NEW ZEALAND DATA SHEET

TRISUL

1. Product Name

TRISUL, 80 mg / 400 mg tablets

2. Qualitative and Quantitative Composition

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

11 mm flat bevelled edge white tablet, marked “80|400” on one side and “R” on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

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

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

Urinary tract infections

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

Respiratory tract infections

Treatment of otitis media. TRISUL is not indicated for prophylactic or prolonged administration in otitis media.

Treatment of acute exacerbations of chronic bronchitis.

Treatment and prevention of *Pneumocystis jirovecii* pneumonitis (PJP) (see section 4.2 and section 4.8).

Genital tract infections

Treatment of gonorrhoea, including oro-pharyngeal and ano-rectal infection (see section 4.2).

This regimen is less effective in some parts of the world due to disease caused by resistant organisms (WHO 1991).

Treatment of chancroid (see section 4.2). This regimen may be less effective in some parts of the world due to disease caused by resistant organisms (WHO 1991).

Treatment granuloma inguinale (venereum) (see section 4.2).

Gastrointestinal tract infections

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

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

Treatment of shigellosis, this regimen may be less effective in some parts of the world due to resistant organisms.

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

Other bacterial infections caused by sensitive organisms

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

Treatment and prophylaxis of toxoplasmosis, treatment of nocardosis.

4.2 Dose and method of administration

It may be preferable to take TRISUL with some food or drink to minimise the possibility of gastrointestinal disturbances.

Acute infections

Adults and children over 12 years

STANDARD DOSAGE – 2 tablets every 12 hours.

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

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

As an alternative to STANDARD DOSAGE for acute uncomplicated lower urinary tract infections, short term therapy of 1 to 3 days' duration has been shown to be effective.

Special populations

Hepatic impairment

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

Elderly

See section 4.4. Unless otherwise specified STANDARD DOSAGE applies.

Special dosage recommendations

Unless otherwise specified STANDARD DOSAGE applies.

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

Renal impairment

Adults and children over 12 years: (No information is available for children under 12 years of age).

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

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 160mg Sulfamethoxazole and 800mg Trimethoprim**
Above 25	Men <260 Women <170	STANDARD DOSAGE 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 - 15	Men 260 to 600 Women 170 to 400	Half the STANDARD DOSAGE frequency from Day 4 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	Not recommended 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)].

(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) Measurements of plasma concentration of sulfamethoxazole at intervals of 3 days are recommended in samples obtained 12 hours after administration of TRISUL. If the concentration of total sulfamethoxazole exceeds 150 micrograms/ml then treatment must be interrupted until the value falls below 120 micrograms/ml.

(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.

Pneumocystis jirovecii pneumonitis

Treatment

A higher dosage is recommended, using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg body weight per day in two or more divided doses for two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of greater than or equal to 5 micrograms/ml (See section 4.8).

Prevention

Adults

The following dose schedules may be used:

160 mg trimethoprim / 800 mg sulfamethoxazole daily 7 days per week.

160 mg trimethoprim / 800 mg sulfamethoxazole three times per week on alternate days.

320 mg trimethoprim / 1600 mg sulfamethoxazole per day in two divided doses three times per week on alternate days.

Children

The following dose schedules may be used for the duration of the period at risk (see Acute infections):

STANDARD DOSAGE taken in two divided doses, seven days per week

STANDARD DOSAGE taken in two divided doses, three times per week on alternate days

STANDARD DOSAGE taken in two divided doses, three times per week on consecutive days

STANDARD DOSAGE taken as a single dose, three times per week on consecutive days

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m^2/day and 750 mg sulfamethoxazole/m^2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Gonorrhoea

In uncomplicated cases 4 tablets every 12 hours for two days; *or*

5 tablets followed by a further 5 tablets eight hours later; *or*

10 tablets once daily for 3 days.

If poor patient compliance is expected a single dose of 8 tablets taken under supervision may be employed.

Oro-pharyngeal gonococcal infection

2 tablets three times daily for seven days.

Ano-rectal gonorrhoea

The STANDARD DOSAGE recommendations for gonorrhoea are applicable.

Chancroid

2 tablets twice daily for 7 days; if no evidence of healing is apparent after 7 days a further 7 days' treatment can be considered, however, physicians should be aware that failure to respond may indicate that the disease is caused by a resistant organism.

Granuloma inguinale

2 tablets twice daily for up to 2 weeks.

Nocardiosis

There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 tablets daily for up to 3 months have been used.

Toxoplasmosis

There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition. The decision should be based on clinical experience.

For prophylaxis, however, the dosages suggested for prevention of *Pneumocystis jirovecii* pneumonitis may be appropriate.

4.3 Contraindications

Hypersensitivity to the active substances, trimethoprim, or sulfamethoxazole, any sulfonamides, or with documented megaloblastic anaemia secondary to folate deficiency. or to any of the excipients listed in section 6.1.

Contraindicated in patients showing marked liver parenchymal damage, blood dyscrasias and severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.

TRISUL should not be given to premature babies nor to full term infants during the first 8 weeks of life, as sulfamethoxazole may interfere with the serum albumin binding of bilirubin to produce kernicterus

Contraindicated in patients with a history of drug-indicated immune thrombocytopenia with use of trimethoprim and/or sulphonamides.

Contraindicated in patients with acute porphyria.

Contraindicated for 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 trimethoprim/sulfamethoxazole than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

4.4 Special warnings and precautions for use

Serious adverse reactions

Fatalities, although very rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract. Sulfamethoxazole/trimethoprim 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.

- Life-threatening cutaneous reactions Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfamethoxazole (one of the active ingredients in TRISUL).
- 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 signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, TRISUL treatment should be discontinued (see section 4.8).
- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS or TEN with the use of sulfamethoxazole or TRISUL, TRISUL must not be re-started in this patient at any time.

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.

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, severe allergies or bronchial asthma.

Use in treatment of *Pneumocystis jirovecii* pneumonia in Human Immunodeficiency Virus (HIV) – positive patients

Because of their unique immune dysfunction, HIV-positive patients may not tolerate or respond to sulfamethoxazole/trimethoprim in the same manner as non- HIV-positive patients. The incidence of side effects, particularly rash, fever, neutropenia, thrombocytopenia, raised liver enzymes and leucopoenia necessitating cessation of therapy, with sulfamethoxazole/trimethoprim therapy in HIV-positive 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-HIV positive patients. Such adverse effects have occurred in up to 80% of HIV-positive 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 re-challenge 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.

Use in glucose-6-phosphate dehydrogenase deficiency

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients, haemolysis may occur. This may be dose related

Pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including sulfamethoxazole and trimethoprim. A toxin produced with *Clostridium difficile*, appears to be the primary cause. The severity of the colitis may range from mild to life threatening. 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). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement 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.

Use in renal impairment

For patients with known renal impairment special measures should be adopted (see section 4.2).

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 the risk may be increased.

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 must be maintained in order to prevent crystalluria and stone formation.

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 may induce hyperkalaemia (see section 4.5). Severe and symptomatic hyponatraemia 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.

Folate deficiency

Because of the possible interference with folate metabolism, regular monthly blood counts are advisable when sulfamethoxazole/trimethoprin is given for long periods, or to patients predisposed 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, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. 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, leucovorin may be administered.

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

Use in the elderly

Particular care is *always* advisable when treating elderly patients because, as a group, they are more susceptible to 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 and/or concomitant use of other medicines. Severe skin reactions, or generalised bone marrow suppression (see section 4.8) 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 section 4.2).

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.

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.

Paediatric population

See sections 4.2 and 4.3.

Sulfamethoxazole/trimethoprin should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic *streptococci*; eradication of these organisms from the oropharynx is less effective than with penicillin.

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

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

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

Except under careful supervision sulfamethoxazole/trimethoprin should not be given to patients with serious haematological disorders (see section 4.8). Sulfamethoxazole/trimethoprim has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

The combination of antibiotics in sulfamethoxazole/trimethoprin should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risk; consideration should be given to the use of a single effective antibacterial agent.

4.5 Interaction with other medicines and other forms of interaction

Interaction with laboratory tests:

trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

Methotrexate:

Sulfamethoxazole/trimethoprim combinations may increase the free plasma levels of methotrexate by displacing the methotrexate from protein binding sites. Cases of pancytopenia have been reported in patients taking the combination of sulfamethoxazole/trimethoprim and methotrexate. If sulfamethoxazole/trimethoprim combinationis considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4).

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacilius casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

Para-aminobenzoic acid (PABA) or its derivatives

May antagonise the antibacterial effects of sulfamethoxazole.

Urinary acidifiers

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

Warfarin

Sulfamethoxazole/trimethoprim combination has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin

from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with sulfamethoxazole/trimethoprin is advisable.

Phenytoin

Sulfamethoxazole/trimethoprim combination prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect and side effects (folate deficiencies). Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Cross sensitisation

May exist between sulfamethoxazole/trimethoprim and some antithyroid agents, diuretics (acetazolamide and the thiazides) and oral hypoglycaemic drugs.

Sulfonylurea hypoglycaemic agents

interaction with sulfonylurea hypoglycaemic agents is uncommon but potentiation has been reported. Concomitant use may result in potentiation of hypoglycaemia in occasional patients. Diuretics (thiazides):

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Cyclosporin

Reversible deterioration in renal function has been observed in patients treated with sulfamethoxazole/trimethoprim combination and cyclosporin following renal transplantation.

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 combination be prescribed concurrently.

Digoxin

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

Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium **sparing diuretics, prednisolone**

Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone and prednisolone. Concomitant use of trimethoprim-sulfamethoxazole may result in clinically relevant hyperkalaemia (see section 4.4).Zidovudine

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

Lamivudine

Administration of trimethoprim/sulfamethoxazole 160 mg / 800 mg causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Rifampicin

Concurrent use of rifampicin and sulfamethoxazole/trimethoprim combination results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

Repaglinide

Trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

Folinic acid

Folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

Contraceptives

Oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive, or choose another method of contraception.

Azathioprine

There are conflicting clinical reports of interactions between azathioprine and trimethoprim-sulfamethoxazole, resulting in serious haematological abnormalities.

Drugs that form cations

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

Fertility

No data available.

Pregnancy

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

Trimethoprim and sulfamethoxazole cross the placenta and their safety in pregnant woman has not been established. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim 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. (see section 5.3).

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus for the first month of life, when sulfamethoxazole/trimethoprim combination is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency. Sulfonamides should therefore be avoided as far as possible during the last month of pregnancy.

Breast-feeding

Trimethoprim and sulfamethoxazole are excreted into breast milk at concentrations comparable or somewhat lower than those in the blood. Administration of sulfamethoxazole/trimethoprim combination should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of sulfamethoxazole/trimethoprim combination should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia. Although the quantity of sulfamethoxazole/trimethoprim ingested by a breast-fed infant is small, it is recommended that the age of the infant be considered and the possible risks be balanced against the expected therapeutic effect.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of sulfamethoxazole/trimethoprim combinations on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless, the clinical status of the patient and the adverse events profile of sulfamethoxazole/trimethoprim combination should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

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. Sulfamethoxazole/trimethoprim 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.

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

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

The following convention has been used for the classification of adverse events in terms of frequency: Very common ≥ 1/10, common ≥ 1/100 and < 1/10, uncommon ≥ 1/1000 and < 1/100, rare ≥ 1/10,000 and < 1/1000, very rare < 1/10,000, not known – cannot be estimated from the available data.

Infections and infestations

Common: Overgrowth fungal, Pseudomembranous colitis

Blood and lymphatic system disorders

Haematological changes have been observed in some patients, particularly the elderly. The great majority of these changes were mild, asymptomatic and proved reversible on withdrawal of the drug.

Very rare: Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, hypothrombinaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, bone marrow depression, purpura, haemolysis in certain susceptible G-6-PD deficient patients.

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 HIV-positive patients.

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).

Fatalities have been recorded in at-risk patients and these patients should be observed carefully.

Immune system disorders

Very rare: Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus

Severe hypersensitivity reactions associated with PJP (see effects associated with *Pneumocystis jirovecii* pneumonitis (PJP) management), rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis

Metabolism and nutrition disorders

Very common: Hyperkalaemia
Very rare: Hypoglycaemia, hyponatraemia, anorexia, metabolic acidosis

Close supervision is recommended when sulfamethoxazole/trimethoprim combination is used in elderly patients or in patients taking high doses of sulfamethoxazole/trimethoprim combination as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

Psychiatric disorders

Very rare: Depression, hallucination
Not known: Psychotic disorder

Nervous system disorders

Common: Headache
Very rare: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, dizziness, insomnia, fatigue, apathy, nervousness, muscle weakness, vertigo, tinnitus, mental depression, seizures and hallucinations.

Aseptic meningitis was rapidly reversible on withdrawal of the drug but recurred in a number of cases on re-exposure to either sulfamethoxazole/trimethoprim combination or to trimethoprim alone.

Tremor and other neurologic manifestations (e.g. ataxia, ankle clonus, apathy) developed during sulfamethoxazole/trimethoprim therapy in several HIV-positive patients; although such manifestations have also been associated with the underlying disease process, they resolved in these patients within 2-3 days after discontinuing the drug.

Respiratory, thoracic and mediastinal disorders

Very rare: Cough, shortness of breath, pulmonary infiltrates

Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Gastrointestinal disorders

Common: Nausea, Uncommon: Vomiting
Very rare: Glossitis, stomatitis, abdominal pain, pancreatitis, diarrhoea

Eye disorders

Very rare: Uveitis

Hepatobiliary disorders

Rare: Elevation in alkaline phosphatase and serum transaminases, elevation of blood bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

Jaundice is usually mild and transient, frequently occurring in patients with a past history of infectious hepatitis.

Skin and subcutaneous tissue disorders

Common: Mild skin rashes
Very rare: Photosensitivity reactions, angioedema, exfoliative dermatitis, fixed drug eruption, erythema multiforme, severe cutaneous adverse reactions (SCARs, see section 4.4): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis.

Sensitivity reactions:

Several cases of Stevens-Johnson syndrome (erythema multiforme bullosa) and Lyell's syndrome (toxic epidermal necrolysis) 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 anaphylaxis, arthralgia, erythema multiforme, Henoch-Schönlein purpura, pruritis, urticaria, periorbital oedema, corneal ring infiltrates, conjunctival and scleral redness and oedema, and photosensitivity. Mild to moderate rashes, when they occur, usually appear within 7-14 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. HIV-positive patients appear to be at particular risk of developing rash (usually diffuse, erythematous and maculopapular) during sulfamethoxazole/trimethoprim therapy.

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia, myalgia

Renal and urinary disorders

Very rare: Impaired renal function (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis

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 toxic nephrosis have been reported. Crystalluria and stone formation have occurred in patients receiving sulfamethoxazole/trimethoprim. Diuresis has occurred rarely in patients receiving sulfonamides.

Effects associated with *Pneumocystis jirovecii* pneumonitis (PJP) management

Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia, hyponatraemia, rhabdomyolysis

At the high dosages used for *Pneumocystis jirovecii* pneumonitis (PJP) management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to sulfamethoxazole/trimethoprim combination, sometimes after a dosage interval of a few days.

Rhabdomyolysis has been reported in HIV positive patients receiving trimethoprim-sulfamethoxazole for prophylaxis or treatment of PJP.

Miscellaneous:

Other adverse effects reported with sulfamethoxazole/trimethoprim include drug fever, chills, myalgia, pulmonary infiltrates, cough, shortness of breath, hypotension, periarteritis nodosa and a positive lupus erythematous phenomenon. Vision problems, alopecia and epistaxis have been reported rarely.

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://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

Symptoms

Nausea, vomiting, dizziness, confusion, mental and visual disturbances, petechiae, purpura, pyrexia, haematuria and crystalluria are likely signs/symptoms of overdosage. Blood dyscrasias and jaundice are late complications. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment

Stop therapy. Force fluids orally or parenterally if renal function is normal. In extreme overdosage in patients with impaired renal function, consider haemodialysis which is moderately effective in removing sulfamethoxazole and trimethoprim. Peritoneal dialysis is ineffective.

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.

If vomiting has not occurred, induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete in approximately two hours. This may not be the case in gross overdosage. Dependant on the status of renal function, administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: combinations of sulfonamides and trimethoprim, including derivatives

ATC code: J01EE01

Mechanism of action

TRISUL is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim it interferes with the bacterial synthesis of tetrahydrofolic acid, an essential stage in the production of thymidine, purines and subsequently nucleic acids. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity *in vitro* between the two agents. Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

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.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination that with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase in the concentration of PABA and thereby out-compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

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

Many common pathogenic bacteria are susceptible *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antibiotics, however, *in vitro* activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

Susceptibility testing breakpoints

EUCAST

Enterobacteriaceae:	S≤ 2 R> 4
S. maltophilia:	S≤ 4 R> 4
Acinetobacter:	S≤ 2 R> 4
Staphylococcus:	S≤ 2 R> 4
Enterococcus:	S≤ 0.032 R> 1
Streptococcus ABCG:	S≤ 1 R> 2
Streptococcus pneumoniae:	S≤ 1 R> 2
Hemophilus influenza:	S≤ 0.5 R> 1

Moraxella catarrhalis: S≤ 0.5 R >1
Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*

S = susceptible, R = resistant.

*These are CLSI breakpoints since no EUCAST breakpoints are currently available for these organisms.

Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as trimethoprim concentration.

Antibacterial spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not.

Trimethoprim/sulfamethoxazole susceptibility against a number of bacteria are shown in the table below:

Commonly susceptible species:
Gram-positive aerobes: *Staphylococcus aureus* *Staphylococcus saprophytics* *Streptococcus pyogenes*
Gram-negative aerobes: *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Salmonella* spp. *Stenotrophomonas maltophilia* *Yersinia* spp.
Species for which acquired resistance may be a problem:
Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium* *Nocardia* spp. *Staphylococcus epidermidis* *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter* spp. *Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella pneumonia* *Proteus mirabilis* *Proteus vulgaris* *Providencia* spp. *Serratia marcesans*
Inherently resistant organisms:
Gram-negative aerobes:

Pseudomonas aeruginosa *Shigella* spp. *Vibrio cholera*

5.2 Pharmacokinetic properties

Absorption

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady-state levels in adults are reached after dosing for 2 to 3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Distribution

Approximately 44% of trimethoprim in the plasma is protein bound.
Trimethoprim is a weak base with a pKa of 7.4. It is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 70% of sulfamethoxazole in the plasma is protein bound.
Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in amniotic fluid, aqueous humor, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluid is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sulfamethoxazole accounts for 15 – 30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72 hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite. Sulfamethoxazole/trimethoprim is metabolised in the liver. Trimethoprim is metabolised to oxide and hydroxylated metabolites, while sulfamethoxazole is acetylated and conjugated with glucuronic acid.

Elimination

The half-life of sulfamethoxazole in humans is approximately 9 to 11 hours in the presence of normal renal function. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 ml/minute.

The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

The half-life of trimethoprim in humans is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in the elderly compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely.

The pharmacokinetics in the paediatric population with normal renal function of both components of sulfamethoxazole/trimethoprim combinations, are age dependent. Elimination of sulfamethoxazole/trimethoprim is reduced in neonates, during the first two months of life, thereafter both sulfamethoxazole and trimethoprim show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

Special patient population

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of sulfamethoxazole/trimethoprim combination should be reduced (see section 4.2).

Hepatic impairment

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

Elderly patients

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

Paediatric population

See special dosage regimen (see section 4.2).

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

At doses in excess of recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6. Pharmaceutical Particulars

6.1 List of excipients

TRISUL tablets also contain:

- Povidone
- Sodium starch glycollate
- Magnesium stearate
- Docusate sodium

TRISUL is gluten, lactose and sugar free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

Protect from light.

6.5 Nature and contents of container

HDPE bottle with PP closure. Pack-size of 500 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Customer Services Freephone: 0800 579 811

9. Date of First Approval

17 May 1979

10. Date of Revision of the Text

15 February 2021

Summary table of changes

Section	Summary of new information
4.2	Updated renal patient dosing
4.3	Additional contraindications, some minor editorial updates for better flow and replacement of Sulfamethoxazole/trimethoprim combinations for co-trimoxazole
4.4	Additional warnings and precautions or new information on: Serious adverse reactions, use in treatment of Pneumocystis jirovecii pneumonia in Human Immunodeficiency Virus (HIV) – positive patients, Use in glucose-6-phosphate dehydrogenase deficiency, Pseudomembranous colitis, Use in renal impairment, Electrolyte

	abnormalities, Folate deficiency, Use in the elderly, Effects on laboratory tests and Paediatric population Some minor editorial updates, movement of text for better flow, replacement of Sulfamethoxazole/trimethoprim combinations for co-trimoxazole
4.5	Additional Interactions or new information on interactions for: Methotrexate, Para-aminobenzoic acid (PABA) or its derivatives, Urinary acidifiers, Phenytoin, Cross sensitisation, Sulfonylurea hypoglycaemic agents and Pyrimethamine, Some minor editorial updates, movement of text for better flow, replacement of Sulfamethoxazole/trimethoprim combinations for co-trimoxazole and formatting of headings
4.6	Additional information or new information for: pregnancy and breast-feeding and deletion of some information in pregnancy Some minor editorial updates, movement of text for better flow, replacement of Sulfamethoxazole/trimethoprim combinations for co-trimoxazole and formatting of headings
4.7	Minor editorial updates, replacement of Sulfamethoxazole/trimethoprim combinations for co-trimoxazole
4.8	Additional information or new information for undesirable effects: general effects, Blood and lymphatic system disorders, Metabolism and nutrition disorders, Nervous system disorders, Gastrointestinal disorders, Hepatobiliary disorders, Skin and subcutaneous tissue disorders, Renal and urinary disorders and miscellaneous Some minor editorial updates, movement of text for better flow, replacement of Sulfamethoxazole/trimethoprim combinations for co-trimoxazole and formatting of headings
4.9	Additional information for symptoms and treatment
5.1	Additional information for Mechanism of action
5.2	Additional information or updated information for: Distribution, Biotransformation, Some minor editorial updates to replace Sulfamethoxazole/trimethoprim combinations for co-trimoxazole and/or TMP-SMZ
5.3	Minor editorial updates to add heading to align with current data sheet format standard headings
8	Minor editorial update to change the Sponsor contact telephone number
10	New date of revision