

Septrin™

For Infusion

Strong Sterile Co-trimoxazole Solution

To make Co-trimoxazole Intravenous Infusion BP.

To the Medical and Pharmaceutical Professions

Presentation

Septrin for Infusion contains 80 mg Trimethoprim BP and 400 mg Sulphamethoxazole BP in each 5 ml ampoule. The infusion is a faintly yellow aqueous solution and contains 45 percent w/v propylene glycol together with ethyl alcohol. It has a pH of approximately 10.

Uses

Septrin is an antibacterial agent. Septrin is effective *in vitro* against a wide range of gram-positive and gram-negative organisms. It is not active against *Mycobacterium tuberculosis*, *Mycoplasma*, or *Treponema pallidum*. *Pseudomonas aeruginosa* is usually insensitive. In general, the indications for the use of Septrin for Infusion are the same as those for 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 co-trimoxazole is useful in critically ill patients, there may be no therapeutic advantage over the oral preparation.

Septrin for Infusion has been investigated clinically in the following indications amongst others:

Respiratory tract infections: Pneumonia and *Pneumocystis carinii* pneumonitis.

Genito-urinary tract infections:

Gastro-intestinal tract infections: Shigellosis and typhoid fever. Other bacterial infections caused by sensitive organisms: Brucellosis, septicaemia, intra-abdominal sepsis, meningitis, osteoarticular infections, paediatric soft tissue and skeletal infections.

Dosage and administration

Administration: Septrin for Infusion is for administration ONLY by the intravenous route and 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 Septrin for Infusion (5 ml) to 125 ml infusion solution.

Two ampoules Septrin for Infusion (10 ml) to 250 ml infusion solution.

Three ampoules Septrin for Infusion (15 ml) to 500 ml infusion solution.

Septrin for Infusion is known to be compatible, when diluted as schedules 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 Injection BP (6% w/v) in glucose (5% w/v) or normal saline.

Dextran 40 Injection BP (10% w/v) in glucose (5% w/v) or normal saline.

Ringer's Solution for Injection BPC 1959.

NO OTHER SUBSTANCE SHOULD BE MIXED WITH THE INFUSION. The duration of the infusion should be approximately one to one and a half hours, but this should 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 solution should be infused over a period not exceeding one hour.

Discard any unused diluted solution.

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 sulphamethoxazole per kg 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.

Special Dosage Recommendations:

Dosage recommendations in impaired renal function: Adults and children over 12 years (no information is available for children under 12 years of age):

Creatinine clearance (ml/min)	Serum creatinine (µmol/l)	Recommended Dosage
Above 25	men < 265 women < 175	STANDARD DOSAGE.
15 – 25	men 265 - 620 women 175 – 400	STANDARD DOSAGE for maximum of 3 days followed by half the standard daily dosage.
Below 15	men >620 women >400	Not recommended unless haemodialysis facilities are available when half the standard daily dosage may be given.

Measurements of plasma concentrations of sulphamethoxazole 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 sulphamethoxazole exceeds 150 micrograms/ml then treatment should be interrupted until the value falls below 120 micrograms/ml (see Further information).

Dosage in Pneumocystis carinii pneumonitis:

Treatment:

20 mg trimethoprim and 100 mg sulphamethoxazole per kg bodyweight 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 ≥ 5 micrograms/ml (See Side- and adverse effects).

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

Acute 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.

Use in the elderly: No specific studies have been carried out in the elderly, although Septrin has been widely used in older people. See Precautions for further information.

Contra-indications, warnings, etc.

Contra-indications: Septrin should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim or co-trimoxazole. Septrin for Infusion is contra-indicated in patients showing marked liver parenchymal damage. Except under careful supervision Septrin for Infusion should not be given to patients with serious haematological disorders. Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Septrin for Infusion is contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed. Septrin for Infusion should not be given to premature babies nor to full-term infants during the first six weeks of life.

Precautions: Septrin for Infusion should be discontinued if a skin rash appears.

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 cardiopulmonary 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 malnutrition the risk may be increased.

For patients with known renal impairment special measures should be adopted (See Dosage recommendations in impaired renal function).

Regular monthly blood counts are advisable when Septrin is given for long periods 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 folic acid (5 to 10 mg/day) without interfering with the antibacterial activity.

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.

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.

In treatment of tonsillo-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 sulphamethoxazole) have been associated with clinical exacerbation of porphyria.

Drug interactions: Co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulphamethoxazole may displace warfarin from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with Septrin is advisable. Co-trimoxazole 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 hypoglycemic 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 co-trimoxazole and cyclosporin following renal transplantation.

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

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

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.

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

Side- and adverse effects: As Septrin contains trimethoprim and a sulphonamide, the type and frequency of adverse reactions associated with such compounds may be expected. At the recommended dosages Septrin is usually well tolerated.

Of the reported adverse reactions most are mild and comprise nausea, with or without vomiting, and skin rashes. More severe skin sensitivity such as erythema multiforme bullosa (Stevens Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) have occurred rarely; the latter condition carries a high mortality.

Haematological changes have been reported, the majority being mild and reversible when treatment was stopped. The changes are mainly leucopenia, neutropenia, thrombocytopenia and, less commonly, agranulocytosis, megaloblastic anaemia and purpura. Although most of the changes cause no clinical symptoms they may become severe in isolated cases, especially in the elderly, in those with hepatic or renal dysfunction or in those with poor folate status; such patients should be observed carefully. Septrin may induce haemolysis in certain susceptible G-6-PD deficient patients but this does not appear to be dose related.

Aseptic meningitis has been reported in association with the administration of co-trimoxazole. The condition 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.

Hepatic changes including cholestatic jaundice and hepatic necrosis have been reported rarely and may be fatal. Local thrombophlebitis may occasionally be a problem at the site of injection.

Diarrhoea, glossitis and stomatitis are uncommon. Pseudomembranous colitis has been reported rarely.

Monial overgrowth is also very rare.

Impaired renal function has been reported rarely following the administration of co-trimoxazole, but

its relationship to therapy remains unproven. Allergic reactions including serum sickness and mild anaphylaxis have been reported rarely.

There have been a few reports of subjective experiences such as headache, depression, dizziness and hallucinations but their relationship to therapy remains unproven.

At the high dosages used for the therapy of *Pneumocystis carinii* pneumonitis in patients with Acquired Immune Deficiency Syndrome, rash, fever, neutropenia, thrombocytopenia and raised liver enzymes have been reported, necessitating cessation of therapy. Concomitant administration of intravenous diphenhydramine may permit continued infusion.

Use in pregnancy and lactation: The safety of Septrin in human pregnancy has not been established. The drug should not be given during pregnancy. Animal studies have shown teratogenic effects typical of a folate antagonist in rats but not rabbits at high doses; these were prevented by administration of dietary folates.

Sulphonamide-containing products should not be administered in late pregnancy because of the risk of kernicterus.

The usual caution in prescribing any drug for women of child-bearing age should be exercised with Septrin. Despite the excretion of sulphamethoxazole into breast milk, the administration of Septrin to lactating women represents a negligible risk to the suckling infant.

Toxicity and treatment of overdose: The maximum tolerated dose in humans is unknown.

Nausea, vomiting, dizziness and confusion are likely symptoms of overdose.

In cases of known, suspected, or accidental overdose, stop therapy.

Acidification of the urine will increase the elimination of trimethoprim. Including diuresis plus alkalisation of urine will enhance elimination of sulphamethoxazole. 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 sulphamethoxazole are dialysable by renal dialysis.

Pharmaceutical precautions

Store below 30° C. Protect from light.

Legal category

POM

Package quantities

Box of 10 ampoules.

Further information

Septrin does not affect incubating syphilis.

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

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. Cotrimoxazole may affect the results of thyroid function tests but this is probably of little or no clinical significance.

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

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For Glaxo Wellcome Inc., Mississauga, Ontario, Canada