

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 nocardiosis.

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).

Creatinine clearance (ml/min)	Recommended dosage
> 30	STANDARD DOSAGE
15 – 30	Half the STANDARD DOSAGE
< 15	Not recommended

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 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 should be interrupted until the value falls below 120 micrograms/ml.

***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/m²/day and 750 mg sulfamethoxazole/m²/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 sulfonamides, trimethoprim, co-trimoxazole or to any of the excipients listed in section 6.1.

Contraindicated in patients showing marked liver parenchymal damage.

Contraindicated in 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 6 weeks of life except for the treatment/prophylaxis of PJP in infants 4 weeks of age or greater.

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

Contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

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.

- 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.

Particular care is *always* advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other medicines.

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.

Regular monthly blood counts are advisable when TRISUL is given for long periods, or to folate deficient patients or to the elderly; since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. Supplementation with folic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficiency (see section 4.5).

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.

TRISUL should be given with caution to patients with severe allergy or bronchial asthma.

TRISUL 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 TRISUL 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.

Close monitoring of serum potassium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

TRISUL 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 TRISUL should not be given to patients with serious haematological disorders (see section 4.8). Co-trimoxazole 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 TRISUL 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: co-trimoxazole may increase the free plasma levels of methotrexate. If co-trimoxazole 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 *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co-trimoxazole be prescribed concurrently.

Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Lamivudine: administration of trimethoprim/sulfamethoxazole 160 mg / 800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.

Warfarin: co-trimoxazole 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 TRISUL is advisable.

Phenytoin: co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Sulfonylurea hypoglycaemic agents: interaction with sulfonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Rifampicin: concurrent use of rifampicin and co-trimoxazole 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.

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.

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

Hyperkalaemia: 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. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) may result in clinically relevant hyperkalaemia.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities.

Co-trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if co-trimoxazole is used in pregnancy (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, when co-trimoxazole 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.

Breast-feeding

Trimethoprim and sulfamethoxazole are excreted into breast milk. Administration of co-trimoxazole 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 co-trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of co-trimoxazole 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 co-trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

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.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency.

The following convention has been used for the classification of adverse events in terms of frequency: Very common $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$,

rare $\geq 1/10,000$ and $< 1/1000$, very rare $< 1/10,000$, not known – cannot be estimated from the available data.

Infections and infestations

Common: Overgrowth fungal
Very rare: Pseudomembranous colitis

Blood and lymphatic system disorders

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

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 co-trimoxazole is used in elderly patients or in patients taking high doses of co-trimoxazole 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

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

Ear and labyrinth disorders

Very rare: Vertigo, tinnitus

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, diarrhoea

Uncommon: Vomiting
Very rare: Glossitis, stomatitis, pancreatitis

Eye disorders

Very rare: Uveitis

Hepatobiliary disorders

Very rare: Elevation of transaminases, elevation of blood bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders

Common: 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)

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

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 co-trimoxazole, 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.

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 and confusion are likely signs/symptoms of overdose. Bone marrow depression has been reported in acute trimethoprim overdose.

Treatment

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 overdose. 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. 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.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination than 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

<i>Enterobacteriaceae</i> :	S ≤ 2 R > 4
<i>S. maltophilia</i> :	S ≤ 4 R > 4
<i>Acinetobacter</i> :	S ≤ 2 R > 4

<i>Staphylococcus:</i>	S ≤ 2 R > 4
<i>Enterococcus:</i>	S ≤ 0.032 R > 1
<i>Streptococcus ABCG:</i>	S ≤ 1 R > 2
<i>Streptococcus pneumoniae:</i>	S ≤ 1 R > 2
<i>Haemophilus influenza:</i>	S ≤ 0.5 R > 1
<i>Moraxella catarrhalis:</i>	S ≤ 0.5 R > 1
<i>Pseudomonas aeruginosa</i> 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: <i>Staphylococcus aureus</i> <i>Staphylococcus saprophyticus</i> <i>Streptococcus pyogenes</i>
Gram-negative aerobes: <i>Enterobacter cloacae</i> <i>Haemophilus influenzae</i> <i>Klebsiella oxytoca</i> <i>Moraxella catarrhalis</i> <i>Salmonella</i> spp. <i>Stenotrophomonas maltophilia</i> <i>Yersinia</i> spp.
Species for which acquired resistance may be a problem:
Gram-positive aerobes: <i>Enterococcus faecalis</i> <i>Enterococcus faecium</i> <i>Nocardia</i> spp. <i>Staphylococcus epidermidis</i> <i>Streptococcus pneumoniae</i>
Gram-negative aerobes: <i>Citrobacter</i> spp. <i>Enterobacter aerogenes</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Klebsiella pneumonia</i> <i>Proteus mirabilis</i> <i>Proteus vulgaris</i>

<i>Providencia</i> spp. <i>Serratia marcesans</i>
Inherently resistant organisms:
Gram-negative aerobes: <i>Pseudomonas aeruginosa</i> <i>Shigella</i> spp. <i>Vibrio cholera</i>

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 50% 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 66% 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.

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 co-trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ 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 co-trimoxazole 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

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
Telephone 09-579-2792

9. Date of First Approval

17 May 1979

10. Date of Revision of the Text

10 December 2018

Summary table of changes

Section	Summary of new information
3	Changed description of pharmaceutical form