SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Trimoxazole 16 mg/80 mg per ml for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Septrin 16 mg/80 mg per ml for Infusion contains 80 mg Trimethoprim and 400 mg Sulfamethoxazole.

Excipient(s) with known effect:

This product contains 1.7 mmoles of sodium, 13.2 vol % ethanol (alcohol) per 5 ml and sodium metabisulphite..

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion

A clear liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-Trimoxazole for Infusion is indicated in children (≥6 weeks) and adults for the treatment of the following infections when owing to sensitive organisms (see section 5.1):

- Acute uncomplicated urinary tract infection: It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than a combination such as Co-Trimoxazole for Infusion.
- Treatment and prevention of *Pneumocystis jirovecii* pneumonitis or “PJP”.
- Treatment and prophylaxis of toxoplasmosis.
- Treatment of nocardiosis.

- In general, the indications for the use of Co-Trimoxazole for Infusion are the same as those for oral presentations.

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
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%.

Adults and children over 12 years:
STANDARD DOSAGE: 2 ampoules (10 ml) every 12 hours

Children aged 12 years and under:
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.

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 patients:

See section 4.4

Impaired hepatic function:

No data are available relating to dosage in patients with impaired hepatic function.

Impaired renal function:

Dosage recommendation:

Adults and children over 12 years:

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

No information 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 Co-Trimoxazole, TMP and SMZ.

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 2 to 3 days are recommended in samples obtained 12 hours after administration of Co-Trimoxazole 16 mg/80 mg per ml 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.

Pneumocystis jirovecii pneumonitis:

Treatment:
15-20 mg trimethoprim and 75-100 mg sulfamethoxazole per kg of 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 greater than or equal to 5 microgram/ml (verified in patients receiving 1-hour infusions of intravenous Co-Trimoxazole). (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 6 to 8 tablets daily for up to 3 months have been used (one tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim).

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**.** For prophylaxis, however, the dosages suggested for prevention of *Pneumocystis jirovecii* pneumonitis may be appropriate.

Method of administration:

Co-Trimoxazole for Infusion is for administration only by the intravenous route and must be diluted before administration.

It is intended that Co-Trimoxazole 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 Co-Trimoxazole 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

- Hypersensitivity to the active substance(s) sulphonamides, trimethoprim, co-trimoxazole or to any of the excipients listed in section 6.1.
- Co-Trimoxazole 16 mg/80 mg per ml for Infusion is contra-indicated in patients with severe impairment of liver function
- Co-Trimoxazole 16 mg/80 mg per ml for Infusion is contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- Co-Trimoxazole 16 mg/80 mg should not be given to patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- Co-Trimoxazole 16 mg/80 mg should not be given to patients with acute porphyria.
- Co-Trimoxazole 16 mg/80 mg should not be given to infants during the first 6 weeks of life.
- First trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Life threatening adverse reactions

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 with systemic symptoms (DRESS) have been reported with the use of Co-Trimoxazole (see section 4.8).
- 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, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, Co-Trimoxazole treatment should be discontinued (see section 4.8) and an alternative treatment considered (as appropriate).
- 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 Co-Trimoxazole, the treatmentmust not be re-started in this patient at any time.
- At the start of treatment, 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.

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

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 malnutrition the risk may be increased.

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

Folate
Regular monthly blood counts are advisable when Co-Trimoxazole 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 folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

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 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
Co-Trimoxazole should be given with caution to patients with severe atopy or bronchial asthma.

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

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

Ethanol
This medicinal product contains 13.2 vol % ethanol (alcohol), i.e. up to 521 mg per dose. This is equivalent to 13.2 ml of beer, or 5.5 ml of wine. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, paediatrics and high-risk groups such as patients with liver disease, or epilepsy.

Sodium metabisulphite
This medicinal product contains sodium metabisulphite, which may rarely cause severe hypersensitivity reaction and bronchospasm.

Sodium
This medicinal product contains 1.7 mmoles (or 38.87 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet.

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

The combination of the antibiotics in Co-Trimoxazole for Infusion 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with laboratory tests: 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.

Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and ciclosporin following renal transplantation.

Rifampicin: concurrent use of rifampicin and Co-Trimoxazole 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.

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

Pyrimethamine: 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.

Warfarin: co-trimoxazole 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 Co-Trimoxazole is advisable.

Phenytoin: 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.

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

Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate. If Co-Trimoxazole is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4).

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.

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

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

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.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Trimethoprim is contraindicated during the first trimester of pregnancy (see section 4.3). Studies in animals have shown a teratogenic effect.

Epidemiological studies have shown an increased risk of spontaneous abortion and congenital malformations, in particular neural tube defects, oral clefts and cardiovascular defects, in children of mothers treated with trimethoprim during the first trimester of pregnancy. The presumed mechanism of action is thought to be interference with folates.

In the second and third trimesters, use should be avoided, unless clinically necessary.

Trimethoprim and sulfamethoxazole cross the placenta and their safety in pregnant women has not been established. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see section 5.3).

Folate supplementation should be considered if Co-Trimoxazole for Infusion 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 newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when Co-Trimoxazole for Infusion 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

The components of Co-Trimoxazole for Infusion (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Co-Trimoxazole for Infusion 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 Co-Trimoxazole for Infusion 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

There have been no studies to investigate the effect of Septrin on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless the clinical status of the patient and the adverse events profile of Septrin should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

Summary of the safety profile
As co-trimoxazole 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.

Tabulated list of adverse reaction

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.
	Very rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients.
Immune system disorders	Very rare	Serum sickness, anaphylactic reaction, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus. Severe hypersensitivity reactions associated with PJP*, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.
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
Vascular disorders	Not known	Circulatory shock*
Respiratory, thoracic and	Very rare	Cough*, dyspnoea*, lung

mediastinal disorders		infiltration.*
Gastrointestinal disorders	Common	Nausea, diarrhoea.
	Uncommon	Vomiting.
	Very rare	Glossitis, stomatitis, 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, dermatitis exfoliative, angiodema, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) *, toxic epidermal necrolysis (TEN) *. Acute generalised exanthematous pustulosis (AGEP).
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), Drug reaction with eosinophilia and systemic symptoms (DRESS)*
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.

* 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 (see section 4.4).

Hepatobiliary disorders

Jaundice cholestatic and hepatic necrosis may be 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).

Effects associated with Pneumocystis jirovecii pneumonitis (PJP) management

Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.

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 trimethoprim-sulfamethoxazole for prophylaxis or treatment of PJP.

For the management of the hypersensitivity reactions associated with Co-Trimoxazole therapy concomitant administration of intravenous diphenhydramine may permit continued infusion when Co-Trimoxazole is used for the treatment of PJP.

Circulatory shock
Cases of circulatory shock, often accompanied by fever and not responding to standard treatment for hypersensitivity, have been reported with sulfamethoxazole + trimethoprim, mainly in immunocompromised patients.

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and Signs

The maximum tolerated dose in humans is unknown.

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

Treatment

Dependent on the status of renal function, administration of fluids is recommended if urine output is low. Both trimethoprim and active sulfamethoxazole are dialysable by renal dialysis. Peritoneal dialysis is not effective.

In cases 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use - Sulphonamides and trimethoprim, 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 that 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.

Many common pathogenic bacteria are susceptible 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 antibiotics, however, in vitro activity does not necessarily imply that clinical efficacy

has been demonstrated and it must be noted that satisfactory susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

Susceptibility testing breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing) limits
Enterobacteriaceae: S≤ 2 R> 4
S. maltophilia: S≤ 4 R> 4
Acinetobacter: S≤ 2 R> 4
Staphylococcus: S≤ 2 R> 4
Enterococcus: S≤ 0.032 R> 1
Streptococcus ABCG: S≤ 1 R> 2
Streptococcus pneumoniae: S≤ 1 R> 2
Hemophilus influenza: S≤ 0.5 R> 1
Moraxella catarrhalis: S≤0.5 R >1
Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*

S = susceptible, R = resistant. *These are CLSI breakpoints since no EUCAST breakpoints are currently available for these organisms.

Trimethoprim: sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as trimethoprim concentration.

Antibacterial Spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not.

Trimethoprim/sulfamethoxazole susceptibility against a number of bacteria are shown in the table below:

Commonly susceptible species:
Gram-positive aerobes: *Staphylococcus aureus* *Staphylococcus saprophyticus* *Streptococcus pyogenes*
Gram-negative aerobes: *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Salmonella* spp. *Stenotrophomonas maltophilia* *Yersinia* spp.

Species for which acquired resistance may be a problem:
Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium* *Nocardia* spp. *Staphylococcus epidermidis* *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter* spp. *Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella pneumonia* *Proteus mirabilis* *Proteus vulgaris* *Providencia* spp. *Serratia marcesans*
Inherently resistant organisms:
Gram-negative aerobes: *Pseudomonas aeruginosa* *Shigella* spp. *Vibrio cholera*

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.

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 Co-Trimoxazole 16 mg/80 mg per ml for Infusion than after oral administration of an equivalent dose of a Co-Trimoxazole 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 humour, 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.

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. 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 older 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 of sulfamethoxazol 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. In older patients there is a reduced renal clearance of sulfamethoxazole.

Special patient population

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of Co-Trimoxazole should be reduced (see section 4.2).

Elderly patients

In elderly 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 Co-Trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ 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

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 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 (E1520)
Tromethamine
Sodium Hydroxide (E524)
Sodium Metabisulphite (E223)
Ethanol
Water for Injections

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

Neutral glass ampoules (5ml nominal fill volume)
Pack size: 10 x 5ml ampoules

6.6 Special precautions for disposal

Co-Trimoxazole for Infusion must be diluted before administration.

DILUTION SHOULD BE CARRIED OUT IMMEDIATELY BEFORE USE. After adding Co-Trimoxazole 16 mg/80 mg per ml for Infusion to the infusion solution shakes 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 Co-Trimoxazole 16 mg/80 mg per ml 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.

Co-Trimoxazole 16 mg/80 mg per ml 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.

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, Co-Trimoxazole 16 mg/80 mg per ml 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 solution.

7. Marketing Authorisation Holder

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