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SEPTRIN™

GlaxoSmithKline

Trimethoprim-Sulfamethoxazole

QUALITATIVE AND QUANTITATIVE COMPOSITION

Sterile solutions containing trimethoprim 80 mg and sodium sulfamethoxazole 400 mg (as the sodium salt) per 5 ml ampoule, used for the preparation of intravenous infusions.

PHARMACEUTICAL FORM

Solution for injection.

CLINICAL PARTICULARS

Indications

In general the indications for the use of SEPTRIN for Infusion are the same as those for oral presentations (See the Prescribing Information for SEPTRIN Oral Presentations).

It is intended that SEPTRIN for Infusion should be used only during such a period as the patient is unable to accept oral therapy, where initiation of treatment is particularly urgent or for convenience if the patient is already receiving intravenous fluids. Although intravenous SEPTRIN is useful in critically ill patients, there may be no therapeutic advantage over the oral preparation.

SEPTRIN should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

The in vitro susceptibility of bacteria to antibiotics varies geographically and with time; the local situation should always be considered when selecting antibiotic therapy.

SEPTRIN for Infusion has been investigated clinically in the following indications amongst others.

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.

Respiratory Tract Infections

Treatment and prevention of Pneumocystis jiroveci (P. carinii) pneumonia (see Dosage and Administration and Adverse Reactions).

Gastrointestinal Tract Infections

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

Treatment of shigellosis; this regimen may be less effective in some parts of the world due to resistant organisms.

Other Bacterial Infections Caused By Sensitive Organisms

There are a number of other bacterial infections caused by sensitive organisms for which treatment with SEPTRIN may be appropriate; the use of SEPTRIN in such conditions should be based on clinical experience and local in vitro data. SEPTRIN for Infusion may be useful in:

- septicaemia
- intra-abdominal sepsis
- meningitis
- nocardiosis
- toxoplasmosis
- brucellosis (second-line therapy), when used in combination with gentamicin or rifampicin
- melioidosis, when used in combination with ceftazidime or cefoperazone/sulbactam.

Dosage and Administration

SEPTRIN for Infusion is for administration ONLY by the intravenous route and must be diluted before administration (see Instructions for Use/Handling).

The duration of the infusion should be approximately 1 to 1.5 hours, but this needs to be balanced against the fluid requirements of the patient.

When fluid restriction is necessary, SEPTRIN for Infusion may be administered at a higher concentration, 5 ml diluted with 75 ml of glucose 5% w/v in water. The resultant solution, whilst being clear to

the naked eye, may on occasion exceed the BP limits set for particulate matter in large volume parenterals. The solutiperiod not exceeding an hour.

Acute Infections

• Adults and children over 12 years

STANDARD DOSAGE: - 2 ampoules (10 ml) every 12 hours.

• Children aged 12 years and under

The recommended dosage is approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kilogram bodyweight per 24 hours, given in two equally divided doses. As a guide, the following schedules may be used diluted as described above:

6 weeks to 5 months 1.25 ml every 12 hours
6 months to 5 years 2.5 ml every 12 hours
6 to 12 years 5.0 ml every 12 hours.

For severe infections in all age groups dosage may be increased by 50%.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days.

• Elderly

See Warnings and Precautions

• Renal impairment

Adults and children over 12 years (no information is available for children under 12 years of age).

Creatinine Clearance (ml/min)	Recommended Dosage
>30	STANDARD DOSAGE.
15 to 30	Half the STANDARD DOSAGE.
<15	Not recommended.

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of SEPTRIN for Infusion. If the concentration of total sulfamethoxazole exceeds 150 micrograms/ml then treatment should be interrupted until the value falls below 120 micrograms/ml (see Pharmacokinetics).

Pneumocystis jiroveci (P. carinii) pneumonitis

Treatment:

15 to 20 mg SEPTRIN and 75 to 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses. Therapy should be changed to the oral route as soon as possible and continued for a total treatment period of 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).

Prevention:

STANDARD DOSAGE (i.v. or oral as appropriate) for the duration of the period at risk.

Brucellosis

It may be advisable to use a higher than standard dosage initially when the intravenous route may be preferred. Treatment should continue for a period of at least four weeks and repeated courses may be beneficial. SEPTRIN should be given in combination with gentamicin or rifampicin.

Melioidosis

8 mg/kg/day trimethoprim and 40 mg/kg/day sulfamethoxazole in divided doses, 3 or 4 times per day, given in combination with ceftazidime or cefoperazone/sulbactam.

Therapy should be changed to the oral route as soon as possible and continued for a total treatment period of 6 months.

Contraindications

SEPTRIN for Infusion should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole or any excipients of SEPTRIN.

SEPTRIN for Infusion should not be given to premature babies nor to full term infants in the neonatal period.

Warnings and Precautions

Fatalities, although very rare, have occurred due to severe reactions including Stevens- Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), fulminant hepatic necrosis, agranulocytosis,

aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

SEPTRIN for Infusion should be discontinued at the first appearance of a skin rash (see Adverse Reactions).

SEPTRIN for Infusion contains sulphite. This may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible individuals.

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 sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from hypoalbuminaemia the risk may be increased.

For patients with known renal impairment special measures should be adopted (see Dosage and Administration).

Exercise caution when treating patients with severe hepatic parenchymal damage as changes may occur in the absorption and metabolism of trimethoprim and sulfamethoxazole.

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, eg. impaired kidney and/or liver function and/or concomitant drugs.

Regular monthly blood counts are advisable when SEPTRIN is given for long periods, or to folate deficient patients or to the elderly, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. These changes may be reversed by administration of folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity.

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.

SEPTRIN should be given with caution to patients with severe allergy or bronchial asthma.

SEPTRIN should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci, eradication of these organisms from the oropharynx is less effective than with penicillin.

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

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.

Close monitoring of serum potassium and sodium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

Except under careful supervision SEPTRIN should not be given to patients with serious haematological disorders (see Adverse Reactions). Trimethoprim-sulfamethoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Interactions

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk 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.

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

Administration of trimethoprim /sulfamethoxazole 160 mg/800 mg (SEPTRIN) causes a 40% increase in lamivudine exposure because of the trimethoprim component.

Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

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. This is not thought to be of clinical significance.

Reversible deterioration in renal function has been observed in patients treated with SEPTRIN 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.

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

SEPTRIN may increase the free plasma levels of methotrexate.

If SEPTRIN is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see Warnings and Precautions).

Laboratory tests interactions

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of the order of 10%.

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

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from Lactobacillus casei is used in the assay. No interference occurs if methotrexate is measured by radio immune assay.

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

Pregnancy and Lactation

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 foetal abnormalities (see Pre-clinical Safety Data). Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Therefore SEPTRIN should be avoided in pregnancy, particularly in the first trimester, unless the potential benefit to the mother outweighs the potential risk to the foetus; folate supplementation should be considered if SEPTRIN 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 SEPTRIN 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.

Trimethoprim and sulfamethoxazole are excreted in breast milk. Administration of SEPTRIN 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 SEPTRIN should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

Effects on Ability to Drive and Use Machines
No data.

Adverse Reactions
As SEPTRIN contains trimethoprim and a sulphonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency. In addition, adverse events may vary in their incidence depending on the indication.

The following convention has been used for the classification of adverse events in terms of frequency:

very common:	≥1 in 10
common:	≥1 in 100 and <1 in 10
uncommon:	≥1 in 1,000 and <1 in 100
rare:	≥1 in 10,000 and <1 in 1,000
very rare:	<1/10,000.

Infections and Infestations
Common: Monilial overgrowth.

Blood and lymphatic system disorders
Very rare: Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients.

Immune system disorders
Very rare: Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus.

Metabolism and nutrition disorders
Very common: Hyperkalaemia
Very rare: Hypoglycaemia, hyponatraemia, anorexia

Psychiatric disorders
Very rare: Depression, hallucinations.

Nervous system disorders
Common: Headache.
Very rare: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness.

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

Vascular disorders
Common: Local thrombophlebitis at the site of injection.

Respiratory, thoracic and mediastinal disorders
Very rare: Cough, shortness of breath, pulmonary infiltrates.

Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Gastrointestinal disorders
Common: Nausea, diarrhoea.
Uncommon: Vomiting.
Very rare: Glossitis, stomatitis, pseudomembranous colitis, pancreatitis.

Eye disorders
Very rare: Uveitis

Hepatobiliary disorders
Very rare: Cholestatic jaundice, hepatic necrosis Hepatic changes including fatalities have been recorded in at-risk patients. Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders
Common: Skin rashes.
Very rare: Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis)

Lyell's syndrome carries a high mortality.

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia, myalgia.

Renal and urinary disorders
Very rare: Impaired renal function (sometimes reported as renal failure), interstitial nephritis.

Effects associated with Pneumocystis jiroveci (P. carinii) pneumonitis (PCP) management
Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, rhabdomyolysis.

At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5 to 10 mg/day).

Severe hypersensitivity reactions have been reported in PCP patients on re-exposure to SEPTRIN, sometimes after a dosage interval of a few days. Rhabdomyolysis has been reported in HIV positive patients receiving SEPTRIN for prophylaxis or treatment of PJP.

Concomitant administration of intravenous diphenhydramine may permit continued infusion.

Overdose
The maximum tolerated dose in humans in unknown.

Nausea, vomiting, dizziness and confusion are likely symptoms/signs of overdosage.

Bone marrow depression has been reported in acute trimethoprim overdosage.

Dependent on the status of renal function administration of fluids is recommended if urine output is low.

In case of known, suspected, or accidental overdosage stop therapy.

Acidification of the urine will increase the elimination of trimethoprim. Inducing diuresis plus alkalinisation of urine will enhance the elimination of sulfamethoxazole.

Alkalinisation will reduce the rate of elimination of trimethoprim. Calcium folinate (5 to 10 mg/day) will reverse any folate deficiency effect of trimethoprim on the bone marrow should this occur. General supportive measures are recommended.

Both trimethoprim and active sulfamethoxazole are dialysable by renal dialysis.

Peritoneal dialysis is not effective.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics

In Vitro Activity

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. Depending on the conditions the effect may be bactericidal. 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.

The majority of common pathogenic bacteria are sensitive in vitro to trimethoprim sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antimicrobial agents in vitro activity does not necessarily imply that clinical efficacy has been demonstrated. These organisms include:

Gram Negative
Brucella spp.
Citrobacter spp.
Escherichia coli (including enterotoxigenic strains)
Haemophilus ducreyi
Haemophilus influenzae (including ampicillin-resistant strains)
Klebsiella/Enterobacter spp.

Legionella pneumophila
Morganella morganii (previously Proteus morganii)
Neisseria spp.
Proteus spp.
Providencia spp. (including previously Proteus rettgeri)
Certain Pseudomonas spp. except aeruginosa
Salmonella spp. including S. typhi and paratyphi
Serratia marcescens
Shigella spp.
Vibrio cholerae
Yersinia spp.

Gram Positive
Listeria monocytogenes
Nocardia spp.
Staphylococcus aureus
Staphylococcus epidermidis and saprophyticus
Enterococcus faecalis
Streptococcus pneumoniae
Streptococcus viridans.

Many strains of Bacteroides fragilis are sensitive. Some strains of Campylobacter fetus subsp. jejuni and Chlamydia are sensitive without evidence of synergy. Some varieties of non-tuberculous mycobacteria are sensitive to sulfamethoxazole but not trimethoprim.

Mycoplasmas, Ureaplasma urealyticum, Mycobacterium tuberculosis and Treponema pallidum are insensitive.

Satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

Pharmacokinetics

Plasma or serum levels of sulfamethoxazole and trimethoprim may be determined by high-performance liquid chromatography.

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

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. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity.

Trimethoprim passes into amniotic fluid and fetal tissues reaching concentrations approximating those at maternal serum.

Approximately 50% of trimethoprim in the plasma is protein. The half life in man is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 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.

Trimethoprim does not induce its own metabolism and therefore no dose modification is required on this account during long-term treatment.

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% of sulfamethoxazole in the plasma is protein bound. The half life in man is approximately 9 to 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 principle 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.

Pre-clinical Safety Data

Reproductive toxicology: At doses in excess of the recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by co-administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

PHARMACEUTICAL PARTICULARS

List of Excipients

Aqueous vehicle containing:
propylene glycol 40% w/v
ethanol
benzyl alcohol.

Incompatibilities

SEPTRIN for Infusion should only be mixed with the recommended diluent (see Instructions for Use/Handling). NO OTHER SUBSTANCE SHOULD BE MIXED WITH THE INFUSION.

Shelf Life

As registered locally.

Special Precautions for Storage

Protect from light.

Nature and Contents of Container

Clear glass 5 ml ampoule.

Instructions for Use/Handling

SEPTRIN for Infusion must be diluted before administration.

DILUTION SHOULD BE CARRIED OUT IMMEDIATELY BEFORE USE. After adding SEPTRIN for Infusion to the infusion solution shake thoroughly to ensure complete mixing.

If visible turbidity or crystallisation appears at any time before or during an infusion, the mixture should be discarded.

It is recommended that SEPTRIN for Infusion is diluted according to the following schedules:

one ampoule (5 ml) added to 125 ml infusion solution
two ampoules (10 ml) added to 250 ml infusion solution
three ampoules (15 ml) added to 500 ml infusion solution.

SEPTRIN for Infusion is known to be compatible, when diluted as recommended above, with the following fluids:

Glucose Intravenous Infusion BP (5% w/v and 10% w/v);
Sodium Chloride Intravenous Infusion BP (0.9% w/v);
Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP;
Dextran 70 Intravenous Infusion BP (6% w/v) in glucose (5% w/v) or normal saline;
Dextran 40 Intravenous Infusion BP (10% w/v) in glucose (5% w/v) or normal saline;
Ringer's Solution for Injection BPC 1959.

The pH of the solution is in the range 9.5 to 11.0.

If higher concentrations are required, one ampoule (5 ml) may be diluted with 75 ml of glucose 5% w/v in water.

Not all presentations are available in every country.

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