SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINALPRODUCT

Trimethoprim 200mg Tablets

2 QUALITATIVE AND QUANTITATIVECOMPOSITION

Each tablet contains Trimethoprim 200 mg.

Excipients with known effect

Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Uncoated tablet

Flat white tablet, with bevelled edges and embossed with 'TR200' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of susceptible infections caused by trimethoprim sensitive organisms including urinary and respiratory tract infections.

Prophylaxis of recurrent urinary tract infections.

4.2 Posology and method of administration

Acute infections:
Treatment should continue for a period of between 3 days (e.g., uncomplicated bacterial cystitis in women) to 2 weeks depending on the nature and severity of the infection.

The first dose may be doubled.
Adults: 200mg twice daily

Paediatric population
Children over 12 years: same as adult dose
Children 6 - 12 years: 100mg twice daily

Children under 6 years: This dosage form is not suitable for use in children younger than 6 years.
Elderly: Dosage is dependent on renal function. See special dosage schedule below.

Advised dosage schedule where there is reduced kidney function:

eGFR (ml/min)	Dosage advised
Over 30	Normal
15 - 30	Normal for 3 days then half dose
Under 15	Half the normal dose

Monitoring of renal function and serum electrolytes should be considered particularly with longer term use, in patients with impaired renal function.

Trimethoprim should only be initiated and used in dialysis patients under close supervision from specialists in both infectious disease and renal medicine. Trimethoprim is removed by dialysis.

Monitoring trimethoprim plasma concentration may be considered with long term therapy but the value of this in individual cases should first be discussed with specialists in infectious disease and renal medicine.

Long-term treatment and prevention therapy:
Adults: 100mg at night
Children over 12 years: Same as adult dose

Children 6-12 years: 50mg at night. Where a single daily dose is required, dosage at bedtime may maximise urinary concentrations. The approximate dosage in children is 2mg trimethoprim per kg body weight per day.

Elderly: Dose depends on renal function. Refer to special dosage schedule above.

Method of administration
For oral administration.

4.3 Contra-indications

Severe hepatic insufficiency.
Megaloblastic anaemia and other blood dyscrasias.
Trimethoprim should not be administered to premature infants or children under 4 months of age.
Trimethoprim should not be administered to pregnant women.

Hypersensitivity to trimethoprim or any other constituents of the medication. (listed in section 6.1)

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 haematological effect.

Monitoring of renal function and serum electrolytes should be considered particularly

with longer term use.

Trimethoprim should only be initiated and used in dialysis patients under close supervision from specialists in both infectious disease and renal medicine.

Regular haematological tests should be undertaken in patients receiving long term treatment and those predisposed to folate deficiency. The elderly may be more susceptible to folate deficiency and a lower dose may be advisable.

Patients and their carers should be told how to recognize signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. Particular care should be exercised in the haematological monitoring of children on long term therapy. Porphyria.

Elevations in serum potassium have been observed in some patients treated with trimethoprim. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, poorly controlled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, renin angiotensin system inhibitors (e.g.: ACE inhibitors or renin angiotensin receptor blockers), or those patients taking other drugs associated with increases in serum potassium (e.g., heparin). If concomitant use of the above-mentioned agents is deemed appropriate, monitoring of serum potassium is recommended (see section 4.5).

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

This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free

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 hematologic toxicity when given with trimethoprim.

Special care is necessary in patients receiving pyrimethamine in addition to trimethoprim due to increased risk of antifolate effect.

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 and increases the antifolate effect of phenytoin..

Rifampicin may decrease trimethoprim concentrations.

Diuretics: In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopenia with purpura.

Concomitant use of drugs that may increase serum potassium levels may lead to a significant increase in serum potassium. Potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, renin-angiotensin system inhibitors (e.g.: ACE inhibitors or renin angiotensin receptor blockers) and other potassium increasing substances (e.g.: heparin). Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Cyclosporin: Increased risk of nephrotoxicity.

Procainamide: Trimethoprim increases plasma concentrations of procainamide.

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

Repaglinide: Trimethoprim may enhance the hypoglycaemic effects of repaglinide.

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

Antibacterials: Plasma concentration of trimethoprim is possibly reduced by rifampicin. Plasma concentration of both drugs may increase when trimethoprim is given with dapsone.

Antimalarials: Increased antifolate effect when trimethoprim is given with pyrimethamine.

4.6 Fertility, pregnancy and lactation

Pregnancy
The usual caution in prescribing any drug for women of child-bearing age should be exercised with Trimethoprim.

Breast-Feeding
Trimethoprim is not contra-indicated for short-term use in lactating mothers, although the drug is excreted in breast milk.

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 most frequent adverse effects at usual doses are pruritus and skin rash (in about 3 to 7% of patients) and mild gastrointestinal disturbances including nausea, vomiting and

glossitis. These effects are generally mild and quickly reversible on withdrawal of the drug.

Infections and Infestations

Common: Monilial overgrowth

Blood and lymphatic system disorders

Very rare: Leucopenia, neutropenia, thrombocytopenia, pancytopaenia, bone marrow depression, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, purpura, haemolysis,
Unknown: Megaloblastic anaemia, methaemoglobinaemia, hyperkalaemia (particularly in the elderly and in HIV patients), methaemoglobinaemia. Trimethoprim therapy may effect haematopoiesis.

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, anaphylactoid reaction 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 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 behavior, 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 Trimethoprim 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.
Unknown: Sore mouth, Gastro-intestinal disturbance

Hepatobiliary disorders

Very rare: Disturbance in liver enzymes, 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 nodusum, Stevens-Johnson Syndrome, toxic epidermal necrolysis, bullous dermatitis, purpura, angioedema
Unknown: Pruritis
Lyell's syndrome (toxic epidermal necrolysis) carries a high mortality.

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia and myalgia

Renal and urinary disorders
Very rare: Impaired renal function (sometimes reported as renal failure), haematuria
Unknown: Raised serum creatinine and blood urea nitrogen levels. It is not known however, whether this represents inhibition of creatinine tubular secretion or genuine renal dysfunction.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Treat symptomatically, gastric lavage and forced diuresis can be used.
Depression of haematopoiesis by trimethoprim can be counteracted by intramuscular injections of calcium folinate.

5 PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Systemic antibacterial. ATC Code: J01EA01

Mechanisms of action

Trimethoprim is a dihydrofolate reductase inhibitor which affects the nucleoprotein metabolism of micro-organisms by interference in the folic-folinic acid systems, 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. Trimethoprim may be bactericidal or bacteriostatic depending on growth conditions.

In vitro trimethoprim has effects 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.

Mechanism(s) 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.

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

EUCAST Species-related breakpoints (Susceptible□/Resistant>) Units:		
Enterobacteriac	***Staphylococcu***	***Enterococcus***
□2/>4	□2/>4	□0.032/>1*

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

5.2 Pharmacokinetic Properties

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal track and peak concentration in the circulation occur about 1-4 hours after an oral dose. Peak plasma concentrations of about 1µg/ml have been reported after a single dose of 100mg. Approximately 40-70% 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 60% of a dose is excreted in the urine within 24 hours (mainly as unchanged drug) together with metabolites; hence, patients with impairment of renal function such as the elderly may require a reduction in dosage due to accumulation. Urinary concentrations are generally well above the MIC of common

pathogens for more than 24 hours after the last dose. The half-life is approximately 8- 10 hours. It appears in breast milk.

5.3 Preclinical Safety Data

Not relevant

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K30
Crospovidone
Sodium starch glycolate (Type A)
Magnesium stearate
Purified water

6.2 Incompatibilities

None reported

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25^{o}C in a dry place. Protect from light.

6.5 Nature and contents of container

Polypropylene securitainer of 14/15/18/20/21/28/30/100/500 100 or 500 tablets with appropriate bellows or polyurethane foam wads.
Also available in a PVC blister with aluminium lidding foil containing 6, 14 and 28 tablets.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited,
2nd Floor, Connect 38,
1 Dover Place, Ashford, Kent, England, TN23 1FB.

8 MARKETING AUTHORISATION NUMBER

PL 51463/0119

9 DATE OF FIRST AUTHORISATION/RENEWAL OFAUTHORISATION

22/09/2005

10 DATE OF REVISION OF TEXT

19th July 2023