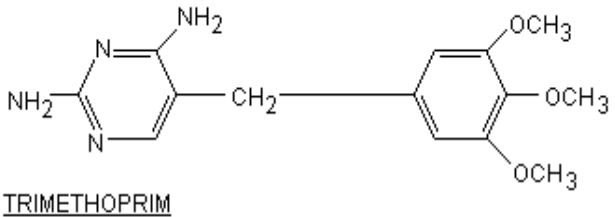
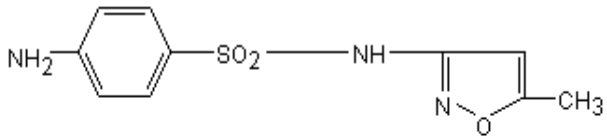
NAME OF THE MEDICINE

BACTRIM®

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



TRIMETHOPRIM



SULFAMETHOXAZOLE

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^{O}C. Trimethoprim is a white to cream-coloured powder that has an aqueous solubility of 300 mg/L at 20^{O}C.

Each tablet contains the inactive ingredients povidone, docusate sodium, sodium starch glycollate 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 jirovecii (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)

BACTERIA	TMP ALONE	SMX ALONE	TMP/SMX (1:20)	
			TMP	SMX
Escherichia coli	0.05 - 1.5	1.0 - 245	0.05 - 0.5	0.95 - 9.5
Proteus species (indole positive)	0.5 - 5.0	7.35 - 300	0.05 - 1.5	0.95 - 28.5
Proteus mirabilis	0.5 - 1.5	7.35 - 30	0.05 - 0.15	0.95 - 2.85
Klebsiella-enterobacter	0.15 - 5.0	2.45 - 245	0.05 - 1.5	0.95 - 28.5

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. Absorption is complete as reflected by the absolute oral bioavailability reaching 100% for both trimethoprim and sulfamethoxazole. The mean serum half-lives of trimethoprim and sulfamethoxazole are 10 hours and 8 - 10 hours, respectively.

Distribution: The volume of distribution is approximately 1.6 L/kg for trimethoprim and approximately 0.26 L/kg for sulfamethoxazole, while the plasma protein binding reaches 37%

for trimethoprim and 53% for sulfamethoxazole. 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 (see Use in Pregnancy).

Metabolism: Around 30% of a trimethoprim dose is metabolised. The cytochrome P450 isoenzymes involved in the oxidative metabolism of trimethoprim have not been identified. The principal trimethoprim metabolites are 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives; some metabolites are active.

Around 80% of a sulfamethoxazole dose is metabolised in the liver, predominantly to the N_4 acetyl-derivative (≈40% of the dose) and to a lesser extent by glucuronide conjugation. Sulfamethoxazole also undergoes oxidative metabolism. The first step of the oxidative pathway, which leads to the formation of the hydroxylamine derivative, is catalysed by CYP2C9. 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. Around two thirds of the trimethoprim dose and one quarter of the sulfamethoxazole dose are excreted unchanged into the urine. The total plasma clearance of trimethoprim equals 1.9 mL/min/kg. The total plasma clearance of sulfamethoxazole equals 0.32 mL/min/kg. A small part of the substances is eliminated via the faeces.

Pharmacokinetics in Special Populations

Children and adolescents: In children aged 1 to 9 years the total plasma clearance of trimethoprim is around three-fold larger than in adults. As a consequence the half-life of trimethoprim in children is less than half of that observed in adults. Similar observations have been made for sulfamethoxazole (see DOSAGE AND ADMINISTRATION).

Hepatic impairment: The pharmacokinetics of trimethoprim and sulfamethoxazole in patients with moderate or severe hepatic impairment are not significantly different from those observed in healthy subjects. (See PRECAUTIONS and ADVERSE REACTIONS for advice and experience of use in patients with impaired liver function.)

Patients with cystic fibrosis: The renal clearance of trimethoprim and the metabolic clearance of sulfamethoxazole are increased in patients with cystic fibrosis. Consequently, the total plasma clearance is increased and the elimination half-life is decreased for both drugs.

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, characterised by creatinine clearance <15 ml/min (see *Dosage and Administration*).

BACTRIM should not be given to patients with a history of hypersensitivity to the active ingredients or the excipients, or other sulfonamides.

BACTRIM must not be given to premature babies, nor during the first six 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 INTERACTIONS WITH OTHER MEDICINES).

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 jirovecii 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 jirovecii 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.

Serious Adverse Reactions

Fatalities, although rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias.

Hypersensitivity and allergic reactions

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.

Pulmonary infiltrates reported in the context of eosinophilic or allergic alveolitis may manifest through symptoms such as cough or shortness of breath. Should such symptoms appear or unexpectedly worsen, the patient should be re-evaluated and discontinuation of BACTRIM therapy considered.

Renal Impairment

In patients with renal impairment, a reduced or less frequent dosage is recommended in order to avoid accumulation of trimethoprim in the blood. Non-ionic diffusion is the main factor in the renal handling of trimethoprim, and as renal failure advances, trimethoprim excretion decreases. See the special dosage table for use in renal impairment. Patients with severe renal impairment who are receiving BACTRIM should be closely monitored for symptoms and signs of toxicity such as nausea, vomiting and hyperkalemia. BACTRIM should be given with caution to patients with impaired renal function and to those with underlying disorders such as: possible folate deficiency; hypoglycaemia; electrolyte abnormalities (hyperkalemia).

Electrolyte Abnormalities

Close monitoring of serum potassium and renal function is warranted in patients receiving high-dose BACTRIM, as used in patients with Pneumocystis jirovecii pneumonia, or in patients receiving standard-dose BACTRIM with underlying disorders of potassium metabolism or renal insufficiency, or who are receiving drugs which induce hyperkalaemia (see *Interactions with Other Medicines*). Severe and symptomatic hyponatremia can occur in patients receiving BACTRIM, particularly for the treatment of P. jiroveci pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications.

Sulfonamides, including BACTRIM, may induce diuresis, particularly in patients with oedema of cardiac origin.

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.

Long-term treatment
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.

Patients on Peritoneal Dialysis

Peritoneal dialysis results in minimal clearance of administered trimethopim and sulfamethoxazole. Use of trimethoprim and sulfamethoxazole in patients receiving peritoneal dialysis is not recommended.

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 (see Pharmacokinetics – *Distribution*). 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. BACTRIM should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. If BACTRIM is used during pregnancy, or if the patient becomes pregnant while taking this drug, folic acid supplementation may be required. The patient should be appropriately counselled.

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 (see Pharmacokinetics - *Distribution*). 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 MEDICINES

Pharmacokinetic interactions
Trimethoprim is an inhibitor of the Organic Cation Transporter 2 (OCT2), and a weak inhibitor of CYP2C8. Sulfamethoxazole is a weak inhibitor of CYP2C9.

Systemic exposure to drugs transported by OCT2 may increase when co-administered with BACTRIM. Examples include dofetilide, amantadine,memantine and lamivudine.

Pharmacokinetic interactions	
Drug class *drug name*	**Clinical comment**
Antiarrhythmics *dofetilide* *amiodarone*	BACTRIM must not be given in combination with dofetilide (see CONTRAINDICATIONS). 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. Amiodarone has a narrow therapeutic index and is metabolised primarily by CYP2C8. Therefore concomitant administration with BACTRIM is not recommended. Systemic exposure may increase when co-administered with BACTRIM.
Antivirals *amantadine/memantine*	Patients receiving amantadine or memantine may be at increased risk of neurological adverse events such as delirium and myoclonus.
Antialzheimer's *memantine*	Co-administration may increase the risk of neurological adverse events such as delirium and myoclonus.
Antineoplastic agents *paclitaxel*	Paclitaxel has a narrow therapeutic index and is metabolised primarily by CYP2C8. Therefore concomitant administration with BACTRIM is not recommended. Systemic exposure may increase when co-administered with BACTRIM.
Antibiotics *dapsone* *rifampicin*	Metabolised primarily by CYP2C8. Systemic exposure may increase when co-administered with BACTRIM. Both dapsone and BACTRIM can cause methaemoglobinemia, and there is therefore potential for both pharmacokinetic and pharmacodynamic interactions. Patients receiving dapsone and BACTRIM concurrently should be monitored for methaemoglobinemia. Alternative therapies should be considered if possible. Concurrent use of rifampicin and BACTRIM results in a shortening of the plasma half-life of trimethoprim after a period of about one week.
Oral hypoglycaemic agents *repaglinide, rosiglitazone or pioglitazone* *Sulfonylurea derivatives*	BACTRIM potentiates the effect of oral hypoglycaemic agents that are metabolized by CYP2C8 (e.g. pioglitazone, repaglinide, and rosiglitazone or CYP2C9 *(*e.g. glipizide) or eliminated renally via OCT2. Systemic exposure may increase when co-administered with BACTRIM. Patients should be monitored regularly for hypoglycaemia.

(glibenclamide,gliclazide, glipizide,chlorpropamide, and tolbutamide)	
Anticoagulants *warfarin, acenocoumarol, phenprocoumon*	Systemic exposure to drugs metabolised primarily by CYP2C9 may increase when co-administered with BACTRIM. BACTRIM has been shown to potentiate the anticoagulant activity of warfarin via stereo selective inhibition of its metabolism. Coagulation should be monitored in patients receiving coumarins. Sulfamethoxazole may displace warfarin from plasma albumin protein binding sites in vitro.
Antiepileptics *phenytoin*	Systemic exposure to drugs metabolised primarily by CYP2C9 may increase when co-administered with BACTRIM. 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.
Cardiovascular agents *digoxin*	Increased digoxin blood levels can occur with concomitant BACTRIM therapy, especially in elderly patients. Serum digoxin levels should be monitored.
Other agents *PABA*	PABA or its derivatives antagonise sulfamethoxazole. Increased sulfamethoxazole blood levels may occur in patients who are also receiving urinary acidifiers, oral anticoagulants, phenylbutazone, oxyphenbutazone, sulfinpyrazone or salicylates.
Pharmacodynamic interactions and interactions of undefined mechanism	
Antipsychotics *clozapine*	Co-administration with clozapine, a drug known to have substantial potential for causing agranulocytosis, should be avoided.
Diuretics *primarily thiazides*	An increased incidence of thrombocytopenia has been observed in elderly patients concurrently receiving certain diuretics, primarily thiazides. Platelets should be monitored regularly in patients receiving diuretics.
Antimalarials *pyrimethamine*	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.
Antimetabolites *methotrexate*	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, especially in the presence of risk factors such as old age, hypoalbuminemia, impaired renal function and decreased bone marrow reserve, and in patients receiving high doses of methotrexate. At risk patients should be treated with calcium folinate to counteract the effect of methotrexate on haematopoesis. Methotrexate may increase the antibacterial activity of sulfamethoxazole.
Antibacterials *sulfonamides*	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

polymyxin	exposure to methotrexate, or increasing the antibacterial activity of sulfamethoxazole. It has been shown in-vitro that polymyxin combined with BACTRIM produces an enhanced antibacterial effect.
Antithyroid agents, diuretics, oral hypoglycaemic drugs	Cross sensitivities may exist with BACTRIM and some antithyroid agents, diuretics (acetazolamide and the thiazides) and oral hypoglycaemic drugs.
Antidepressants *tricyclic antidepressants*	The efficacy of tricyclic antidepressants can decrease when co-administered with BACTRIM.
Antivirals *Zidovudine*	Zidovudine (anti-HIV agent), and less commonly BACTRIM, is known to induce haematological abnormalities. Hence, there is potential for an additive pharmacodynamic effect. Patients receiving BACTRIM and zidovudine should be monitored for haematological toxicity, and dosage adjustment may be needed.
Immunosuppressants *azathioprine, mercaptopurine* *cyclosporin*	Incidence rate and severity of myelotoxic and nephrotic adverse reactions may be increased when BACTRIM is administered concomitantly with other drugs known to be myelosuppressive or associated with renal impairment such as nucleoside analogues, tacrolimus, azathioprine or mercaptupurine. Co-administration with azathioprine or mercaptopurine may increase the risk of haematological adverse events, particularly in patients who receive BACTRIM for an extended period, or who are at an increased risk of folic acid deficiency. Therefore alternatives to BACTRIM should be considered for patients receiving azathioprine or mercaptopurine. If BACTRIM is used in combination with such drugs, patients should be monitored for haematological and/or renal toxicity. A reversible deterioration of renal function has been observed in patients with renal transplants receiving concomitant cyclosporin.
Angiotensin converting-enzyme inhibitors and angiotensin receptor blockers	Due to the potassium-sparing effects of BACTRIM, caution should be used when BACTIRM is co-administered with other agents that increase serum potassium, such as angiotensin converting-enzyme inhibitors and angiotensin receptor blockers, potassium sparing diuretics and prednisolone (see PRECAUTIONS)..

Drug/Laboratory Test Interactions

Two laboratory procedures, namely the Lactobacillus casei serum folate assay and the L. leishmanii serum vitamin B_{12} 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, methaemoglobinaemia, 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 jirovecii 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. Cases of hyponatraemia have also been reported.

Allergic Reactions:
Skin and systemic reactions may occur. Stevens-Johnson syndrome, fixed drug reaction, morbilliform rash, erythema 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, , drug fever, chills, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schoenlein purpura, serum sickness-like syndrome, generalised allergic reactions, photosensitivity, conjunctival and scleral injection. In addition, polyarteritis 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.

General disorders and administration site conditions
Venous pain and phlebitis

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

Neurologic:
Aseptic meningitis, meningitis-like symptoms, convulsions, neuropathy (including peripheral neuritis and paraesthesia), ataxia, vertigo, tinnitus, headache and uveitis, vasculitis cerebral

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, pulmonary vasculitis.

Vascular disorders
Vasculitis, necrotizing vasculitis, granulomatosis with polyangiitis.

Miscellaneous:
Weakness, fatigue, insomnia and fungal infections, such as candidiasis, retinal vasculitis

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 jirovecii 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 (see *Contraindications*):

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.

Criteria of kidney function (non-protein nitrogen is unsuitable)		Recommended dosage regimens
Creatinine clearance mL/min	Serum[1] Creatinine µmol/L	One standard dose for adults = 1 BACTRIM DS tablet containing a total of 160 mg TMP + 800 mg SMX
Above 25	Men < 265 Women < 180	Dosage as for patients with normal kidney functions ie 1 standard dose every 12 hours up to 14 days; later on 1/2 standard dose every 12 hours; no necessity for control analyses of drugs in plasma.
15 - 25	Men 265 - 620 Women 180 - 400	1 standard dose every 12 hours for 3 days; later on 1 standard dose every 24 hours as long as allowed by control analyses.[2]
Below 15	Men > 620 Women > 400	BACTRIM should not be used (See *Contraindications).*

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.

2 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. Alkalinisation 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

Roche Products Pty Limited
ABN 70 000 132 865
4-10 Inman Road
Dee Why NSW 2099

Customer enquiries: 1800 233 950

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

18 August 2005

DATE OF MOST RECENT AMENDMENT

27 September 2016