SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimethoprim 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

200mg Trimethoprim B.P
Also contains lactose. For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Uncoated Tablets

White, flat bevelled edged tablets embossed T/200 on one face and 'PV' on the other face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For treatment of susceptible infections (urinary and respiratory tract infection) caused by trimethoprim-sensitive organisms which are most gram-positive and gram-negative aerobic organisms, including Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumonia, Staphylococcus aureus, Eschersichia coli, Enterobacter, Proteus and Streptococcus faecalis.

Exceptions include anaerobic bacteria. Mycobacterium tuberculosis, Neisseria gonorrhoeae, pseudomonas aeruginosaand Treponema pallidum.

Prophylaxis of recurrent urinary tract infections.

Route of administration: Oral

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

4.2 Posology and method of administration

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: For urinary tract and respiratory tract infections; 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 in this age group.
Elderly: Dosage is dependent upon kidney function; see special dosage schedule

For long-term and prophylactic therapy of urinary tract infections

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 maximise urinary concentrations. The approximate dosage in children is 2mg trimethoprim per kg body weight per day.

Elderly: Dosage is dependent upon kidney; 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 the value of this in individual cases should first be discussed with specialists in infectious disease and renal medicine.

Route of administration: For oral administration.

4.3 Contra-indication:

Hypersensitivity to trimethoprim or to any other component of the formulation. Should not be given to patients with severe hepatic insufficiency, megaloblastic Anaemia and other blood dyscrasias.

Should not be administered to pregnant women, premature infants or during the first four months of life.

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

4.4 Special warning and precautions for use:

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.

Special precautions should be exercised in-patients with a predisposition to folate deficiency. Administration of a 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.

Regular haematological tests should be undertaken in patients receiving long term
treatment and those predisposed to folate deficiency. 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.

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).

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

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

This medicine contains less than 1 mmol sodium (12mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction:

Anti-arrhythmics - Trimethoprim increases plasma concentrations of procainamide.

Bone marrow depressants – trimethoprim may increase the potential for bone marrow aplasia.

Trimethoprim causes an increased anti-folate effect when given to patients between courses of antineoplastic agents and immunosuppressants.

Patients receiving pyrimethamine as malarial prophylaxis at doses in excess of 25mg weekly may develop megaloblastic anaemia should trimethoprim be prescribed concurrently. Special care is necessary for patients receiving pyrimethamine therapy in addition to trimethoprim.

Cytotoxics - Increased risk of haematological toxicity when trimethoprim is given with azathioprine or mercaptopurine.

Trimethoprim may potentiate the anticoagulant effect of warfarin.

Trimethoprim may increase the elimination half-life of phenytoin and if co-administered an excessive phenytoin effect may be observed.

Digoxin – the patient should be carefully controlled as trimethoprim may increase the elimination half-life of digoxin.

Reversible deterioration in renal function, in renal transplant patients, treated with trimethoprim and cyclosporin (nephrotoxicity may be increased).

Concurrent use of rifampicin and trimethoprim may increase elimination and shorten the plasma half-life of trimethoprim.

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).

Trimethoprim has been noted to impair phenylalanine metabolism.

In patients with severe hepatic parenchymal damage, changes may occur in the absorption and metabolism of trimethoprim.

Accumulation in patients with marked impairment of renal function may result in adverse haematological effects.

Caution in patients predisposed to folate deficiency.

Repaglinide- trimethoprim may enhance the hypoglycaemic effects of repaglinide

4.6 Pregnancy and lactation:

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

Breast-feeding
Although trimethoprim is excreted in the 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 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.

<u>Infections and Infestations</u>
Common: Monilial overgrowth

<u>Blood and lymphatic system disorders</u>
Very rare: Leucopenia, neutropenia, thrombocytopenia, pancytopaenia, bone marrow depression, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, purpura, haemolysis,
Unknown: Megaloblastic anaemia, methaemoglobinaemia, hyperkalaemia (particularly in the elderly and in HIV patients), methaemoglobinaemia.
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.

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: Disturbance in liver enzymes, 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 nodosum, Stevens-Johnson Syndrome, toxic epidermal necrolysis, bullous dermatitis, purpura, angioedema
Unknown: Pruritis,

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

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.

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

Symptoms of overdose include diarrhoea and vomiting. Treatment is symptomatic and gastric lavage and forced diuresis may be used. Intramuscular injections of calcium folinate may be used to counteract any effect of trimethoprim on bone-marrow.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antibacterial

ATC Code: J01EA01

Trimethoprim is a dihydrofolate reductase inhibitor, which affects the neuclo-protein metabolism of micro-organisms by interference in the folic/folinic acid systems; and this presents the synthesis of tetrahydrofolic acid from dihydrofolic acid. The anti-microbial activity of trimethoprim is similar to that of sulphonamides. Trimethoprim is also used in the treatment of bacterial infections.

5.2 Pharmacokinetic properties

Trimethoprim is readily and almost completely absorbed from the gastrointestinal tract and peak plasma concentrations in the circulation occur at about 1-4 hours after an oral 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 concentration is reported to be higher than serum concentrations with particular high concentration occurring in the kidneys and lungs but concentrations in the cerebral spinal fluid are about one half of those in the blood. The half is approximately 8 to 10 hours.

Trimethoprim may cause an apparent rise in serum creatinine levels due to competition in the tubular secretory mechanisms.

Approximately 40 to 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. It appears in breast milk.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose	165.0mg
Polyvinylpyrrolidone	1.0mg
Starch	19.0mg
Sodium starch glycollate	8.0mg
Magnesium stearate	1.0mg
Sodium lauryl sulphate	1.0mg
Stearic acid	1.0mg
Polyethylene Glycol 4000	4.0mg

6.2. Incompatibilities

None.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 25°C in dry place, protect from light.

6.5 Nature and contents of container

Securitainer with polypropylene lids containing trimethoprim tablets.(material of the container complies to EEC directives for plastic in contact with drugs and food stuff). In the packs of 14, 28, 30, 100, 250, 500 and 1000

Not all pack sizes may be marketed

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

Pharmvit Limited,
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Derby Road,
Greenford,
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UB6 8UJ

8. MARKETING AUTHORISATION NUMBER

PL 04556/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/03/2009

10 DATE OF REVISION OF THE TEXT

09/09/2024