

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.

TMP 300 mg tablets contain 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. Each tablet contains 300 mg trimethoprim.

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**

It may be preferable to take TMP before retiring to bed with some food or drink which will minimise the possibility of gastrointestinal disturbances.

**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**

TMP should be discontinued if a skin rash appears. 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. These changes may be reversed by administration of folic acid (5 to 10 mg/day) without interfering with the antibacterial activity of trimethoprim.

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

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.

The administration of TMP to patients known or suspected to be at risk of acute porphyria should be avoided as trimethoprim has been associated with clinical exacerbation of porphyria.

## **Use in renal and hepatic impairment**

Exercise caution when treating patients with impaired renal function or severe hepatic parenchymal damage as changes may occur in the absorption and metabolism of trimethoprim.

## **Use in elderly**

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result.

## **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).

## **Interference with laboratory tests**

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in the overestimation of serum/plasma creatinine of the order of 10%. Functional inhibition of the renal tubular secretion of creatinine may produce a spurious fall in the estimated rate of creatinine clearance.

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

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

Occasional reports suggest that patients receiving pyrimethamine as malarial prophylaxis at doses in excess of 25 mg weekly may develop megaloblastic anaemia should cotrimoxazole be prescribed concurrently. The same interaction is likely if trimethoprim be prescribed concurrently.

Trimethoprim may potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Careful control of the anticoagulant therapy during treatment with TMP is advisable.

Trimethoprim 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.

Concurrent use of rifampicin and trimethoprim results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

Reversible deterioration in renal function has been observed in patients treated with trimethoprim and cyclosporin following renal transplantation.

When trimethoprim is administered simultaneously with medicines that form cations at physiological pH, and are also partly excreted by active renal secretion (eg. 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.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

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

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 arrangements 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.

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

### **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.

### **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. Haematologic reactions**

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.

### **Miscellaneous reactions**

Fever, elevation of serum transaminases and bilirubin, 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 overdosage with trimethoprim may appear following ingestion of 1 gram or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression.

### Treatment

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 overdosage.

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. General supportive measures are recommended.

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 folic 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: Sulfonamides and trimethoprim, 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.

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:

#### Gram-Negative:

*Escherichia coli*

*Haemophilus influenzae*

*Proteus mirabilis*

*Salmonella* spp. including *S.typhi* and *S.paratyphi*

*Shigella* spp.

*Vibrio cholerae*

**Gram-Positive:**

*Listeria monocytogenes*

*Staphylococcus aureus*

*Staphylococcus epidermidis* and *saprophyticus*

*Streptococcus faecalis*

*Streptococcus pyogenes*

*Streptococcus viridans*

**Variable sensitivity:**

*Klebsiella / Enterobacter* spp.

*Proteus* spp. (indole positive)

*Providencia* spp.

*Serratia marcescens*

*Streptococcus pneumoniae*

*Yersinia* spp.

**Relatively insensitive:**

*Brucella* spp.

*Clostridium* spp.

*Neisseria* spp.

**Organisms which are insensitive include:**

*Bacteroides* spp.

*Lactobacillus* spp.

*Mycobacteria*

*Mycoplasmas*

*Pseudomonas* spp.

*Ureaplasma urealyticum*

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

## **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.

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## **6. Pharmaceutical Particulars**

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### **6.1 List of excipients**

TMP 300mg tablets 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.

# **7. Medicines Schedule**

Prescription Medicine

# **8. Sponsor Details**

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

# **9. Date of First Approval**

30 October 1986

# **10. Date of Revision of the Text**

20 July 2018

Section	Summary of changes
4.3	Updated information with regards to hematological disorders
4.4	Addition of electrolyte abnormalities precaution
4.5	Additional interactions
4.6	Section updated

4.8	Section updated
4.9	Addition of acute and chronic overdose
5.2	Section updated