

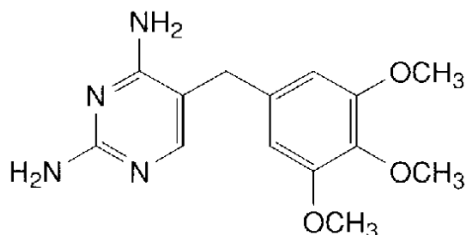
## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Active ingredient: Trimethoprim

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

Structural formula:



Molecular formula: C<sub>14</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>

Molecular weight: 290.3

CAS Registry No.: 738-70-5

### DESCRIPTION

Synthetic antibacterial.

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

Each Alprim tablet contains trimethoprim 300 mg as the active ingredient. Alprim tablets also contain the following inactive ingredients: lactose monohydrate, povidone, sodium starch glycollate, talc – purified, magnesium stearate.

### PHARMACOLOGY

Trimethoprim is rapidly absorbed following oral administration.

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

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.

## Microbiology

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 susceptible organisms

Bacteria	Trimethoprim MIC mcg/mL (range)
<i>Escherichia coli</i>	0.05 - 1.5
<i>Proteus mirabilis</i>	0.5 - 1.5
Proteus sp. (indole positive)	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 (eg. 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.

## INDICATIONS

Treatment of acute urinary tract infections caused by sensitive organisms.

## 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.

## PRECAUTIONS

Use with caution in the following circumstances:

- *Possible Folate Deficiency.* Administration of folate supplementation should be considered.
- *Impaired Renal Function.* Trimethoprim may cause a significant, reversible increase in serum creatinine. Tubular secretion of creatinine is inhibited by trimethoprim. It should not be given in severe impairment unless blood concentrations can be monitored.
- *Impaired Hepatic Function.*
- *Elderly Patients.*
- *Skin Rash.* It should be discontinued if a skin rash appears.

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.

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

### Use in 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.

*Australian categorisation definition of Category B3.* Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

### 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.

## INTERACTIONS WITH OTHER MEDICINES

There is the possibility of megaloblastic anaemia developing in patients prescribing 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, lamivudine.

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

*Rifampicin.* Rifampicin may decrease the trimethoprim concentration.

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

*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.

*ACE Inhibitors.* Severe hyperkalaemia has been noted in patients given trimethoprim (or co-trimoxazole) together with an ACE inhibitor.

If Triprim is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see PRECAUTIONS).

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 folic acid supplement (see PRECAUTIONS).

## ADVERSE EFFECTS

The adverse effects encountered most often with trimethoprim are rash and pruritus. Other adverse effects reported involved the gastrointestinal and haematopoietic systems.

*Dermatological Reactions.* Rash, pruritus and exfoliative dermatitis. Rarely: erythema multiforme, 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.

*Haematological 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.

*Miscellaneous Reactions.* Fever, elevation of serum transaminases and bilirubin, and increases in BUN and

serum creatinine levels.

## DOSAGE AND 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 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 concentrations 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.

## OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126.

*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 **Overdosage, Chronic**; following).

*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.

## PRESENTATION AND STORAGE CONDITIONS

Alprim 300 mg tablets are white, normal convex, marked “TM/300” on one side, “G” on reverse.

Available in blister packs and bottle of 7 tablets.

Store below 30°C.

Not all pack types may be available.

## **NAME AND ADDRESS OF THE SPONSOR**

**Alphapharm Pty Limited**

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## **POISON SCHEDULE OF THE MEDICINE**

S4 (Prescription Only Medicine)

## **DATE OF FIRST INCLUSION IN THE ARTG (the AUSTRALIAN REGISTER OF THERAPEUTIC GOODS):**

Alprim 300 mg tablet bottle: 13th January 1993

Alprim 300 mg tablet blister pack: 6th April 1998

**DATE OF MOST RECENT AMENDMENT:** 6th October 2016