Elderly Patients
Elderly patients are more likely to get serious side effects when receiving SEPTRA® Injection. This is increased if you have kidney or liver disease or are taking some types of other medicines, such as diuretics.

Pregnancy and Breastfeeding
Talk to your doctor before taking this medicine if you are planning to get pregnant or planning to breastfeed. You should not receive SEPTRA® Injection if you are pregnant or are breastfeeding.

Use in Patients with Acquired Immunodeficiency Syndrome (AIDS)
If you have AIDS, you may be more likely to get side effects when receiving SEPTRA® Injection. These may include rash, severe allergic reactions, fever or low blood cell counts.

Gastrointestinal - C. difficile colitis
SEPTRA® Injection may increase your risk of being infected with a bacteria called *C. difficile*. Symptoms include watery diarrhea that happens three or more times per day or diarrhea associated with abdominal cramping.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SEPTRA® Injection:

- Diuretics known as water pills, for example spironolactone. Diuretics are used to remove excess water from the body;
- Pyrimethamine, used to treat malaria;
- Medicines to treat Human Immunodeficiency Virus (HIV), called zidovudine or lamivudine;
- Medicines used to thin the blood, such as warfarin;
- Phenytoin, used to treat epilepsy (fits);
- Methotrexate, a medicine used to treat cancer or arthritis;
- Medicines to treat heart conditions, such as digoxin or procainamide;
- Medicines that can increase the amount of potassium in your blood, such as steroids (like prednisolone);
- Cyclosporin, used after organ transplantation;
- Amantadine, used to treat Parkinson's disease, multiple sclerosis, the flu or shingles;
- Medicines for diabetes, such as glibenclamide, glipizide or tolbutamide (sulphonylureas);
- Rifampicin, an antibiotic.

Drug-Food Interactions

- Tell your healthcare professional if you have special dietary needs, especially if you are following a potassium rich diet. Potassium rich foods include beans, dark leafy greens, potatoes, squash, yogurt, fish, avocados, mushrooms and bananas.

How to take SEPTRA® Injection:

- SEPTRA® Injection will be given to you by a healthcare professional.
- It will be given to you as a continuous infusion into your vein. This is where a medicine is slowly given to you over a period of time.
- Your healthcare professional will dilute SEPTRA® Injection before giving it to you.
- You should drink plenty of fluids while receiving SEPTRA® Injection.

Usual dose:

- Your healthcare professional will decide how much SEPTRA® Injection you will receive.
- The dose you are given and how often you are given it will depend on:
- your infection;
- your weight;
- your age.

Overdose:

If you have been given too much SEPTRA® Injection you may have the following signs or symptoms:

- loss of appetite;
- colic (severe pain in the abdomen caused by gas);
- nausea and vomiting;
- dizziness, drowsiness or confusion;
- fainting;
- headache;
- fever.

If you think you have taken too much SEPTRA® Injection, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Your healthcare professional will inject this medicine into you. If you miss a scheduled injection talk to your healthcare professional as soon as possible.

What are possible side effects from using SEPTRA® Injection?

These are not all the possible side effects you may feel when taking SEPTRA® Injection. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Feeling weak or tired;
- Trouble sleeping;
- Vision problems;
- Hair loss;
- Nose bleed;
- Inflammation at the site of injection;
- Swelling of body tissues with fluid;
- Chills;
- Sensitivity to sunlight;
- Palpitations (heart beat that feels too fast, strong or irregular);
- Cold sores and ulcers or soreness of your tongue;
- Dry mouth;
- Heartburn;
- Abdominal pain or gas;
- Constipation;
- Nausea, vomiting and diarrhea;
- Loss of appetite;
- Passing more or less urine than usual; blood or cloudiness in your urine; difficulty reaching bathroom in time;
- Muscle pain or muscle weakness;
- Tingling or numbness in your hands and feet;
- Problems controlling your movements;
- Uncontrollable shaking;
- Vertigo (sensation of movement or feeling off balance);
- Ringing or other unusual sounds in your ears;
- Headache;
- Inflammation of your eye that causes pain and redness;
- Depression;
- Apathy (indifference and a lack of motivation);
- Feeling unsteady or dizzy.

SEPTRA® Injection can cause abnormal blood test results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic reactions including: swelling of face, mouth, tongue or throat which may be red and painful and/or cause difficulty in swallowing; red patches on the skin; rash; hives; fever (high temperature); joint pain; feeling sick (nausea); being sick (vomiting); chest pain.			√
Steven-Johnson syndrome and toxic epidermal necrolysis (**severe life-threatening skin reactions**); stop taking SEPTRA and get immediate medical help if any of the following occur: fever and flu-like symptoms, red or purple rash that spreads, unexplained widespread skin pain, blisters on the skin, inside the mouth, nose or genitals, shedding of the skin, nausea, vomiting.			√
Difficulty breathing, cough, wheezing, shortness of breath, tightness of the chest.			√
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection), including sudden headache or stiffness of your neck, accompanied by fever, nausea, vomiting, sensitivity to light.			√
Acute inflammation of the small and large intestine (*Pseudomembranous colitis*); including watery or bloody diarrhea, abdominal cramps, pain or tenderness, fever, nausea, dehydration.			√
Fits (convulsions or seizures);			√
Heart problems (stop taking			√

SEPTRA and get immediate medical help if any of the following occur: Increased heart rate, chest pain, shortness of breath).			
Acute inflammation of the pancreas (**Pancreatitis**), including upper abdominal pain that spreads to the back, swollen and tender abdomen, nausea, vomiting, fever.			√
Hypoglycaemia (an abnormally low level of sugar in the blood), including dizziness or light-headedness, shakiness, nervousness or anxiety, feeling confused, sweating, chills.			√
Problems with your urine; pain or difficulty passing urine, blood or cloudiness in your urine.			√
Jaundice (yellowing of the skin and whites of the eyes).			√
An infection called thrush or candidiasis which can affect your mouth or vagina.			√
Seeing, hearing, smelling, tasting or feeling things that don't exist outside your mind (**hallucinations**).			√
Immune thrombocytopenia, including being easily bruised, a rash on the skin that appears tiny pinpoint-sized reddish or purple spots, usually on the lower legs, bleeding from the gums or nose, and blood in the urine or stool.			√
Aplastic anemia, including feeling tired, feeling short of breath, pale skin, unexplained or easy bruising, fever, chills, sore throat, and a general feeling of being unwell.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store SEPTRA® Injection between 15° and 30°C. Protect from light.
Keep out of reach and sight of children.

If you want more information about SEPTRA® Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.aspenpharma.ca), or by calling 1-844-330-1213.

This leaflet was prepared by
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