

## TMP

*Trimethoprim*



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## Presentation

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TMP Tablets 300 mg: 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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## Uses

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### **Actions**

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.

## **Pharmacokinetics**

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.

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.

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.

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.

## **Indications**

TMP Tablets are indicated:

- for the treatment of acute urinary tract infections;
- for long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following -- sterilisation of the urine.

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## **Dosage and Administration**

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

### ***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 approximates to 2 mg/kg bodyweight/day.

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

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

Dosage recommendations for patients with impaired renal function:

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 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.

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## **Contraindications**

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

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.

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## Warnings and Precautions

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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 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.

### ***Use during Pregnancy and Lactation:***

The safety of trimethoprim in human pregnancy has not been established. 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.

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

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## Adverse Effects

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Minor gastrointestinal disturbances such as nausea with or without vomiting, glossitis or sore mouth have been reported.

Skin rashes, including fixed medicine eruption, may occur but are usually mild.

Pruritus with or without an associated rash has been reported.

Although an effect on folate metabolism is possible, interference with haematopoiesis occurs rarely at the recommended dosage. If any such change is seen folinic acid should reverse the effect. Elderly patients may be more susceptible and a lower dosage may be advisable.

Aseptic meningitis has been reported in association with the administration of trimethoprim. The condition 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.

Allergic reactions including mild anaphylaxis have been reported rarely.

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## Interactions

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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 (see Warnings and Precautions).

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## Overdosage

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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.

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## Pharmaceutical Precautions

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Store below 25°C. Protect from light.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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TMP 300 mg: 50 tablets

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## Further Information

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

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

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

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## Name and Address

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## Date of Preparation

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2 February 2009