AUSTRALIAN PRODUCT INFORMATION

ALPRIM®

(trimethoprim) tablet

1 NAME OF THE MEDICINE

Trimethoprim

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg of trimethoprim as the active ingredient.

Excipients with known effect: lactose and trace quantities of sulfites.

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

3 PHARMACEUTICAL FORM

ALPRIM 300 mg tablets: 9.5mm white normal convex tablet marked TM/300 on one side, G on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of acute urinary tract infections caused by sensitive organisms.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and Children over 12 years

One tablet daily for 7 days.

Children over 6 years

Half a tablet daily for 7 days.

Children under 6 years

There is no information available at present concerning the appropriate dose of trimethoprim in children under the age of 6 years.

Renal Failure

The use of trimethoprim in patients with creatinine clearance of less than 15 mL/minute is not recommended. If the creatinine clearance is between 15 and 30 mL/minute, a reduced dose should be considered.

In the treatment of acute urinary tract infection due to susceptible organisms it is not necessary to use trimethoprim for longer than 7 days.

To ensure maximal urinary concentration, it may be advantageous to take the dose before bedtime. The dose may be taken with some food to minimise the possibility of gastrointestinal disturbance.

4.3 CONTRAINDICATIONS

Trimethoprim should not be given to patients with a history of trimethoprim hypersensitivity, or hypersensitivity to any other constituents of this medicine (see to Section 6.1 LIST OF EXCIPIENTS).

Patients with severely impaired renal function (creatinine clearance less than 10 mL/min) should not be prescribed trimethoprim unless the plasma concentration of trimethoprim is monitored repeatedly during treatment.

Severe hepatic insufficiency.

Trimethoprim should not be given to patients with severe haematological disorders or documented megaloblastic anaemia due to folate deficiency.

Trimethoprim should not be administered to premature infants or children under 4 months of age.

Trimethoprim should not be administered to pregnant women and during the nursing period.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Possible Folate Deficiency

Care should be exercised in treating suspected folate deficient patients. Folate supplementation should be considered. Folinic acid (3 – 6 mg/day) as calcium folinate, may be administered without interfering with the antibacterial activity of trimethoprim, except in Enterococci infections.

Regular monthly blood counts are advisable when trimethoprim is given for long periods since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate.

Electrolyte Abnormalities

Close monitoring of serum electrolytes is advised in patients at risk of hyperkalaemia. Elevations in serum potassium have been observed in some patients treated with trimethoprim. Patients at risk for the development of hyperkalaemia include older patients those with renal insufficiency, poorly controlled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, renin angiotensin system inhibitors (e.g. ACE inhibitors or renin angiotensin receptor blockers) or those taking other medicines that are known to increase serum potassium (e.g. heparin). If concomitant use of the above-mentioned agent is deemed appropriate, monitoring of serum potassium is recommended (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Skin Rash

Trimethoprim should be discontinued if a skin rash appears.

Porphyria

Trimethoprim has been associated with acute attacks of porphyria and is considered unsafe in porphyria patients.

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

Rare incidents of serious hypersensitivity reactions have been reported in patients on trimethoprim therapy.

Depression of Haemopoiesis

Rare incidents of trimethoprim interfering with haematopoiesis have been reported, especially when administered in large doses and/or for prolonged periods. Regular haematological tests should be undertaken in patients receiving long term treatment and those predisposed to folate deficiency, (e.g. the elderly), to check for possible pancytopaenia as an effect on folate metabolism is possible. If any such change is seen, folinic acid should reverse the effect.

Blood Glucose

Monitoring of blood glucose is advised if co-administered with repaglinide (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Rare Hereditary Conditions

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in Hepatic Impairment

Trimethoprim should be used cautiously in patients with impaired hepatic function.

Use in Renal Impairment

Trimethoprim may cause a significant, reversible increase in serum creatinine. It is unclear if this represents inhibition of tubular secretion of creatinine or genuine renal dysfunction. It should not be given in severe impairment unless blood concentrations can be monitored. Care should be taken to avoid accumulation and resulting adverse haematological effect.

Monitoring of renal function and serum electrolytes should be considered particularly with longer term use.

Trimethoprim should only be initiated and used in dialysis patients under close supervision from specialists in both infectious disease and renal medicine.

Trimethoprim should be used cautiously in patients with impaired renal function.

Use in the Elderly

Care should be exercised in treating elderly patients.

Elderly people may be more susceptible and a lower dose may be advisable. Patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. If there is evidence of folic acid deficiency, calcium folinate should be administered and response checked by haematologic monitoring. It may be necessary to discontinue trimethoprim.

Paediatric Use

Trimethoprim should not be administered to premature infants or infants during the first few weeks of life (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Particular care should be exercised in the haematological monitoring of children on long term therapy.

Effects on Laboratory Tests

Regular monthly blood counts are advisable when trimethoprim is given for long periods since there exists a possibility of symptomatic changes in haematological laboratory indices due to lack of available folate.

Trimethoprim may cause depression of haemopoiesis.

Trimethoprim may interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of normal values.

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Antimalarials

There is the possibility of megaloblastic anaemia developing in patients prescribed trimethoprim whilst taking pyrimethamine for malarial prophylaxis. Increased antifolate effect when trimethoprim is given with pyrimethamine.

Warfarin and other coumarins

Trimethoprim may potentiate the anticoagulant activity of warfarin and other coumarins though the precise mechanism is unclear. Careful control of anticoagulant therapy during treatment with trimethoprim is advisable.

Phenytoin, Digoxin, Procainamide

Trimethoprim may increase serum concentrations and potentiate the effect of phenytoin, digoxin and procainamide. Close monitoring of the patient's condition and serum levels is advisable.

Zidovudine, Zalcitabine, Lamivudine

Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine and lamivudine.

Dapsone

Trimethoprim and dapsone increase each other's serum concentration when given concomitantly.

Repaglinide

Trimethoprim may enhance the hypoglycaemic effects of repaglinide.

Rifampicin

Rifampicin may decrease the trimethoprim concentration.

Ciclosporin

An increased risk of nephrotoxicity has been reported with use of trimethoprim or co-trimoxazole and ciclosporin.

Medicines that form cations

When trimethoprim is administered simultaneously with medicines 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 medicines.

Diuretics

In patients given trimethoprim who were also receiving diuretics, hyponatraemia has been reported. In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopenia with purpura.

Bone Marrow Depressants

Use of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression or bone marrow aplasia and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors, such as pyrimethamine or methotrexate.

Cytotoxic agents such as azathioprine, mercaptopurine and methotrexate increase the risk of haematologic toxicity when given with trimethoprim due to increased risk of antifolate effect.

If trimethoprim is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cases of pancytopenia have been reported in patients taking trimethoprim in combination with methotrexate. Most of these patients were on long term methotrexate therapy, and/or predisposed to folate deficiency, and none of them were reported to have received a prophylactic folinic acid supplement (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Folate antagonists and anticonvulsants

Trimethoprim may induce folate deficiency in patients predisposed to folate deficiency such as those receiving concomitant folate antagonists or anticonvulsants.

If trimethoprim is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

ACE Inhibitors

Concomitant use of medicines known to increase serum potassium, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics, potassium supplements, potassium containing salt substitutes, renin-angiotensin system inhibitors (e.g. ACE inhibitors or renin angiotensin receptor blockers) and other potassium increasing substances (e.g. heparin) may result in severe hyperkalaemia. Monitoring of potassium should be undertaken as appropriate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B3

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.

Trimethoprim is contraindicated in pregnant women, premature infants or infants during the first few weeks of life. If trimethoprim is given during pregnancy, folic acid supplementation may be required.

The usual caution in prescribing any drug for women of child-bearing age should be exercised with trimethoprim.

Use in Lactation

Trimethoprim is excreted in human milk. When trimethoprim is administered to a nursing mother, alternative arrangements should be made for feeding the infant.

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 a part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse effects encountered most often with trimethoprim are rash and pruritus. Other adverse effects reported involve mild gastrointestinal disturbances including nausea, vomiting and glossitis and haematopoietic systems. These effects are generally mild and quickly reversible on withdrawal of the drug.

Dermatologic Reactions

Rash, pruritus and exfoliative dermatitis.

Rarely: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

At the recommended dose of 300 mg daily, the incidence of rash is 7.9%. These rashes were maculopapular, morbilliform, pruritic and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

Common: urticaria, skin rashes.

Very rare: photosensitivity, fixed drug eruption, erythema nodosum, bullous dermatitis, purpura, angioedema, exfoliative dermatitis, erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis.

Unknown: pruritus, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Lyell's syndrome (toxic epidermal necrolysis) carries a high mortality.

Infections and Infestations

Common: monilial overgrowth.

Gastrointestinal Reactions

Epigastric distress, nausea, vomiting and glossitis.

Common: diarrhoea.

Very rare: constipation, stomatitis, pseudomembranous colitis, pancreatitis.

Unknown: sore mouth, gastrointestinal disturbance.

Blood and Lymphatic System Disorders

Thrombocytopenia, leukopenia, neutropenia, megaloblastic anaemia and methaemoglobinaemia.

Although an effect on folate metabolism is possible, interference with haematopoiesis occurs rarely at the recommended dosage. If any such change is seen, calcium folinate may be administered. Elderly patients may be more susceptible and a lower dosage may be advisable.

Fatalities have been reported (especially in the elderly, or those with impairment of renal or hepatic function in whom careful monitoring is advised – refer to Section 4.3 CONTRAINDICATIONS), however the majority of haematological changes are mild and reversible when treatment is stopped.

Very rare: pancytopenia, bone marrow depression, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, purpura, haemolysis.

Unknown: hyperkalaemia (particularly in the elderly and in HIV patients). Trimethoprim therapy may affect haematopoiesis.

Metabolism and Nutritional Disorders

Hyperkalaemia, hyponatraemia.

Very rare: hypoglycaemia, anorexia.

Close supervision is recommended when trimethoprim is used in elderly patients, patients with renal impairment or patients taking high doses as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

Psychiatric Disorders

Very rare: depression, hallucinations, confusional states, agitation, anxiety, abnormal behaviour, insomnia and nightmares.

Nervous System Disorders

Common: headache.

Very rare: dyskinesias, aseptic meningitis, tremor, ataxia, dizziness, lethargy, syncope, paraesthesia, convulsions, peripheral neuritis, vertigo, tinnitus.

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 or trimethoprim-containing agents.

Eye Disorders

Very rare: uveitis.

Respiratory, Thoracic and Mediastinal Disorders

Very rare: cough, shortness of breath, wheeze, epistaxis.

Musculoskeletal and Connective Tissue Disorders

Very rare: arthralgia and myalgia.

Renal and Urinary Disorders

Very rare: impaired renal function (sometimes reported as renal failure), haematuria.

Unknown: Raised serum creatinine and blood urea nitrogen levels. It is not known, however, whether this represents inhibition of creatinine tubular secretion or genuine renal dysfunction.

Immune System Disorders

Anaphylaxis and anaphylactoid reactions, hypersensitivity, angioedema, drug fever, allergic vasculitis.

Very rare: hypersensitivity, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus.

Hepatobiliary Disorders

Very rare: disturbance in liver enzymes, elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis. Cholestatic jaundice and hepatic necrosis may be fatal.

Miscellaneous Reactions

Fever, increases in blood urea nitrogen (BUN) and serum creatinine levels, abdominal cramps, stomatitis.

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

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

Acute

Signs of acute overdosage with trimethoprim may appear following ingestion of 1 g or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression (see Overdose - Chronic below).

Treatment

General supportive measures and the use of activated charcoal (where physicochemical appropriate) have generally been seen as acceptable recommendations. Acidification of the urine will increase renal elimination of trimethoprim. Peritoneal dialysis is not effective and haemodialysis only moderately effective in eliminating the drug.

Chronic

Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anaemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given folinic acid as calcium folinate, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal haematopoiesis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Trimethoprim is a synthetic antibacterial.

Trimethoprim blocks the formation of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. Its affinity for the bacterial dihydrofolate reductase enzyme is much stronger than for the corresponding mammalian enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Trimethoprim is active *in vitro* against the common urinary tract pathogens.

Representative Minimum Inhibitory Concentrations (MIC) for trimethoprim in susceptible organisms:

Bacteria	Trimethoprim MIC mcg/mL (range)
Escherichia coli	0.05 – 1.5
Proteus mirabilis	0.5 – 1.5
Proteus sp. (indole positive)	0.5 – 5.0
Klebsiella pneumoniae	0.5 – 5.0

It is not active against *Pseudomonas spp.*

Normal vaginal and faecal flora are the source of most pathogens causing urinary tract infections. It is therefore relevant to consider the suppressive effect of trimethoprim at these sites.

Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentration of simultaneously obtained serum samples.

Sufficient trimethoprim is excreted in the faeces to markedly reduce or eliminate trimethoprim susceptible organisms from the faecal flora.

In vitro resistance develops rapidly when susceptible bacteria are passed through increasing concentrations of the drug. However, following clinical use, there have been conflicting reports on the development of resistance to trimethoprim when used alone. The possibility of increasing resistance to trimethoprim cannot at present be ruled out. Generally, resistance is more likely to occur in hospital than in domiciliary use. Plasmid mediated as well as chromosomal resistance to trimethoprim have been reported.

Microbiology, Susceptibility Tests

Dilution or Diffusion Techniques

Either quantitative (MIC) or breakpoint should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Immediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applications in body sites where the drug is physiologically concentrated or in situations where high dosage of the drug is used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Note: the prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Trimethoprim is rapidly absorbed following oral administration.

Distribution

Approximately 44% of the drug is protein bound in the blood.

Metabolism

Time to peak concentration in the circulation occur about 0.6 to 4 hours after an oral dose. Food decreases the area under the plasma concentration-time curve by approximately 20%. The half-life of trimethoprim ranges from 8 to 12 hours in the presence of normal renal function.

Excretion

Excretion of trimethoprim is chiefly by the kidneys through glomerular filtration and tubular secretion. Urine concentrations are considerably higher than are the concentrations in the blood. After oral administration 50% to 60% of trimethoprim is excreted in the urine within 24 hours, approximately 80% of this being unmetabolised trimethoprim. Less than 4% appears in the faeces. Concentrations of trimethoprim exceed those in plasma in the case of prostatic tissue and fluid, and vaginal secretions.

In subjects receiving a single dose of 100 mg trimethoprim, the urinary concentration ranged from 30 to 160 mcg/mL, zero to 4 hours after the dose, and from 18 to 90 mcg/mL 8 to 24 hours after the dose. Increasing the dose of trimethoprim to 200 mg will double the urinary concentration.

Elimination is delayed in patients with renal insufficiency. The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/minute is not recommended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ALPRIM tablets contain the following inactive ingredients: lactose monohydrate, povidone, sodium starch glycollate, purified talc and 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 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container Type: PVC/PVDC/Al blister pack of 7 tablets.

Australian Register of Therapeutic Goods (ARTG)

AUST R 63518 – ALPRIM trimethoprim 300 mg tablet blister pack.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

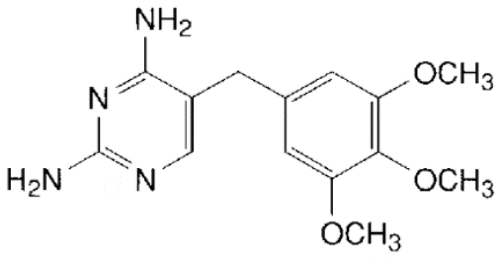
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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

738-70-5

Melting point about 200°C. Solubility 1:2500 of water, 1:300 in ethanol (96%), 1:55 of chloroform and 1:80 of methyl alcohol.

It is a white, or yellowish-white powder, odourless or almost odourless. Practically insoluble in ether.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

06/04/1998

10 DATE OF REVISION

15/06/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.8	Undesirable effect added for drug rash with eosinophilia and systemic symptoms (DRESS) under dermatologic reaction.
5.2	Editorial update to excretion section.

ALPRIM® is a Viatris company trade mark

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