SEPTRIN ORAL
GlaxoSmithKline

Trimethoprim-Sulfamethoxazole

QUALITATIVE AND QUANTITATIVE COMPOSITION

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Trimethoprim content</th>
<th>Sulfamethoxazole content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Tablet</td>
<td>80 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Dispersible</td>
<td>80 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Double Strength (Forte) Tablets</td>
<td>160 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Paediatric Tablets</td>
<td>20 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Capsules</td>
<td>80 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Adult Oral Suspension</td>
<td>80 mg per 5 ml</td>
<td>400 mg per 5 ml</td>
</tr>
<tr>
<td>Paediatric Oral Suspension</td>
<td>40 mg per 5 ml</td>
<td>200 mg per 5 ml</td>
</tr>
</tbody>
</table>

PHARMACEUTICAL FORM
- Tablets.
- Dispersible tablets.
- Capsules.
- Oral suspension.

CLINICAL PARTICULARS

Indications
SEPTRIN should only be used where, in the judgment of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

The in vitro susceptibility of bacteria to antibiotics varies geographically and with time; the local situation should always be considered when selecting antibiotic therapy.

Urinary tract infections
Treatment of acute uncomplicated urinary tract infections. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Respiratory tract infections
Treatment of otitis media. SEPTRIN is not indicated for prophylactic or prolonged administration in otitis media.

Treatment of acute exacerbations of chronic bronchitis.

Treatment and prevention of Pneumocystis jiroveci (P. carinii) pneumonitis (see Dosage and Administration and Adverse Reactions).

Genital tract infections
- Treatment of gonorrhoea, including oro-pharyngeal and ano-rectal infection (see Dosage and Administration). This regimen is less effective in some parts of the world due to disease caused by resistant organisms.
- Treatment of chancroid (see Dosage and Administration). This regimen may be less effective in some parts of the world due to disease caused by resistant organisms.
- Treatment of granuloma inguinale (venereum) (see Dosage and Administration).

Gastrointestinal tract infections
Clinicians should be aware that first line therapy in the management of all patients with diarrhoeal disease is the maintenance of adequate hydration.

Treatment of cholera, as an adjunct to fluid and electrolyte replacement, when the organism has been shown to be sensitive in vitro.

Treatment of shigellosis, this regime may be less effective in some parts of the world due to disease caused by resistant organisms.

Treatment of travellers’ diarrhoea (including gastroenteritis due to enterotoxigenic E. coli).

Other bacterial infections caused by sensitive organisms
There are a number of other bacterial infections caused by sensitive organisms for which treatment with SEPTRIN may be appropriate; the use of SEPTRIN in such conditions should be based on clinical experience and local in vitro data.

Treatment of nocardiosis (see Dosage and Administration).
SEPTRIN may be useful in:
- toxoplasmosis
- brucellosis (second-line therapy), when used in combination with gentamicin or rifampicin
- melioidosis, when used in combination with ceftazidime or cefoperazone/sulbactam.

Dosage and Administration
It may be preferable to take SEPTRIN with some food or drink to minimise the possibility of gastrointestinal disturbances.

Unless otherwise specified STANDARD DOSAGE applies.

Where dosage is expressed as “tablets” this refers to the adult tablet, i.e. 80 mg trimethoprim and 400 mg sulfamethoxazole. If other formulations are to be used appropriate adjustment should be made.

Acute Infections
• Adults and children over 12 years

<table>
<thead>
<tr>
<th>STANDARD DOSAGE</th>
<th>Tablets/Capsules</th>
<th>Double Strength Tablets</th>
<th>Adult Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 every 12 hours</td>
<td>1 every 12 hours</td>
<td>10 ml every 12 hours</td>
</tr>
</tbody>
</table>

• Children aged 12 years and under

<table>
<thead>
<tr>
<th>STANDARD DOSAGE</th>
<th>Age</th>
<th>Paediatric Tablets</th>
<th>Paediatric Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 to 12 years</td>
<td>4 every 12 hours</td>
<td>10 ml every 12 hours</td>
</tr>
<tr>
<td></td>
<td>6 months to 5 years</td>
<td>2 every 12 hours</td>
<td>5 ml every 12 hours</td>
</tr>
<tr>
<td></td>
<td>6 weeks to 5 months</td>
<td>-</td>
<td>2.5 ml every 12 hours</td>
</tr>
</tbody>
</table>

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

• Elderly
See Warnings and Precautions.

• Renal impairment
Adults and children over 12 years (no information is available for children under 12 years of age).

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>STANDARD DOSAGE</td>
</tr>
<tr>
<td>15 to 30</td>
<td>Half the STANDARD DOSAGE</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

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 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 or equal to 5 micrograms/ml (verified in patients receiving 1 hour infusions of intravenous SEPTRIN) (see Adverse Reactions).

Prevention:
• Adults
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
The following dose schedules may be used for the duration of the period at risk (see Dosage and Administration, Acute Infections, Children):
  – 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/m2/day and 750 mg sulfamethoxazole/m2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Gonorrhoea
In uncomplicated cases 4 tablets every 12 hours for two days or 5 tablets followed by a further 5 tablets eight hours later or 10 tablets once daily for 3 days. If poor patient compliance is expected a single dose of 8 tablets taken under supervision may be employed.

Oro-pharyngeal gonococcal infection: 2 tablets three times daily for seven days.

Chancroid
2 tablets twice daily for 7 days. If no evidence of healing is apparent after 7 days a further 7 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
2 tablets twice daily for up to 2 weeks.

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 gentamicin or rifampicin.

Melioidosis
8 mg/kg/day trimethoprim and 40 mg/kg/day sulfamethoxazole in divided doses, 3 or 4 times per day for 6 months given in combination with ceftazidime or cefoperazone/sulbactam.

Contraindications
SEPTRIN should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole or any excipients of SEPTRIN.

SEPTRIN should not be given to premature babies or to full-term infants in the neonatal period.

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

SEPTRIN should be discontinued at the first appearance of skin rash (see Adverse Reactions).

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.

For patients with known renal impairment special measures should be adopted (see Dosage and Administration).

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.

Exercise caution when treating patients with severe hepatic parenchymal damage as changes may occur in the absorption and metabolism of trimethoprim and sulfamethoxazole.

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.
These changes may be reversed by administration of folic acid (5 to 10 mg/day) without interfering with the antibacterial activity.

A folate supplement should also be considered with prolonged high dosage of SEPTRIN (see Interactions).

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

SEPTRIN should be given with caution to patients with severe allergy or bronchial asthma.

SEPTRIN 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.

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

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

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

Except under careful supervision SEPTRIN should not be given to patients with serious haematological disorders (see Adverse Reactions). Trimethoprim-sulfamethoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Interactions

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia.

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

In some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to SEPTRIN. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Administration of trimethoprim /sulfamethoxazole 160 mg/800 mg (SEPTRIN) causes a 40% increase in lamivudine exposure because of the trimethoprim component.

Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

SEPTRIN 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.

SEPTRIN prolongs the half-life of phenytoin and if co-administered the prescriber should be alert for excessive phenytoin effect. Close monitoring of the patient’s condition and serum phenytoin levels is advisable.

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

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.

Reversible deterioration in renal function has been observed in patients treated with SEPTRIN 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.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.
Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia. SEPTRIN 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 Warnings and Precautions).

**Laboratory tests interactions**

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 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. SEPTRIN may affect the results of thyroid function tests but this is probably of little or no clinical significance.

**Pregnancy and Lactation**

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 have been shown to cause foetal abnormalities (see Pre-clinical Safety Data). Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Therefore SEPTRIN should be avoided in pregnancy, particularly in the first trimester, unless the potential benefit to the mother outweighs the potential risk to the foetus; folate supplementation should be considered if SEPTRIN is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As 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.

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.

**Effects on Ability to Drive and Use Machines**

No data.

**Adverse Reactions**

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 reactions 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:** \( \geq 1 \text{ in } 10 \)
- **common:** \( \geq 1 \text{ in } 100 \) and \( <1 \text{ in } 10 \)
- **uncommon:** \( \geq 1 \text{ in } 1,000 \) and \( <1 \text{ in } 100 \)
- **rare:** \( \geq 1 \text{ in } 10,000 \) and \( <1 \text{ in } 1,000 \)
- **very rare:** \( <1/10,000 \).

**Infections and Infestations**

**Common:** Monilial overgrowth.

**Blood and lymphatic system disorders**

Very rare: Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobin-
drug eruption, erythema multiforme, Stevens-Johnson syndrome, Lyell’s syndrome (toxic epidermal necrolysis) Lyell’s syndrome carries a high mortality.

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia, myalgia.

Renal and urinary disorders
Very rare: Impaired renal function (sometimes reported as renal failure), interstitial nephritis. Effects associated with Pneumocystis jiroveci (P. carinii) pneumonitis (PCP) management
Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, rhabdomyolysis, hyperkalaemia, hyponatraemia.

At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5 to 10 mg/day).

Severe hypersensitivity reactions have been reported in PCP patients on re-exposure to SEPTRIN, 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.

Overdose
Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage.

Bone marrow depression has been reported in acute trimethoprim overdosage.

If vomiting has not occurred induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete in approximately two hours. This may not be the case in gross overdosage.

Dependent on the status of renal function, administration of fluids is recommended if urine output is low. Both trimethoprim and active sulfamethoxazole are dialysable by haemodialysis.

Peritoneal dialysis is not effective.
**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

**In Vitro Activity**

Sulfamethoxazole competitively inhibits the utilization 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.

The affinity of trimethoprim for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

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 has been demonstrated. These organisms include:

**Gram Negative**
- Brucella spp.
- Citrobacter spp.
- Escherichia coli (including enterotoxigenic 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
- Shigella spp.
- Vibrio cholerae
- Yersinia spp.

**Gram Positive**
- Listeria monocytogenes
- Nocardia spp.
- Staphylococcus 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.

**Pharmacokinetics**

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 to 3 days.

Neither component has an appreciable effect on the concentrations achieved in the blood by the other. Trimethoprim is a weak base with a pKa of 7.4. It is lipophilic. 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; middle ear fluid synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and fetal tissues reaching concentrations approximating those of maternal serum. Approximately 50% of trimethoprim in the plasma is protein bound. The half-life 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. Sulfamethoxazole is a weak acid with a pKa of 6.0. 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. Approximately 66% of sulfamethoxazole in the plasma is protein bound. The half-life in man is approximately 9 to 11 hours in the presence of normal renal function. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 ml/minute. The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

**Pre-clinical 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.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**
As registered locally.

**Incompatibilities**
No data.

**Shelf Life**
As registered locally.

**Special Precautions for Storage**
Protect all SEPTRIN products from light.
Keep SEPTRIN dispersible tablets and capsules dry.

**Nature and Contents of Container**
As registered locally.

**Instructions for Use/Handling**
SEPTRIN Adult and Paediatric Suspensions 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.
Not all presentations are available in every country.

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