NEW ZEALAND DATA SHEET

TRISUL

1. Product Name

TRISUL, 400 mg / 80 mg tablets

2. Qualitative and Quantitative Composition

Each tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

11 mm flat bevelled edge white tablet, marked “80I400” 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) The concentration of total sulfamethoxazole 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 sulfamethoxazole exceeds 150 micrograms/mL As soon as the value of total sulfamethoxazole 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.

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 to any of the excipients listed in section 6.1.

Contraindicated in patients with documented megaloblastic anaemia secondary to folate deficiency.

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.

Concomitant administration with dofetilide (see section 4.5).

4.4 Special warnings and precautions for use

Life-threatening adverse reactions

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

Life-threatening cutaneous reactions Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia with systemic symptoms (DRESS) have been reported with the use of trimethoprim/sulfamethoxazole.

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, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, TRISUL treatment should be discontinued (see section 4.8).

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 TRISUL, TRISUL must not be re-started in this patient at any time.

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.

Severe cutaneous adverse reactions

Sulfamethoxazole/trimethoprim should be discontinued if a skin rash appears. Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking certain antibiotics. When SCAR is suspected, Sulfamethoxazole 400 mg and Trimethoprim 80 mg should be discontinued immediately and an alternative treatment should be considered. Clinical signs such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions.

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

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.

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). 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* 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.

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

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

Monitoring

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 monthly blood counts are advisable in patients on long-term therapy, in those who are predisposed to folate deficiency (i.e. the elderly, chronic alcoholics and 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, 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 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 medicines. Severe skin reactions, or generalised bone marrow suppression (see section 4.8) 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). The trimethoprim component of sulfamethoxazole/trimethoprim medicines may cause hyperkalaemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or when given concomitantly with drugs known to induce hyperkalaemia, 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 population

See sections 4.2 and 4.3.

Effects on laboratory tests

Two laboratory procedures, namely the *Lactobacillus casei* serum folate assay and the *L. leishmanii* serum vitamin B_{12} 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.

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.

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, severe allergies or bronchial asthma.

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

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.

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/trimethoprim 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

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.

If sulfamethoxazole/trimethoprim combination is 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.

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 half-life of phenytoin 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 (folate deficiencies). Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Sulfonylurea hypoglycaemic agents

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

Diuretics (thiazides):

An increased risk 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 deterioration nephrotoxicity with co-administration of sulfamethoxazole/trimethoprim and cyclosporin in renal transplant recipients.

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.

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 and potassium-sparing diuretics and prednisolone are co-administered (see section 4.4). 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.

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.

Tricyclic antidepressants

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

Increased sulfamethoxazole blood levels

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.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin, have also been reported.

Dofetilide

Concurrent administration is contraindicated (see section 4.3). 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*

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.

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

Fertility

No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole, doses roughly two times the recommended human daily dose on a body surface area basis.

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.*

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 foetus.

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 foetus (see section 4.4).

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.

Breast-feeding

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 administered to nursing women, 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.

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

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, toxic epidermal necrolysis, 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). 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 to7% 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 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.

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, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, 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-Schoenlein purpura, periarteritis nodosa, systemic lupus erythromatosus, 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, decrease appetite, metabolic acidosis
Psychiatric disorders	Very rare	Depression, hallucination
	Unknown	Psychotic disorder
Nervous system disorders	Common	Headache
	Very rare	Meningitis aseptic, seizures, 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.
	Common	Rash

System Organ Class	Frequency	Side Effects
Skin and subcutaneous tissue disorders	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

* 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 medicine. The reported changes consist primarily of neutropenia and thrombocytopenia. Leucopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia, hypothrombinaemia, aplastic anaemia, 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 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

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 angioedema, serum sickness-like syndrome, generalised allergic reactions, generalised skin eruptions, anaphylaxis, erythema multiforme, drug fever, chills Henoch-Schönlein purpura, pruritis,

urticaria, periorbital oedema, corneal ring infiltrates, conjunctival and scleral redness and oedema, and photosensitivity. In addition, periarteritis nodosa, and a positive lupus erythematosus phenomenon, and systemic lupus erythromatosus have been reported.

Mild to moderate rashes, when they occur, usually appear within 7 to14 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.

Hepatobiliary disorders

Hepatitis, hepatic changes (as indicated by abnormal elevations in alkaline phosphatase and serum transaminases 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.

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).

Nervous system disorders

Aseptic meningitis, seizures, peripheral neuritis, ataxia, vertigo, tinnitus headache .fatigue. 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.

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.

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, acute eosinophilic pneumonia, acute and delayed lung injury, interstitial lung disease, and acute respiratory failure. Epistaxis has been reported rarely.

Skin and subcutaneous tissue disorders

Acute generalised exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis have been reported with certain antibiotics. Alopecia has been reported rarely

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported to be life-threatening (see Section 4.4).

Vascular disorders

Hypotension

Eye disorders

Vision problems have been reported rarely. Uveitis reported very rarely.

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

4.9 Overdose

Acute

Symptoms

Signs and symptoms of overdosage with include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, haematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage. Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion, 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 which is moderately effective in removing sulfamethoxazole and trimethoprim. 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.

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.

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 anaemia. If signs of bone marrow depression occur, the patient should be given leucovorin; 5 to 15 mg leucovorin daily has been recommended by some investigators.

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 inhibits the formation of dihydrofolatic acid from p-aminobenzoic acid. Trimethoprim inhibits the action of the enzyme dihydrofolate reductase, thus preventing the synthesis of tetrahydrofolate from dihydrofolaic 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.

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 and 70% of sulfamethoxazole are protein bound in the blood.
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.

Biotransformation

Sulfamethoxazole/trimethoprim is metabolised in the liver. Trimethoprim is metabolised to oxide and hydroxylated metabolites, while sulfamethoxazole is acetylated and conjugated with glucuronic acid. 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

See section 4.6.

6. Pharmaceutical Particulars

6.1 List of excipients

TRISUL tablets also contain:

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

Contains sulfites

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or 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

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

17 May 1979

10. Date of Revision of the Text

10 February 2023

Summary table of changes

Section	Summary of new information
2 and 6.1	Moved Contains sulfites to section 6.1 Deleted “Excipient(s) with known effect Deleted allergen statement “contain benzoates”
4.4, 4.8	Minor editorial updates: formatting, subheading
4.4	Addition of information on haemophagocytic lymphohistiocytosis (HLH)
4.8	Addition of haemophagocytic lymphohistiocytosis
10	New date of revision of the text