NEW ZEALAND DATA SHEET

TMP

1. Product Name

TMP 300 mg tablets.

2. Qualitative and Quantitative Composition

Each tablet contains 300 mg of trimethoprim.

Excipients with known effect: lactose monohydrate; povidone and sodium starch glycollate (source of sulfites).

Allergen Declaration: contains lactose and sulfites.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

TMP 300 mg tablets are white, normal convex, imprinted TM/300 on one side, and G on the other side.

This product is not able to deliver all approved dose regimens.

4. Clinical Particulars

4.1 Therapeutic indications

TMP tablets are indicated for the treatment of acute urinary tract infections.

TMP tablets are also indicated for long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following sterilisation of the urine.

4.2 Dose and method of administration

This product is not able to deliver all approved dose regimens.

Dose

Acute urinary tract infections

Adults and children over 12 years: 300 mg once daily

Children aged 6 to 12 years: 150 mg once daily

Children aged 6 months to 5 years: 75 mg once daily

Children aged 6 weeks to 5 months: 40 mg once daily

This dosage approximates to 6 mg/kg bodyweight/day. The recommended duration of treatment will vary according to medical practice in different countries.

Long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following sterilisation of the urine

Adults and children over 12 years: 100 mg once daily

Children aged 6 to 12 years: 50 mg once daily

Children aged 6 months to 5 years: 25 mg once daily

This dosage approximated to 2 mg / kg bodyweight/day.

Treatment may be continued for 3 to 12 months or more as appropriate.

Trimethoprim does not induce its own metabolism and therefore no dose modification is required on this account during long term treatment.

Special populations

Renal impairment

When a patient is known to have a creatinine clearance below 15 to 20 ml/minute trimethoprim plasma levels should be monitored after approximately 3 days of treatment. When clearance is below 10 ml/minute TMP should not be administered unless plasma concentrations can be estimated regularly and haemodialysis facilities are available.

Method of administration

To ensure maximal urinary concentrations it may be advantageous to take the dose before bedtime. The dose may be taken with food to minimise the possibility of gastrointestinal disturbance.

4.3 Contraindications

Trimethoprim should not be given to patients with a history of trimethoprim hypersensitivity, or a hypersensitivity to any of the excipients listed in section 6.1.

Severe hepatic insufficiency. Megaloblastic anaemia and other blood dyscrasias.

Patients with severely impaired renal function (creatinine clearance less than 10 ml/minute) should not be prescribed trimethoprim unless the plasma concentration of trimethoprim is monitored repeatedly during treatment.

Trimethoprim should not be given to patients with severe haematological disorders or documented megaloblastic anaemia due to folate deficiency.

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

Possible folate deficiency

Care should be exercised in treating suspected folate deficient patients. Folate supplementation should be considered. Folinic acid (3 to 6 mg/day) as calcium folinate, may be administered without interfering with the antibacterial activity of trimethoprim, except in *Enterococci* infections.

Regular monthly blood counts are advisable when trimethoprim is given for long periods since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate.

Electrolyte abnormalities

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 older patients 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 medicines 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 sections 4.5)

Skin rash

Trimethoprim should be discontinued if a skin rash appears.

Porphyria

Trimethoprim has been associated with acute attacks of porphyria and is considered unsafe in porphyria patients.Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

Rare incidents of serious hypersensitivity reactions have been reported in patients on trimethoprim therapy.

Depression of haemopoiesis

Rare incidents of trimethoprim causing depression of haemopoiesis . have been reported, especially when administered in large doses and/or for prolonged periods. 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 as an effect on folate metabolism is possible. If any such change is seen, folinic acid should reverse the effect.

Blood glucose

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

Rare hereditary conditions

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

Use in hepatic impairment

Trimethoprim should be used cautiously in patients with impaired hepatic function.

Use in renal impairment

Trimethoprim may cause a significant, reversible increase in serum creatinine. It is unclear if this represents inhibition of tubular secretion of creatinine or genuine renal dysfunction. It should not be given in severe impairment unless blood concentrations can be monitored.

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 should be used cautiously in patients with impaired renal function.

Use in elderly

Care should be exercised in treating elderly.

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. 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.

Paediatric use

Trimethoprim should not be administered to premature infants or infants during the first few weeks of life (see Section 4.2).

Particular care should be exercised in the haematological monitoring of children on long term therapy.

Effects on laboratory results

Regular monthly blood counts are advisable when trimethoprim is given for long periods since there exists a possibility of symptomatic changes in haematological laboratory indices due to lack of available folate.

Trimethoprim may cause depression of haemopoiesis.

Trimethoprim may interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of normal values.

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay.

Pregnancy

Trimethoprim should not be administered to pregnant women nor during the breastfeeding period.

4.5 Interaction with other medicines and other forms of interaction

Antimalarials

There is the possibility of megaloblastic anaemia developing in patients prescribed trimethoprim whilst taking pyrimethamine for malarial prophylaxis. Increased antifolate effect when trimethoprim is given with pyrimethamine.

Warfarin and other coumarins

Trimethoprim may potentiate the anticoagulant activity of warfarin and other coumarins though the precise mechanism is unclear. Careful control of the anticoagulant therapy during treatment with trimethoprim is advisable.

Phenytoin, digoxin, procainamide

Trimethoprim may increase serum concentrations and potentiate the effect of phenytoin, digoxin and procainamide. Close monitoring of the patient's condition and serum levels is advisable.

Zidovudine, zalcitabine, lamivudine

Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine, lamivudine.

Dapsone

Trimethoprim and dapsone increase each other's serum concentration when given concomitantly.

Repaglinide

Trimethoprim may enhance the hypoglycaemic effects of repaglinide.

Rifampicin

Rifampicin may decrease the trimethoprim concentration.

Antibacterials

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

Ciclosporin

An increased risk of nephrotoxicity has been reported with use of trimethoprim or co-trimoxazole and ciclosporin.

Medicines that form cations

When trimethoprim is administered simultaneously with medicines that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the medicines.

Diuretics

In patients given trimethoprim who were also receiving diuretics, hyponatraemia has been reported. In elderly patients taking diuretics, particularly thiazides, there is an increased incidence of thrombocytopaenia with purpura.

Folate antagonists and anticonvulsants

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

If trimethoprim is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (see section 4.4).

Bone marrow depressants

Use of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression and bone marrow aplasia, and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors, such as pyrimethamine or methotrexate.

Cytotoxic agents such as azathioprine, mercaptopurine and methotrexate increase the risk of haematologic toxicity when given with trimethoprim.

If trimethoprim is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (see Section 4.4).

Cases of pancytopenia have been reported in patients taking trimethoprim in combination with methotrexate. Most of these patients were on long term methotrexate therapy, and/or predisposed to folate deficiency, and none of them were reported to have received a prophylactic folinic acid supplement (see section 4.4).

ACE Inhibitors

Concomitant use of medicines known to increase serum potassium such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and potassium sparing diuretics, potassium supplements, potassium containing salt substitutes, renin-angiotensin system inhibitors (e.g.: ACE inhibitors or renin angiotensin receptor blockers) and other potassium increasing substances (e.g.: heparin) may results in severe hyperkalaemia. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Trimethoprim may interfere with folic acid metabolism and animal experiments have shown that administration of very high doses of trimethoprim during organ development may give rise to birth defects typical of folic acid antagonism.

Trimethoprim is contraindicated in pregnant women, premature infants or infants during the first few weeks of life.

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

Breastfeeding

Trimethoprim is excreted in human milk. When trimethoprim is administered to a nursing mother alternative arrangement should be made for feeding the infant.

Fertility

For pre-clinical pregnancy data refer to section 5.3.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed.

4.8 Undesirable effects

The adverse effects encountered most often with trimethoprim are rash and pruritus. Other adverse effects reported involved the gastrointestinal i and haematopoietic systems.

Skin and subcutaneous tissue disorders

Rash, pruritus and exfoliative dermatitis.

Rarely: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. At the recommended dose of 300 mg daily the incidence of rash is 7.9%. These rashes were maculopapular, morbilliform, pruritic and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

Common: urticaria, skin rashes

Very Rare: Photosensitivity, fixed drug eruption, erythema nodusum, bullous dermatitis, purpura, angioedema, exfoliative dermatitis, erythema multiforme, Sevens-Johnsons syndrome, toxic epidermal necrolysis.

Unknown: Pruritus.

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

Infections and Infestations

Common: Monilial overgrowth

Gastrointestinal disorders

Epigastric distress, nausea, vomiting and glossitis.

Common: diarrhoea.

Very rare: Constipation, stomatitis, pseudomembranous colitis, pancreatitis.

Unknown: Sore mouth, gastrointestinal disturbance

Blood and lymphatic system disorders

Thrombocytopenia, leucopenia, neutropenia, megaloblastic anaemia and methaemoglobinaemia,

Although an effect on folate metabolism is possible, interference with haematopoiesis occurs rarely at the recommended dosage. If any such change is seen calcium folinate may be administered. Elderly patients may be more susceptible and a lower dosage may be advisable.

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, however the majority of haematological changes are mild and reversible when treatment is stopped.

Very rare: pancytopaenia, bone marrow, depression, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, purpura, haemolysis,

Unknown: hyperkalaemia (particularly in the elderly and in HIV patients). Trimethoprim therapy may affect haematopoiesis.

Metabolism and nutrition disorders

Hyperkalaemia, hyponatraemia.

Very rare: Hypoglycaemia, anorexia.

Close supervision is recommended when trimethoprim is used in elderly patients, patients with renal impairment 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: Dyskinesia, aseptic meningitis, tremor, ataxia, dizziness, lethargy, syncope, paraesthesiae, convulsions, peripheral neuritis, vertigo, tinnitus.

Aseptic meningitis was rapidly reversible on withdrawal of the medicine but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone or to trimethoprim-containing agents.

Eye disorders

Very rare: Uveitis.

Respiratory, thoracic and mediastinal disorders

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

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.

Immune system disorders

Anaphylaxis, anaphylactoid reactions, hypersensitivity, angioedema, drug fever, allergic vasculitis

Very rare: Hypersensitivity, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus.

Miscellaneous reactions

Fever, disturbance in liver enzymes, elevation of serum transaminases and bilirubin, increases in blood urea nitrogen (BUN) and serum creatinine levels, abdominal cramps, stomatitis, cholestatic jaundice, hepatic necrosis. Cholestatic jaundice and hepatic necrosis may be fatal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Acute

Signs of acute overdosage with trimethoprim may appear following ingestion of 1000 mg or more of the medicine and include nausea, vomiting, dizziness, headaches, mental depression, confusion, and bone marrow depression (see Chronic section).

Treatment

Treatment consists of general supportive measures.

Acidification of the urine will increase renal elimination of trimethoprim.

Peritoneal dialysis is not effective and haemodialysis only moderately effective in eliminating the medicine.

Chronic

Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anaemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given folinic acid as calcium filinate, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal haematopoiesis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Trimethoprim and derivates

ATC code: J01EA01

Mechanism of action

Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR). It 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. Depending on the growth conditions the effect may be bactericidal or bacteriostatic.

Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

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 *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)		
Enterobacteriac	***Staphylococ***	***Enterococc***
-2/>4	-2/>4	-0.032/>1*

*The activity of trimethoprim is uncertain against enterococci. Hence the wild type population is categorised as intermediate.

The majority of common pathogenic bacteria are sensitive *in vitro* to trimethoprim at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. These organisms include:

Organism	Trimethoprim representative Minimum Inhibitory Concentration (MIC)
Sensitive:	
Gram-Negative:	
Escherichia coli	0.05 – 1.5 microg/mL
Haemophilus influenzae	
Proteus mirabilis	0.5 – 1.5 microg/mL
Salmonella spp. including *S.typhi* and *S.paratyphi*	
Shigella spp.	
Vibrio cholerae	
Gram-Positive:	
Listeria monocytogenes	
Staphylococcus aureus	
Staphylococcus epidermidis and saprophyticus	
Streptococcus faecalis	
Streptococcus pyogenes	
Streptococcus viridans	
Variable sensitivity:	
Klebsiella spp. including Klebsiella pneumoniae	0.5 – 5.0 microg/mL
Enterobacter spp.	
Proteus spp. (indole positive)	0.5 – 5.0 microg/mL
Providencia spp.	
Serratia marcescens	
Streptococcus pneumoniae Yersinia spp.	
Relatively insensitive:	
Brucella spp.	
Clostridium spp.	
Neisseria spp.	
Insensitive:	
Bacteroides spp.	
Lactobacillus spp.	
Mycobacteria	
Mycoplasmas	
Pseudomonas spp.	
Ureaplasma urealyticum	

Satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

Normal vaginal and faecal flora are the source of most pathogens causing urinary tract infections. It is therefore relevant to consider the suppressive effect of trimethoprim at these sites.

Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentration of simultaneously obtained serum samples.

Sufficient trimethoprim is excreted in the faeces to markedly reduce or eliminate trimethoprim susceptible organisms from the faecal flora.

In vitro resistance develops rapidly when susceptible bacteria are passed through increasing concentrations of the medicine. However, following clinical use there have been conflicting reports on the
development of resistance to trimethoprim when used alone. The possibility of increasing resistance to trimethoprim cannot at present be ruled out. Generally, resistance is more likely to occur in hospital than in domiciliary use. Plasmid mediated as well as chromosomal resistance to trimethoprim have been reported.

Clinical efficacy and safety

No data available.

5.2 Pharmacokinetic properties

Absorption

After oral administration trimethoprim is rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Peak plasma concentrations of about 1µg/ml have been reported after a single dose of 100mg.Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady-state levels in adults are reached after dosing for 2 to 3 days.

Distribution

Approximately 40 -70% of the medicine is protein bound in the blood. Trimethoprim is a weak base with a pKa of 7.3. It is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations but concentrations in the cerebrospinal fluid are about one half of those in the blood. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and fetal tissues reaching concentrations approximating those of maternal serum.

Biotransformation

Approximately 50% of trimethoprim in the plasma is protein bound. The half-life in humans is in the range 8.6 to 10 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in the elderly compared with young patients.

Elimination

Excretion of trimethoprim is chiefly by the kidneys through glomerular filtration and tubular secretion. Urine concentrations are considerably higher than are the concentrations in the blood. After oral administration 40% to 60% of trimethoprim is excreted 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. approximately 80% of this being unmetabolised trimethoprim. Several metabolites have been identified in urine. Urinary concentrations of

trimethoprim vary widely. Within 2 hours of any therapeutic dose the concentrations achieved are greatly in excess of the minimum inhibitory concentration (MIC) of most pathogenic bacteria responsible for urinary tract infections. High concentrations usually persist in the urine for 24 hours or more after a single dose. Even in patients undergoing chronic haemodialysis levels of trimethoprim achieved in the urine exceed the MIC for most of the urinary tract pathogens. Less than 4% appears in the faeces. Concentrations of trimethoprim exceed those in plasma in the case of prostatic tissue and fluid, and vaginal secretions. It appears in breast milk.

5.3 Preclinical safety data

Pregnancy

At doses greatly in excess of the recommended human therapeutic dose trimethoprim has been reported to be teratogenic in rats with effects typical of a folate antagonist and preventable by administration of dietary folate. No significant medicine-related malformations have been demonstrated in rabbits but at doses approximately ten times in excess of the human therapeutic dose an increase in fetal deaths was noted.

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. Pharmaceutical Particulars

6.1 List of excipients

TMP tablets also contain:

- lactose monohydrate
- magnesium stearate
- povidone
- purified talc
- sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle with a PP cap. Pack size of 50 tablets.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

30 October 1986

10. Date of Revision of the Text

18 November 2024

Summary table of changes

Section	Summary of new information
4.4, 4.5, 4.6, 4.8, 4.9	Minor Editorial changes Rearrangement of sections, minor typographical error corrections
2	Clearer identification of excipients with known effect and moved and consolidated Allergen declaration from section 6.1
4.4	Addition of exception statement for *Enterococci i*nfections in folate deficiency. Updated information on folate metabolism in depression of haemopoiesis. Addition of statement for recognition of signs of blood disorders and advised to seek immediate when used in elderly patients' medical attention. Addition of statement not to be used during nursing period. Deletion of statement about intravenous use as product is only for oral use.
4.5	Addition of statement Increased antifolate effect when trimethoprim is given with pyrimethamine. Addition of statement in bone marrow depressants subsection for consideration of folate supplementation in patients receiving other anti-folate medicines such as methotrexate. Updated ACE inhibitor information
4.6	Added information on premature infants and infants during the first few weeks of life. Removed the pregnancy category B3

Section	Summary of new information
	Removed the wording 'If trimethoprim is given during pregnancy, folic acid supplementation may be required'
4.8	Editorial updates to the section introduction Addition of some ADRs for Skin and subcutaneous tissue disorders, Gastrointestinal disorders, Nervous system disorders and Miscellaneous reactions.
4.9	Removal of information on when to stop therapy and determination of plasma and serum levels.
6.1	Allergen information moved to and consolidated into Section 2
10	Updated Date of Revision of Text