Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Septrin Paediatric 40 mg/200 mg per 5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 40 mg Trimethoprim and 200 mg Sulfamethoxazole.

Excipients with known effect:

Contains 2.3 g of sorbitol (E 420) per 5 ml, 13.50 µL of ethanol per 5 ml, 5 mg of methyl hydroxybenzoate (E218) per 5 ml, 10.95 mg of sodium per 5 ml (inclusive of 5mg of sodium benzoate E 211), vanilla flavour with 0.00015 µL sulphur dioxide per 5 ml and 750 mg of glycerol per 5ml.

For the full list of excipients, see section 6.1,

3 PHARMACEUTICAL FORM

Oral suspension

An off-white, banana and vanilla flavoured syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Septrin Paediatric Suspension is indicated in infants and children aged 6 weeks to 12 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 antimicrobial agent is the preferred treatment. Since trimethoprim is also as efficacious as Septrin for the prophylaxis of recurrent urinary tract infections, Septrin is not indicated for prophylactic use.
- *Respiratory tract infections:* Septrin 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 (PJP)*.
- Septrin may be used in the management of other serious conditions such as nocardiasis, 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
Treatment should be continued until the patient has been symptom free for two days; acute infections will require treatment for at least 5 days. If clinical improvement is not evident after 7 days therapy, the patient should be reassessed.

Standard dosage recommendations for acute infections
Children aged 6 weeks to 12 years old :

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 table below:

STANDARD DOSAGE	
Age	**Paediatric Suspension**
6 to 12 years	10 ml every 12 hours

6 months to 5 years	5 ml every 12 hours
6 weeks to 5 months	2.5 ml every 12 hours

As an alternative to standard dosage for acute uncomplicated lower urinary tract infections, short-term therapy of 1 to 3 days' duration has been shown to be effective.

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**
>30	10 ml every 12 hours
15 to 30	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 trimethoprim-sulfamethoxazole.

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of Septrin. 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 – Infants and children aged 6 weeks to 12 years old:

A higher dosage is recommended using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day (see table below) in two or more divided doses for 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 Septrin) (See section 4.8).

Prevention – Infants and children aged 6 weeks to 12 years old:

Age	**Paediatric Suspension**
6 to 12 years	10 ml every 12 hours, seven days per week
6 to 12 years	10 ml every 12 hours, three times per week on alternative days
6 to 12 years	10 ml every 12 hours, three times per week on consecutive days
6 to 12 years	20 ml once a day, three times per week on consecutive days
6 months to 5 years	5 ml every 12 hours, seven days per week
6 months to 5 years	5 ml every 12 hours, three times per week on alternative days
6 months to 5 years	5 ml every 12 hours, three times per week on consecutive days
6 months to 5 years	10 ml once a day, three times per week on consecutive days
6 weeks to 5 months	2.5 ml every 12 hours, seven days per week
6 weeks to 5 months	2.5 ml every 12 hours, three times per week on alternative days
6 weeks to 5 months	2.5 ml every 12 hours, three times per week on consecutive days
6 weeks to 5 months	5 ml once a day, three times per week on consecutive days

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m2/day and 750 mg sulfamethoxazole/m2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

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. 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
Oral

It may be preferable to take Septrin with some food or drink to minimise the possibility of gastrointestinal disturbances.

4.3 Contraindications

Septrin Paediatric suspension 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 renal insufficiency where repeated measurements of the plasma drug concentration cannot be performed.
- severe impairment of liver function.
- a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- acute porphyria.
- First trimester of pregnancy (see section 4.6).

Septrin 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.

- Severe cutaneous adverse reactions (SCARs):
- Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with Septrin Paediatric Suspension treatment (see section 4.8).
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions.
- If signs and symptoms suggestive of these reactions appear, Septrin Paediatric Suspension should be withdrawn immediately and an alternative treatment considered (as appropriate).
- If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of Septrin Paediatric Suspension, the treatment must not be restarted 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 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).

Patients with glucose-6-phosphate dehydrogenase deficiency
In glucose-6-phosphate dehydrogenase (G-6-PD) deficient 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.

Excipients with known effects
- 2.3 g sorbitol in each 5 ml which is equivalent to 0,46 g/ml. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

- 5 mg sodium benzoate (E 211) in each 5 ml. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
- 0.01 mg of ethanol in each 5 ml oral suspension which is equivalent to 0.002 mg/ml. The amount in 5ml of this medicine 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.
- sulphur dioxide (E 220) which may rarely cause severe hypersensitivity reactions and bronchospasm
- methyl p-hydroxybenzoate (E 218), which may cause allergic reactions (possibly delayed).
- This medicinal product contains 10.95 mg sodium per 5ml dose , equivalent to 0.55% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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.

Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should trimethoprim-sulfamethoxazole be prescribed concurrently.

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

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.

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.

Phenytoin: trimethoprim-sulfamethoxazole prolongs the half-life of phenytoin and if co-administered the prescriber should be alert for excessive phenytoin effects. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

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

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.

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

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.

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

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.

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

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 *Lactobacilluscasei* is used in the assay. No interference occurs if methotrexate is measured by radio-immune 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%.
Functional inhibition of the renal tubular secretion of creatinine may produce a spurious fall in the estimated rate of creatinine clearance.

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.

Folate supplementation should be considered if Septrin is used in pregnancy

Sulfamethoxazole crosses the placenta and its safety in human pregnancy has not been established. In animal studies, it has been shown to cause foetal abnormalities (see section 5.3).

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significant maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when Septrin is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6- phosphate dehydrogenase deficiency.

Breast Feeding

Trimethoprim and sulfamethoxazole are excreted in breast milk. Administration of Septrin should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of Septrin should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

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.

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 ³1/10,
Common ³1/100 and <1/10,
Uncommon ³1/1000 and <1/100,
Rare ³1/10,000 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	Leucopenia, 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 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, rhabdomyolosis, 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.
Vascular disorders	Not Known	Circulatory shock*
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.
General disorders and administration 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 Septrin 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).

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.

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:

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.

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 sulfonamides 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. Thu,s 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. The affinity of trimethoprim 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.

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
Brucellaspp.
Citrobacter spp.
Escherichiacoli(includingampicillin-resistant strains)
Haemophilusducreyi
Haemophilusinfluenzae(includingampicillin-resistant strains) Klebsiella/Enterobacter spp.
Legionellapneumophila
Morganellamorganii(previouslyProteusmorganii)
Neisseriaspp.

Proteusspp. *Providenciaspp.(includingpreviouslyProteusrettgeri)* *CertainPseudomonas spp.exceptaeruginosa* *Salmonellaspp.including*S. *typhiandparatyphi.* *Serratiamarcescens.* *Shingellaspp.* *Vibriocholerae* *Yersiniaspp.*
Gram positive
Listeriamonocytogenes. *Nocardiaspp.* *Staohylococcusaureus.* *Staphylococcusepidermidisandsaprophyticus* *Enterococcusfaecalis.* *Streptococcuspneumoniae.* *Streptococcusviridans.*

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:
After oral administration trimethoprim - sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady state levels in adults are reached after dosing for 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

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, saliva, sputum and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and 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 20-50% of the plasma concentration.

Biotransformation:
Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72-hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite.

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 the elderly 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 concentration of trimethoprim varies widely.

The half-life of sulfamethoxazole in man is approximately 9-11 hours in the presence of normal renal function. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 ml/minute.

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

Special patient populations
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 Septrin should be reduced (see section 4.2).

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, trimethoprim and 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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol E420
Glycerol
Dispersible cellulose
Carmellose sodium
Polysorbate 80
Methyl hydroxybenzoate E218
Sodium Benzoate E211
Saccharin Sodium
Ethanol
Banana Flavour
Vanilla flavour containing sulphur dioxide E220
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Once opened: use within 6 weeks.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the bottle in the outer carton in order to protect from light.
Once opened: use within 6 weeks

6.5 Nature and contents of container

Amber glass bottles, with plastic child resistant closures (CRC) made of polypropylene with a polyethylene liner and a polypropylene double ended spoon.
Bottles of 50 and 100 ml.
This pack contains a polypropylene double-ended 5 ml/2.5 ml spoon.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Septrin Paediatric Suspension may be diluted with Syrup BP. Although they may show some sedimentation such dilutions remain stable for at least a month. Shake thoroughly before use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/010/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th November 1975

Date of last renewal: 14th November 2005

10 DATE OF REVISION OF THE TEXT

September 2026