AUSTRALIAN PRODUCT INFORMATION

RESPRIM
RESPRIM FORTE

Sulfamethoxazole/Trimethoprim tablets

1 NAME OF THE MEDICINE

Sulfamethoxazole/trimethoprim

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RESPRIM tablet contains 400 mg of sulfamethoxazole and 80 mg of trimethoprim as the active ingredients. Each RESPRIM FORTE tablet contains 800 mg of sulfamethoxazole and 160 mg of trimethoprim as the active ingredients.

Excipients with known effect: sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

RESPRIM	:	Sulfamethoxazole 400 mg with trimethoprim 80 mg tablet: white, scored, marked 80|400 on one side, R on reverse.
RESPRIM FORTE	:	Sulfamethoxazole 800 mg with trimethoprim 160 mg tablet: white, biconvex, elongated, marked 160|800 on one side, RF on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Upper and lower respiratory tract infections; renal and urinary tract infections; skin and wound infections; septicaemias and other infections caused by sensitive organisms.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

In acute infections, trimethoprim/sulfamethoxazole should be given for at least 5 days or until the patient has been symptom-free for 2 days.

Adults and children over 12 years:

Standard dosage: 2 RESPRIM tablets or 1 RESPRIM FORTE tablet every 12 hours.

For severe infections: 3 RESPRIM tablets or 1½ RESPRIM FORTE tablets every 12 hours. This is the maximum daily dosage.

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

Attention should be paid to the folate status of the patient should treatment be prolonged.

Children under 12 years (see Section 4.3 CONTRAINDICATIONS):

Alternative dosage form is available from other brands for use in children under 12 years of age.

Patients with reduced renal function:

The following dosage regimens are based on published information for the administration of trimethoprim/ sulfamethoxazole to patients with reduced kidney function.

Criteria of kidney function (non- protein nitrogen is unsuitable)		**Recommended dosage regimens for adults and children over 12 years (no information is available for children under 12 years of age)**
Creatinine clearance mL/min	**Serum creatinine [1] µmol/L**	**(One standard dose for adults = 1 RESPRIM FORTE tablet, or 2 RESPRIM tablets, containing a total of 160 mg TMP + 800 mg SMX)**
Above 25	men < 265 women < 180	Dosage as for patients with normal kidney functions, i.e. 1 standard dose every 12 hours up to 14 days; later on ½ standard dose every 12 hours; no necessity for control analyses of drugs in plasma.
15 to 25	men 265-620 women 180-400	1 standard dose every 12 hours for 3 days; later on 1 standard dose every 24 hours as long as allowed by control analyses[2].
Below 15	men > 620 women > 400	RESPRIM should not be used (see **Section 4.3 CONTRAINDICATIONS**).

1) The serum creatinine can be used as the basis of dosing only in cases of chronic renal impairment, but not of acute or subacute kidney failure.

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

4.3 CONTRAINDICATIONS

Trimethoprim/sulfamethoxazole is contraindicated in patients showing marked liver parenchymal damage, blood dyscrasias, megaloblastic bone marrow or severe renal insufficiency, characterised by creatinine clearance <15 ml/min (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Trimethoprim/sulfamethoxazole should not be given to patients with a history of hypersensitivity to the active ingredients or the excipients, or other sulfonamides.

Trimethoprim/sulfamethoxazole should not be given to premature babies, nor during the first six weeks of life, because of the risk of producing kernicterus. It should probably not be given to infants less than 3 months of age.

Trimethoprim/sulfamethoxazole should not be used in 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.

Trimethoprim/sulfamethoxazole must not be given in combination with dofetilide (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in treatment of Pneumocystis jirovecii pneumonitis in patients with acquired immunodeficiency syndrome (AIDS)

Because of their unique immune dysfunction, AIDS affected patients may not tolerate or respond to trimethoprim/sulfamethoxazole in the same manner as non-AIDS affected patients. The incidence of side effects, particularly rash, fever, and leucopenia, with trimethoprim/sulfamethoxazole therapy in AIDS affected 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 trimethoprim/sulfamethoxazole in non-AIDS affected patients.

Use in glucose-6-phosphate dehydrogenase deficiency

In glucose-6-phosphate dehydrogenase deficient individuals haemolysis may occur. This may be dose related. Trimethoprim/sulfamethoxazole should not be given to patients with a glucose-6-phosphate dehydrogenase deficiency unless absolutely essential, and then only in minimal doses.

Pseudomembranous colitis

The use of RESPRIM can lead in very rare instances to the development of severe colitis as a result of colonisation with *Clostridium difficile*, a toxin producing organism. The colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can be fatal. If significant diarrhoea occurs (this may, however, begin up to several weeks after the cessation of antibiotic therapy) trimethoprim/sulfamethoxazole should be discontinued. This may be sufficient treatment in the early stages although cholestyramine orally may help by binding the toxin in the colonic lumen. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered.

Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Even if an organism is sensitive to trimethoprim, if it is not sensitive to sulfamethoxazole the combination should not be used, to avoid unnecessary exposure to the potential side effects of the sulfonamide component.

Serious Adverse Reactions

Fatalities, although rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias.

Hypersensitivity and allergic reactions

The trimethoprim/sulfamethoxazole 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.

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 this risk may be increased.

As with other sulfonamide preparations, critical appraisal of benefit versus risk should be made in patients with liver damage, renal damage, urinary obstruction, blood dyscrasias, allergies or bronchial asthma.

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 trimethoprim/sulfamethoxazole therapy considered.

Long-term treatment

If trimethoprim/sulfamethoxazole is given over a prolonged period, regular blood counts are required. If a significant reduction in count of any formed blood element is noted, RESPRIM should be discontinued.

As with all medicines containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

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

Electrolyte Abnormalities

Close monitoring of serum potassium and renal function is warranted in patients receiving high-dose trimethoprim/sulfamethoxazole, as used in patients with *Pneumocystis jirovecii* pneumonia, or in patients receiving standard-dose trimethoprim/sulfamethoxazole with underlying disorders of potassium metabolism or renal insufficiency, or who are receiving drugs which induce hyperkalaemia (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). Severe and symptomatic hyponatremia can occur in patients receiving RESPRIM, particularly for the treatment of *P. jirovecii* pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life- threatening complications.

Sulfonamides, including trimethoprim/sulfamethoxazole, may induce diuresis, particularly in patients with oedema of cardiac origin.

Cross sensitivity is known to occur among sulfonamides (see **Section 4.3 CONTRAINDICATIONS**).

Except under careful supervision, trimethoprim/sulfamethoxazole should not be given to patients with serious haematological disorders. Trimethoprim/sulfamethoxazole has been given to patients receiving cytotoxic therapy.

Because of possible interference with folate metabolism, regular 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 rheumatoid arthritics), in malabsorption syndromes, malnutrition states, or during the treatment of epilepsy with anticonvulsant medicines such as phenytoin, primidone or barbiturates. Changes indicative of folic acid impairment have, in certain specific situations, been reversed by folinic acid therapy.

Urine analysis and renal function tests should be performed during long-term therapy, particularly in patients with reduced renal function.

Special care should be exercised in treating elderly or suspected folate-deficient patients; folate supplementation should be considered.

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

Trimethoprim has been noted to impair phenylalanine metabolism in some patients.

Use in Renal Impairment

In patients with 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. See the special dosage table for use in renal impairment. Patients with severe renal impairment who are receiving RESPRIM should be closely monitored for symptoms and signs of toxicity such as nausea, vomiting and hyperkalaemia. Trimethoprim/sulfamethoxazole 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).

Patients on Peritoneal Dialysis

Peritoneal dialysis results in minimal clearance of administered trimethoprim and sulfamethoxazole. Use of trimethoprim and sulfamethoxazole in patients receiving peritoneal dialysis is not recommended.

Use in the Elderly

The use of trimethoprim/sulfamethoxazole in elderly patients carries an increased risk of severe adverse effects. In rare instances, fatalities have occurred. The risk of severe adverse effects is particularly greater when complicating conditions exist, e.g. impaired kidney and/or liver function, or concomitant use of other medicines.

Severe skin reactions or generalised bone marrow suppression [see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**] or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

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

Paediatric Use

No data available.

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 trimethoprim/sulfamethoxazole.

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

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Trimethoprim is an inhibitor of the Organic Cation Transporter 2 (OCT2), and a weak inhibitor of CYP2C8. Sulfamethoxazole is a weak inhibitor of CYP2C9.

Systemic exposure to drugs transported by OCT2 may increase when co-administered with trimethoprim/sulfamethoxazole. Examples include dofetilide, amantadine, memantine and lamivudine.

Pharmacokinetic interactions	
Drug class *drug name*	**Clinical comment**
Antiarrhythmics *dofetilide*	Trimethoprim/sulfamethoxazole must not be given in combination with dofetilide (see **Section 4.3 CONTRAINDICATIONS**). Elevated plasma levels of dofetilide have been reported following co-administration of trimethoprim and dofetilide. Increased plasma concentrations of dofetilide may cause serious ventricular arrhythmias associated with QT interval prolongation, including torsades de pointes.

Pharmacokinetic interactions	
Drug class *drug name*	**Clinical comment**
amiodarone	Amiodarone has a narrow therapeutic index and is metabolised primarily by CYP2C8. Therefore concomitant administration with RESPRIM is not recommended. Systemic exposure may increase when co-administered with trimethoprim/sulfamethoxazole. An alternative antibiotic medication is recommended in patients receiving therapies with amiodarone**.**
Antivirals *amantadine/memantine*	Patients receiving amantadine or memantine may be at increased risk of neurological adverse events such as delirium and myoclonus.
Antialzheimer's *memantine*	Co-administration may increase the risk of neurological adverse events such as delirium and myoclonus.
Antineoplastic agents *paclitaxel*	Paclitaxel has a narrow therapeutic index and is metabolised primarily by CYP2C8. Therefore concomitant administration with RESPRIM is not recommended. Systemic exposure may increase when co-administered with trimethoprim/sulfamethoxazole. An alternative antibiotic medication is recommended in patients receiving therapies with paclitaxel.
Antibiotics *dapsone*	Metabolised primarily by CYP2C8. Systemic exposure may increase when co-administered with trimethoprim/sulfamethoxazole. Both dapsone and trimethoprim/sulfamethoxazole can cause methaemoglobinemia, and there is therefore potential for both pharmacokinetic and pharmacodynamic interactions. Patients receiving dapsone and trimethoprim/sulfamethoxazole concurrently should be monitored for methaemoglobinemia. Alternative therapies should be considered if possible.
rifampicin	Concurrent use of rifampicin and trimethoprim/sulfamethoxazole results in a shortening of the plasma half-life of trimethoprim after a period of about one week.
Oral hypoglycaemic agents *repaglinide, rosiglitazone or pioglitazone* *sulfonylurea derivatives (glibenclamide, gliclazide, glipizide, chlorpropamide and tolbutamide)*	Trimethoprim/sulfamethoxazole potentiates the effect of oral hypoglycaemic agents that are metabolized by CYP2C8 (e.g. pioglitazone, repaglinide, and rosiglitazone or CYP2C9 *(*e.g. glipizide) or eliminated renally via OCT2. Systemic exposure may increase when co-administered with RESPRIM. Patients should be monitored regularly for hypoglycaemia.
Anticoagulants *warfarin, acenocoumarol, phenprocoumon*	Systemic exposure to drugs metabolised primarily by CYP2C9 may increase when co-administered with trimethoprim/ sulfamethoxazole. Trimethoprim/sulfamethoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo selective inhibition of its metabolism. Coagulation should be monitored in patients receiving coumarins. Sulfamethoxazole may displace warfarin from plasma albumin protein binding sites in vitro.
Antiepileptics *phenytoin*	Systemic exposure to drugs metabolised primarily by CYP2C9 may increase when co-administered with trimethoprim/sulfamethoxazole. Trimethoprim/sulfamethoxazole prolongs the half-life of phenytoin and if co-administered the prescriber should be alert for excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Pharmacokinetic interactions	
Drug class *drug name*	**Clinical comment**
Cardiovascular agents *digoxin*	Increased digoxin blood levels can occur with concomitant trimethoprim/sulfamethoxazole therapy, especially in elderly patients. Serum digoxin levels should be monitored.
Other agents *PABA*	PABA or its derivatives antagonise sulfamethoxazole. Increased sulfamethoxazole blood levels may occur in patients who are also receiving urinary acidifiers, oral anticoagulants, phenylbutazone, oxyphenbutazone, sulfinpyrazone or salicylates.

Pharmacodynamic interactions and interactions of undefined mechanism	
Drug class *drug name*	**Clinical comment**
Antipsychotics *clozapine*	Co-administration with clozapine, a drug known to have substantial potential for causing agranulocytosis, should be avoided.
Diuretics *primarily thiazides*	An increased incidence of thrombocytopenia has been observed in elderly patients concurrently receiving certain diuretics, primarily thiazides. Platelets should be monitored regularly in patients receiving diuretics.
Antimalarials *pyrimethamine*	Occasional reports suggest that patients receiving pyrimethamine as malarial prophylaxis at doses in excess of 25 mg weekly may develop megaloblastic anaemia should trimethoprim/sulfamethoxazole be prescribed concurrently.
Antimetabolites *methotrexate*	Cases of pancytopenia have been reported in patients taking trimethoprim-sulfamethoxazole in combination with methotrexate. Trimethoprim has a low affinity for human dihydrofolate reductase but may increase the toxicity of methotrexate, especially in the presence of risk factors such as old age, hypoalbuminemia, impaired renal function and decreased bone marrow reserve, and in patients receiving high doses of methotrexate. At risk patients should be treated with calcium folinate to counteract the effect of methotrexate on haematopoesis. Methotrexate may increase the antibacterial activity of sulfamethoxazole.
Antibacterials *sulfonamides*	Sulfonamides, including sulfamethoxazole, can compete with protein binding and also with the renal transport of methotrexate, thus increasing the free methotrexate fraction and the systemic exposure to methotrexate, or increasing the antibacterial activity of sulfamethoxazole.
polymyxin	It has been shown in-vitro that polymyxin combined with trimethoprim/sulfamethoxazole produces an enhanced antibacterial effect.
Antithyroid agents, diuretics, oral hypoglycaemic drugs	Cross sensitivities may exist with trimethoprim/sulfamethoxazole and some antithyroid agents, diuretics (acetazolamide and the thiazides) and oral hypoglycaemic drugs.
Antidepressants *tricyclic antidepressants*	The efficacy of tricyclic antidepressants can decrease when co-administered with trimethoprim/sulfamethoxazole.
Antivirals *Zidovudine*	Zidovudine (anti-HIV agent), and less commonly trimethoprim/sulfamethoxazole, is known to induce haematological abnormalities. Hence, there is potential for an additive pharmacodynamic effect. Patients receiving trimethoprim/sulfamethoxazole and zidovudine should be monitored for haematological toxicity, and dosage adjustment may be needed.

Pharmacodynamic interactions and interactions of undefined mechanism	
Drug class *drug name*	**Clinical comment**
Immunosuppressants *azathioprine,* *mercaptopurine*	Incidence rate and severity of myelotoxic and nephrotic adverse reactions may be increased when RESPRIM is administered concomitantly with other drugs known to be myelosuppressive or associated with renal impairment such as nucleoside analogues, tacrolimus, azathioprine or mercaptopurine. Co-administration with azathioprine or mercaptopurine may increase the risk of haematological adverse events, particularly in patients who receive trimethoprim/sulfamethoxazole for an extended period, or who are at an increased risk of folic acid deficiency. Therefore alternatives to trimethoprim/sulfamethoxazole should be considered for patients receiving azathioprine or mercaptopurine. If trimethoprim/sulfamethoxazole is used in combination with such medicines, patients should be monitored for haematological and/or renal toxicity.
ciclosporin	A reversible deterioration of renal function, manifested by increased serum creatinine, has been observed in patients with renal transplants receiving concomitant ciclosporin.
Angiotensin converting-enzyme inhibitors and angiotensin receptor blockers	Due to the potassium-sparing effects of trimethoprim/sulfamethoxazole, caution should be used when trimethoprim/sulfamethoxazole is co-administered with other agents that increase serum potassium, such as angiotensin converting- enzyme inhibitors and angiotensin receptor blockers, potassium sparing diuretics and prednisolone (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: C

Sulfonamides may cross the placenta and cause jaundice and haemolytic anaemia in the newborn. 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 (see **Section 5.2 PHARMACOKINETIC PROPERTIES**). 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. Two large observational studies have suggested a 2 to 3.5-fold increased risk of spontaneous abortion in women treated with trimethoprim alone and in combination with sulfamethoxazole during the first trimester compared to either no exposure to antibiotics or to exposure to penicillins. RESPRIM should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. If a trimethoprim/sulfonamide combination is given during pregnancy, or if the patient becomes pregnant while taking this drug, folic acid supplementation may be required. The patient should be appropriately counselled.

Use in Lactation

Both trimethoprim and sulfamethoxazole are excreted in breast milk at concentrations comparable or somewhat lower than that in the blood.

Although the quantity of trimethoprim/sulfamethoxazole ingested by a breast-fed infant is small, it is recommended that the possible risks should be balanced against the expected therapeutic effect (see **Section 5.2 PHARMACOKINETIC PROPERTIES**). Consideration should be made of the infant's age (see **Section 4.3 CONTRAINDICATIONS).**

A folate supplement *may* be considered with prolonged high dose of trimethoprim/sulfamethoxazole.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, aplastic anaemia and other blood dyscrasias (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Haematologic

Agranulocytosis, aplastic anaemia, thrombocytopenia, leukopenia, neutropenia, haemolytic anaemia, autoimmune anaemia, megaloblastic anaemia, hypoprothrombinaemia, methaemoglobinaemia, eosinophilia, purpura, bone marrow depression, granulocytopenia and pancytopenia. Haematological changes have been observed particularly in the elderly. The great majority of these changes were mild, asymptomatic, and proved reversible on withdrawal of the drug which was, in some instances, necessary before therapy could be completed.

High doses of trimethoprim as used in patients with *Pneumocystis jirovecii* pneumonia induces progressive but reversible increase in 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.

Allergic Reactions

Skin and systemic reactions may occur. Stevens-Johnson syndrome, fixed drug reaction, morbilliform rash, erythema and toxic epidermal necrolysis (Lyell's syndrome) have been reported.

The following have been reported rarely; eosinophilic or allergic alveolitis, anaphylaxis, allergic myocarditis, exfoliative dermatitis, angioedema, erythema multiforme, drug fever, chills, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schoenlein purpura, serum sickness-like syndrome, generalised allergic reactions, photosensitivity, conjunctival and scleral injection. In addition, polyarteritis nodosa and systemic lupus erythematosus have been reported.

Congenital disorders and Pregnancy, puerperium and perinatal conditions

Spontaneous abortion

Gastrointestinal

Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, isolated cases of vanishing bile duct syndrome, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhoea, anorexia, moniliasis. Jaundice has occurred rarely and has usually been mild and transient, frequently occurring in patients with a past history of infectious hepatitis.

General disorders and administration site conditions

Venous pain and phlebitis

Genitourinary

Renal failure, impaired renal function, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

Neurologic

Aseptic meningitis, meningitis-like symptoms, convulsions, neuropathy (including peripheral neuritis and paraesthesia), ataxia, vertigo, tinnitus, headache, uveitis and vasculitis cerebral.

Psychiatric

Hallucinations, depression, apathy, nervousness.

Endocrine

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

Musculoskeletal

Arthralgia, myalgia and isolated cases of rhabdomyolysis.

Respiratory

Pulmonary infiltrates, pulmonary vasculitis.

Vascular disorders

Vasculitis, necrotising vasculitis, granulomatosis with polyangiitis.

Miscellaneous

Weakness, fatigue, insomnia, fungal infections such as candidiasis, retinal vasculitis.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute

Symptoms: The amount of a single dose of trimethoprim/sulfamethoxazole that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides 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 and bone marrow depression.

Treatment: Treatment of overdose should consist of general supportive measures. General principles of treatment include the prevention of further absorption, forcing of oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Alkalinisation of the urine may aid the elimination of the sulfamethoxazole component of trimethoprim/sulfamethoxazole but may decrease the elimination of the trimethoprim component. 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. On cessation of therapy calcium folinate, 3 mg to 6 mg intramuscularly for five to seven days may be given to counteract the effects of trimethoprim on haematopoiesis.

Peritoneal dialysis is not effective and haemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

Chronic

Use of trimethoprim/sulfamethoxazole at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leucopenia and/or megaloblastic anaemia. Other blood dyscrasias may occur due to folinic acid deficiency. If signs of bone marrow depression occur, the patient should be given leucovorin 5 to 15 mg daily until normal haematopoiesis is restored.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives, ATC code: J01 EE01

Mechanism of Action

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of nucleic acids and proteins essential to bacteria.

Microbiology

Trimethoprim/sulfamethoxazole is effective against a wide range of Gram-negative and Gram-positive organisms, including: *E. coli*, Neisseria, Salmonella, Klebsiella, Enterobacter, Shigella, *Vibrio cholerae, Bordetella pertussis*, Streptococcus, Staphylococcus, Pneumococcus. Trimethoprim/sulfamethoxazole is usually active against the problem organisms *Haemophilus influenzae* and Proteus.

Trimethoprim/sulfamethoxazole is also active against the protozoan *Pneumocystis jirovecii* (see special dosage instructions).

Trimethoprim/sulfamethoxazole is not active against *Mycobacterium tuberculosis* and *Treponema pallidum. Pseudomonas aeruginosa* is frequently insensitive.

Representative minimum inhibitory concentration (MIC) values for susceptible organisms (microgram/mL)				
Bacteria	**TMP**	**SMX**	**TMP/SMX (1:20)**	
			TMP	**SMX**
Escherichia coli	0.05 - 1.5	1.0 - 245	0.05 - 0.5	0.95 - 9.5
Proteus species (indole positive)	0.5 - 5.0	7.35 - 300	0.05 - 1.5	0.95 - 28.5
Proteus mirabilis	0.5 - 1.5	7.35 - 30	0.05 - 0.15	0.95 - 2.85
Klebsiella-enterobacter sp.	0.15 - 5.0	2.45 - 245	0.05 - 1.5	0.95 - 28.5
TMP = Trimethoprim SMX = Sulfamethoxazole				

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Trimethoprim/sulfamethoxazole is rapidly absorbed on oral administration reaching peak blood levels after 1 to 4 hours, which correspond to those achieved when each component is given alone. The mean serum half-lives of trimethoprim and sulfamethoxazole are 10 hours and 8 – 10 hours, respectively.

Distribution

The volume of distribution of trimethoprim is about 130 litres and that of sulfamethoxazole is about 20 litres. At the above concentrations, about 42 – 45% of trimethoprim and 66% of sulfamethoxazole is bound to plasma proteins. The free forms of trimethoprim and sulfamethoxazole are considered to be the therapeutically active forms.

Studies in both animals and man have shown that diffusion of trimethoprim/sulfamethoxazole into the tissue is good. Large amounts of trimethoprim and smaller amounts of sulfamethoxazole pass from the bloodstream into the interstitial fluid and other extravascular body fluids.

In humans, trimethoprim and sulfamethoxazole were detected in the foetal placenta, umbilical cord blood, amniotic fluid and foetal tissues (liver, lung), indicating placental transfer of both drugs (see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION**).

Metabolism

Approximately 50 – 70% of the trimethoprim dose and 10-30% are excreted unchanged. The principal trimethoprim metabolites are 1- and 3-oxides and the 3'- and 4'- hydroxyl derivatives; some metabolites are active.

Sulfamethoxazole is metabolised in the liver, predominantly by N4-acetylation and to a lesser extent by glucuronide conjugation; the metabolites are inactive.

Excretion

The elimination half-lives of the two components are very similar (a mean of 10 hours for trimethoprim and 11 hours for sulfamethoxazole).

Both substances, as well as their metabolites, are eliminated almost entirely by the kidneys through both glomerular filtration and tubular secretion, giving urine concentrations of both active substances considerably higher than the concentration in the blood. Around two thirds of the trimethoprim dose and one quarter of the

sulfamethoxazole dose are excreted unchanged into the urine. The total plasma clearance of trimethoprim equals 1.9 mL/min/kg. The total plasma clearance of sulfamethoxazole equals 0.32 mL/min/kg. A small part of the substances is eliminated via the faeces.

Pharmacokinetics in Special Populations

Children and adolescents

In children aged 1 to 9 years the total plasma clearance of trimethoprim is around three-fold larger than in adults. As a consequence the half-life of trimethoprim in children is less than half of that observed in adults. Similar observations have been made for sulfamethoxazole (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Hepatic impairment

The pharmacokinetics of trimethoprim and sulfamethoxazole in patients with moderate or severe hepatic impairment are not significantly different from those observed in healthy subjects. [See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)** for advice and experience of use in patients with impaired liver function.]

Patients with cystic fibrosis

The renal clearance of trimethoprim and the metabolic clearance of sulfamethoxazole are increased in patients with cystic fibrosis. Consequently, the total plasma clearance is increased and the elimination half-life is decreased for both drugs.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

RESPRIM and RESPRIM FORTE tablets contain the following inactive ingredients:

- povidone
- docusate sodium
- sodium starch glycollate
- magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

RESPRIM	:	Blister pack (Al/PVC/PVDC) of 10* tablets. Blister pack (Al/PVC/PVDC) of 20 and 30 tablets for hospital only; Bottle (HDPE) of 10, 20 and 30 tablets.
RESPRIM FORTE	:	Blister pack (Al/PVC/PVDC) of 10* and 100 tablets for hospital only; Bottle (HDPE) of 4, 10 and 500 tablets.

Some pack sizes and/or pack types may not be marketed.

*Currently marketed in Australia.

Australian Register of Therapeutic Goods (ARTG)

AUST R 17681 – RESPRIM trimethoprim/sulfamethoxazole 80 mg/400 mg tablet blister pack

AUST R 17682 – RESPRIM FORTE trimethoprim/sulfamethoxazole 160 mg/800 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Sulfamethoxazole is a white or almost white, odourless crystalline powder. It is practically insoluble in water; sparingly soluble in ethanol (96%), freely soluble in acetone, slightly soluble in chloroform and in ether. It dissolves in dilute solutions of sodium hydroxide. Melting point 167°C to 172°C.

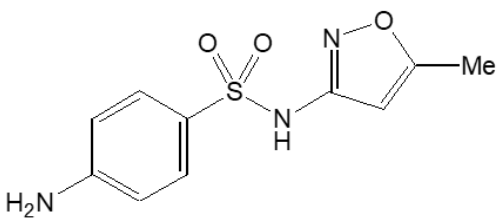
Trimethoprim is a white or yellowish-white powder; odourless or almost odourless. It is very slightly soluble in water; slightly soluble in ethanol (96%), sparingly soluble in chloroform, practically insoluble in ether. Melting point 199°C to 203°C.

Chemical Structure

Active ingredient : Sulfamethoxazole

Chemical name : 4-Amino-N-(5-methylisoxazol-3-yl)benzenesulphonamide

Molecular formula :

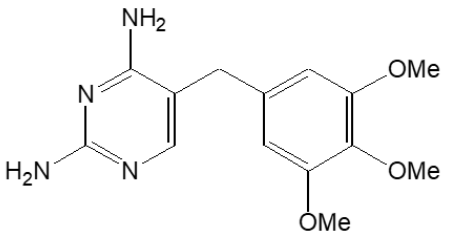


Molecular formula : $C_{10}H_{11}N_3O_3S$ Molecular weight : 253.3

Active ingredient : Trimethoprim

Chemical name : 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine

Structural formula :



Molecular formula : $C_{14}H_{18}N_4O_3$ Molecular weight : 290.3

CAS Number

Sulfamethoxazole : 723-46-6

Trimethoprim : 738-70-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Limited as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

11/10/1994

10 DATE OF REVISION

16/12/2021

Summary Table of Changes

Section Changed	Summary of New Information

2, 4.2, 4.4, 4.6, 5.1, 5.2	Minor editorial update
4.4	Update to warning of acute generalized exanthematous pustulosis (AGEP)
6.5	Include AUST R numbers
8	Update to Sponsor details

RESPRIM&RESPRIMFORTE_pi\Dec21/00