NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Bactrim® 400/80 (sulfamethoxazole 400 mg/5 ml and trimethoprim 80 mg/5 ml concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bactrim® 400/80: One ampoule of 5 mL contains 400 mg sulfamethoxazole and 80 mg trimethoprim (=480 mg sulfamethoxazole/trimethoprim), which is 80 mg sulfamethoxazole per mL and 16 mg trimethoprim per mL.

Excipients with known effect
Bactrim® 400/80 contains 2050 mg propylene glycol, 500 mg ethanol absolute and 58.55 mg sodium hydroxide.
For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion. The concentrate is clear and colourless to slightly yellowish.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral administration of Bactrim® 400/80 is indicated where oral dosage is not desirable or practical, e.g. pre- and post-operative infections associated with surgery, trauma or gynaecology; septicaemia and other infections due to sensitive organisms such as typhoid and paratyphoid.

4.2 Dose and method of administration

Dosage for adults and children over 12 years
Standard dose: 10 mL diluted and infused twice daily.
For severe infections: 15 mL diluted and infused twice daily.

Dosage for children to 12 years
The recommended dosage is approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg bodyweight per day, divided into two equal doses, morning and evening. As a guide, the following doses of Bactrim® may be used:
2 months to 5 months: 1.25 mL diluted and infused twice daily.
6 months to 5 years: 2.5 mL diluted and infused twice daily.
6 years to 12 years: 5 mL diluted and infused twice daily.

The recommended dosage for patients with documented *Pneumocystis jirovecii pneumonitis* is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days.

Dosage in reduced renal function
In patients with impaired renal function, the dosage and/or frequency of administration of sulfamethoxazole/trimethoprim needs to be modified.

The following dosage regimens have been published for the administration of sulfamethoxazole/ trimethoprim tablets to patients with reduced kidney function. In view of the close similarity of plasma levels of trimethoprim and sulfamethoxazole when sulfamethoxazole/trimethoprim is given orally and

intravenously, there is no reason to suppose that these regimens cannot be followed with Bactrim®.

Criteria of kidney function

(non-protein nitrogen is unsuitable)		**Recommended Dosage Regimens**
Creatinine Clearance mL/min	**Serum Creatinine micromol/L (a)**	**One Standard Dose for Adults 160 mg TMP + 800 mg SMX**
Above 25	Men < 260 Women < 170	Dosage as for patients with normal kidney function, i.e. 1 standard dose every 12 hours for up to 14 days; thereafter half standard dose every 12 hours; no necessity of control analyses of drugs in plasma.
25 to 15	Men 260 to 600 Women 170 to 400	One standard dose every 12 hours for 3 days; thereafter one standard dose every 24 hours for as long as allowed by control analyses (b).
Below 15	Men > 600 Women > 400	Until further experience is gained, the combination should be given only if patients can undergo haemodialysis when necessary (c); under this condition one standard dose may be administered every 24 hours as long as allowed by control analyses (b).

TMP = Trimethoprim
SMX = Sulfamethoxazole

(a) Serum creatinine levels can be used as the basis of dosing only in cases of stable chronic renal impairment, but not acute or subacute kidney failure.

(b) The concentration of total SMX should be measured in plasma samples obtained 12 hours after every third day of treatment. Treatment must be interrupted if at any time the determined plasma level of total SMX exceeds 150 micrograms/mL. As soon as the value of total SMX drops again below 120 micrograms/mL (e.g. in patients undergoing haemodialysis), treatment can be continued as recommended.

(c) Both trimethoprim and sulfamethoxazole are readily dialysable, leading to a significantly shortened half-life for each drug during dialysis. It is suggested that patients undergoing haemodialysis receive a dose just before and at the end of the procedure.

Duration of treatment

Bactrim® 400/80 should be used ONLY during such periods as the patient is unable to accept oral therapy. In general, administration is unlikely to be required for more than a few days, and it is recommended that it be restricted to no more than three successive days.

For further information, please refer to section 6.6

4.3 Contraindications

Sulfamethoxazole/trimethoprim is contraindicated in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides and in patients showing marked hepatic damage, blood dyscrasias or with severe renal insufficiency and oliguria, where repeated measurements

of the plasma concentrations cannot be performed. It should not be given to patients with known hypersensitivity to the active substance (trimethoprim, sulfonamides or cotrimoxazole) or to one of the excipients listed in section 6.1 List of excipients, or with documented megaloblastic anaemia secondary to folate deficiency.

Bactrim® must not be given in combination with dofetilide (see section 4.5 Interactions with other medicines and other forms of interactions).

Premature babies and newborn babies during the first eight weeks of life should not be given sulfamethoxazole/trimethoprim, as sulfamethoxazole may interfere with the serum albumin- binding of bilirubin to produce kernicterus.

Use of Bactrim® for treatment of streptococcal pharyngitis is contraindicated (See section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Sulfamethoxazole/trimethoprim should only be used for the prevention or treatment of infections caused by micro-organisms that are proven to be sensitive to sulfamethoxazole/trimethoprim or for which there is strong evidence that they are sensitive. In the absence of such data, local epidemiological data and susceptibility patterns may help in the choice of an appropriate antibiotic. In order to exclude resistance, especially if infections are (probably) caused by partially sensitive organisms, the isolate should be tested for susceptibility to sulfamethoxazole/trimethoprim.

Hypersensitivity and allergic reactions
Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment. 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 sulfamethoxazole/trimethoprim therapy considered.

Life-threatening adverse reactions
FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS (TEN), DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS), FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANAEMIA, OTHER BLOOD DYSCRASIAS, ACUTE AND DELAYED LUNG INJURY, HYPERSENSITIVITY OF THE RESPIRATORY TRACT, AND CIRCULATORY SHOCK.

Severe cutaneous adverse reactions
Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia with systemic symptoms (DRESS) 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 SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions), AGEP or DRESS (e.g. fever, eosinophilia) are present, Bactrim® 400/80 treatment should be discontinued immediately (see Section 4.8 Adverse effects (undesirable effects)) and an alternative treatment should be considered.

The best results in managing SJS, TEN or DRESS come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS, TEN or DRESS with the use of Bactrim® 400/80, Bactrim® 400/80 must not be re-started in this patient at any time.

At the start of treatment, the occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of AGEP (see section 4.8 Adverse effects (undesirable effects); it requires cessation of treatment and contraindicates any new administration of Bactrim alone or in combination with other drugs.

Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH have been reported very rarely in patients treated with sulfamethoxazole/trimethoprim. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, sulfamethoxazole/trimethoprim treatment should be discontinued.

Respiratory tract
Cough, shortness of breath, and pulmonary infiltrates potentially representing hypersensitivity reactions of the respiratory tract have been reported in association with trimethoprim-sulfamethoxazole treatment.

Other severe pulmonary adverse reactions occurring within days to week of trimethoprim-sulfamethoxazole initiation and resulting in prolonged respiratory failure requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), lung transplantation or death have also been reported in patients and otherwise healthy individuals treated with trimethoprim-sulfamethoxazole products.

Circulatory shock
Circulatory shock with fever, severe hypotension, and confusion requiring intravenous fluid resuscitation and vasopressors has occurred within minutes to hours of re-challenge with trimethoprim-sulfamethoxazole in patients with history of recent (days to weeks) exposure to sulfamethoxazole-trimethoprim.

Acute respiratory failure including acute eosinophilic pneumonia has been reported in healthy adolescents with sulfamethoxazole/trimethoprim treatment.

Sulfamethoxazole/trimethoprim should be discontinued immediately as soon as there are symptoms of a skin rash (e.g. exanthema) or other serious side effects. Clinical signs such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions.

Thrombocytopenia
Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole/trimethoprim.

Streptococcal infections and rheumatic fever
The sulfonamides should not be used for the treatment of group A beta-haemolytic streptococcal infections (see section 4.3 Contraindications). In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

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 sulfamethoxazole/trimethoprim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, neutropenia, thrombocytopenia, raised liver enzymes and leucopenia necessitating cessation of therapy, with sulfamethoxazole/trimethoprim 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 sulfamethoxazole/trimethoprim in non-AIDS patients. Such adverse effects have occurred in up to 80% of AIDS patients receiving the drug, usually during the second week of therapy. The exact mechanism(s) of this increased risk of sulfamethoxazole/trimethoprim toxicity has not been determined, but may be immunologically based. These adverse effects usually recur following rechallenge with the drug, although cautious desensitisation has been performed successfully in some patients in whom continued sulfamethoxazole/trimethoprim therapy was considered necessary. Some evidence indicates that sulfamethoxazole/trimethoprim may be better tolerated in HIV infected children than adults. Adverse effects are usually less severe in patients receiving the drug for prophylaxis of Pneumocystis jirovecii pneumonia compared with those receiving sulfamethoxazole/trimethoprim for treatment of the disease.

Adjunctive treatment with leucovorin for Pneumocystis jirovecii pneumonia
Treatment failure and excess mortality were observed when sulfamethoxazole/trimethoprim was used concomitantly with leucovorin for the treatment of HIV positive patients with Pneumocystis jirovecii pneumonia in a randomized placebo-controlled trial. Co-administration of sulfamethoxazole/trimethoprim and leucovorin during treatment of Pneumocystis jirovecii pneumonia should be avoided.

Use in glucose-6-phosphate dehydrogenase deficiency
In individuals with glucose-6-phosphate dehydrogenase deficiency, haemolysis may occur. This is frequently dose-related.

Clostridioides difficile associated diarrhoea (CDAD)
Clostridioides difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including sulfamethoxazole and trimethoprim, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy).

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against C. difficile should be considered. Fluids, electrolytes and protein replacement, antibiotic treatment of C. difficile, and surgical evaluation should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Hypoglycaemia
Cases of hypoglycaemia in non-diabetic patients treated with sulfamethoxazole/trimethoprim have been reported, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of sulfamethoxazole/trimethoprim are particularly at risk.

Electrolyte abnormalities
Close monitoring of serum potassium and renal function is warranted in patients receiving high-dose sulfamethoxazole/trimethoprim, as used in patients with Pneumocystis jirovecii pneumonia, or in patients receiving standard-dose sulfamethoxazole/trimethoprim with underlying disorders of potassium metabolism or renal insufficiency, or who are receiving drugs which induce hyperkalaemia (see Section 4.5 Interactions with other medicines and other forms of interactions). Severe and symptomatic hyponatremia can occur in patients receiving sulfamethoxazole/trimethoprim, particularly for the treatment of P. jirovecii pneumonia. Evaluation for hyponatremia and appropriate correction is necessary

in symptomatic patients to prevent life-threatening complications.

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

Laboratory Tests
Complete blood counts should be done frequently in patients receiving sulfamethoxazole/trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole/trimethoprim should be discontinued.

Folate deficiency
Because of the possible interference with folate metabolism, regular blood counts are advisable in patients on long term therapy, in those who are pre-disposed to folate deficiency (i.e. the elderly, chronic alcoholics and those with rheumatoid arthritis), in malabsorption syndromes, malnutrition states or during the treatment of epilepsy with anticonvulsant drugs such as phenytoin, primidone and barbiturates. Folic acid may be administered during sulfamethoxazole/trimethoprim therapy and will not interfere with the drugs’ antibacterial effect. Megaloblastic anaemia and occasionally neutropenia and thrombocytopenia may be reversed by administration of calcium leucovorin (folinic acid). If signs of bone marrow suppression occur in patients receiving sulfamethoxazole/trimethoprim, Bactrim® administration should be ceased; leucovorin may be administered.

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

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

Use in renal impairment
In 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. For such patients, serum assays are necessary.
Patients with severe renal impairment who are receiving sulfamethoxazole/trimethoprim should be closely monitored for symptoms and signs of toxicity such as nausea, vomiting and hyperkalaemia. Sulfamethoxazole/trimethoprim 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 (hyperkalaemia).

Urinalysis with careful microscopic examination and renal function tests should be performed frequently, particularly for those patients with impaired renal function. Adequate fluid intake and urinary output must be maintained in order to prevent crystalluria and stone formation. In patients with renal impairment, a reduced or less frequent dosage is recommended to avoid accumulation of trimethoprim in the blood.

Use in the elderly
The use of sulfamethoxazole/trimethoprim 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, possible folate deficiency, or concomitant use of other drugs. Severe skin reactions, or generalised bone marrow suppression (see Section 4.8 Adverse effects (undesirable effects)) or a specific decrease in platelets (with or without purpura), and hyperkalaemia 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. Increased digoxin blood levels can occur with concomitant sulfamethoxazole/trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored. Haematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folinic acid therapy. Appropriate dosage adjustments

should be made for patients with impaired kidney function and duration of use should be as short as possible to minimise risks of undesired reactions (see Section 4.2 Dose and method of administration). The trimethoprim component of sulfamethoxazole/trimethoprim may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or when given concomitantly with drugs known to induce hyperkalemia, such as angiotensin converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of sulfamethoxazole/trimethoprim treatment is recommended to help lower potassium serum levels.

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

Paediatric use
See Sections 4.2 Dose and method of administration and 4.3 Contraindications.

Effects on laboratory tests
Two laboratory procedures, namely the Lactobacillus casei serum folate assay and the L. leishmanii serum vitamin B12 assay are affected by sulfamethoxazole/trimethoprim.

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

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

Other
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.

The possibility of superinfection with a non-sensitive organism should be borne in mind.

4.5 Interaction with other medicines and other forms of interaction

Methotrexate: Sulfonamides such as sulfamethoxazole may displace methotrexate from protein binding sites and can compete with the renal transport of methotrexate, thereby increasing free methotrexate levels. Cases of pancytopenia have been reported in patients taking the combination of sulfamethoxazole/trimethoprim and methotrexate.

Para-aminobenzoic acid (PABA) or its derivatives: may antagonise the antibacterial effects of sulfamethoxazole.

Warfarin/anticoagulants: Anticoagulant activity may be increased by concurrent treatment with sulfamethoxazole/trimethoprim. It has been reported that sulfamethoxazole/trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin (a CYP2C9 substrate). This interaction should be kept in mind when sulfamethoxazole/trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Phenytoin: Increased effects and side effects of phenytoin (folate deficiencies) could occur when sulfamethoxazole/trimethoprim is given concurrently. Sulfamethoxazole/trimethoprim may inhibit the hepatic metabolism of phenytoin (a CYP2C9 substrate). Oral sulfamethoxazole/trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonylureas: Concomitant use may result in potentiation of hypoglycaemia in occasional patients.

Diuretics: An increased incidence of thrombocytopenia is reported when this combination is used in the elderly.

Ciclosporin: Deterioration in renal function in patients with renal transplants. There have been reports of marked but reversible nephrotoxicity with co-administration of sulfamethoxazole/trimethoprim and ciclosporin in renal transplant recipients.

Amiodarone: Sulfamethoxazole/trimethoprim may increase the plasma concentration of amiodarone. Therefore, concomitant use of Bactrim® with amiodaraone is not recommended.

Paclitaxel: Sulfamethoxazole/trimethoprim may increase the plasma concentration of paclitaxel. Therefore, caution is advised for concomitant administration of paclitaxel and Bactrim®.

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

Dapsone: Both dapsone and sulfamethoxazole/trimethoprim may cause methemoglobinemia and the effect of dapsone may be further strengthened by the pharmacokinetic and pharmacodynamic interaction with sulfamethoxazole/trimethoprim. If possible, alternative therapies should be considered. If sulfamethoxazole/trimethoprim and dapsone are used concomitantly, caution should be exercised and careful monitoring on methemoglobinemia is recommended, especially for high risk patients with significant comorbidities or in patients receiving a high dose of one of both agents.

Digoxin: Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients. Serum digoxin levels should be monitored.

Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics, prednisolone: Due to the potassium sparing effects of sulfamethoxazole/trimethoprim, caution should be used when other agents that increase serum potassium, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics and prednisolone, are co-administered (see Section 4.4 Special warnings and precautions for use). In the literature, two cases of hyperkalaemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and an angiotensin converting enzyme inhibitor.

Tricyclic antidepressants: The efficacy of tricyclic antidepressants can decrease when co- administered with sulfamethoxazole/trimethoprim.

Increased sulfamethoxazole blood levels: may occur in patients who are also receiving urinary acidifiers, oral anticoagulants, phenylbutazone, oxyphenbutazone and indomethacin.

Cross sensitisation: may exist between sulfamethoxazole/trimethoprim and some antithyroid agents, diuretics (acetazolamide and the thiazides) and oral hypoglycaemic drugs. Trimethoprim is an inhibitor of CYP2C8 as well as an OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when Sulfamethoxazole/trimethoprim is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2. Sulfamethoxazole/trimethoprim potentiates the effect of oral hypoglycaemics that are metabolised by CYP2C8 (e.g. pioglitazone, repaglinide, and rosiglitazone) or CYP2C9 (e.g. glipizide and glyburide) or eliminated renally via OCT2 (e.g. metformin). Additional monitoring of blood glucose may be warranted.

Dofetilide: Concurrent administration is contraindicated (see Section 4.3 Contraindications). Elevated plasma concentrations of dofetilide have been reported following concurrent administration of trimethoprim and dofetilide. Increased plasma concentrations of dofetilide may cause serious ventricular arrhythmias associated with QT interval prolongation, including torsade de pointes.

In the literature, some cases of toxic delirium and myoclonus have been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine, metformin, dofetilide, amantadine and lamivudine have also been reported.

Others: 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.

4.6 Fertility, pregnancy and lactation

Effects on fertility
No data available.

Use in pregnancy - Pregnancy Category C
Category C - Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

If sulfamethoxazole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the fetus.

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. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, Sulfamethoxazole/trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see section 4.4 Special warnings and precautions for use).

Trimethoprim and sulfamethoxazole, alone and in combination, have produced teratogenic effects (cleft palate) in some studies in rats receiving dosages exceeding the usual human dosage.

Human data:
While there are no large prospective, well-controlled studies in pregnant women and their babies, some retrospective epidemiologic studies suggest an association between first trimester exposure to sulfamethoxazole/trimethoprim with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular abnormalities, urinary tract defects, oral clefts, and club foot. These studies, however, were limited by the small number of exposed cases and the lack of adjustment for multiple statistical comparisons and confounders. These studies are further limited by recall, selection, and information biases, and by limited generalisability of their findings. Lastly, outcome measures varied between studies, limiting cross-study comparisons.

Alternatively, other epidemiologic studies did not detect statistically significant associations between sulfamethoxazole/trimethoprim exposure and specific malformations. A retrospective study reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester.
In a separate survey, no congenital abnormalities were found in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Use in lactation

Levels of sulfamethoxazole/trimethoprim in breast milk are approximately 2-5% of the recommended daily dose for infants over 2 months of age. Although the quantity of sulfamethoxazole/trimethoprim ingested by a breast-fed infant is small, caution should be exercised when sulfamethoxazole/trimethoprim is administered to a nursing woman, especially when breastfeeding jaundiced, ill, stressed, or premature infants because of the potential risk of bilirubin displacement and kernicterus, and it is recommended that the age of the infant be considered and the possible risks be balanced against the expected therapeutic effect.

An increased risk of hyperbilirubinemia should be considered in premature neonates and children with glucose-6-phosphate dehydrogenase deficiency.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

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

Fatalities, associated with the administration of sulfonamides although rare, have occurred due to severe reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias, hypersensitivity of the respiratory tract, acute and delayed lung injury, and circulatory shock (see section 4.4 Special warnings and precautions for use). Treatment with sulfamethoxazole/trimethoprim must be stopped immediately as soon as there are symptoms of skin rash (e.g. exanthema) or other serious side effects. Clinical signs such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions.

Adverse reactions have been reported in approximately 5 to 7% of patients treated in the published literature. In general, the adverse reactions correspond to those of a sulfonamide of moderately low toxicity.

Tabulated list of adverse reactions
The following convention has been used for the classification of adverse reactions in terms of frequency:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1,000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
Very rare < 1/10,000
Not known – cannot be estimated from the available data.

System Organ Class	Frequency	Side effects
Infections and infestations	Common	Overgrowth - fungal
	Very rare	Pseudomembranous colitis.
Blood and lymphatic system disorders	Very rare	Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia,

System Organ Class	Frequency	Side effects
		purpura, haemolysis in certain susceptible G-6-PD deficient patients.
Immune system disorders	Very rare	Serum sickness, anaphylactic reaction, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schönlein-purpura, periarteritis nodosa, systemic lupus erythematosus, haemophagocytic lymphohistiocytosis. Severe hypersensitivity reactions associated with *Pneumocystis jirovecii* pneumonia*, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.
Metabolism and nutrition disorders	Very common	Hyperkalaemia.
	Very rare	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis
Psychiatric disorders	Very rare	Depression, hallucination.
	Not Known	Psychotic disorder.
Nervous system disorders	Common	Headache
	Very rare	Meningitis aseptic*, seizure, neuropathy peripheral, ataxia, dizziness.
Ear and labyrinth disorders	Very rare	Vertigo, tinnitus.
Eye disorders	Very rare	Uveitis.
Respiratory, thoracic and mediastinal disorders	Very rare	Cough*, dyspnoea*, lung infiltration*.
Gastrointestinal disorders	Common	Nausea, diarrhoea.
	Uncommon	Vomiting.
	Very rare	Glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders	Very rare	Jaundice cholestatic*, hepatic necrosis*. Transaminases increased, blood bilirubin increased.
Skin and subcutaneous tissue disorders	Common	Rash.
	Very rare	Photosensitivity reaction, dermatitis exfoliative, angioedema, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS)*, toxic epidermal necrolysis (TEN)*, acute generalised exanthematous pustulosis (AGEP).
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), Drug reaction with eosinophilia and systemic symptoms (DRESS)*.
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia, myalgia.
Renal and urinary disorders	Very rare	Renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis.
	Not known	Urolithiasis*

* See description of selected adverse events.

Description of selected adverse reactions

Gastrointestinal disorders: Nausea and vomiting are the most frequent gastrointestinal reactions to sulfamethoxazole/trimethoprim, but glossitis, stomatitis, abdominal pain, pancreatitis, pseudomembranous colitis and diarrhoea have also been reported.

Blood and lymphatic system disorders: Haematological changes have been observed in some patients, particularly the elderly. The majority of these changes were mild, asymptomatic and proved reversible on withdrawal of the drug. The reported changes consist primarily of neutropenia and thrombocytopenia. Leucopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia, hypoprothrombinaemia, aplastic and haemolytic anaemia, purpura, agranulocytosis and bone marrow depression have been observed less frequently. Haematological toxicity may occur with increased frequency in folate depleted patients including geriatric, malnourished, alcoholic, pregnant or debilitated patients; in patients receiving anti-folates (e.g. phenytoin or methotrexate) or diuretics; in patients with haemolysis or impaired renal function; and in patients receiving sulfamethoxazole/trimethoprim in high dosages and/or for prolonged periods (e.g. longer than 6 months). In geriatric patients receiving some diuretics (principally thiazides) and sulfamethoxazole/trimethoprim concomitantly, an increased incidence of thrombocytopenia with purpura has been reported. The risk of leucopenia, neutropenia and thrombocytopenia also appear to be increased in patients with AIDS.

Congenital disorders and Pregnancy, puerperium, and perinatal conditions: spontaneous abortion have been observed.

Immune system disorders: Several cases of Stevens-Johnson syndrome (erythema multiforme bullosa) and toxic epidermal necrolysis (TEN) have been reported. Together with exfoliative dermatitis, serum sickness and allergic myocarditis, these are the most severe allergic reactions reported with sulfonamides alone, or in combination with trimethoprim. Other reported allergic and anaphylactoid reactions include angioedema, serum sickness-like syndrome, generalised allergic reactions, generalised skin eruptions, anaphylaxis, erythema multiforme, drug fever, chills, Henoch-Schönlein purpura, pruritus, urticaria, periorbital oedema, corneal ring infiltrates, conjunctival and scleral redness and oedema, and photosensitivity. In addition, periarteritis nodosa and a positive lupus erythematous phenomenon, and systemic lupus erythromatosus have been reported.

Mild to moderate rashes, when they occur, usually appear within 7 to 14 days after initiation of sulfamethoxazole/trimethoprim. Rashes are generally erythematous, maculopapular, morbilliform, and/or pruritic. Generalised pustular dermatosis and fixed drug eruption have also been reported. Patients with AIDS appear to be at particular risk of developing rash (usually diffuse, erythematous and maculopapular) during sulfamethoxazole/trimethoprim therapy.

Hepatobiliary disorders: Hepatitis, hepatic changes (as indicated by abnormal elevations in alkaline phosphatase and serum transaminase levels) including cholestatic jaundice and hepatic necrosis have been reported rarely and may be fatal. Jaundice rarely occurs and has usually been mild and transient, frequently occurring in patients with a past history of infectious hepatitis. Elevation of bilirubin levels has also been reported.

Renal and urinary disorders: Dysuria, oliguria, anuria, haematuria, urgency and functional kidney changes (as indicated by abnormal elevations in serum urea, serum creatinine and urine protein concentrations) have been reported occasionally. Renal failure, interstitial nephritis and nephrotoxicity in association with ciclosporin have been reported. Crystalluria and stone formation have occurred in patients receiving sulfamethoxazole/trimethoprim. Cases of urolithiasis have been reported in patients treated with co-trimoxazole. Renal stones formed by N-acetylsulfamethoxazole crystals aggregation (either 100% or partial) have been described. A causal association is defined specifically for urolithiasis composed from Bactrim metabolites (either 100% or partial), when specific patient risk factors, like crystalluria or reduced urinary output, are met.

Metabolism and nutrition disorders: Anorexia.

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 (see Section 4.4 Special warnings and precautions for use).

Nervous system disorders: Aseptic meningitis, seizures, peripheral neuritis, ataxia, vertigo, tinnitus, headache. Tremor and other neurologic manifestations (e.g. ataxia, ankle clonus, apathy) developed during sulfamethoxazole/trimethoprim therapy in several patients with AIDS; although such manifestations have also been associated with the underlying disease process, they resolved in these patients within 2 to 3 days after discontinuing the drug.

Psychiatric disorders: Adverse nervous system effects of sulfamethoxazole/trimethoprim include, insomnia, apathy, nervousness, mental depression and hallucinations.

Endocrine disorders: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycaemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycaemia has occurred rarely in patients receiving sulfonamides.

Infections and infestations: Fungal infections (such as candidiasis) were reported.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia, muscle weakness. Cases of rhabdomyolysis have been reported with sulfamethoxazole/trimethoprim, mainly in AIDS patients.

Respiratory, thoracic and mediastinal disorders: Cough, shortness of breath, pulmonary infiltrates, pulmonary vasculitis, acute eosinophilic pneumonia, acute and delayed lung injury, interstitial lung disease, and acute respiratory failure. Epistaxis has been reported rarely.

General disorders and administration site conditions: Weakness, fatigue, pain, local irritation, inflammation, and thrombophlebitis may occasionally occur with intravenous sulfamethoxazole/trimethoprim, especially if extravasation of the drug occurs.

Skin and subcutaneous tissue disorders:
Acute febrile neutrophilic dermatosis has been reported with certain antibiotics. Alopecia has been reported rarely.

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life-threatening. Acute generalised exanthematous pustulosis (AGEP) has been reported with certain antibiotics. See Section 4.4 Special warnings and precautions for use.

Vascular disorders: hypotension.

Eye disorders: Vision problems have been reported rarely. Uveitis and retinal vasculitis have been reported.

Post-marketing experience
The following adverse reactions have been identified during post-approval use of sulfamethoxazole/trimethoprim. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Thrombotic thrombocytopenia purpura

- Idiopathic thrombocytopenic purpura
- QT prolongation resulting in ventricular tachycardia and *torsade de pointes.*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Acute

Symptoms
Signs and symptoms of overdosage with include anorexia, diarrhoea, colic, nausea, vomiting, dizziness, headache, mental and visual disturbances, drowsiness, and unconsciousness. Pyrexia, haematuria, anuria and crystalluria may be noted. Bone marrow depression (manifested as thrombocytopaenia or leucopaenia) and 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
Stop therapy. Treatment of overdose is supportive and symptomatic care. Force fluids orally or parenterally if renal function is normal. In extreme overdosage in patients with impaired renal function, consider haemodialysis (peritoneal dialysis is ineffective) which is moderately effective in removing sulfamethoxazole and trimethoprim, monitoring of blood count and electrolytes. Acidification of the urine will increase renal elimination of trimethoprim. 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. Peritoneal dialysis is ineffective.

Chronic
Use of sulfamethoxazole/trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin.

No known antidote for sulfonamide poisoning exists, however, calcium folinate (the equivalent of 3 mg to 6 mg folinic acid intramuscularly for 5 to 7 days) is an effective antidote for adverse effects in the haemopoietic system caused by trimethoprim.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sulfamethoxazole is a white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96%). It dissolves in dilute solutions of sodium hydroxide and in dilute acids. Melting point is 169-172°C. Trimethoprim is a white or yellowish-white powder. It is very slightly soluble in water, slightly soluble in ethanol (96%). Melting point is 199-203ºC.

Mechanism of action
Sulfamethoxazole/trimethoprim interferes with the bacterial synthesis of tetrahydrofolic acid, an essential stage in the production of thymidine, purines and subsequently nucleic acids.

Sulfamethoxazole inhibits the formation of dihydrofolic acid from p-aminobenzoic acid; trimethoprim inhibits the action of the enzyme dihydrofolate reductase, thus preventing the synthesis of tetrahydrofolic

acid from dihydrofolic acid. Thus the combination of trimethoprim and sulfamethoxazole blocks two consecutive steps within the bacterial metabolic pathway of the biosynthesis of nucleic acids and proteins.

Sulfamethoxazole/trimethoprim usually shows in vitro activity against the following gram- negative and gram-positive organisms, e.g. E. coli, Neisseria, Salmonella, Klebsiella, Enterobacter, Shigella, Vibrio cholerae, Bordetella pertussis, Streptococcus, Staphylococcus, Pneumococcus, Haemophilus influenzae and Proteus.

Sulfamethoxazole/trimethoprim is also active against the protozoan Pneumocystis jirovecii. However, Mycobacterium tuberculosis, Treponema pallidum, Mycoplasma and Pseudomonas aeruginosa are frequently resistant to sulfamethoxazole/trimethoprim.

Clinical trials
No data available.

5.2 Pharmacokinetic properties

Absorption
Concentrations of at least 0.5 microgram/mL trimethoprim and 20 microgram/mL sulfamethoxazole are reached within 30 minutes after the start of an infusion and are maintained for at least 12 hours. Mean peak steady state serum concentrations of approximately 9 and 105 microgram/mL of trimethoprim and sulfamethoxazole, respectively, are reached after intravenous (IV) infusion of 160 mg trimethoprim and 800 mg sulfamethoxazole every 8 hours in adults with normal renal function. Steady state trough concentrations reached with this intravenous (IV) dose are approximately 6 microgram/mL of trimethoprim and 70 microgram/mL of sulfamethoxazole. The administration of a trimethoprim/ sulfamethoxazole ratio of 1:5 achieves trimethoprim/sulfamethoxazole concentrations in the blood of about 1:20.

Distribution
Sulfamethoxazole/trimethoprim is widely distributed into body tissues. Sulfamethoxazole is distributed mainly in the extracellular body fluids while trimethoprim, which has lipophilic properties, concentrates in the tissues. Approximately 44% of trimethoprim and 70% of sulfamethoxazole are protein bound in the blood.

Excretion
Sulfamethoxazole/trimethoprim is rapidly excreted in the urine.

5.3 Preclinical safety data

Genotoxicity
No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monoethanolamine

Propylene glycol

Ethanol absolute

Sodium hydroxide

Water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate. Do not freeze.

If stored at low temperatures precipitation may occur and solutions in which precipitation has occurred should be discarded.

6.5 Nature and contents of container

Bactrim® 400/80 is supplied as a 5 mL ampoule (made of type 1 glass) containing 400 mg sulfamethoxazole and 80 mg trimethoprim in packs of 10 ampoules.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Bactrim® 400/80 has been found to be stable for 6 hours at room temperature under normal daylight conditions when admixed with the following solutions in a concentration of 0.03 mL/mL and 0.04 mL/mL:
5% Glucose
10% Glucose
0.9% Sodium Chloride
2.5% Glucose/0.45% Sodium Chloride
Ringer's solution
Dextran 70 (6%) in glucose (5%)
10% Xylitol

No other agent should be added to or mixed with the infusion.
Do not add any products to Bactrim® 400/80 other than the infusion fluids listed above, and especially no products that lower the pH to less than 8 as this may result in precipitation.

Levulose 5%, Hartmann solution and sodium bicarbonate 1.4% solution must not be used to dilute Bactrim® 400/80.

The solution for infusion containing Bactrim® 400/80 must be administered to the patient within 6 hours of preparation

Method of administration

Bactrim® 400/80 must be diluted prior to administration. Sulfamethoxazole/trimethoprim should be administered intravenously only in the form of an infusion solution, and may not be injected undiluted either intravenously or direct into the infusion tube.

Bactrim® 400/80 may be mixed only with the following solutions for infusion:

5% Glucose
10% Glucose
0.9% Sodium Chloride
2.5% Glucose/0.45% Sodium Chloride
Ringer's solution
Dextran 70 (6%) in glucose (5%)
10% Xylitol
No other agent should be added to or mixed with the infusion.

It is important to adhere to the following minimum dilution scheme, which is based on a proportion of 1 mL Bactrim® 400/80 to 25 to 30 mL solution for infusion. Add one ampoule (5 mL) to 125 mL infusion solution; two ampoules (10 mL) to 250 mL infusion solution; or three ampoules (15 mL) to 500 mL infusion solution or an equivalent dilution.

The prepared infusion should be shaken well to ensure thorough mixing. Should visible turbidity or crystallisation appear in the solution during its preparation or infusion, it must be discarded and replaced by a freshly prepared solution.

It is recommended that infusion of sulfamethoxazole/trimethoprim be commenced within half an hour of preparation and the duration of infusion should not exceed 1.5 hours. However, this should be balanced against the fluid requirements of the patient.

Infusions containing Bactrim® 400/80 must be administered to the patient within 6 hours of preparation. Bactrim® 400/80 contains no antimicrobial agent and is for single use in one patient only. Discard any residue. Do not refrigerate prepared solution.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Ltd
t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
Auckland 2022
Telephone (09) 918 5100
Fax: (09) 918 5101

9. DATE OF FIRST APPROVAL

24 September 2026

10. DATE OF REVISION OF THE TEXT

24 September 2026

Summary table of changes

Section changed	Summary of new information
All	Compilation of initial data sheet version