Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Septrin 80 mg/400 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

Contains 2.25 mg of sodium per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablets, debossed with S2 on one side and scored on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Septrin tablets should only be used where, in the judgement of the physician, the benefit of treatment outweighs any possible risks, and where there is good reason to prefer the combination to a single antimicrobial agent.

Septrin tablets are indicated in adults and children over 12 years 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 or "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
General DosageRecommendations
Where dosage is expressed as "tablets" this refers to the adult tablet, i.e. 80 mg Trimethoprim BP and 400 mg Sulfamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Standard dosage recommendations for acute infections
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.

Adults and children over 12 years:
STANDARD DOSAGE: 2 tablets 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.

Treatment for acute brucellosis should be maintained for a period of at least 4 weeks, while nocardiosis requires longterm therapy.

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.

Elderly patients:
See section 4.4.

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

Impairedrenalfunction
Dosage recommendation:
Adults and children over 12 years:

Creatinine Clearance(ml/min)	**RecommendedDosage**
> 30	2 tablets every 12 hours
15 to 30	1 tablet 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 jiroveciipneumonitis:
Treatment - Adults and children over 12 years:
A higher dosage is recommended, using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses for two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of greaterthanorequalto 5 microgram/ml (verified in patients receiving 1-hour infusions of intravenous trimethoprim – sulfamethoxazole). (See section 4.8).

Prevention: Adults and children over 12 years:
The following dose schedules may be used:

- 160 mg trimethoprim/800 mg sulfamethoxazole daily seven days per week
- 160 mg trimethoprim/800 mg sulfamethoxazole three times per week on alternate days
- 320 mg trimethoprim/1600 mg sulfamethoxazole per day in two divided doses three times per week on alternate days.

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 daily dose given on a treatment day approximates to 150 mg trimethoprim/m^2/day and 750 mg sulfamethoxazole/m^2/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 6 to 8 tablets daily for up to 3 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 tablets are 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 the use of trimethoprim and/or sulphonamides.
- acute porphyria.

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.

- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or 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 and 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 and 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
n 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 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.

Excipients with known effects
Septrin contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

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 25mg 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 patients conditions and serum phenytoin levels is 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 - 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 Lactobacillus casei 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 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 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 trimethoprim - sulfamethoxazole is used in pregnancy.

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 hyperbilrubinaemia, 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 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
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 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 (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 (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 trimethoprim - sulfamethoxazole 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 sulphonamides and trimethoprim, incl. derivatives, ATC Code: J01EE0l

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 effects 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 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
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.
Nocardias pp.
Staohylococcus aureus.
Staphylococcus epidermidis and saprophyticus

Enterococcus faecalis. *Streptococcus pneumoniae.* *Streptococcus viridans.*

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 and 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 in 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, salvia, sputum and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal; middle ear fluid synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and fetal tissue reaching concentrations approximately 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 principle 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 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 25ml/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
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 generally in excess of the recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, finding 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

Sodium starch glycolate type A
Povidone K30
Docusate sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/Aluminium foil blister packs.

Packs of 100 and 500 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1691/010/001

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

August 2025