

ALPRIM

Trimethoprim tablets

1 NAME OF THE MEDICINE

Trimethoprim

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: lactose and traces of sulfites and galactose.

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

3 PHARMACEUTICAL FORM

ALPRIM (trimethoprim) 300 mg: 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 table daily for 7 days.

Children under 6 years

There is no information available at present concerning the appropriate dose of ALPRIM 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 ALPRIM 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

ALPRIM should not be given to patients with a history of trimethoprim hypersensitivity.

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

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

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.

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.

Electrolyte Abnormalities

Close monitoring of serum electrolytes is advised in patients at risk of hyperkalaemia. These include older patients, those with renal impairment and those taking other medicines that are known to increase serum potassium (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.

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 represent inhibition of tubular secretion of creatinine or genuine renal dysfunction. It should not be given in severe impairment unless blood concentrations can be monitored.

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

Use in the Elderly

Care should be exercised in treating elderly patients.

Paediatric Use

see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on Laboratory Tests

Regular monthly blood counts are advisable when ALPRIM 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 interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of normal values.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There is the possibility of megaloblastic anaemia developing in patients prescribed trimethoprim whilst taking pyrimethamine for malarial prophylaxis.

Warfarin

Trimethoprim may potentiate the anticoagulant activity of warfarin 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.

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.

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.

Diuretics

In patients given trimethoprim who were also receiving diuretics, hyponatraemia has been reported.

Bone Marrow Depressants

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

If ALPRIM 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).

ACE Inhibitors

Concomitant use of medicines known to increase serum potassium, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and potassium sparing diuretics may result in severe hyperkalaemia.

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. If trimethoprim is given during pregnancy, folic acid supplementation may be required.

Use in Lactation

Trimethoprim is excreted in human milk. When ALPRIM 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 involved the gastrointestinal and haematopoietic systems.

Dermatologic Reactions

Rash, pruritus and exfoliative dermatitis.

Rarely: erythema multiform, Steven-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.

Gastrointestinal Reactions

Epigastric distress, nausea, vomiting and glossitis.

Haematologic Reactions

Thrombocytopenia, leucopenia, 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.

Metabolism and Nutrition Disorders

Hyperkalaemia, hyponatraemia.

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.

Immune System Disorders

Anaphylaxis and anaphylactoid reactions.

Eye Disorders

Very rare: Uveitis.

Miscellaneous Reactions

Fever, elevation of serum transaminases and bilirubin and increases in BUN and serum creatinine levels.

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

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, leucopenia and/or megaloblastic anaemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given folic acid as calcium folinate, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal haematopoiesis.

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

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 an 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)
<i>Escherichia coli</i>	0.05 – 1.5
<i>Proteus mirabilis</i>	0.5 – 1.5
<i>Proteus sp. (indole positive)</i>	0.5 – 5.0
<i>Klebsiella pneumoniae</i>	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

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

ALPRIM: PVC/PVDC/Al blister pack of 7s

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

Australian Register of Therapeutic Goods (ARTG)

AUST R 63518 – ALPRIM trimethoprim 300 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

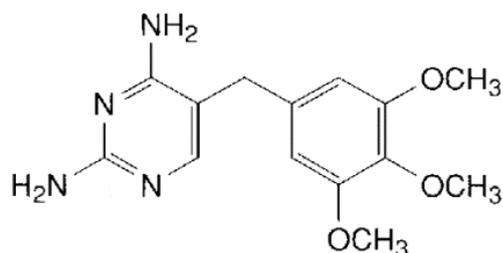
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

5-(3,4,5-trimethoxybenzyl)-pyrimidine-2, 4-diamine

Structural formula



Molecular formula: C₁₄H₁₈N₄O₃

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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9 DATE OF FIRST APPROVAL

06/04/1998

10 DATE OF REVISION

06/05/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Editorial changes
2	Updated description to align with TGO 91
3	Editorial changes and description aligned with ARTG
4.8	Added Eye Disorder for Uveitis as a very rare effect associated with trimethoprim
6.5	Editorial changes and added AUST R number
8	Update to sponsor details

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