

SUMMARY OF PRODUCT CHARACTERISTICS

1 TRADE NAME OF THE MEDICINAL PRODUCT

Trimoptin Tablets 200 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains trimethoprim 200 mg.

Also contains 20mg lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Flat, white bevelled-edge tablets embossed 'TR 200'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of infections caused by trimethoprim-sensitive organisms including urinary and respiratory tract infections and prophylaxis of recurrent urinary tract infections.

4.2 Posology and Method of Administration

Trimoptin 200mg tablets are not recommended for use in children under 12 years of age. Other suitable dosage forms are available for this patient population.

1. Treatment of respiratory and urinary tract infections

Adults: 200mg twice daily for 7 – 10 days

The first dosage on the first day can be doubled.

Children

Over 12 years same as adult dose.

Not recommended for use in children under 12 years.

2. Prophylaxis of recurrent urinary tract infection:

Adults: The usual dose is 100mg at night. An extra 100mg may be taken in the morning if necessary.

Children

Over 12 years: same as adult dose.

Not recommended for use in children under 12 years.

3. Dosage in renal impairment

Creatinine Clearance (ml/sec)	Plasma creatinine (Micromole/l)	Dosage advised
Over 0.45	Men <250 Women <175	Normal
0.25 - 0.45	Men 250-600 Women 175-400	Normal for 3 days then half dose
Under 0.25	Men >600 Women >400	Half the normal dose

Trimethoprim is removed by dialysis. However, it should not be administered to dialysis patients unless plasma concentrations can be estimated regularly.

Route of administration: oral.

4.3 Contraindications

Hypersensitivity to Trimethoprim or any of the excipients. Severe hepatic insufficiency. Severe renal insufficiency, unless plasma levels can be monitored regularly. Megaloblastic anaemia and other blood dyscrasias. Trimethoprim should not be administered to premature infants or children under 6 weeks of age. Trimoptin should not be administered to pregnant women, (see section 4.6).

Patients with fragile X chromosome

Patients with porphyria

4.4 Special warnings and precautions for use

Patients with marked impairment of renal function: care should be taken to avoid accumulation and resulting adverse hepatological effect.

Trimethoprim may cause depression of haemopoiesis. Regular haematological tests should be undertaken in patients receiving long-term treatment and those predisposed to folate deficiency, (e.g. the elderly) to check for possible pancytopenia. If there is evidence of folic acid deficiency, calcium folinate should be administered and response checked by haematological monitoring. It may be necessary to discontinue trimethoprim. Particular care should be exercised in the haematological monitoring of children on long term therapy.

Close monitoring of serum electrolytes is advised in patients at risk of hyperkalaemia (see section 4.8).

Monitoring of blood glucose is advised if co-administered with rapaglinide (see section 4.5)

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Discontinue treatment if rash develops.

Prolonged use of an anti-infective may result in the development of super infection due to organisms resistant to that anti-infective.

4.5 Interaction with other medicinal products and other forms of interaction

Folate antagonists and anticonvulsants: Trimethoprim may induce folate deficiency in patients predisposed to folate deficiency such as those receiving concomitant folate antagonists or anticonvulsants.

Bone marrow depressants: Trimethoprim may increase the risk for bone marrow aplasia. Cytotoxic agents such as azathioprine, mercaptopurine and methotrexate increase the risk of haematologic toxicity when given with trimethoprim.

Phenytoin and Digoxin: Careful monitoring of patients treated with digoxin or phenytoin is advised as trimethoprim may increase plasma concentration of these agents by increasing their elimination half-life.

Rifampicin may decrease trimethoprim concentration.

Procainamide: Trimethoprim increases plasma concentration of procainamide

Diuretics: In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopenia with purpura. Rare cases of hyponatraemia have been reported in patients treated with trimethoprim and potassium sparing diuretics and/or thiazide diuretics. Hyperkalaemia may be exacerbated by concomitant administration of diuretics, particularly potassium sparing diuretics and/or thiazide diuretics and aldosterone antagonists (eplerenone).

Dapsone: Plasma concentrations of trimethoprim and dapsone may increase when taken together.

Repaglinide: Trimethoprim may enhance the hypoglycaemic effects of repaglinide, (see section 4.4).

Anticoagulants: Trimethoprim may potentiate the anticoagulant effect of warfarin and other coumarins.

ACE inhibitors: The likelihood of hyperkalaemia is increase when ACE inhibitors are taken with Trimethoprim.

Amiodarone: Increased risk of ventricular arrhythmia

Oral typhoid vaccine: Inactivated by antibacterials

Potassium-sparing diuretics and aldosterone antagonists: Increased risk of hyperkalaemia

Oral contraceptive: Reports of contraceptive failure after taking trimethoprim

Others: Increased risk of haematological toxicity with azathioprine, methotrexate, mercaptopurine, and pyrimethamine.

Dofetilide: Serum levels increased with trimethoprim

An increased risk of nephrotoxicity has been reported with the use of trimethoprim and cyclosporin.

Trimoptin may interfere with diagnostic tests including serum methotrexate assay where dihydrofolate reductase is used and the Jaffe reaction for creatinine.

4.6 Pregnancy and lactation

Trimoptin should not be given to pregnant women, premature infants or infants during the first few weeks of life.

Trimoptin is excreted in breast milk. This should be kept in mind when considering administration to breast-feeding women.

4.7 Effects on ability to drive and use machines

None that are known.

4.8 Undesirable effects

The following list of undesirable effects have been reported by health care professionals. Sometimes it may be difficult to distinguish reactions caused by the condition being treated from adverse drug reactions, which means that not all the listed reactions were caused by drug administration.

The frequencies of the undesirable effects listed below are categorised as follows:

Common: $\geq 1\%$ but $\leq 10\%$

Rare: $\geq 0.01\%$ but $\leq 0.1\%$

Very rare: $\leq 0.01\%$

Infections and Infestations

Common: Monilial overgrowth

Blood and lymphatic system disorders

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

Fatalities have been reported (especially in the elderly, or those with impairment of renal or hepatic function in whom careful monitoring is advised- refer to Section 4.3 Contraindications), however 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 resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus.

Metabolism and nutrition disorders

Very common: Hyperkalaemia

Very rare: Hypoglycaemia, hyponatraemia, anorexia

Close supervision is recommended when Trimoptin 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: Dyskinesias, aseptic meningitis, tremor, ataxia, dizziness, lethargy, syncope, paraesthesiae, convulsions, peripheral neuritis, vertigo, tinnitus.

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to Trimoptin alone.

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. Cholestatic jaundice and hepatic necrosis may be fatal.

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.

Lyell's syndrome (toxic epidermal necrolysis) carries a high mortality.

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia, myalgia

Renal and urinary disorders

Very rare: Impaired renal function (sometimes reported as renal failure), haematuria

Trimethoprim may affect haemopoiesis (See sections 4.4 & 4.5)

4.9 Overdose

Treat symptomatically, gastric lavage and forced diuresis can be used.

Depression of haematopoiesis by Trimoptin can be counteracted by intramuscular injections of calcium folinate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antibacterial.

ATC Code J01EA01

Mode of action

Trimethoprim is a dihydrofolate reductase inhibitor, inhibiting the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid, required for the synthesis of some amino acids.

Its effects are considerably greater on the cells of micro-organisms than on the mammalian cells.

In vitro trimethoprim has effect on most Gram-positive and Gram-negative aerobic organisms, including enterobacteria such as *E Coli*, *Proteus*, *Klebsiella pneumoniae*, *Streptococcus faecalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*.

It has no effect on *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, *Treponema pallidum*, *Brucella abortis* or anaerobic bacteria.

Mechanisms of resistance

Resistance to trimethoprim may be due to several mechanisms. Clinical resistance is often due to plasmid mediated dihydrofolate reductases that are resistant to trimethoprim: such genes may become incorporated into the chromosome via transposons. Resistance may also be due to overproduction of dihydrofolate reductase, changes in cell permeability, or bacterial mutants, which are intrinsically resistant to trimethoprim because they depend on exogenous thymidine and thymine for growth. Emergence of resistance to trimethoprim does not appear to be any higher in areas where it is used alone than in areas where trimethoprim is used in combination with sulphonamides. Nonetheless, trimethoprim resistance has been reported in many species, and very high frequencies of resistance have been seen in some developing countries, particularly among Enterobacteriaceae.

Breakpoints

EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens are:

EUCAST Species-related breakpoints (Susceptible\leq/Resistant$>$) Units: mg/L		
<i>Enterobacteriaceae</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>
$\leq 2 / > 4$	$\leq 2 / > 4$	$\leq 0.032 / > 1^*$

* The activity of trimethoprim is uncertain against enterococci. Hence the wild type population is categorized as intermediate.

Breakpoints for *S. pneumoniae* and *H. Influenzae* are not defined.

5.2 Pharmacokinetic properties

Trimoptin is readily absorbed from the gastro-intestinal tract and peak concentrations in the circulation occur about 3 hours after a dose is taken. It is bound to plasma proteins. Tissue concentrations are reported to be higher than serum concentrations with particularly high concentrations occurring in the kidneys and lungs but concentrations in the cerebrospinal fluid are about one half of those in the blood. About 40 to 50% of a dose is excreted in the urine within 24 hours mainly as unchanged drug; hence patients with impaired renal function, such as the elderly, may require a reduction in dosage due to accumulation. It appears in breast milk. Urinary concentrations are generally well above the MIC of common pathogens for more than 24 hours after the last dose

5.3 Preclinical safety data

Not relevant

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Povidone

Crospovidone

Sodium starch glycolate

Magnesium stearate

6.2 Incompatibilities

None applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package. Protect from light.

6.5 Nature and contents of container

Polypropylene tablet container with a high-density/low-density polyethylene blend cap and low-density polyethylene snap filler.

Pack sizes: 14, 15, 18, 20, 21, 28, 30, 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Athlone Laboratories Limited

Ballymurray

Co. Roscommon

Ireland

8 MARKETING AUTHORISATION NUMBER

PA 298/14/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 30 July 2004

Date of last renewal: 30 July 2009

10 DATE OF PARTIAL REVISION OF TEXT

17/01/2012