PRODUCT INFORMATION

SEPTRIN

NAME OF THE DRUG

SEPTRIN 80/400 (trimethoprim/sulfamethoxazole) tablets
SEPTRIN FORTE 160/800 (trimethoprim/sulfamethoxazole) tablets
SEPTRIN 40/200 (trimethoprim/sulfamethoxazole) oral liquid

The structural formula of Trimethoprim (CAS 738-70-5) is

Trimethoprim is a 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine. It is a white to light yellow, odourless, bitter compound with a molecular weight of 290.3 and the molecular formula C_{14}H_{18}N_{4}O_{3}.

The structural formula of Sulfamethoxazole (CAS 723-46-6) is

Sulfamethoxazole is N^{1}-(5-methyl-3-isoxazolyl) sulphanilamide. It is an almost white, odourless, tasteless compound with a molecular weight of 253.28, and the molecular formula C_{10}H_{11}N_{3}O_{3}S.

Septrin is a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim. (CAS8064-90-2)

DESCRIPTION

Septrin in an antibacterial combination containing trimethoprim and sulfamethoxazole in a ratio of 1:5.
SEPTRIN tablets are white, biconvex, round, scored and embossed “ septrin” on the upper face. Bottom face plain. Each SEPTRIN tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole and the excipient ingredients, Magnesium stearate, Docusate sodium ( 0.4 mg per tablet), sodium starch glycollate and Povidone
SEPTRIN-FORTE tablets are white, elliptical, biconvex and embossed “SEPTRIN FORTE” on the upper face. Bottom face plain and scored along the shorter axis. Each SEPTRIN FORTE tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole and the excipient ingredients, Magnesium stearate, Docusate sodium (0.8 mg per tablet), sodium starch glycollate and Povidone
SEPTRIN Sugar Free Oral liquid is cherry flavoured. Each 5 mL of SEPTRIN sugar free oral liquid contains contains 40 mg trimethoprim and 200 mg sulfamethoxazole and the excipient ingredients sorbitol, preservatives methyl hydroxybenzoate and sodium benzoate, ethanol, flavours and colours: cherry, sunset yellow and allura red, citric acid, cellulose, glycerol, polysorbate 80, sodium carmellose and saccharin sodium.

PHARMACOLOGY

Microbiology
The majority of common gram-negative and gram-positive pathogenic bacteria are sensitive in vitro to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. These organisms include: E. coli, Neisseria, Salmonella, Klebsiella, Enterobacter, Shigella, Vibrio cholerae and Bordetella pertussis, Streptococcus, Staphylococcus, Pneumococcus. Septrin is usually active against the problem organisms: Haemophilus influenzae and Proteus.

Representative minimum inhibitory concentration values for susceptible organisms (MIC - microgram/mL)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Trimethoprim alone</th>
<th>Sulfamethoxazole alone</th>
<th>TMP/SMX (1:20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>0.05 - 1.5</td>
<td>1.0 - 245</td>
<td>0.05 - 0.5</td>
</tr>
<tr>
<td>Proteus species (indole positive)</td>
<td>0.5 - 5.0</td>
<td>7.35 - 300</td>
<td>0.05 - 1.5</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>0.5 - 1.5</td>
<td>7.35 - 30</td>
<td>0.05 - 0.15</td>
</tr>
<tr>
<td>Klebsiella-Enterobacter</td>
<td>0.15 - 5.0</td>
<td>2.45 - 245</td>
<td>0.05 - 1.5</td>
</tr>
</tbody>
</table>

TMP = Trimethoprim      SMX = Sulfamethoxazole

SEPTRIN is insensitive against Pseudomonas aeruginosa, Mycoplasmas, Ureaplasma urealyticum, Mycobacterium tuberculosis, Bacteroides species, Lactobacillus species and Treponema pallidum
In vitro studies have shown that bacterial resistance develops more slowly with SEPTRIN (trimethoprim + sulfamethoxazole) than with either trimethoprim or sulfamethoxazole alone.
Septrin is also active against the protozoan Pneumocystis carinii (see special dosage instructions).
Satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

Disc Susceptibility Testing
Dilution or diffusion techniques- either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg, NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. 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, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.
Pharmacological Actions
Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents. Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Pharmacokinetics
Absorption
After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Steady state levels in adults are reached after dosing for 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other. Trimethoprim is a weak base with a pKa of 7.3. It is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Trimethoprim is found in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid. Trimethoprim passes into amniotic fluid and foetal tissue reaching concentrations approximating those of maternal serum.

Metabolism
Approximately 44-50% of trimethoprim in the plasma is protein bound. The half-life in man is in the range 8.3-31 hours (mean 14.5 hours) in the presence of normal renal function. It is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. There appears to be no significant difference in the elderly compared with young patients.

Excretion
The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely. Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in amniotic fluid, aqueous humor, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluid is of the order of 20-50% of the plasma concentration. Approximately 66-70% of sulfamethoxazole in the plasma is protein bound. The half-life in man is in the range 6.1-22 hours (mean 11 hours) in the presence of normal renal function. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 mL/minute. The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

INDICATIONS
Upper and lower respiratory tract infections; renal and urinary tract infections; genital tract infections; gastrointestinal tract infections; skin and wound infections; septicaemias, and other infections caused by sensitive organisms.

CONTRAINDICATIONS
- Septrin should not be given to patients with a history of sulphonamide or trimethoprim sensitivity.
- Marked liver parenchymal damage or severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- Except under careful supervision, Septrin should not be given to patients with serious haematological disorders. Septrin has been given to patients receiving cytotoxic therapy (see Interactions with Other Drugs).
- Septrin should not be used in late pregnancy because products containing a sulphonamide may cause kernicterus.
- Septrin should not be given to premature babies or to infants less than 2 months of age.
- Septrin should not be used in the treatment of streptococcal pharyngitis. Clinical studies have documented that patients with Group A Beta-haemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septrin than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

**PRECAUTIONS**

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 anaemia and other blood dyscrasias.

Sulfonamides, including sulfonamide-containing products such as trimethoprim/sulfamethoxazole, should be discontinued at the first appearance of skin rash or any sign of adverse reaction. In rare instances, a skin rash may be followed by a more severe reaction such as Steven-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorder.

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 pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

**Use in the Elderly**

The use of Septrin in elderly patients carries an increased risk of severe adverse reactions. In rare instances fatalities have occurred. The risk of severe adverse reactions is particularly greater when complicating conditions exist, e.g. impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, or generalised bone marrow suppression (see Adverse Reactions section) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see Dosage and Administration section).

In view of the increased risk of severe adverse reactions in the elderly, consideration should be given to whether Septrin is the antibacterial of choice in this age group.

**Use in treatment of pneumocystis carinii pneumonia in patients with Acquired Immunodeficiency Syndrome (AIDS)**

Because of their unique immune dysfunction, AIDS patients may not tolerate or respond to Septrin in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, and leukopenia, with Septrin therapy in AIDS patients who are being treated for Pneumocystis carinii pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of Septrin in non-AIDS patients.

**Use in Glucose-6-phosphate dehydrogenase deficiency**

In individuals with glucose-6-phosphate dehydrogenase deficiency haemolysis may occur. This may be dose related.
Use in Patients known or suspected to be at risk of Acute porphyria
The administration of Septrin to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Effects on Fertility
The effect of SEPTRIN on human fertility is not known. Reproduction studies in rats with oral dosage up to 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole have not revealed evidence of impaired fertility.

Use in Pregnancy (Category C)
Sulphonamides may cross the placenta and cause kernicterus, jaundice and haemolytic anaemia in the newborn (by displacing bilirubin from plasma albumin) and should therefore be avoided as far as possible during the last month of pregnancy. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism and exposure during organ development may give rise to birth defects typical of folic acid antagonism.

Trimethoprim and sulfamethoxazole, alone and in combination, have produced teratogenic effects (cleft palate) in some studies in rats receiving dosages exceeding the usual human dosage. In some rabbit studies, an overall increase in fetal loss was associated with trimethoprim doses 6 times the usual human dose. SEPTRIN should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. If a trimethoprim-sulphonamide combination is given during pregnancy, folic acid supplementation may be required.

Carcinogenicity
Long term studies in animals to evaluate the carcinogenic potential of SEPTRIN have not been performed.

Genotoxicity
Bacterial mutagenic studies have not been performed with SEPTRIN. Trimethoprim did not exhibit mutagenic activity in the Ames test, and no chromosomal damage was observed in human leukocytes cultured in vitro with trimethoprim concentrations exceeding those attained in blood during therapy with the drug.

Pseudomembranous colitis
Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including trimethoprim/sulfamethoxazole. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis (e.g. opiates and diphenoxylate with atropine, Lomotil) may prolong and/or worsen the condition and should not be used.

Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Even if an organism is sensitive to trimethoprim, if it is not sensitive to sulfamethoxazole the combination should not be used, to avoid unnecessary exposure to the potential side effects of the sulphonamide components.

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

As with other sulphonamide preparations, critical appraisal of benefit versus risk should be made in patients with liver damage, renal damage, urinary obstruction, allergies or bronchial asthma. Severe
hepatic parenchymal damage may result in changes in the absorption and metabolism of sulfamethoxazole and trimethoprim. 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. See the special dosage table for use in renal impairment.

Regular blood counts are advisable in patients on long-term therapy, in those who are predisposed to folate deficiency (ie, the elderly, chronic alcoholics and rheumatoid arthritics), in malabsorption syndromes, malnutrition states, or during the treatment of epilepsy with anticonvulsant drugs such as phenytoin, primidone or barbiturates. Changes indicative of folate deficiency may be reversed by administration of folic acid without interfering with the antibacterial activity of trimethoprim.

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

A folate supplement should also be considered with prolonged high dosage of Septrin.

Urine analysis and renal function tests should be performed during long term therapy particularly in patients with reduced renal function.

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

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

Use in Lactation

Both trimethoprim and sulfamethoxazole are excreted in breast milk at concentrations comparable or somewhat lower than that in the blood. Sulfonamides may cause kernicterus, jaundice and haemolytic anaemia in the newborn. It is recommended that the possible risks should be balanced against the expected therapeutic effect. Consideration should be made of the infants age. Premature babies or to infants less than 2 months of age should not be exposed to SEPTRIN (see Contraindications).

Interactions with Other Drugs

In elderly patients concurrently receiving diuretics, mainly thiazides there appears to be an increased incidence of thrombocytopenia with or without purpura.

Occasional reports suggest that patients receiving pyrimethamine as malarial prophylaxis at doses in excess of 25 mg weekly may develop megaloblastic anaemia should Septrin be prescribed concurrently.

Septrin has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites in vitro. Careful control of the anticoagulant therapy during treatment with Septrin is advisable.

Septrin prolongs the half-life of phenytoin and if co-administered the prescriber should be alert for excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels is advisable.

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

Concurrent use of rifampicin and Septrin results in a shortening of the plasma half-life of trimethoprim after a period of about one week.

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

Sulphonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations. If Septrin is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see PRECAUTIONS).

Cases of pancytopenia have been reported in patients taking trimethoprim-sulfamethoxazole in combination with methotrexate. Most of these patients were on long term methotrexate therapy and/or predisposed to folate deficiency, and none of them were reported to have received a prophylactic folic acid supplement (see PRECAUTIONS).

Reversible deterioration in renal function has been observed in patients treated with co-trimoxazole 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. Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

**Drug/Laboratory Test Interactions**

Septrin, 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 Jaffe alkaline picrate reaction assay for creatinine resulting in over-estimations of about 10% in the range of normal values. The *Lactobacillus casei* serum folate assay and the *L. leishmanii* serum vitamin B₁₂ assay are affected by Septrin.

**Paediatric Use**

Safety has not been established in infants less than 2 months old and is not recommended for use. Trimethoprim and sulfamethoxazole should be used with caution in children who have the fragile X chromosome, as folate depletion may worsen the psychomotor regression associated with the disorder. (See CONTRAINDICATIONS)

**ADVERSE REACTIONS**

The following reactions have been reported from the use of oral Septrin. Nausea, vomiting, stomatitis and glossitis may occur. Haematological changes have been observed in some patients, particularly the elderly. The great majority of these changes were mild, asymptomatic, and proved reversible on withdrawal of the drug; in some instances, this was necessary before therapy could be completed. The reported changes consist primarily of neutropenia and thrombocytopenia. Observed less frequently: megaloblastic anaemia, leukopenia, aplastic and haemolytic anaemia, purpura, agranulocytosis and bone marrow depression. Rarely, fatalities have been reported. Skin and systemic reactions may occur. Several cases of Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported. Fatalities have been reported rarely. Jaundice has also rarely occurred and has usually been mild and transient, frequently occurring in patients with a past history of infectious hepatitis. On the whole, however, the nature of adverse reactions generally corresponds with what one would expect from a sulphonamide of moderately low toxicity, when the contraindications are strictly respected and recommended doses are used. Percentage incidence figures cannot be precise but have been estimated from the published literature at 6.8% of cases treated. Sensitivity reactions and gastrointestinal symptoms comprised nearly three-quarters of the adverse reactions reported.

The following have been reported rarely; eosinophilic or allergic alveolitis, anaphylaxis, allergic myocarditis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness like syndrome, generalised allergic reactions, photosensitivity, conjunctival and scleral injection. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported. Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pancreatitis, emesis, abdominal pain, diarrhoea, anorexia, moniliasis, pseudomembranous colitis. Renal failure, intestinal nephritis, blood urea and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria. Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. Hallucinations, depression, apathy, nervousness.
The sulphonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycaemia agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulphonamides.

Arthralgia and myalgia, pulmonary infiltrates, weakness, fatigue, insomnia.

At the high dosages used for the therapy of Pneumocystis carinii pneumonia in patients with acquired immune deficiency syndrome (AIDS), rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia and hyponatraemia have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient may be given calcium folinate supplementation. Severe hypersensitivity reactions have also been reported in HIV-infected patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days.

**DOSAGE AND ADMINISTRATION**

In the majority of acute infections, Septrin should be given for at least 5 days or until the patient has been symptom free for 2 days.

**Adults and Children over 12 years of age**

Standard dosage: one Septrin Forte or 2 Septrin tablets every twelve hours.

**For Severe Infections**

3 Septrin tablets every twelve hours.

Attention should be paid to the folate status of the patient should treatment be prolonged.

**Children under 12 years**

6 to 12 years: 5 to 10 mL Septrin Paediatric Suspension every twelve hours

2 to 5 years: 2.5 to 5 mL Septrin Paediatric Suspension every twelve hours

under 2 years: 2.5 mL Septrin Paediatric Suspension every twelve hours.

These amounts approximate to a dose of 6 mg/kg trimethoprim daily plus 30 mg/kg sulfamethoxazole daily. For severe infections dosage may be increased by 50%.

**Treatment of Pneumocystis carinii pneumonia**

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonia is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The aim is to obtain peak plasma or serum levels of >5 microgram/mL (see Adverse Reactions).

**Use in the Elderly**

See Precautions

**Dosage in Patients with Reduced Renal Function**

The following dosage regimens have been published for the administration of Septrin to patients with reduced kidney function.
Criteria of kidney function (non-protein nitrogen is unsuitable)  

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Serum creatinine(^1) (micromol/L)</th>
<th>Recommended dosage regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 25</td>
<td>men &lt; 265 \ women &lt; 175</td>
<td>Dosage as for patients with normal kidney function, ie, 1 standard dose every 12h up to 14 days. Later on ½ standard dose every 12h; no necessity of control analyses of drugs in plasma.</td>
</tr>
<tr>
<td>25 to 15</td>
<td>men 265-620 \ women 175-400</td>
<td>1 standard dose every 12 h for 3 days; later 1 standard dose every 24 h as long as allowed by control analyses(^2).</td>
</tr>
<tr>
<td>Below 15</td>
<td>men &gt; 620 \ women &gt; 400</td>
<td>Until further experience is gained the combination should be given only if patients can undergo haemodialysis when necessary(^3); under this condition 1 standard dose may be administered every 24h as long as allowed by control analyses(^2).</td>
</tr>
</tbody>
</table>

1. The serum creatinine can be used as the basis of dosing only in cases of chronic renal impairment; not in acute or subacute kidney failure.
2. The concentration of total SMX should be measured in plasma samples obtained 12h after every third day of treatment. Treatment should be interrupted if at any time the determined plasma level of total SMX exceeds 150 microgram/mL. As soon as the value of total SMX drops below 120 microgram/mL (eg. in patients undergoing haemodialysis) treatment can be continued as recommended.

OVERDOSAGE

Acute
The amount of a single dose of Septrin 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 sulphonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, haematuria 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 use of activated charcoal (where physicochemically appropriate), 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 haemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

Chronic
Use of Septrin at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anaemia. If signs of bone marrow depression occur, the patient should be given leucovorin; 5 to 15 mg daily has been recommended by some investigators.

PRESENTATION

Septrin tablets: bottle of 10's.
Septrin Forte tablets: blister packs of 10's.
Septrin Paediatric Suspension sugar free (cherry flavour): 100 mL bottle.

STORAGE

Tablets. Store below 30°C. Protect from light.
Suspension. Store below 30°C. Protect from light.

POISONS SCHEDULE

S4

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharma Pty Ltd
34-36 Chandos Street,
St. Leonards NSW 2065
Australia

Approved by Therapeutic Goods Administration on 7 July 1995
Date of latest safety related change: 22 December 1999
Date of latest amendment: 1 March 2002
Amendments approved by the TGA on 6 January 2006
Date of latest amendment: 03 Aug 2009 (further correspondence 24 June 2010)