SEPTRIN™ FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT

SEPTRIN™ FOR INFUSION, Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml ampoule contains 80mg trimethoprim and 400mg sulfametoxazole.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear faintly yellow to brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bacterial infections of respiratory tract, gastrointestinal tracts and skin, susceptible to the drug

4.2 Dosage and Administration

Dosage and Administration

Trimethoprim- sulfamethoxazole for Infusion is for administration ONLY by the intravenous route and must be diluted before administration (See Use and 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, Trimethoprim- sulfamethoxazole 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 an hour.

ACUTE INFECTIONS

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

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

Populations

- **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 6mg trimethoprim and 30mg sulphamethoxazole 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:

Age	Dosage
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.

- **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
greater than 30	STANDARD DOSAGE.
15 to 30	Half the STANDARD DOSAGE.
less than 15	Not recommended.

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

PNEUMOCYSTIS JIROVECI (CARINII) PNEUMONITIS
Treatment:

15-20mg trimethoprim and 75 - 100 mg sulphamethoxazole per kilogram 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 ≥5 mcg/ml *(See Adverse Reactions)*.

Prevention:

Standard dosage for the duration of the period at risk.

4.3 Contraindications

Septrin presentations should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole or any excipients of the presentations

Contra-indicated in patients with severe renal insufficiency where repeated measurements monitoring of plasma drug concentration cannot be performed.

Use in patients with severe impairment of liver function.

Use in patients with existent or severe blood dyscrasias.

Use in patients with glucose-6-phosphate dehydrogenase deficiency.

Septrin should not be given to premature babies nor to full- term infants during the first 6 weeks of life.

4.4 Special Warnings and Special Precautions for Use

Fatalities, although very rare, have occurred due to severe reactions including fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Septrin. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Septrin treatment should be discontinued *(see 4.8 Undesirable Effects)*.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Septrin, Septrin must not be re-started in this patient at any time.

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 use of other drugs.

For patients with known renal impairment special measures should be adopted *(See 4.2 Dosage and of administration)*. 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. Exercise caution when treating patients with severe hepatic parenchymal damage as changes may occur in the absorption and metabolism of trimethoprim and sulfamethoxazole.

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 (5-10 mg/day) without interfering with the antibacterial activity.

In glucose-6-phosphate dehydrogenase-deficient (G-6-PD) 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 β-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.

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). Septrin has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

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

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

In patients (particularly the elderly) concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with purpura.

The product should be used with care in patients taking concomitant therapy with drugs which are strongly bound, including oral hypoglycaemics and anti-coagulants.

Administration of trimethoprim/sulphamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole.

Sulphonamides may displace methotrexate from protein binding sites and compete with renal transport of methotrexate and may inhibit phenytoin metabolism in the liver increasing the toxicity of each. If co-administered the prescriber should be alert for excessive phenytoin effect. Close monitoring of the patients condition and serum phenytoin levels is advisable.

Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported. Septrin should be used with care in patients on concomitant therapy with these agents.

This product may precipitate folate deficiency in patients liable to folate deficiency such as those taking folate antagonists, or anticonvulsants, or pyrimethamine.

The presence of trimethoprim can interfere with serum methotrexate assays when a bacterial dihydrofolate reductase is used as the binding protein for techniques based on competitive protein binding.

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

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

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

Both trimethoprim and sulfametoxazole may interfere with the Jaffe alkaline picrate reaction assay for creatinine.

4.6 Pregnancy and Lactation

Trimethoprim and sulphamethoxazole 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 Section 5.3 Preclinical Safety Data)*.

Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Therefore co-trimoxazole 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 co-trimoxazole is used in pregnancy.

Sulphamethoxazole 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 sulphamethoxazole are excreted in breast milk. Administration of co-trimoxazole 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 Trimethoprim- sulfamethoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.7 Effects on Ability to Drive and Use Machines

No specific studies have been performed.

4.8 Undesirable Effects

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 ≥1/10,
Common ≥1/100 and <1/10,
Uncommon ≥1/1000 and <1/100,
Rare ≥1/10,000 and <1/1000,
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 Septrin or to trimethoprim alone.

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
Cholestatic jaundice and hepatic necrosis may be fatal.

Very rare: elevation of serum transaminases, elevation of bilirubin levels

Skin and subcutaneous tissue disorders

Common: Skin rashes

Very rare: Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Severe cutaneous adverse reactions (SCARs), Stevens-Johnson syndrome (SJS), and (toxic epidermal necrolysis)(TEN) have been reported (see section 4.4).

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 (carinii) pneumonitis (PJP) management

Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, rhabdomyolysis

At the high dosages used for PJP 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 PJP patients on re-exposure to trimethoprim-sulfamethoxazole, 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.

I.V. Infusion:

Concomitant administration of intravenous diphenhydramine may permit continued infusion

4.9 Overdose

Nausea, vomiting, dizziness and confusion are likely symptoms/signs of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

If vomiting has not occurred, induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. Dependent on the status of renal function administration of fluids is recommended if urine output is low.

Both trimethoprim and sulphamethoxazole are moderately dialysable by haemodialysis.

Peritoneal dialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties

Parmacotherapeutic Group: Antibacterials for systemic use

ATC Code: J01EE01

Co-trimoxazole is a bactericidal in vitro to a wide range of Gram-positive and Gram-negative organisms, including Streptococcus, Staphyloccus, Pneumococcus, Neisseria, B. catarrhalis, Escherichia coli, Klebsiella, Proteus spp., Haemophilus, Salmonella, Shigella, Vibrio cholerae, Brucella , Pneumocystis carinii, Nocardia and Bordetella.

A particular high degree of activity is exhibited against Haemophilis influenzae, Escherichia coli and Proteus spp.

5.2 Pharmacokinetic Properties

A combination of sulfametoxazole and trimethoprim each of which blocks a bacterial enzyme system in the same metabolic pathway of biosynthesis of folinic acid in the micro-organism resulting in a synergistic anti-bacterial effect. Both drugs are widely distributed after reaching peak levels at 1-4 hours. Elimination is via the kidney with a half life of about 12 hours. Both substances are moderately bound to plasma proteins, and are widely distributed in tissues and body fluids including synovial fluid, aqueous human and CSF.

5.3 Preclinical Safety Data

Teratogenicity: At doses generally in excess of the recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to be teratogenic in rats with effects typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients

Propylene Glycol
Tromethamine
Sodium hydroxide
Sodium metabisulphite
Ethanol (96%)
Water for injection

6.2 Incompatibilities

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

6.3 Shelf Life

36 months

6.3 Special Precautions for Storage

Do not store above 30°C, protect from light.

6.4 Nature and Contents of Container

Glass ampoule
10 x 5 ML

6.6 Instructions for Use and 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 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.

It is suggested that the duration should be approximately one to one and a half-hours, but this should be balanced against the fluid requirements of the patient.

Discard any unused diluted solution.

7. MANUFACTURER

Jubilant HollisterStier General Partnership (JHSGP), Canada
Trans–Canada Highway, Kirkland, Quebec

8. LICENSE HOLDER

Perrigo Israel Agencies Ltd.
29 Lehi St., Bnei Brak 51200

9. LICENSE NUMBER

126-27-30623

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