1. Product Name

TMP 300 mg tablets.

2. Qualitative and Quantitative Composition

Each TMP tablet contains 300 mg of trimethoprim.
TMP 300 mg tablets contain lactose.
For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

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.

4. Clinical Particulars

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. Except in rare circumstances TMP should not be given to patients with serious haematological disorders.

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 folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity of trimethoprim.

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.

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.

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.

**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 (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.

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).

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

The safety of trimethoprim in human pregnancy has not been established. For pre-clinical pregnancy data refer to section 5.3.

**Breast-feeding**

Despite its excretion in breast milk the administration of TMP to lactating women represents a negligible risk to the suckling infant.

**Fertility**

No data available.

### 4.7 Effects on ability to drive and use machines

Not relevant.
4.8 Undesirable effects

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 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.

Skin and subcutaneous tissue disorders

Common: Skin rashes, urticaria.

Very rare: Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, erythema nodosum, Stevens-Johnson Syndrome, toxic epidermal necrolysis, bullous dermatitis, purpura.

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia and myalgia.

**Renal and urinary disorders**

Very rare: Impaired renal function, haematuria.

**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/](https://nzphvc.otago.ac.nz/reporting/)

### 4.9 Overdose

The maximum tolerated dose in humans is unknown.

Nausea, vomiting, dizziness and confusion are likely symptoms of overdosage.

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.

Trimethoprim is dialysable by renal dialysis.

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

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

### 5. Pharmacological Properties

#### 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**

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 17 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**

The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged medicine. 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.

### 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.

### 6. Pharmaceutical Particulars

#### 6.1 List of excipients

TMP 300mg tablets contain lactose, magnesium stearate, povidone, purified talc and 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
31 May 2017 Data sheet revised to SmPC format