SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimethoprim DAWA 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg Trimethoprim
One tablet contains 22.80 mg of lactose (see section 4.4).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White coloured, round, flat bevelled edge (8.10mm) tablets embossed with 'Rx' on one side & '100' on 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 on the appropriate use of antibacterial agents.

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) and two weeks according to the nature and severity of infection. The first dose can be doubled.

- Adults and children over 12 years: 200mg twice daily.
- Children 6-12 years: 100mg twice daily.
- Children under 6 years of age: Not recommended; a more suitable dosage form should be used this age group.

- Elderly: Dosage is dependent upon kidney function; see special dosage schedule.

Long-term treatment and prophylactic therapy:

- Adults and children over 12 years: 100mg at night.
- Children 6-12 years: 50mg at night. Where a single daily dose is required, dosage at bedtime may
  maximize urinary concentrations. The approximate dosage in children is 2mg trimethoprim per kg body weight per day.
- Elderly: Dosage is dependent upon kidney function; see special dosage schedule

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 should be discussed with specialists in infectious disease and renal medicine.
Route of administration: Oral.

4.3 Contraindications

Hypersensitivity to trimethoprim or any of the excipients.

First trimester of pregnancy (see section 4.6).

Severe hepatic insufficiency.

Megaloblastic anaemia and other blood dyscrasias.

Trimethoprim should not be administered to premature infants or children under 4 months of age.

4.4 Special warnings and precautions for use

Administer with care to patients with impaired renal function. Monitoring of renal function and serum electrolytes should be considered particularly with

longer term use. In patients with renal impairment, care should be taken to avoid accumulation.
Trimethoprim should only be initiated and used in dialysis patients under close supervision from specialists in both infectious disease and renal medicine.

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).

Trimethoprim may cause depression of haemopoiesis. Regular haematological tests should be undertaken in patients receiving long term treatment and in those with actual or potential folate deficiency (e.g. the elderly) to check for possible pancytopaenia and administration of folate supplement should be considered. 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.

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 Lapp lactase deficiency or glucose-galactose malabsorbtion should not take this medicine.

Trimethoprim has been associated with acute attacks of porphyria. Trimethoprim use in patients with acute porphyria is not recommended.

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

4.5 Interaction with other medicinal products and other forms of interaction

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).

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 :

Special care is necessary patients receiving antimalarial such as pyrimethamine therapy in addition to trimethoprim. Increased antifolate effect when trimethoprim is given with pyrimethamine

Dapsone:

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

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 trimethoprim.

Phenytoin and digoxin.

The patient should be carefully monitored as trimethoprim may increase the elimination half-life of phenytoin and digoxin.

Anticoagulants

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

Other drugs

Ciclosporin may increase the nephrotoxicity of trimethoprim.

Trimethoprim increases plasma concentrations of procainamide.

Trimethoprim may enhance the hypoglycaemic effects of repaglinide.

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.

Breast-feeding

Although trimethoprim is excreted in breast milk, it is not necessarily contraindicated for short- term therapy during lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

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.The adverse affected are displayed by system organ class and frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), (and not known (cannot be estimated from the available data).

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to <1/10)**	**Very rare (<1/10,000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations		Monilial overgrowth		
Blood and lymphatic system disorders[1]			Leucopenia, thrombocytopenia, agranulocyctosis, neutropenia, pancytopaenia, bone marrow depression, aplastic anemia, haemolytic anemia, eosinophilia, purpura, haemolysis	Megaloblastic anaemia, methaemoglobinaemia. Trimethoprim therapy may affect haematopoiesis
Immune system disorders			Hypersensitivity, anaphylaxis, anaphylactoid reaction, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus	
Metabolism and nutrition disorders	Hyperkalemia (particularly in The elderly and in HIV patients),		Hypoglycemia, hyponatraemia[2], anorexia	

Psychiatric disorders			Depression, Hallucinations, confusional states, agitation, anxiety, abnormal behavior, insomnia and nightmares	
Nervous system disorders		Headache.	Dyskinesias, aseptic meningitis[3], tremor, ataxia, dizziness, lethargy, syncope, paraesthesiae, convulsions, peripheral neuritis, vertigo, tinnitus	
Eye disorders			Uveitis	
Respiratory, Thoracic and mediastinal disorder			Cough, shortness of breath, wheeze, epistaxis	
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Glossitis, constipation, stomatitis, pseudomembranous colitis, pancreatitis	Gastrointestinal disturbances, sore mouth
Hepatobiliary disorder			Disturbances in liver enzyme values, elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis[4]	
Skin and subcutaneous disorder		Skin rashes, urticaria	Exfoliative dermatitis, photosensitivity, angioedema, erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis[5], fixed drug eruption, erythema nodusum, bullous dermatitis, purpura	Pruritus, Drug reaction with eosinophilia and systemic symptoms (DRESS).

Musculoskeletal and connective tissue disorders			Myalgia. arthralgia	
Renal and urinary disorders			Impaired renal function (sometimes reported as renal failure), haematuria	Raised serum creatinine and blood urea nitrogen levels[6]

[1] 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.

[2] 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

[3] 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.

[4] Cholestatic jaundice and hepatic necrosis may be fatal.

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

[6] 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**. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

Acute overdose may cause nausea, vomiting, dizziness, ataxia, drowsiness, dysuria, and 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 Treat symptomatically, gastric lavage and forced diuresis may be used. Depression of haematopoiesis by trimethoprim may be countered 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.
Trimethoprim is effective *in vitro* against aerobic gram-negative organisms, including
Escherichia coli, Proteus, Klebsiella pneumonia and many gram-positive cocci.

It is not effective against anaerobes, *Pseudomonas aeruginosa, Treponema pallidum, Mycoplasma* spp., *Mycobacterium tuberculosis, Nocardia species, Neisseria* species and *Brucella abortus.*

Acquired resistance is common in *S. pneumoniae,* enterococci and many enterobacterales.

Mechanism(s) of resistance

Resistance to trimethoprim may be due to several mechanisms: (1) permeability barrier and/or efflux pumps, (2) naturally insensitive target enzymes, (3) regulational changes in the target enzymes, (4) mutational or recombinational changes in the target enzymes, and (5) acquired resistance by drug-resistant target enzymes. The mechanism of greatest clinical importance for TMP is the production of plasmid-encoded, trimethoprim-resistant forms of dihydrofolate reductase. Trimethoprim resistance has been reported in many species.
EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens v. 10.0, valid from 2020-01-01:

EUCAST Species-related breakpoints (Susceptible/ Resistant) #			
Enterobacterales	*Staphylococcus* spp.	*Enterococcus* spp.	*S. agalactiae* (group B streptococci)
S≤4 / R >4	S≤4 / R >4	*	S≤2 / R >2

#Breakpoints are valid for uncomplicated UTI only.

*The activity of trimethoprim is uncertain against enterococci and it is not possible to predict clinical outcome. The ECOFF to categorise isolates as wild type or non-wild type for both *E. faecalis* and *E. faecium* is 1 mg/L.

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.The half life is approximately 8-10 hours. About 40-60% of a dose is excreted unchanged in the urine within 24 hours, together with metabolites; hence, patients with impairment of renal function such as the elderly may require a reduction in dosage due to accumulation. It appears in breast milk.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber additional to that included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Sodium starch glycollate
Microcrystalline cellulose
Povidone K30
Magnesium stearate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Blister pack - Tablets packed in a blister strip made of PVC/PVDC (90GSM) and aluminium foil 0.25µ, White blister pack.

Pack sizes are:
Blister pack- 6, 10, 14, 28 & 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Dawa Limited

5, Sandridge Close,

Harrow, Middlesex,

HA11XD,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30684/0310

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/07/2021

10 DATE OF REVISION OF THE TEXT

10/01/2026