SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimethoprim 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Trimethoprim 200mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet: white coloured flat bevelled edged tablets engraved with 'MT200'.

Slight characteristic odour.

4 CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

4.2. Posology and method of administration

Posology

Acute infections*:*
Treatment should continue for a period of between three days (e.g. uncomplicated bacterial cystitis in women) to two weeks depending on the nature and severity of 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 of age: This dosage form is not suitable for use in children younger than 6 years.
Elderly: Dosage is dependent upon 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

Paediatric Population:
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. Contraindications

Hypersensitivity to trimethoprim or any other constituents of the medication (listed in section 6.1).
Trimethoprim should not be administered to pregnant women.
First trimester of pregnancy (see section 4.6)
Megaloblastic anaemia and other blood dyscrasias.
Severe hepatic insufficiency.
Trimethoprim should not be administered to premature infants or children under 4 months of age.

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 (e.g. the elderly) to check for possible pancytopaenia. Although an effect on folate metabolism is possible, interference with haematopoiesis rarely occurs at the recommended dose. If any such change is seen, folinic acid should reverse the effect.

Elderly people may be more susceptible and a lower dose may be advisable. Patients and their carers should be told how to recognise 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.

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).

Caution should be used in patients with acute porphyria.

Severe cutaneous adverse reactions (SCARs)
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with trimethoprim treatment (see section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, trimethoprim should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of trimethoprim, the treatment must not be restarted in this patient at any time.

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

4.5. Interactions 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.

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

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 due to increased risk of antifolate effect.

Special care is necessary in patients receiving pyrimethamine in addition to trimethoprim.

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

Diuretics: In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopaenia 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 (eg: ACE inhibitors or renin angiotensin receptor blockers) and other potassium increasing substances (eg: heparin). Monitoring of potassium should be undertaken as appropriate (see section 4.4).

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.

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 potentiate the anticoagulant effect of warfarin and other coumarins.

Ciclosporin: Increased risk of nephrotoxicity.

4.6. Fertility, Pregnancy and Lactation

<u>Pregnancy</u>

The usual caution in prescribing any drug for women of child-bearing age should be

exercised with Trimethoprim.

Trimethoprim is contraindicated during the first trimester of pregnancy (see section 4.3). Studies in animals have shown a teratogenic effect.

Epidemiological studies have shown an increased risk of spontaneous abortion and congenital malformations, in particular neural tube defects, oral clefts and cardiovascular defects, in children of mothers treated with trimethoprim during the first trimester of pregnancy. The presumed mechanism of action is thought to be interference with folates.

In the second and third trimesters, use should be avoided, unless clinically necessary.

Breast-feeding
Trimethoprim is not contraindicated 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 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 affect 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 behaviour, insomnia and nightmares.
Very rare: Hallucinations
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 nodosum, Stevens-Johnson Syndrome, toxic epidermal necrolysis, bullous dermatitis, purpura, angioedema
Unknown: Pruritis
Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS)

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 at: 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 PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic Group: Systemic antibacterial. ATC Code: J01EA01

Mechanism 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 microorganisms than on the mammalian cells. Trimethoprim may be bactericidal or bacteriostatic depending on growth conditions.

Trimethoprim is effective *in vitro* against a wide range of Gram-positive and aerobic Gram-negative organisms, including enterobacteria *Escherica coli, Proteus, Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus faecalis, Haemophilus influenzae* and *Staphylococcus aureus*.

It has no effect on *Pseudomonas aeruginosa, Treponema pallidum, Mycobacterium tuberculosis, Neisseria gonorrhoeae, 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.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for trimethoprim and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-micbreakpoints en.xlsx

5.2. Pharmacokinetic Properties

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations 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 40-60% of a dose is excreted unchanged 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 applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose
Povidone 25cps
Crospovidone
Sodium starch glycollate
Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container.

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polythene lids and polyurethane or polythene inserts.

Blister pack - 25 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade) 20 micron hard-tempered aluminium foil coated on the pull side with 6-7gsm heat seal lacquer and printed on the bright side.

Pack sizes: 50, 100, 500, 1000, 5000 (Bulk pack), 6, 14 & 28 (blister pack)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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