SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimethoprim 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of Trimethoprim

Excipient with known effect: Also contains Lactose monohydrate 22.50 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

White to off-white circular, flat bevelled edged uncoated tablets with breakline dividing “TMP” and “200” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Long-term prophylaxis of recurrent urinary tract infections.

Consideration should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology:

Acute infections:

Adults and Children over 12 years: 200 mg twice daily

Children 6 years to 12 years: 100 mg twice daily

Children under 6 years of age: Not recommended; a more suitable dosage form should be used in this age group.

Elderly: Depending on kidney function, see special dosage schedule.

Treatment should continue for a period of between three days (e.g. uncomplicated bacterial cystitis in women) and two weeks according to the nature and severity of the infection. The first dose can be doubled.

Long-term treatment and prophylactic therapy:

Adults and children over 12 years: 100 mg at night

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 2 mg trimethoprim per kg body weight per day.

Children under 6 years of age: Not recommended, a more suitable dosage form should be used in this age group.

Elderly: Dosage is dependent on kidney function, see special dosage schedule.

Dosage advised where there is reduced kidney function:

Creatinine clearance (ml/sec)	Plasma clearance (micromol/l)		Dosage advised
Over 0.45	Men	< 250	Normal
	Women	< 175	
0.25 – 0.45	Men	250 – 600	Normal for three days then half dose
	Women	175 – 400	
Under 0.25	Men	> 600	Half the normal dose
	Women	> 400	

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

Method of administration:

For oral use.

4.3 Contraindications

- Hypersensitivity to trimethoprim or any of the excipients listed in section 6.
- Severe hepatic insufficiency. Severe renal 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.

4.4 Special warnings and precautions for use

Administer with care to patients with impaired renal function.

Trimethoprim may cause depression of haemopoiesis. Regular haematological examination should be performed during long-term therapy and for those

predisposed to folate deficiency (e.g. the elderly), to check for possible pancytopenia.

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. If there is evidence of folic acid deficiency, calcium folinate should be administered and response checked by haematologic monitoring. It may be necessary to discontinue trimethoprim. Particular care should be exercised in the haematological monitoring of children on long term therapy.
In patients with renal impairment, care should be taken to avoid accumulation.

Concomitant use of medicinal products known to cause hyperkalaemia like Trimethoprim with spironolactone may result in severe hyperkalaemia.

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

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

Trimethoprim has been associated with acute attacks of porphyria. Trimethoprim use in patients with acute porphyria is not recommended.
This product contains the excipient lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Rifampicin: Rifampicin may increase the elimination and shorten the elimination half-life of trimethorpim.

Phenytoin and digoxin: The patients should be carefully controlled as trimethoprim may increase plasma concentration of these agents by increasing the elimination half-life of phenytoin and digoxin.

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

Ciclosporin: Ciclosporin may increase the nephrotoxicity of trimethoprim.

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

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

Diuretics: In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopaenia with purpura. Hyperkalaemia may be exacerbated by concomitant administration of diuretics, particularly potassium sparing diuretics and/or thiazide diuretics and eplerenone.

In addition to other medicinal products known to cause hyperkalaemia concomitant use of trimethoprim with spironolactone may result in clinically relevant hyperkalaemia.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Trimethoprim should not be given to pregnant women (see section 4.3), premature infants or infants during the first few weeks of life. There are not any adequate data from the use of trimethoprim in pregnant women. Case-control studies have shown

that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, trimethoprim has been shown to cause foetal abnormalities (see section 5.3)

Lactation

Although Trimethoprim is excreted in breast milk, it is not necessarily contraindicated for short-term therapy during lactation. This should be kept in mind when considering administration to breast- feeding women.

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, , haemolysis,

Unknown: Megaloblastic anaemia, methaemoglobinaemia , hyperkalaemia (particularly in the elderly and in HIV patients), 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.

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, gastrointestinal disturbances

Hepatobiliary disorders
Very rare: Disturbance in liver enzyme values, 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, 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
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.

4.9 Overdose

Symptoms

Acute overdose may cause nausea, vomiting, dizziness, ataxia, drowsiness, dysuria, headache and confusion. Hyperkalaemia and hyponatraemia are also possibilities. Occasionally rashes may occur.

Chronic overdose may cause bone marrow depression and this has been reported in acute overdose.

Management

Gut decontamination is unlikely to be of benefit. Observe these patients for at least 4 hours after ingestion, Check blood Urea &Electrolytes and correct imbalances. Check the full blood count at 48 hours post ingestion in patients who have ingested more than 50 mg/kg.

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: Antibacterial for systemic use

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 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, Nocardia species, 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: mg/L

Enterobacteriaceae	*Staphylococcus*	*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 readily absorbed from the gastro-intestinal tract and peak concentrations in the circulation occur about 1-4 hours after a dose is taken. 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

Reproductive toxicology:

At doses in excess of recommended human therapeutic dose, trimethoprim have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
povidone K-25
crospovidone
sodium starch glycolate

magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blisters: 36 months

HDPE tablet containers: 36 months

6.4 Special precautions for storage

Blisters: Do not store above 25^{o}C. Store in the original package.

HDPE Tablet containers: Do not store above 25^{o}C. Store in the original container. Keep the container tightly closed.

6.5 Nature and contents of container

HDPE tablet containers, pack sizes of 50, 100, 250 and 500 tablets.

Al/PVC Blisters, pack sizes of 14, 28, 56 and 84 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal and other handling**

No special requirements

7 MARKETING AUTHORISATION HOLDER

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11/09/2017