

TMP



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## 1. Product Name

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TMP 300 mg tablets.

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## 2. Qualitative and Quantitative Composition

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Each TMP tablet contains 300 mg of trimethoprim.

Excipients with known effect: lactose.

For the full list of excipients, see section 6.1.

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## 3. Pharmaceutical Form

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TMP 300 mg tablets are white, normal convex, imprinted TM/300 on one side, and G on the other side.

This product is not able to deliver all approved dose regimens.

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## 4. Clinical Particulars

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### **4.1 Therapeutic indications**

TMP tablets are indicated for the treatment of acute urinary tract infections.

TMP tablets are also indicated for long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following sterilisation of the urine.

### **4.2 Dose and method of administration**

This product is not able to deliver all approved dose regimens.

#### **Dose**

##### ***Acute urinary tract infections***

Adults and children over 12 years: 300 mg once daily

Children aged 6 to 12 years: 150 mg once daily

Children aged 6 months to 5 years: 75 mg once daily

Children aged 6 weeks to 5 months: 40 mg once daily

This dosage approximates to 6 mg/kg bodyweight/day. The recommended duration of treatment will vary according to medical practice in different countries.

### ***Long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following sterilisation of the urine***

Adults and children over 12 years: 100 mg once daily

Children aged 6 to 12 years: 50 mg once daily

Children aged 6 months to 5 years: 25 mg once daily

This dosage approximated to 2 mg / kg bodyweight/day.

Treatment may be continued for 3 to 12 months or more as appropriate.

Trimethoprim does not induce its own metabolism and therefore no dose modification is required on this account during long term treatment.

### ***Special populations***

#### **Renal impairment**

When a patient is known to have a creatinine clearance below 15 to 20 ml/minute trimethoprim plasma levels should be monitored after approximately 3 days of treatment. When clearance is below 10 ml/minute TMP should not be administered unless plasma concentrations can be estimated regularly and haemodialysis facilities are available.

#### **Method of administration**

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

### ***4.3 Contraindications***

TMP should not be given to patients with a history of trimethoprim hypersensitivity, or a hypersensitivity to any of the excipients listed in section 6.1.

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

TMP 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***

#### **Skin rash**

TMP should be discontinued if a skin rash appears.

#### **Possible folate deficiency**

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

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

A folate supplement should also be considered when high doses of TMP are administered intravenously (see Interactions).

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

## **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 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.

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

## **Use in elderly**

Care should be exercised in treating elderly because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result.

## **Paediatric use**

See section 4.2

## **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 and 4.8).

## **Effects on laboratory results**

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.

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

## **4.5 Interaction with other medicines and other forms of interaction**

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 the anticoagulant therapy during treatment with TMP 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, 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.

### **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.

### **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 TMP is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (see section 4.4).

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 section 4.4).

### **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**

### **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.

### **Breast-feeding**

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

## **Fertility**

For pre-clinical pregnancy data refer to section 5.3.

### **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.

### **4.8 Undesirable effects**

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

#### **Blood and lymphatic system disorders**

Very rare: Leucopenia, neutropenia, thrombocytopenia, pancytopenia, bone marrow depression, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, purpura, haemolysis, megaloblastic anaemia, and methaemoglobinaemia.

The majority of haematological changes are mild and reversible when treatment is stopped.

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.

#### **Immune system disorders**

Very rare: Hypersensitivity, anaphylaxis, angioedema, drug fever, allergic vasculitis.

#### **Metabolism and nutrition disorders**

Very common: Hyperkalaemia.

Very rare: Hypoglycaemia, hyponatraemia, anorexia.

Close supervision is recommended when trimethoprim is used in elderly patients, patients with renal impairment or in 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: Dyskinesia, aseptic meningitis, tremor, ataxia, dizziness, lethargy, syncope, paraesthesiae, convulsions, peripheral neuritis, vertigo, tinnitus.

Aseptic meningitis was rapidly reversible on withdrawal of the medicine, but recurred in a number of cases on re-exposure to either trimethoprim or to trimethoprim-containing agents.

#### **Eye disorders**

Very rare: Uveitis.

#### **Respiratory, thoracic and mediastinal disorders**

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

## **Gastrointestinal disorders**

Common: Nausea, diarrhoea, vomiting.

Very rare: Constipation, glossitis, stomatitis, pseudomembranous colitis, pancreatitis.

Epigastric distress.

## **Hepatobiliary disorders**

Very rare: Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis.

## **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.

## **Musculoskeletal and connective tissue disorders**

Very rare: Arthralgia and myalgia.

## **Renal and urinary disorders**

Very rare: Impaired renal function, haematuria.

## **Miscellaneous reactions**

Increases in BUN and serum creatinine levels.

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting>.

## **4.9 Overdose**

### **Acute**

Signs of acute overdose with trimethoprim may appear following ingestion of 1000 mg or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression.

### **Treatment**

Treatment consists of general supportive measures.

Stop therapy. If vomiting has not occurred induction of vomiting may be desirable. Gastric lavage may be useful though absorption from the gastrointestinal tract is normally very rapid and complete in approximately two hours. This may not be the case in gross overdose.

Acidification of the urine will increase the elimination of trimethoprim. Calcium folinate (5 to 10 mg/day) will reverse any folate deficiency effect of trimethoprim on the bone marrow should this occur.

Peritoneal dialysis is not effective and haemodialysis only moderately effective in eliminating the drug.

Plasma or serum levels of trimethoprim may be determined by gas liquid chromatography and high performance liquid chromatography.

## 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 filinate, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal haematopoiesis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## 5. Pharmacological Properties

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### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Trimethoprim and derivatives

ATC code: J01EA01

#### Mechanism of action

Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the experimental conditions the effect may be bactericidal or bacteriostatic.

Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

The majority of common pathogenic bacteria are sensitive *in vitro* to trimethoprim at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. These organisms include:

Organism	Trimethoprim representative Minimum Inhibitory Concentration (MIC)
<b>Sensitive:</b>	
<b>Gram-Negative:</b>	
<i>Escherichia coli</i>	0.05 – 1.5 microg/mL
<i>Haemophilus influenzae</i>	
<i>Proteus mirabilis</i>	0.5 – 1.5 microg/mL
<i>Salmonella</i> spp. including <i>S.typhi</i> and <i>S.paratyphi</i>	
<i>Shigella</i> spp.	
<i>Vibrio cholerae</i>	
<b>Gram-Positive:</b>	
<i>Listeria monocytogenes</i>	
<i>Staphylococcus aureus</i>	
<i>Staphylococcus epidermidis</i> and <i>saprophyticus</i>	

<b>Organism</b>	<b>Trimethoprim representative Minimum Inhibitory Concentration (MIC)</b>
<i>Streptococcus faecalis</i>	
<i>Streptococcus pyogenes</i>	
<i>Streptococcus viridans</i>	
<b>Variable sensitivity:</b>	
<i>Klebsiella spp. including Klebsiella pneumoniae</i>	0.5 – 5.0 microg/mL
<i>Enterobacter spp.</i>	
<i>Proteus spp. (indole positive)</i>	0.5 – 5.0 microg/mL
<i>Providencia spp.</i>	
<i>Serratia marcescens</i>	
<i>Streptococcus pneumoniae</i> <i>Yersinia spp.</i>	
<b>Relatively insensitive:</b>	
<i>Brucella spp.</i>	
<i>Clostridium spp.</i>	
<i>Neisseria spp.</i>	
<b>Insensitive:</b>	
<i>Bacteroides spp.</i>	
<i>Lactobacillus spp.</i>	
<i>Mycobacteria</i>	
<i>Mycoplasmas</i>	
<i>Pseudomonas spp.</i>	
<i>Ureaplasma urealyticum</i>	

Satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

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.



## **Clinical efficacy and safety**

No data available.

## **5.2 Pharmacokinetic properties**

### **Absorption**

After oral administration trimethoprim is rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady-state levels in adults are reached after dosing for 2 to 3 days.

### **Distribution**

Approximately 44% of the drug is protein bound in the blood. Trimethoprim is a weak base with a pKa of 7.3. It is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and fetal tissues reaching concentrations approximating those of maternal serum.

### **Biotransformation**

Approximately 50% of trimethoprim in the plasma is protein bound. The half-life in humans is in the range 8.6 to 12 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in the elderly compared with young patients.

### **Elimination**

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. Several metabolites have been identified in urine. Urinary concentrations of trimethoprim vary widely. Within 2 hours of any therapeutic dose the concentrations achieved are greatly in excess of the minimum inhibitory concentration (MIC) of most pathogenic bacteria responsible for urinary tract infections. High concentrations usually persist in the urine for 24 hours or more after a single dose. Even in patients undergoing chronic haemodialysis levels of trimethoprim achieved in the urine exceed the MIC for most of the urinary tract pathogens. 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.

## **5.3 Preclinical safety data**

### **Pregnancy**

At doses greatly in excess of the recommended human therapeutic dose trimethoprim has been reported to be teratogenic in rats with effects typical of a folate antagonist and preventable by administration of dietary folate. No significant medicine-related malformations have been demonstrated in rabbits but at doses approximately ten times in excess of the human therapeutic dose an increase in fetal deaths was noted.

### **Genotoxicity**

No data available.

### **Carcinogenicity**

No data available.

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## 6. Pharmaceutical Particulars

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### 6.1 *List of excipients*

TMP 300 mg tablets also contain:

- lactose
- magnesium stearate
- povidone
- purified talc
- sodium starch glycollate

The tablets are gluten free.

### 6.2 *Incompatibilities*

Not applicable.

### 6.3 *Shelf life*

3 years

### 6.4 *Special precautions for storage*

Store at or below 25°C.

### 6.5 *Nature and contents of container*

HDPE bottle with a PP cap. Pack size of 50 tablets.

### 6.6 *Special precautions for disposal*

Not applicable.

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## 7. Medicines Schedule

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Prescription Medicine

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## 8. Sponsor Details

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Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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## 9. Date of First Approval

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30 October 1986

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## 10. Date of Revision of the Text

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09 July 2019

Section	Summary of changes
-	Minor editorial updates
4.4	Recommended regular blood counts Additional information about renal impairment
4.5	Additional interactions for zidovudine, zalcitabine, lamivudine, dapsone, diuretics and additional information about bone marrow depressants
4.8	Additional effect: epigastric distress
5.1	Inclusion of known MIC levels Additional information about reduced sensitivity and source of pathogens