SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimethoprim 50 mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 50 mg of Trimethoprim

Excipients with known effect
Also contains:
Sodium methyl parahydroxybenzoate (E219) 8.6mg/5ml (0.172 % w/v)
Sodium propyl parahydroxybenzoate (E217) 2.25mg/5ml (0.045%w/v)
Sodium benzoate (E211) 0.06 mg/5ml
Maltitol Liquid 2g/5ml
Polysorbate 80 4.250mg/5ml
See section 4.4

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.
White opaque smooth suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trimethoprim is indicated for the prevention and treatment of urinary tract infections in adults and children, and the treatment of other susceptible infections in adults and children caused by a wide range of trimethoprim sensitive Gm +ve and Gm -ve organisms including *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, E.coli, Enterobacter, Proteus* and *Streptococcus faecalis.*

4.2 Posology and method of administration

Posology

Adults & Children over 12 years of age

Treatment of urinary tract infections and all other susceptible infections: 200 mg (20 ml) twice daily.

Long-term prevention of recurrent urinary tract infections: 100 mg (10 ml) at night.

Children 6 weeks to 12 years of age

Treatment of urinary tract infections is based on a dosage of 8 mg/kg body weight daily, subdivided into two equal doses. Suggested regimens are:

6 weeks - 5 months	-	25 mg (2.5 ml) twice daily
6 months - 5 years	-	50 mg (5 ml) twice daily
6 years - 12 years	-	100 mg (10 ml) twice daily

Long-term prevention of recurrent urinary tract infection is based on 2 mg/kg body weight daily given as a single dose at night. Suggested regimens are:

6 months - 5 years	-	25 mg (2.5 ml) at night
6 years - 12 years	-	50 mg (5 ml) at night

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.

Elderly

Depending on kidney function, see special dosage schedule.

Method of administration

For oral administration

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Trimethoprim is contra-indicated in severe hepatic insufficiency. Trimethoprim is contra-indicated in megaloblastic anaemia and other blood dyscrasias.

Trimethoprim should not be administered to women in their first trimester of pregnancy (see section 4.6), premature infants or children under 4 months.

4.4 Special warnings and precautions for use

Care is necessary in administration to patients with impaired renal function. Regular haematological tests should be performed during long term therapy.

In patients with renal impairment, care should be taken to avoid accumulation. 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.

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 pancytopaenia. 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.

Isolated cases of megaloblastic anaemia during prolonged therapy with trimethoprim in doses higher than those recommended have been reported but these are reversible with discontinuation of therapy and administration of calcium folinate.

If a patient has a known or suspected risk of acute prophyria, treatment with trimethoprim should be avoided.

Close monitoring of serum electrolytes is advised in patients at risk for 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).

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.

Trimethoprim Oral Suspension contains sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217). These may cause allergic reactions (possibly delayed).
It also contains maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicine contains 4.250mg of polysorbate per 5ml of suspension which is equivalent to 0.85mg per ml. Polysorbates in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

This medicine contains 0.06mg of sodium benzoate per 5 ml of suspension which is equivalent to 0.012mg per ml. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

This medicine contains less than 1 mmol sodium (23 mg) per 5ml of suspension, 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 potential for bone marrow aplasia.

Cytotoxics such as azathioprine, mercaptopurine, methotrexate, increase the risk of haematologic toxicity when given with trimethoprim. Special care is necessary in patients receiving pyrimethamine in addition to 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 concentrations.

Diuretics: In elderly patients concurrently taking diuretics, primarily 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 (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).

Ciclosporin: Increased risk of nephrotoxicitiy.

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
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.

Breastfeeding
Trimethoprim is excreted in breast milk. Effects on the suckling child are likely if therapeutic doses are administered to breast-feeding mothers. Trimethoprim is contraindicated if the breastfed infant is less than 4 months of age.

Fertility
Not known

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

The following list of undesirable effects have been reported by healthcare 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.

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: Megaloblastic anaemia, methaemoglobinaemia, depression of

haematopoiesis. Fatalities have been reported (especially in the elderly, or those with impairment of renal or hepatic function in whom careful monitoring 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 arythematosus.

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.

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: 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.
Not known: Pruritus, 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, myalgia and uveitis.

Renal and urinary disorders
Very rare: Impaired renal function (sometimes reported as renal failure), haematuria.

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

Treatment of overdosage: 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

Pharmacotherapeutic group: Systemic antibacterial, ATC code: J01EA01

Mechanism 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. 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/		
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 3 hours after a dose is taken. About 45% 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 CSF are about half that of those in blood. The half life is about 10-16 hours. 40-50% of the dose is excreted unchanged in the urine within 24 hours.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460) and carboxymethyl cellulose sodium (E466)
Xanthan Gum Food grade (E415)
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)
Liquid Maltitol (E965)
Sodium Saccharin (E954)
Polysorbate 80 (E433)
Citric acid anhydrous (E330)
Anise natural AF-3006 Flavour (Acacia Gum (E 414), Dextrose & Maize Starch, Sodium benzoate (E211), Sorbic acid (E 200), Citric acid (E 330), Butylated Hydroxyanisole (E320), Anise Oil (Natural))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months, unopened
Shelf-life after first opening of the bottle: 3 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottle with a polypropylene child-resistant cap with a polypropylene inner liner containing 100ml of suspension.
A polypropylene measuring spoon of 2.5/5 ml is supplied to help measure the dose.
Pack size: 100 ml.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

DAWA Limited
5 Sandridge Close
Harrow
Middlesex
HA1 1XD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30684/0364

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/05/2023

10 DATE OF REVISION OF THE TEXT

21/02/2026