For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

SEPTRAN/ SEPMAX DOUBLE STRENGTH

Co-Trimoxazole Oral Formulations

QUALITATIVE AND QUANTITATIVE COMPOSITION

SEPTRAN TABLETS (Adult)
(Co-trimoxazole Tablets IP)

Each uncoated tablet contains:
Trimethoprim IP 80 mg
Sulphamethoxazole IP 400 mg

SEPTRAN PAEDIATRIC TABLETS
(Co-trimoxazole Tablets IP)

Each uncoated tablet contains:
Trimethoprim IP 20 mg
Sulphamethoxazole IP 100 mg

SEPTRAN PAEDIATRIC SUSPENSION
(Co-trimoxazole Oral Suspension IP)

Each 5 ml suspension contains:
Trimethoprim IP 40 mg
Sulphamethoxazole IP 200 mg in a sweetened syrup base
Colours: Ponceau 4R & Carmoisine

SEPMAX TABLETS DOUBLE STRENGTH
(Co-trimoxazole Tablets IP)

Each uncoated tablet contains:
Trimethoprim IP 160 mg
Sulphamethoxazole IP 800 mg

PHARMACEUTICAL FORM

Uncoated Tablets
Oral Suspension

CLINICAL PARTICULARS

Therapeutic Indications

SEPTRAN/SEPMAX tablets are indicated for the treatment of the following infections when owing to sensitive organisms:

- treatment and prevention of *Pneumocystis jiroveci* pneumonitis or "PJP" (previously known as *Pneumocystis carinii* pneumonia or "PCP")
- treatment and prophylaxis of toxoplasmosis
- treatment of nocardiosis

The following infections may be treated with *SEPTRAN/SEPMAX* where there is bacterial evidence of sensitivity to *SEPTRAN/SEPMAX* and good reason to prefer the combination of antibiotics in *SEPTRAN/SEPMAX* to a single antibiotic:

- acute uncomplicated urinary tract infection
- acute otitis media
- acute exacerbation of chronic bronchitis

Additionaly *SEPTRAN/SEPMAX* may be useful in:

- treatment of chancroid infection (this regimen may be less effective in some parts of the world due to disease caused by resistant organisms)
- treatment of granuloma inguinale (venereum)
- treatment of travellers' diarrhea (including gastroenteritis due to enterotoxigenic *Escherichia coli)*

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

Posology and Method of Administration

It may be preferable to take *SEPTRAN/SEPMAX* with some food or drink to minimise the possibility of gastrointestinal disturbances.

Route of Administration

For oral use.

Standard dosage recommendations for acute infections

Adults and children over 12 years

SEPTRAN TABLETS (Adult)
2 tablets every 12 hours.

SEPMAX TABLETS DOUBLE STRENGTH

1 tablet every 12 hours.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evident after 7 days' therapy, the patient should be reassessed.

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.

Children aged 12 years and under

Below dosage approximates to 6 mg trimethoprim and 30 mg sulfamethoxazole per kilogram body weight per 24 hours.

Children aged 6 to 12 years

SEPTRAN PAEDIATRIC TABLETS
Four tablets every 12 hours.

SEPTRAN PAEDIATRIC SUSPENSION
10 ml oral suspension every 12 hours.

Children aged 6 months to 5 years

SEPTRAN PAEDIATRIC TABLETS
Two tablets every 12 hours.
The use of paediatric oral suspension formulation is recommended in this age group.

SEPTRAN PAEDIATRIC SUSPENSION
5 ml oral suspension every 12 hours.

Children aged 6 weeks to 5 months

SEPTRAN PAEDIATRIC TABLETS
Not recommended.
The use of paediatric oral suspension formulation is recommended in this age group.

SEPTRAN PAEDIATRIC SUSPENSION
2.5 ml oral suspension every 12 hours.

Pneumocystis jiroveci (P.carinii) pneumonitis
Treatment

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 greater than or equal to 5 microgram/ ml (verified in patients receiving 1-hour infusions of intravenous sulfamethoxazole/ trimethoprim) *(see Section Undesirable Effects).*

Prevention

SEPMAX TABLETS DOUBLE STRENGTH
SEPTRAN TABLETS (Adult)

Adults and children over 12 years

The following dose schedules may be used:

- 160 mg trimethoprim/ 800 mg sulfamethoxazole daily 7 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.

Children aged 12 years and under

The following dose schedules may be used for the duration of the period at risk (see *Standard dosage recommendations for acute infections* above in *Posology and Method of Administration*):

- standard dosage taken in two divided doses, seven days per week.
- standard dosage taken in two divided doses, three times per week on alternate days.
- standard dosage taken in two divided doses, three times per week on consecutive days.
- standard dosage taken as a single dose, three times per week on consecutive days.

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 (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 jiroveci pneumonitis may be appropriate.

Chancroid

SEPTRAN TABLETS (Adult)
Two tablets twice daily for seven days.

SEPMAX TABLETS DOUBLE STRENGTH
One tablet twice daily for seven days.

If no evidence of healing is apparent after seven days a further seven days treatment can be considered. However, physicians should be aware that failure to respond may indicate that the disease is caused by a resistant organism.

Granuloma inguinale

SEPTRAN TABLETS (Adult)
Two tablets twice daily for up to two weeks.

SEPMAX TABLETS DOUBLE STRENGTH
One tablet twice daily for up to two weeks.

Elderly

Unless otherwise specified standard dosage applies, *see Section Special Warnings and Special Precautions for Use.*

Renal impairment

Adults and children over 12 years

Creatinine Clearance (ml/min)	**Recommended Dosage**
> 30	STANDARD DOSAGE
15 to 30	Half the STANDARD DOSAGE
<15	Not recommended

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of Sulfamethoxazole/ trimethoprim. If the concentration of total sulfamethoxazole exceeds 150 microgram/ml then treatment should be interrupted until the value falls below 120 microgram/ml.

Children aged 12 years

No data are available relating to dosage in children aged 12 years and under with impaired renal function.

Hepatic impairment

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

Contraindications

SEPTRAN/SEPMAX is contraindicated in:

- patients with a history of hypersensitivity to sulphonamides, trimethoprim, sulfamethoxazole/ trimethoprim or any excipients of this medicinal product,
- severe hepatic parenchymal damage,
- severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed,
- premature babies or full-term infants during the first 6 weeks of life except for the treatment /prophylaxis of PJP (*Pneumocystis jiroveci* pneumonitis) in infants 4 weeks of age or greater,
- patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides,
- patients with acute porphyria (*see Section Special Warnings and Special Precautions for Use*).

Special Warnings and Special Precautions for Use

Severe 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.

Severe Cutaneous Adverse Reactions (SCARs)

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfamethoxazole/ trimethoprim.

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 Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (e.g. progressive skin rash often with blisters or mucosal lesions) are present,

sulfamethoxazole/ trimethoprim treatment should be discontinued *(see Section Undesirable Effects)*.

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

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.

Renal impairment

For patients with known renal impairment special measures should be adopted.

Risk of crystalluria

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.

Haematological changes

Regular monthly blood counts are advisable when sulfamethoxazole/ trimethoprim 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 Interaction with Other Medicaments and Other Forms of Interaction).*

Glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients

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

Severe atopy, bronchial asthma

Sulfamethoxazole/ trimethoprim should be given with caution to patients with severe atopy or bronchial asthma.

Streptococcal pharyngitis

Sulfamethoxazole/ trimethoprim 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.

Phenylketonuric patients

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

Porphyria

The administration of sulfamethoxazole/ trimethoprim 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 (*see Section Contraindications*).

Serum potassium and sodium monitoring

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

Metabolic acidosis

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

Serious haematological disorders

Except under careful supervision sulfamethoxazole/ trimethoprim should not be given to patients with serious haematological disorders *(see Section Undesirable Effects).* Sulfamethoxazole/ trimethoprim has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Use of sulfamethoxazole/ trimethoprim

The combination of antibiotics in sulfamethoxazole/ trimethoprim 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.

Interaction with Other Medicaments 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 sulfamethoxazole/ trimethoprim. 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 sulfamethoxazole/ trimethoprim and cyclosporin following renal transplantation.

Rifampicin

Concurrent use of rifampicin and sulfamethoxazole/ trimethoprim 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.

Procainamide, amantadine

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 *(see Section Special Warnings and Special Precautions for Use).*

Pyrimethamine

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

Warfarin

Sulfamethoxazole/ trimethoprim 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 sulfamethoxazole/ trimethoprim is advisable.

Phenytoin

Sulfamethoxazole/ trimethoprim prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

Digoxin

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

Methotrexate

Sulfamethoxazole/ trimethoprim may increase the free plasma levels of methotrexate. If sulfamethoxazole/ trimethoprim is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered *(see Section Special Warnings and Special Precautions for Use).*

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.

Sulphonylurea hypoglycaemic agents

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 including spironolactone.

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 jiroveci 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.

Pregnancy and Lactation

Pregnancy

SEPTRAN/SEPMAX should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if *SEPTRAN/SEPMAX* is used in pregnancy.

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.

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 *SEPTRAN/SEPMAX* 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.

Lactation

The components of *SEPTRAN/SEPMAX* are excreted in breast milk. Administration of *SEPTRAN/SEPMAX* 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 *SEPTRAN/SEPMAX* should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of sulfamethoxazole/ trimethoprim 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 sulfamethoxazole/ trimethoprim should be borne in mind when considering the patients ability to operate machinery.

Undesirable Effects

Clinical Trial and Post Marketing Data

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

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.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.
Frequencies are defined as:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Infections and infestations
Common: monilial overgrowth

Blood and lymphatic system disorders
Very rare: leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients

Immune system disorders

Very rare: serum sickness, anaphylactic reaction, allergic myocarditis, angioedema, pyrexia, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus

Metabolism and nutrition disorders
Very common: hyperkalaemia
Very rare: hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis, renal tubular acidosis
Psychiatric disorders
Very rare: depression, hallucinations

Nervous system disorders
Common: headache
Very rare: aseptic meningitis*, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness
*Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either Sulfamethoxazole/ trimethoprim or to trimethoprim alone.

Eye disorders
Very rare: uveitis

Respiratory, thoracic and mediastinal disorders
Very rare: cough, dyspnoea, lung infiltration*
*Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Gastrointestinal disorders
Common: nausea, diarrhoea
Uncommon: vomiting
Very rare: glossitis, stomatitis, pseudomembranous colitis, pancreatitis

Hepatobiliary disorders
Very rare: transaminases increased, blood bilirubin increased, cholestatic jaundice, hepatic necrosis (cholestatic jaundice and hepatic necrosis may be fatal)

Skin and subcutaneous tissue disorders
Common: rash
Very rare: photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) *(see Section Special Warnings and Special Precautions for Use)*

Musculoskeletal and connective tissue disorders
Very rare: arthralgia, myalgia

Renal and urinary disorders
Very rare: renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis

Effects associated with Pneumocystis jiroveci (P.carinii) Pneumonitis (PJP) management.
Very rare: 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 sulfamethoxazole/ trimethoprim, 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.

Overdose

Symptoms and Signs

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

Treatment

Absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. Dependant 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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim including derivatives; ATC Code: J01EE01.

Mechanism of Action

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents.

Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Mechanism of 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.

Trimethoprim binds to plasmodial DHFR but less tightly than to bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial 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
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 sulfamethoxazole/ trimethoprim or not.

Sulfamethoxazole/ trimethoprim susceptibility against a number of bacteria are shown 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
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Serratia marcesans

Inherently resistant organisms:

Gram-negative aerobes:
Pseudomonas aeruginosa
Shigella spp.
Vibrio cholerae

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 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 humor, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluid is of the order of 20 to 50% of the plasma concentration.

Metabolism

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 (N-4-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. 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 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 concentrations of trimethoprim vary widely.

The half-life of sulfamethoxazole 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 elderly patients there is a reduced renal clearance of sulfamethoxazole.

Special patient populations

Children

See special dosage regimen in *Posology and Method of Administration* section.

Elderly

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

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 sulfamethoxazole/ trimethoprim should be reduced *(see Section Posology and Method of Administration).*

Hepatic impairment

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

Clinical Studies

Not relevant for this product.

Preclinical Safety Data

Reproductive toxicology

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 *(see Section Pregnancy and Lactation).*

PHARMACEUTICAL PARTICULARS

List of Excipients

SEPTRAN Tablets (Adult) / SEPTRAN Paediatric Tablets / SEPMAX Tablets Double Strength:

Sodium Starch Glycollate, Dioctyl Sodium Sulphosuccinate, Starch Maize, Magnesium Stearate.
SEPTRAN Paediatric Suspension:

Sucrose, Methyl Paraben, Propyl Paraben, Sodium Chloride, Sorbitol Solution, Microcrystalline Cellulose, Sodium Carboxymethylcellulose, Anise oil, Flavour Vanilla, Ponceau 4R, Carmoisine, Saccharin Sodium, Polysorbate 20, Purified Water.

Incompatibilities

There are no relevant data available.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

SEPTRAN Tablets (Adult) / SEPTRAN Paediatric Tablets / SEPMAX Tablets Double Strength:

Store in a dry place at a temperature not exceeding 30 ºC . Protect from light and moisture.

SEPTRAN Paediatric Suspension:

Store in a well closed container at temperatures not exceeding 30ºC. Protect from light. Do not freeze.

Keep out of reach of children.

Nature and Specification of Container

SEPTRAN Tablets (Adult), Paediatric Tablets and *SEPMAX Tablets Double Strength:*

Strips in a carton.

SEPTRAN Paediatric Suspension:

Bottle with a measuring cup.

All presentations may not be marketed in the Country.

Instructions for Use / Handling

There are no special requirements for use or handling of these products.

SEPTRAN Paediatric Suspension:

Shake well before use.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

Trade marks are owned by or licensed to the GSK group of companies.

Version: SEP/PI/IN/2018/01 dated 27 August 2018.

Adapted from Sulfamethoxazole/ trimethoprim (Co-trimoxazole) NCDS 01 dated 08-May-2017.