

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Septrin 80 mg/400 mg per ampoule, concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Contains 38.25 mg of sodium per 5 ml ampoule (inclusive of sodium metabisulphite E 223), 0.5 mg ethanol (alcohol) per 5 ml ampoule and 2.25 g of propylene glycol (E 1520) per 5ml ampoule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Infusion

Clear faintly yellow to brown solution.

The pH of the solution is in the range 9.6 to 10.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In general, the indications for the use of Septrin for Infusion are the same as those for oral presentations. Septrin for Infusion is for use when oral dosage is not possible.

Septrin for Infusion is indicated in children aged 12 years and under (>6 weeks to <12 years old); children over 12 years old (>12 to <18 years old) and adults (>18 years old) for the treatment of the following infections when owing to sensitive organisms (see section 5.1):

- *Urinary tract infections:* For simple urinary tract infections, trimethoprim alone or another single anti-microbial agent is the preferred treatment. Since trimethoprim is also as efficacious as Septrin for Infusion for the prophylaxis of recurrent urinary tract infections, Septrin for Infusion is not indicated for prophylactic use.

- *Respiratory tract infections:* Septrin for Infusion may be used as second line therapy in chronic obstructive airways disease or other respiratory tract infections, including acute otitis media where sensitivity has been demonstrated or is highly probable. (Septrin is not indicated for prophylactic or prolonged administration in otitis media).

- Treatment and prevention of *Pneumocystis jirovecii* pneumonitis or 'PJP.'

- Septrin for Infusion may be used in the management of other serious conditions such as nocardiosis, toxoplasmosis and brucellosis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Standard dosage recommendations for acute infections

Adults (>18 years old):

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STANDARD DOSAGE	
Age	Solution for Infusion
>18 years old	2 ampoules (10 ml) every 12 hours

The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day, given in two equally divided doses. The schedules for children are according to the child's age and provided in the tables below:

Children over 12 years old (>12 to <18 years old):

STANDARD DOSAGE	
Age	Solution for Infusion
>12 to <18 years old	2 ampoules (10 ml) every 12 hours

Children aged 12 years and under (>6 weeks to <12 years old)

Age	Dosage
6 weeks to 6 months	1.25 ml every 12 hours
6 months to 6 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 % for severe 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.

Elderly patients:

See section 4.4

Impaired renal function:

Dosage recommendation:

Adults (>18 years old) and Children over 12 years old (>12 to <18 years old):

Creatinine Clearance (ml/min)	Recommended Dosage
> than 30	2 ampoules (10 ml) every 12 hours
15-30	1 ampoules (5 ml) every 12 hours
< 15	Not recommended.

No information is available for children aged 12 years and under with renal failure. See section 5.2 for the pharmacokinetics in the paediatric population with normal renal function of both components of Septrin.

Impaired hepatic function:

Caution should be exercised when treating patients with severe hepatic impairment as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.

Measurements of plasma concentrations of sulfamethoxazole at intervals of two to three days are recommended in samples obtained 12 hours after administration of Septrin. If the concentration of total sulfamethoxazole exceeds 150 mcg/ml then treatment should be interrupted until the value falls below 120 mcg/ml.

Pneumocystis jirovecii pneumonia (PJP):

Treatment- children aged 12 years and under (>6 weeks to <12 years old); children over 12 years old (>12 to <18 years old) and adults (>18 years old):

20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses. The course is two weeks, but oral therapy should be substituted as soon as it is appropriate. The steady state or serum level of trimethoprim should be maintained at 5 mcg/ml or higher for maximum efficacy. The aim is to obtain peak plasma or serum levels of trimethoprim of greater than or equal to 5 microgram/ml (verified in patients receiving 1-hour infusions of intravenous Septrin). (See section 4.8)

Prevention:

Standard dosage as described under acute infections for the duration of the period at risk.

Nocardiosis:

There is no consensus on the most appropriate dosage. Adult doses of 480 mg trimethoprim/2400 mg sulfamethoxazole to 640 mg trimethoprim/3200 mg sulfamethoxazole daily for up to three months have been used.

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 other agents in line with national treatment guidelines.

Toxoplasmosis:

There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition. The decision should be based on clinical experience. Doses of 480 mg or 960 mg of trimethoprim-sulfamethoxazole twice daily for three months have been used for prophylaxis and 40 mg/kg/day or 120 mg/kg/day for a mean of 25 days for the treatment of toxoplasmosis in patients with HIV.

Method of administration:

Septrin for Infusion is for administration only by the intravenous route and must be diluted before administration.

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 Septrin for Infusion is useful in critically ill patients, there may be no therapeutic advantage over the oral preparation.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

Septrin for infusion is contraindicated in patients with:

- hypersensitivity to the active substance(s) sulphonamides, trimethoprim or to any of the excipients listed in section 6.1.
- severe impairment of liver function.
- severe renal insufficiency where repeated measurements of the plasma drug concentration cannot be performed.
- a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- acute porphyria.

Septrin for infusion should not be given to infants during the first 6 weeks of life.

4.4 Special warnings and precautions for use

Life threatening adverse reaction

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

- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) 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; for DRESS, the risk of occurrence is in the first two to eight weeks after drug administration.
- If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia, rash, lymphadenopathy, abnormal blood/liver function test and/or visceral organ involvement) are present, Septrin treatment should be discontinued (see section 4.8).
- The best results in managing SJS, TEN or DRESS 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, TEN or DRESS with the use of Septrin, Septrin must not be re-started in this patient at any time.
- The occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of acute generalised exanthematous pustulosis (AGEP) (see section 4.8); it requires cessation of treatment and contraindicates any new administration of Co-Trimoxazole alone or in combination with other drugs.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported very rarely in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, co-trimoxazole treatment should be discontinued.

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

Elderly patients

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, e.g. impaired kidney and/or liver function and/or concomitant use of other drugs.

Patients with renal impairment

For patients with known renal impairment special measures should be adopted (see section 4.2).

Urinary output

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.

Folate

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. Supplementation with folic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

Patients with glucose-6-phosphate dehydrogenase deficiency

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

Patients with severe atopy or bronchial asthma

Septrin should be given with caution to patients with severe atopy or bronchial asthma.

Treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci

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.

Phenylalanine metabolism

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

Patients with or at risk of porphyria

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

Patients with hyperkalaemia and hyponatraemia

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

Metabolic acidosis

Septrin has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Patients with serious haematological disorders

Except under careful supervision Septrin should not be given to patients with serious haematological disorders (see section 4.8). Septrin has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Sulphites

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

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

Excipients with known effects

- This medicinal product contains 38.25 mg of **sodium** per 5 ml ampoule, equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- This medicinal product contains **sodium metabisulphite (E 223)**, which may rarely cause severe hypersensitivity reactions and bronchospasm.
- This medicinal product contains 2.25 g of **propylene glycol (E 1520) per 5 ml ampoule** which is equivalent to 450 mg/ml. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol. Therefore, doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis. Medical monitoring is required. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old. This medicine should not be used in children less than 5 years old if the calculated dose for any given indication exceeds a propylene glycol threshold of 500 mg/kg/day.
- This medicinal product contains 0.5 mg of **ethanol** in each 5 ml ampoule which is equivalent to 0.1 mg/ml. The amount in 5 ml of this medicinal product is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without 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.

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

Methotrexate and Phenytoin: 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 patient's condition and serum phenytoin levels is advisable.

If Septrin is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4).

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.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with trimethoprim-sulfamethoxazole and cyclosporin following renal transplantation.

Hyperkalaemia: caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) may result in clinically relevant hyperkalaemia.

Azathioprine: There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and trimethoprim - sulfamethoxazole.

Zidovudine: 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.

Rifampicin: 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.

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.

Warfarin: trimethoprim – sulfamethoxazole 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.

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

Repaglinide: trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

Contraceptives: oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive, or choose another method of contraception.

Interaction with laboratory tests:

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 radioimmuno assay.

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

4.6 Fertility, pregnancy and lactation

Pregnancy

Trimethoprim and sulfamethoxazole cross the placenta and their safety in human pregnancy has not been established. Trimethoprim is a folate antagonist and, in animal studies, both agents established have been shown to cause foetal abnormalities (see section 5.3). 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 significantly maternally derived drug levels persist for several days in the new-born, 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.

Breast-Feeding

Trimethoprim and sulfamethoxazole are excreted in breast milk. Administration of trimethoprim-sulfamethoxazole 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.

See also section 4.4 for more information about ethanol content in this formulation.

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

See also section 4.4 for more information about ethanol and propylene glycol (E1520) content in this formulation.

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,

not known: cannot be estimated from the available data.

System Organ Class	Frequency	Side effects
Infections and infestations	Common	Overgrowth fungal
Blood and lymphatic system disorders*	Very rare	Leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia, methemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients
Immune system disorders	Very rare	Serum sickness, anaphylactic reactions, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus. Severe hypersensitivity reactions associated with PJP* including rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, rhabdomyolysis, hyperkalaemia, hyponatraemia
Metabolism and nutrition disorders	Very common	Hyperkalaemia
	Very rare	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis
Psychiatric disorders	Very rare	Depression, hallucination
	Not known	Psychotic disorder
Nervous system disorders	Common	Headache
	Very rare	Meningitis aseptic*, seizure, neuropathy peripheral, ataxia, dizziness
Ear and labyrinth disorders	Very rare	Vertigo, tinnitus

Eye disorders	Very rare	Uveitis
Respiratory, thoracic and mediastinal disorders	Very rare	Cough*, dyspnoea*, lung infiltration*
Gastrointestinal disorders	Common	Nausea, diarrhoea
	Uncommon	Vomiting
	Very rare	Glossitis, stomatitis, pseudomembranous colitis, pancreatitis
Hepatobiliary disorders	Very rare	Jaundice cholestatic*, hepatic necrosis*, transaminases increased, blood bilirubin increased
Skin and subcutaneous tissue disorders*	Common	Rash
	Very rare	Photosensitivity reaction, angioedema, dermatitis exfoliative, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS)*, toxic epidermal necrolysis (TEN)*, Acute generalised exanthematous pustulosis (AGEP).
	Not Known	Drug reaction with eosinophilia and systemic symptoms (DRESS)*, Acute febrile neutrophilic dermatosis (Sweet's syndrome).
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia, myalgia.
Renal and urinary disorders	Very rare	Renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis
General disorders and administrations site conditions	Very rare	Pyrexia

* see description of selected adverse reactions

Description of selected adverse reactions

Aseptic meningitis

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

Pulmonary hypersensitivity reactions

Cough, dyspnoea, and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life threatening (see Section 4.4).

As with any other drug, allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of the drug. Very rare cases of acute generalised exanthematous pustulosis (AGEP) have been observed (see section 4.4).

Hepatobiliary disorders

Jaundice cholestatic and hepatic necrosis may be fatal.

*Effects associated with *Pneumocystis jirovecii* (*P. carinii*) pneumonitis (PJP) management*

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. 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.

IV Infusion

Concomitant administration of intravenous diphenhydramine may permit continued infusion.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Symptoms

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

The maximum tolerated dose in humans is unknown.

Management

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

Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

In cases of known, suspected or accidental overdose, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **ANTIBACTERIALS FOR SYSTEMIC USE – SULFONAMIDES AND TRIMETHOPRIM** Combinations of sulphonamides and trimethoprim, incl. derivatives, ATC code: J01EE01.

Mechanism of action

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.

Resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out-compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme. Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

Susceptibility testing breakpoints

Testing of trimethoprim - sulfamethoxazole was performed using the common dilution series to assess the Minimum Inhibitory Concentration (MIC). The MIC breakpoints for resistance are those recommended by CLSI (Clinical and Laboratory Standards Institute – formerly the National Committee for Clinical Laboratory Standards (NCCLS) and EUCAST guidelines.

Pharmacodynamic effects

The majority of common 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. In common with other antimicrobial agents *in vitro* activity does not necessarily imply that clinical efficacy had been demonstrated. These organisms include:

Gram Negative

Brucella spp.
Citrobacter spp.
Escherichia coli (including ampicillin-resistant 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.
Shingella spp.
Vibrio cholerae
Yersinia spp.

Gram positive

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

5.2 Pharmacokinetic properties

Absorption

Peak plasma levels of trimethoprim and sulfamethoxazole are higher and achieved more rapidly after one hour of intravenous infusion of Septrin for infusion 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.

Distribution

Approximately 50% of trimethoprim in the plasma is protein bound.

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, sputum, and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 66% of sulfamethoxazole in the plasma is protein bound.

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 to 50% of the plasma concentration.

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

Biotransformation

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

Elimination

The half-life of trimethoprim in man is in the range 8.6 to 17 hours in the presence of normal renal function. There appears to be no significant difference in elderly patients compared with young patients.

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.

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 principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form.

Special patient populations

Renal impairment

When the creatinine clearance falls below 30 mL/min the dosage of Septrin should be reduced (see section 4.2).

Hepatic impairment

Caution should be exercised when treating patients with severe hepatic impairment as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.

Older patients

In older patients, a slight reduction in renal clearance of sulfamethoxazole but not trimethoprim has been observed.

Paediatric population

The pharmacokinetics in the paediatric population with normal renal function of both components of Septrin for infusion, trimethoprim – sulfamethoxazole are age dependent. Elimination of trimethoprim - sulfamethoxazole is reduced in neonates, during the first two months of life, thereafter both trimethoprim and sulfamethoxazole show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

5.3 Preclinical safety data

Teratogenicity: 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 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
Trometamol
Sodium Hydroxide
Sodium Metabisulphite (E223)
Ethanol (96%)
Water for Injections

6.2 Incompatibilities

Septrin for Infusion should only be mixed with the recommended diluent (see section 6.6)

NO OTHER SUBSTANCE SHOULD BE MIXED WITH THE INFUSION.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the ampoule in the outer carton to protect from light.

6.5 Nature and contents of container

5ml Type 1, clear-neutral glass ampoule.

Pack size: Box of 10x5ml ampoules.

6.6 Special precautions for disposal and other 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 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.

If higher concentrations are required, one ampoule (5 ml) may be 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 solution.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
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Dublin 24
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8 MARKETING AUTHORISATION NUMBER

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