

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Deprim oral suspension, sulfamethoxazole 200 mg and trimethoprim 40 mg per 5 mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Deprim contains 200 mg Sulfamethoxazole and 40 mg trimethoprim per 5 mL.

Excipients with known effect: For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

Deprim Suspension is a pink, raspberry flavoured suspension containing 200 mg Sulfamethoxazole and 40 mg trimethoprim per 5 mL.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Deprim has a broad spectrum of antibacterial activity and may be indicated for the following:
Gastrointestinal tract infections:

- 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 (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
- Genital tract infections:
- Treatment of gonorrhoea including oro-pharyngeal and ano-rectal infection
- Treatment of chancroid (may be less effective in some parts of the world due to resistant organisms)
- Treatment of granuloma inguinale (venereum)

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. Deprim is not indicated for prophylactic or prolonged administration in otitis media
- Treatment of acute exacerbations of chronic bronchitis
- Treatment and prevention of Pneumocystis jirovecii

Other:

- Treatment and prophylaxis of toxoplasmosis

- Treatment of nocardosis

There are a number of other bacterial conditions caused by sensitive organisms for which treatment with Deprim may be appropriate. The use of Deprim should be based on clinical experience and local in vitro data.

Deprim should only be used where in the judgement of the physician the benefits of the 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.

4.2 Dose and method administration

Deprim should be administered at 12 hourly intervals, ideally after the morning and evening meals. Maintenance of an adequate fluid intake is essential. Deprim may be used in children and in adults who are unable to take co-trimoxazole tablets.

Acute infections:

Deprim should be administered for at least 5 days or until the patient remains symptom free for at least 2 days. If clinical improvement is not evident after 7 days therapy, the patient should be reassessed. For acute uncomplicated lower urinary tract infections short term therapy of 1-3 days has been shown to be effective.

The following table indicates standard dosage:

Age	Recommended dosing schedule
Adults and children over 12 years	20 mL every 12 hours
6 to 16 years	10 mL every 12 hours
6 months to 5 years	5 mL every 12 hours
8 weeks to 5 months	2.5 mL every 12 hours

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

Elderly

Care is recommended because as a group, elderly patients 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 functions and/or concomitant use of other medications.

Impaired renal function:

The dosage schedule used should reflect the creatinine clearance rate. The following table indicates dosing schedule suitability for varying rates of renal impairment in adults and children aged over 12 years (no information is available for children under 12 years)

Creatinine clearance (mL/min)	Recommended dosage schedule
> 30	Standard dose: 20 mL twice daily
15-30	Minimum dose: 10 mL twice daily
< 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 Deprim. If the concentration of the total Sulfamethoxazole exceeds 150 micrograms/mL then treatment should be interrupted until the value falls below 120 micrograms/mL.

Pneumocystis Jirovecii:

A higher dosage is recommended using 20 mg trimethoprim and 100 mg sulfamethoxazole (2.5 mL) per kilogram bodyweight per day taken in two or more divided doses for 2 weeks. Peak plasma levels of 5 mcg/mL are required.

Prevention for Adults: Use one of the following dosage schedules:

- Standard dose (20 mL) daily 7 days per week
- Standard dose (20 mL) 3 times per week on alternate days
- Twice the standard dose (40 mL) per day in two divided doses three times per week on alternate days.

The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole (40 mL).

Prevention for Children under 12 years of age: Use one of the following dose schedules for the duration of the period at risk

- Standard dose taken in 2 divided doses 7 days per week
- Standard dose taken in 2 divided doses three times per week on alternate days
- Standard dose taken in 2 divided doses three times per week on consecutive days
- Standard dosage taken as a single dose three times per week on consecutive days.

The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole (40 mL).

Gonorrhoea: For uncomplicated cases 40 mL every 12 hours for two days, or 50 mL followed by a further 50 mL eight hours later, or 100 mL once daily for three days. A single dose of 80 mL taken under supervision can be used if patient compliance is not expected.

Oro-pharyngeal gonococcal infection: 20 mL three times a day for 7 days.

Ano-rectal gonorrhoea: The standard dosage recommendations for gonorrhoea are applicable.

Chancroid: 20 mL twice daily for 7 days. If there is no evidence of healing after 7 days a further 7 days treatment can be considered. However, it should be kept in mind that failure to respond may indicate that the disease is caused by a resistant organism.

Granuloma inguinale: 20 mL twice daily for up to 2 weeks.

Nocardiosis: There is no consensus on the most appropriate dosage. Adult doses of 60 to 80 mL daily have been used.

Toxoplasmosis: There is no consensus on appropriate dosage for the treatment or prophylaxis of this disease. The decision should be based on clinical experience. For prophylaxis, the dosages suggested for the prevention of Pneumocystis jirovecii may be appropriate.

4.3 Contraindications

- Hypersensitivity to trimethoprim, sulphonamides or co-trimoxazole

- Premature babies or newborn babies during the first eight weeks of life (see section 4.6).
- With a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides
- Premature babies or full term infants in the neonatal period
- Severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed
- Patients showing marked liver parenchymal damage
- Patients with severe haematological disorders unless under careful supervision. Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

4.4 Special warnings and precautions for use

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.

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

There is an increased risk of severe adverse reactions in elderly patients or when complicating conditions exist e.g. impaired kidney and/or liver function or concomitant use of other medicines.

Regular blood counts are advisable for patients receiving long term Deprim therapy to monitor any asymptomatic changes in haematological properties that could develop from folate deficiency. Most haematological disorders resulting from folate deficiency respond to administration of calcium folinate or removal of Deprim treatment.

An adequate urinary output must be maintained at all times especially when malnutrition is suspected. Urine samples should be inspected routinely to prevent the development of crystalluria.

The appearance of skin rashes, particularly in elderly patients, warrants the immediate removal of co-trimoxazole treatment.

Folate deficiency: A suitable folic acid supplement should be considered when treating elderly patients, patients with suspected folate deficiencies, and patients receiving prolonged high doses of Deprim treatment.

A suitable folate supplement should be considered when treating elderly patients, patients with suspected folate deficiencies, and patients receiving prolonged high doses of Deprim.

Trimethoprim impairs phenylalanine metabolism, but this has been demonstrated to be of no clinical significance to phenylketonuric patients with appropriate dietary restrictions.

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

Haemolysis may occur in glucose-6-phosphate dehydrogenase deficient (G-6-PD) patients.

Deprim should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci – penicillin is more effective in eradicating these organisms from the oropharynx.

The administration of Deprim to patients known or suspected to be at risk of acute porphyria should be avoided as both trimethoprim and sulphonamides have been associated with clinical exacerbation of porphyria.

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

Life-threatening adverse reactions

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 co-trimoxazole.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, co-trimoxazole 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 co-trimoxazole, co-trimoxazole must not be re-started in this patient at any time.

4.5 Interaction with other medicines and other forms of interaction

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

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.

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

Administration of Deprim 20 mL causes a 40% increase in lamivudine exposure because of the trimethoprim content. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

A reversible deterioration in renal function presented with increased levels of serum creatinine has been observed in patients treated with Deprim and cyclosporin following renal transplantation.

Deprim 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. Careful control of the anticoagulant therapy during treatment with Deprim is advisable.

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

Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Concurrent use of rifampicin and Deprim results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is thought to be of clinical significance.

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partially 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.

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

Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia.

Deprim may increase the free plasma levels of methotrexate.

If Deprim is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered.

4.6 Fertility, pregnancy and lactation

Category C

Both trimethoprim and sulfamethoxazole cross the placenta and their safety in human pregnancy has not been established.

It is known that trimethoprim in excessive doses, is teratogenic to rats, producing foetal malformations typical of folate antagonists. Studies have shown there may be an association between exposure to folate antagonists and birth defects in humans. It is believed such teratogenic effects may be prevented by adequate folate supplementation during pregnancy, however the use of Deprim during pregnancy (especially in the first trimester) should be avoided unless the potential benefit to the mother outweighs the potential risk to the foetus. Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally deprived drug levels persist for several days in the new born, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia with an associated theoretical risk of kernicterus when Deprim is administered to the mother near the time of delivery. The potential risk is particularly relevant in infants at an increased risk of hyperbilirubinaemia e.g. those who are pre-term or with glucose-6-phosphate dehydrogenase deficiency.

Sulfamethoxazole and trimethoprim are distributed in breast milk. Although levels are very low, the risk of neonatal kernicterus and hypersensitivity exists, and administration of Deprim should be avoided when the infant is at particular risk of hyperbilirubinaemia or is less than 8 weeks old.

4.7 Effect on ability to drive and use machines

Deprim is unlikely to have any effect on the patient's ability to drive or handle 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 > 1/10, common >1/100 and < 1/10, uncommon > 1/1000 and < 1/100, rare > 1/10,000 and < 1,000, very rare < 1/10,000.

Infections and Infestations

Common: Monilial overgrowth

Blood and lymphatic disorders

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

The majority of haematological changes are mild and reversible when treatment is stopped. Most of the changes cause no clinical symptoms although they may become severe in isolated cases, especially in the elderly, in those with hepatic or renal dysfunction or in those with poor folate status. 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.

Metabolism and nutrition disorders

Very common: Hyperkalaemia

Very rare: Hypoglycaemia. Hyponatraemia, anorexia

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, hallucinations.

Nervous system disorders

Common: Headache

Very rare: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, 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.

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, pseudomembranous colitis, pancreatitis

Hepatobiliary disorders

Very rare: Elevation of serum transaminases, elevation of 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, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis).

Lyell's syndrome carries a high mortality.

Drug reaction with eosinophilia and systemic symptoms (DRESS).

Frequency: not known

Severe cutaneous adverse reactions (SCARs)

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

Renal and urinary disorders

Very rare: Impaired renal function (sometimes reported as renal failure), interstitial nephritis

Effects associated with P. Jirovecii management

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

At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10 mg/day). Severe hypersensitivity reactions have been reported in PCP 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 deprim for prophylaxis or treatment of PCP.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Acute overdosage of co-trimoxazole commonly presents with nausea, vomiting, vertigo, dizziness, mental and visual disturbances, diarrhoea, crystalluria, haematuria, and in severe cases, anuria. Bone marrow depression has been reported in acute trimethoprim overdosage.

Chronic overdosage of co-trimoxazole may result in leucopenia, thrombocytopenia, and other blood dyscrasias due to continual folic acid depletion.

Treatment

Symptomatic treatments indicated for co-trimoxazole overdosage includes: emesis; gastrolavage; forced diuresis of Sulfamethoxazole by alkalinisation of the urine; forced diuresis of trimethoprim by acidification of the urine; haemodialysis; renal dialysis; specific treatment for significant complications of blood dyscrasia or jaundice. Peritoneal dialysis is not effective. Ongoing haematological assessment and monitoring of electrolytes is required in cases of overdosage. The haematopoietic effects of trimethoprim may be countered by administration of calcium folinate 3-6 mg by intramuscular injection for 5-7 days.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sulfamethoxazole - a substituted sulphonamide, interferes with the synthesis of nucleic acids in sensitive microorganisms by blocking the conversion of p-aminobenzoic acid to the co-enzyme dihydrofolic acid, a reduced form of folic acid. In man, dihydrofolic acid is obtained from dietary folic acid so sulphonamides do not affect human cells. Their action is primarily bacteriostatic although they may be bactericidal where concentrations of thymine are low in the surrounding medium. The sulphonamides have a broad spectrum of action but the development of widespread resistance has greatly reduced their usefulness and susceptibility often varies widely even among nominally sensitive pathogens.

Trimethoprim - a diaminopyrimidine antibiotic, is used for the treatment of infections due to sensitive organisms. Trimethoprim is a dihydrofolate reductase inhibitor. It inhibits the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid which is necessary for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA synthesis. It acts in the same metabolic pathway as the sulphonamides. The binding affinity of trimethoprim for bacterial dihydrofolate reductase enzymes is estimated to be 50000 greater than for the corresponding mammalian enzyme group.

Because Sulfamethoxazole and trimethoprim act at consecutive points of the folate metabolic pathway a potent synergy exists in vitro with an increase of up to about 10-fold in antibacterial activity and a frequently bactericidal action where individually they are generally bacteriostatic. The minimum inhibitory concentration (MIC) of each agent is reduced.

The majority of common pathogenic bacteria are sensitive in vitro to co-trimoxazole at concentrations significantly lower than those attained in vivo following the administration of recommended doses. Microorganisms that are sensitive include:

Gram-negative:

Brucella spp.; *Citrobacter* spp.; *Enterobacter* spp.; *Escherichia coli* (including enterotoxigenic strains); *Haemophilus ducreyi*; *Haemophilus influenzae* (including ampicillin-resistant strains); *Klebsiella* spp.; *Legionella pneumophila*; *Morganella morganii* (previously *Proteus morganii*); *Neisseria* spp.; *Proteus* spp.; *Providencia* spp. (including previously *Proteus rettgeri*); Certain *Pseudomonas* spp. (except *P. aeruginosa*); *Salmonella* spp. (including *S. typhi* and *paratyphi*); *Serratia marcescens*; *Shigella* spp.; *Vibrio cholerae*; *Yersinia* spp.

Gram-positive:

Listeria monocytogenes; *Nocardia* spp.; *Staphylococcus aureus*; *Staphylococcus epidermidis* and *saprophyticus*; *Streptococcus faecalis*; *Streptococcus pneumoniae*; *Streptococcus viridans*.

Many strains of *Bacteroides fragilis* are sensitive. Some strains of *Campylobacter fetus* subspecies *jejuni*, and *Chlamydia* (especially *C. trachomatis*) are sensitive without evidence of synergy. Some varieties of non-tuberculous mycobacteria are sensitive to Sulfamethoxazole but not trimethoprim.

Mycoplasmas, *Ureaplasma urealyticum*, *Mycobacterium tuberculosis* and *Treponema pallidum* are insensitive.

In vitro activity does not necessarily imply that clinical efficacy has been demonstrated and it should be noted that satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

5.2 Pharmacokinetic properties

Sulfamethoxazole and trimethoprim have very similar pharmacokinetic properties. The individual pharmacokinetic profile of each agent is not altered in the presence of the other agent.

Sulfamethoxazole and trimethoprim are both rapidly and almost completely absorbed following oral administration with or without food. Peak plasma levels of each agent are attained within 1-4 hours after ingestion and effective levels for antibacterial activity persist up to 24 hours after a therapeutic dose. Steady state levels in adults are attained after dosing for 2-3 days. Plasma levels are a function of dose for each agent.

Approximately 65% of the Sulfamethoxazole is bound to plasma proteins with a plasma half-life is 6-12 hours. It is prolonged in patients with severe renal impairment. Sulfamethoxazole diffuses freely throughout the body tissues and may be detected in the urine, saliva, sweat, bile, in the cerebrospinal, peritoneal, ocular and synovial fluids, and in pleural and other effusions. It crosses the placenta into the foetal circulation and low concentrations have been detected in breast milk. Sulfamethoxazole is a weak acid ($pK_a=6.0$), insoluble at physiological pH, and levels in extravascular fluids represent only 20-50% of plasma levels. The apparent volume of distribution is 20 litres. Sulfamethoxazole undergoes conjugation mainly in the liver, chiefly to the inactive N4-acetyl derivative which represents about 15% of the total amount of Sulfamethoxazole in the blood. Glucuronide conjugation also occurs but to a lesser extent. Elimination in the urine is dependent on pH. About 80-100% of a dose is excreted in the urine of which about 60% is in the form of the acetyl derivative with the remainder as unchanged drug and glucuronide. Sulfamethoxazole is also oxidised to the hydroxylamine, a metabolite that has been implicated in adverse reactions to sulphonamides.

Approximately 45% of trimethoprim is bound to plasma proteins. Trimethoprim is widely distributed to various tissues and fluids including kidneys, liver, lung and bronchial secretions, saliva, aqueous humour, prostatic tissue and fluid, and vaginal secretions. Concentrations in many of these tissues are reported to be higher than serum concentrations but concentrations in the CSF are about one-quarter to one-half of those in the blood. Trimethoprim readily crosses the placenta and it appears in breast milk. The half-life is about 8-11 hours in adults and somewhat less in children but is prolonged in severe renal impairment and in neonates whose renal function is immature. Trimethoprim is a lipophilic weak base ($pK_a=7.3$) which is relatively insoluble at physiological pH and has an apparent volume of distribution of 130 litres. About 10-20% of trimethoprim is metabolised in the liver mainly via the oxidation and hydroxylation pathways with the principal metabolites being 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives with some metabolites being active. Small amounts are excreted in the faeces via the bile but most is excreted in urine predominantly as unchanged drug. About 40-60% is excreted in urine within 24 hours. Trimethoprim is removed from the blood by haemodialysis to some extent.

Both Sulfamethoxazole and trimethoprim are almost exclusively eliminated by renal excretion via glomerular filtration and tubular secretion processes. Biliary excretion of each agent accounts for a relatively minor amount of a therapeutic dose. In patients with severely impaired renal function (creatinine clearance 15-30 mL/min) dosage adjustment is required.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colouring

Ponceau 4R (e124)

Flavour

Raspberry flavour E_0026934

Other excipient

Carmellose sodium, citric acid, anhydrous, dispersible cellulose, glycerol, sodium citrate, polysorbate 80, purified water q.s., syrup.

Other excipient, preservative

Sodium propyl hydroxybenzoate, Sodium methylhydroxybenzoate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Packs of 100 mL.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd

PO Box 33-203

Takapuna

Auckland 0740

Phone: 0800 423 823

Email: customer.service@aftpharm.com

9. DATE OF FIRST APPROVAL

23 April 2009

10. DATE OF REVISION OF THE TEXT

8 August 2025

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
July 2025	4.2	Minimum age changed to 8 weeks.