SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trimethoprim 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of trimethoprim.

Excipients with known effect

Each tablet contains 67.5 mg lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, normal biconvex tablets, engraved Berk 2H7 or 2H7 with a breakline on reverse.
The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trimethoprim is indicated for the treatment of susceptible infections caused by trimethoprim-sensitive organisms including urinary tract and respiratory tract infections.

Trimethoprim is also indicated for the prevention of recurrent urinary tract infections.

4.2 Posology and method of administration

Posology

Acute infections:
Adults and children over 12 years of age: 200 mg twice daily
Children 6 years to 12 years: 100 mg twice daily
Children under 6 years of age: This dosage form is not suitable for use in children younger than 6 years, a more suitable dosage form (such as a suspension) should be used in this age group.
Elderly: Depending on kidney function, see special dosage schedule.

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 can be doubled.

Long-term treatment and prophylactic therapy:
Adults and children over 12 years: 100 mg at night
Children 6 years to 12 years of age: 50 mg at night. Where a single dose is required, dosage at bedtime may maximise urinary concentrations. The approximate dosage in children is 2mg trimethoprim per kg body weight per day. This dosage form is not suitable for use in children younger than 12 years, a more suitable dosage form (such as a suspension) should be used in this age group.
Elderly: Depending on kidney function, see special dosage schedule.

Dosage advised 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.

Method of administration:
For oral administration.

4.3 Contra-indications

Trimethoprim is contra-indicated in pregnancy, hypersensitivity to trimethoprim or to any of the excipients listed in section 6.1, megaloblastic anaemia and blood dyscrasias and severe hepatic insufficiency.

4.4 Special warnings and precautions for use

In patients with marked impairment of renal function, care should be taken to avoid accumulation and resulting adverse haematological effects. 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.

Caution should be exercised in the administration of trimethoprim to patients with actual or potential folate deficiency (e.g. the elderly). Administration of a folate supplement should be considered. Although an effect on folic acid metabolism is possible, interference with haematopoiesis rarely occurs at the recommended dose. If any such change occurs, folinic acid should reverse the effect. Elderly people may be more susceptible and a lower dose may be advisable.

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. 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 haematological monitoring. It may be necessary to discontinue trimethoprim. Particular care should be exercised in the haematological monitoring of children on long term therapy. The usual caution in prescribing any drug for women of child bearing age should be exercised with trimethoprim.

Trimethoprim should be used under careful medical supervision in neonates.

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

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

Caution should be used in patients with acute porphyria.

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

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, 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.

Anti-arrhythmics: Trimethoprim increases plasma concentrations of procainamide.

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

Cytotoxics: Increased risk of haematological toxicity when trimethoprim is given with azathioprine or mercaptopurine. Trimethoprim increases the antifolate effect of methotrexate therefore use should be avoided. Special care is necessary in patients receiving pyrimethamine in addition to trimethoprim.

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

Bone marrow depressants: Trimethoprim may increase the potential for bone marrow aplasia.

Digoxin and phenytoin: Trimethoprim may increase the elimination half-life of phenytoin and digoxin therefore patients should be carefully controlled.

Ciclosporin may increase the nephrotoxicity of trimethoprim.

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

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

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.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy
Trimethoprim is contra-indicated in pregnant women, premature infants or infants during the first few weeks of life.

Breast-feeding
Trimethoprim is excreted in breast milk but is not contra-indicated for short term use in lactating mothers.

This should be kept in mind when considering administration to breast-feeding women.

4.7 Effects on ability to drive and use machines

There are no reported effects on the ability to drive or operate machines.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

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.

Not Known: Isolated cases of megaloblastic anaemia during prolonged therapy with trimethoprim, with higher doses than those recommended, have been reported. These effects are reversible with discontinuation of therapy and administration of calcium folinate.

Not Known: Trimethoprim 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 (see section 4.3)), 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 (particularly in the elderly and in HIV patients)

Very Rare: Hypoglycaemia, hyponatraemia, anorexia.

Close supervision is recommended when Trimethoprim Tablets 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 Tablets alone.

Eye disorders

Very Rare: Uveitis.

Respiratory, thoracic and mediastinal disorders

Very Rare: Cough, shortness of breath, wheeze, epistaxis.

Gastrointestinal disorders

Rare: Nausea, vomiting, gastrointestinal disturbances

Very Rare: Constipation, glossitis, stomatitis, pseudomembranous colitis, pancreatitis

Not Known: Sore mouth

Hepatobiliary disorders

Very Rare: Disturbances in liver enzyme values, elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

Renal and Urinary disorders

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

Not Known: 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

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.

Not Known: Pruritus

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

Musculoskeletal system disorders

Very Rare: Myalgia, arthralgia

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

Symptomatic treatment, gastric lavage and forced diuresis can be used. Depression of haematopoiesis by trimethoprim can be counteracted by intramuscular administration of calcium folinate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01EA01 Sulfonamides And Trimethoprim (*Trimethoprim and derivatives*)

Mechanism of action
Trimethoprim inhibits dihydrofolate reductase and thus prevents the synthesis of tetrahydrofolic acid from dihydrofolic acid, required for the synthesis of some amino acids. It therefore affects the nucleoprotein metabolism of micro-organisms by interference in the folic-folinic acid systems.

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.

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: 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 categorised 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 per ml have been reported after a single dose of 100mg. About 40 to 70% is bound to plasma proteins. Tissue concentrations are reported to be higher than serum concentrations with particularly high concentrations in the kidneys and lungs. Concentrations in the cerebrospinal fluid (CSF) are about half that of those in bloodAbout 40-60 % of the 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

Preclinical information has not been included because the safety profile of trimethoprim has not been established after many years of clinical use. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet contains:
Lactose Monohydrate
Maize Starch
Microcrystalline Cellulose
Sodium Starch Glycolate (Type A)
Povidone
Colloidal Anhydrous Silica
Magnesium Stearate
Stearic Acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 24 months
Containers/buckets: 36 months.

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

Blister strips in packs of 7, 10, 14, 20, 21, 28, 30, 56, 60, 70, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

Polythene container with lid in a pack of 5000 tablets.

HDPE or polypropylene containers with caps or child resistant closures in packs of 28, 100 and 500 tablets.

6.6 Instructions for use/handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road, Hampden Park,
Eastbourne, East Sussex, BN22 9AG

8. MARKETING AUTHORISATION NUMBER

PL 00289/0196

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

25/07/96

10. DATE OF REVISION OF THE TEXT

16/01/2023