NAME OF THE MEDICINE

BACTRIM®
Sulfamethoxazole (CAS registry number: 723-46-6)
Trimethoprim (CAS registry number: 738-70-5)

DESCRIPTION

BACTRIM is a synthetic antibacterial combination product.

BACTRIM is available as white to almost white, oblong, biconvex tablets for oral administration in an 800mg/160mg strength (sulfamethoxazole/trimethoprim).

BACTRIM is also available as a light beige oral suspension in a 200mg/40mg per 5mL strength (sulfamethoxazole/trimethoprim).

The chemical name for sulfamethoxazole is 3-(4-aminobenzenesulfonamido)-5-methylisoxazole having a molecular weight of 253.28 and a pKa 5.9. The chemical name for trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine having a molecular weight of 290.3 and a pKa 7.3.

Sulfamethoxazole is a white to off-white powder and is virtually insoluble in water at 20°C. Trimethoprim is a white to cream-coloured powder that has an aqueous solubility of 300 mg/L at 20°C.

Each tablet contains the inactive ingredients povidone, docusate sodium, sodium starch glyccollate and magnesium stearate.
The oral suspension contains the inactive ingredients dispersible cellulose, methyl hydroxybenzoate, propyl hydroxybenzoate, sorbitol, polysorbate 80, banana flavour, vanilla flavour and water.

**PHARMACOLOGY**

**Actions**

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus BACTRIM blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to bacteria.

BACTRIM is effective against a wide range of Gram-negative and Gram-positive organisms; for example, E. coli, Neisseria, Salmonella, Klebsiella-Enterobacter, Shigella, Vibrio cholerae and Bordetella pertussis, Streptococcus, Staphylococcus, Pneumococcus. BACTRIM is usually active against the problem organisms Haemophilus influenzae and Proteus.

BACTRIM is also active against the protozoan Pneumocystis carinii (see special dosage instructions). BACTRIM is not active against Mycobacterium tuberculosis and Treponema pallidum. Pseudomonas aeruginosa is frequently insensitive.

**Representative minimum inhibitory concentration values for BACTRIM - Sensitive Organisms (MIC microgram /mL)**

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>TMP ALONE</th>
<th>SMX ALONE</th>
<th>TMP/SMX (1:20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0.05 - 1.5</td>
<td>1.0 - 245</td>
<td>0.05 - 0.5</td>
</tr>
<tr>
<td>Proteus species</td>
<td>0.5 - 5.0</td>
<td>7.35 - 300</td>
<td>0.05 - 1.5</td>
</tr>
<tr>
<td>(indole positive)</td>
<td></td>
<td></td>
<td>0.95 - 28.5</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>0.5 - 1.5</td>
<td>7.35 - 30</td>
<td>0.05 - 0.15</td>
</tr>
<tr>
<td>Klebsiella-enterobacter</td>
<td>0.15 - 5.0</td>
<td>2.45 - 245</td>
<td>0.05 - 1.5</td>
</tr>
</tbody>
</table>

TMP = Trimethoprim

SMX = Sulfamethoxazole
Pharmacokinetics

Absorption: BACTRIM is rapidly absorbed on oral administration reaching peak blood levels after 1 to 4 hours, which correspond to those achieved when each component is given alone. The mean serum half-lives of trimethoprim and sulfamethoxazole are 10 hours and 8 - 10 hours respectively.

Distribution: The volume of distribution of trimethoprim is about 130 litres and that of sulfamethoxazole is about 20 litres. At the above concentrations, about 42 - 45% of trimethoprim and 66% of sulfamethoxazole is bound to plasma proteins. The free forms of trimethoprim and sulfamethoxazole are considered to be the therapeutically active forms.

Studies in both animals and man have shown that diffusion of BACTRIM into the tissue is good. Large amounts of trimethoprim and smaller amounts of sulfamethoxazole pass from the bloodstream into the interstitial fluid and other extravascular body fluids.

In humans, trimethoprim and sulfamethoxazole were detected in the foetal placenta, umbilical cord blood, amniotic fluid and foetal tissues (liver, lung), indicating placental transfer of both drugs.

Metabolism: Approximately 50 - 70% of the trimethoprim dose and 10 - 30% are excreted unchanged. The principal trimethoprim metabolites are 1- and 3-oxides and the 3’- and 4’-hydroxy derivatives; some metabolites are active.

Sulfamethoxazole is metabolised in the liver, predominantly by N^4-acetylation and to a lesser extent by glucuronide conjugation; the metabolites are inactive.

Excretion: The elimination half-lives of the two components are very similar (a mean of 10 hours for trimethoprim and 11 hours for sulfamethoxazole).

Both substances, as well as their metabolites, are eliminated almost entirely by the kidneys through both glomerular filtration and tubular secretion, giving urine concentrations of both active substances considerably higher than the concentration in the blood. A small part of the substances is eliminated via the faeces.

INDICATIONS

Upper and lower respiratory tract infections; renal and urinary tract infections; genital tract infections; gastrointestinal tract infections; skin and wound infections; septicaemias and other infections caused by sensitive organisms.

CONTRAINDICATIONS

BACTRIM is contraindicated in patients showing marked liver parenchymal damage, blood dyscrasias, megaloblastic bone marrow or severe renal insufficiency, where repeated measurements of the plasma concentration cannot be performed.
BACTRIM should not be given to patients with a history of sulfonamide or trimethoprim sensitivity.

BACTRIM should not be given to premature babies nor during the first few weeks of life because of the risk of producing kernicterus. It should probably not be given to children under 3 months of age.

BACTRIM should not be used in the treatment of streptococcal pharyngitis. Clinical studies have documented that patients with Group A β-haemolytic (Sp) streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with BACTRIM than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

BACTRIM must not be given in combination with dofetilide (See PRECAUTIONS: Interactions with other Drugs).

**PRECAUTIONS**

**Use in the Elderly**

The use of BACTRIM in elderly patients carries an increased risk of severe adverse reactions. In rare instances fatalities have occurred. The risk of severe adverse reactions is particularly greater when complicating conditions exist, e.g. impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, or generalised bone marrow suppression (see Adverse Reactions section) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see Dosage and Administration section).

In view of the increased risk of severe adverse reactions in the elderly, consideration should be given to whether BACTRIM is the antibacterial of choice in this age group.

**Use in treatment of pneumocystis carinii pneumonitis in patients with Acquired Immunodeficiency Syndrome (AIDS)**

Because of their unique immune dysfunction, AIDS patients may not tolerate or respond to BACTRIM in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, and leucopenia, with BACTRIM therapy in AIDS patients who are being treated for Pneumocystis carinii pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of BACTRIM in non-AIDS patients.
**Use in glucose-6-phosphate dehydrogenase deficiency**

In glucose-6-phosphate dehydrogenase deficient individuals haemolysis may occur. This may be dose related. BACTRIM should not be given to patients with a glucose-6-phosphate dehydrogenase deficiency unless absolutely essential, and then only in minimal doses.

**Pseudomembranous Colitis**

The use of BACTRIM can lead in very rare instances to the development of severe colitis as a result of colonisation with C. difficile, a toxin producing organism. The colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can be fatal. If significant diarrhoea occurs (this may, however, begin up to several weeks after the cessation of antibiotic therapy) BACTRIM should be discontinued. This may be sufficient treatment in the early stages although cholestyramine orally may help by binding the toxin in the colonic lumen. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against C. difficile should be considered.

Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Even if an organism is sensitive to trimethoprim, if it is not sensitive to sulfamethoxazole the combination should not be used, to avoid unnecessary exposure to the potential side effects of the sulfonamide component.

Fatalities, although rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias. BACTRIM should be discontinued if a skin rash appears. Clinical signs such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions.

An adequate urinary output should be maintained at all times. Evidence of crystalluria in-vivo is rare, although sulfonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition this risk may be increased.

As with other sulfonamide preparations, critical appraisal of benefit versus risk should be made in patients with liver damage, renal damage, urinary obstruction, blood dyscrasias, allergies or bronchial asthma.

In patients with renal impairment, a reduced or less frequent dosage is recommended in order to avoid accumulation of trimethoprin in the blood. Non-ionic diffusion is the main factor in the renal handling of trimethoprin, and as renal failure advances, trimethoprin excretion decreases. For such patients, serum assays are necessary. See the special dosage table for use in renal impairment.

Cross sensitivity is known to occur among sulfonamides (see Contraindications).

Except under careful supervision, BACTRIM should not be given to patients with serious haematological disorders. BACTRIM has been given to patients receiving cytotoxic therapy.
Because of possible interference with folate metabolism, regular blood counts are advisable in patients on long-term therapy, in those who are predisposed to folate deficiency (i.e. the elderly, chronic alcoholics and rheumatoid arthritics), in malabsorption syndromes, malnutrition states, or during the treatment of epilepsy with anticonvulsant drugs such as phenytoin, primidone or barbiturates. Changes indicative of folic acid impairment have, in certain specific situations, been reversed by folinic acid therapy.

Urine analysis and renal function tests should be performed during long term therapy particularly in patients with reduced renal function.

The possibility of superinfection with a nonsensitive organism should be borne in mind.

Trimethoprim has been noted to impair phenylalanine metabolism in some patients.

If BACTRIM is given over a prolonged period, regular blood counts are required. If a significant reduction in count of any formed blood element is noted, BACTRIM should be discontinued.

As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

Patients who are “slow acetylators” may be more prone to idiosyncratic reactions to sulfonamides.

**Use in Pregnancy** Category C.

Sulfonamides may cause jaundice and haemolytic anaemia in the newborn. Sulfonamides may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulfonamides should therefore be avoided as far as possible during the last month of pregnancy. Trimethoprim may interfere with folic acid metabolism and animal experiments have shown that administration of very high doses of trimethoprim during organ development may give rise to birth defects typical of folic acid antagonism. If a trimethoprim-sulfonamide combination is given during pregnancy, folic acid supplementation may be required.

**Use During Lactation**

Both trimethoprim and sulfamethoxazole are excreted in breast milk at concentrations comparable or somewhat lower than that in the blood. Although the quantity of BACTRIM ingested by a breast-fed infant is small, it is recommended that the possible risks should be balanced against the expected therapeutic effect. Consideration should be made of the infants age (see Contraindications).

A folate supplement may be considered with prolonged high dose of BACTRIM.
**Interactions with other drugs**

An increased incidence of thrombocytopenia with purpura has been observed in elderly patients concurrently receiving certain diuretics, primarily thiazides.

Increased digoxin blood levels can occur with concomitant BACTRIM therapy, especially in elderly patients. Serum digoxin levels should be monitored.

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

BACTRIM 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 BACTRIM is advisable.

BACTRIM 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.

Concurrent use of rifampicin and BACTRIM results in a shortening of the plasma half-life of trimethoprim after a period of about one week.

A reversible deterioration of the renal function, manifested by increased serum creatinine, has been observed in patients with renal transplants receiving concomitantly cyclosporin. This combined effect is presumably due to the trimethoprim component.

Sulfonamides, including sulfamethoxazole, can compete with protein binding and also with the renal transport of methotrexate, thus increasing the free methotrexate fraction and the systemic exposure to methotrexate, or increasing the antibacterial activity of sulfamethoxazole. Cases of pancytopenia have been reported in patients taking trimethoprim-sulfamethoxazole in combination with methotrexate. Trimethoprim has a low affinity for human dihydrofolate reductase but may increase the toxicity of methotrexate and may lead to the possibility of haematological adverse drug interactions with methotrexate, especially in the presence of other risk factors such as old age, hypoalbuminemia, impaired renal function and decreased bone marrow reserve. Such adverse drug reactions may occur especially with methotrexate given in a high dose regimen. Calcium folinate may be used to treat those patients to counteract the effect on haematopoiesis.

Sulfonylurea oral hypoglycaemics and methotrexate may increase the antibacterial activity of sulfamethoxazole.

PABA or its derivatives antagonise sulfamethoxazole. Increased sulfamethoxazole blood levels may occur in patients who are also receiving urinary acidifiers, oral anticoagulants, phenylbutazone, oxyphenbutazone, indomethacin, sulfinpyrazone or salicylates.

Cross sensitivities may exist with BACTRIM and some antithyroid agents, diuretics (acetazolamide and the thiazides) and oral hypoglycaemic drugs.
It has been shown in-vitro that polymyxin combined with BACTRIM produces an enhanced antibacterial effect.

Elevated plasma levels of dofetilide have been reported following co-administration of trimethoprim and dofetilide. Increased plasma concentrations of dofetilide may cause serious ventricular arrhythmias associated with QT interval prolongation, including torsades de pointes. The concurrent administration of dofetilide and trimethoprim is contraindicated.

**Drug/Laboratory Test Interactions**

Two laboratory procedures, namely the Lactobacillus casei serum folate assay and the L. leishmanii serum vitamin B₁₂ assay are affected by BACTRIM.

BACTRIM, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

**ADVERSE REACTIONS**

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash (including maculopapular), pruritus and urticaria).

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, aplastic anaemia and other blood dyscrasias (see Warnings section).

**Haematologic:**
Agranulocytosis, aplastic anaemia, thrombocytopenia, leukopenia, neutropenia, haemolytic anaemia, autoimmune anaemia, megaloblastic anaemia, hypoprothrombinaemia, methaemoglobinemia, eosinophilia, purpura, bone marrow depression, granulocytopenia and pancytopenia. Haematological changes have been observed particularly in the elderly. The great majority of these changes were mild, asymptomatic, and proved reversible on withdrawal of the drug which was, in some instances, necessary before therapy could be completed.

High doses of trimethoprim as used in patients with Pneumocystis carinii pneumonia induces progressive but reversible increase of serum potassium concentration in a substantial number of patients. Even treatment with recommended doses may cause hyperkalaemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalaemia are given concomitantly.

Close monitoring of serum potassium is warranted in these patients. Cases of hyponatraemia have also been reported.
Allergic Reactions:
Skin and systemic reactions may occur. Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported.

The following have been reported rarely; eosinophilic or allergic alveolitis, anaphylaxis, allergic myocarditis, exfoliative dermatitis, angioedema, erythema multiforme, exfoliative dermatitis, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalised allergic reactions, photosensitivity, conjunctival and scleral injection. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.

Gastrointestinal:
Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, isolated cases of vanishing bile duct syndrome, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhoea, anorexia, moniliasis. Jaundice has occurred rarely and has usually been mild and transient, frequently occurring in patients with a past history of infectious hepatitis.

Genitourinary:
Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

Neurologic:
Aseptic meningitis, convulsions, neuropathy (including peripheral neuritis and paraesthesia), ataxia, vertigo, tinnitus, headache and uveitis.

Psychiatric:
Hallucinations, depression, apathy, nervousness.

Endocrine:
The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cases of hypoglycemia in non-diabetic patients treated with BACTRIM are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of BACTRIM are particularly at risk.

Musculoskeletal:
Arthralgia, myalgia and isolated cases of rhabdomyolysis.

Respiratory:
Pulmonary infiltrates.

Miscellaneous:
Weakness, fatigue, insomnia and fungal infections, such as candidiasis.
DOSAGE AND ADMINISTRATION

In acute infections BACTRIM (in any form) should be given for at least five days or until the patient has been symptom-free for two days.

Adults and children over 12 years of age: Standard dosage.
1 BACTRIM DS (double strength) tablet morning and evening after meals.

Minimum dosage: ½ a BACTRIM DS (double strength) tablet twice daily (see below).

Maximum dosage (for particularly severe infections): 1½ BACTRIM DS (double strength) tablets twice daily.

The recommended dose for patients with documented Pneumocystis carinii pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole/24 hours given in equally divided doses every six hours for 14 days.

Children under 12 years:

Under 2 years 2.5 mL of syrup twice daily
2-5 years 2.5-5.0 mL of syrup twice daily
6-12 years 5.0-10.0 mL of syrup twice daily

Adjustment of this dose can be made in the case of children whose body weight is particularly high or low.

Patients with reduced renal function:
The following dosage regimens are based on published information for the administration of BACTRIM DS tablets to patients with reduced kidney function.

<table>
<thead>
<tr>
<th>Criteria of kidney function (non-protein nitrogen is unsuitable)</th>
<th>Recommended dosage regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance mL/min</td>
<td>Serum¹ Creatinine µmol/L</td>
</tr>
<tr>
<td>Above 25</td>
<td>Men &lt; 265 Women &lt; 180</td>
</tr>
<tr>
<td>15 - 25</td>
<td>Men 265 - 620 Women 180 - 400</td>
</tr>
<tr>
<td>Below 15</td>
<td>Men &gt; 620 Women &gt; 400</td>
</tr>
</tbody>
</table>

¹ The serum creatinine can be used as the basis of dosing only in cases of chronic renal impairment, but not of acute or subacute kidney failure.
The concentration of total SMX should be measured in plasma samples obtained 12 hours after every third day of treatment. Treatment will be interrupted if at any time the determined plasma level of total SMX exceeds 150µg/mL. As soon as the value of total SMX drops again below 120µg/mL (e.g. in patients undergoing haemodialysis) treatment can be continued as recommended.

**OVERDOSAGE**

**Acute**

*Symptoms:* The amount of a single dose of BACTRIM that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, haematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

*Treatment:* Treatment of overdose should consist of general supportive measures. General principals of treatment include the prevention of further absorption, forcing of oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Alkalisation of the urine may aid the elimination of the sulfamethoxazole component of BACTRIM but may decrease the elimination of the trimethoprim component. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. On cessation of therapy calcium folinate, 3 mg to 6 mg intramuscularly for five to seven days may be given to counteract the effects of trimethoprim on haematopoiesis.

Peritoneal dialysis is not effective and haemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

**Chronic**

Use of BACTRIM at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anaemia. Other blood dyscrasias may occur due to folinic acid deficiency. If signs of bone marrow depression occur, the patient should be given leucovorin 5 to 15 mg daily until normal haematopoiesis is restored.

Contact the Poisons Information Centre for advice on management of overdosage.
PRESENTATION AND STORAGE CONDITIONS

BACTRIM DS tablets: sulfamethoxazole 800 mg, trimethoprim 160 mg in an oblong, biconvex, white to almost white tablet, scored on one side, marked ROCHE 800 + 160 on the other. BACTRIM DS tablets are available in a pack of 10.

BACTRIM oral suspension: each 5 mL contains sulfamethoxazole 200 mg, trimethoprim 40 mg and includes sorbitol 63% w/v. BACTRIM oral suspension is available in a bottle containing 100 mL suspension.

Storage: Store below 30°C.
Shelf life: Oral suspension: 5 years, Tablets: 5 years.

SPONSOR

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DATE OF MOST RECENT AMENDMENT

4 July 2011