Summary of Product Characteristics

1. Name of the Medicinal Product: Co-Trimoxazole tablets BP 960 mg
2. Qualitative and Quantitative Composition

Each uncoated tablet contains

Sulfamethoxazole	BP	800 mg
Trimethoprim	BP	160 mg
Excipients		q.s.

3. Pharmaceutical Form

Oral Tablets

White colored. caplet shaped uncoated tablet having break line on one side and other side plain. 10 × 10 Tablets Alu-PVC Blister Packed in a Carton

4. Clinical Particulars

4.1 Therapeutic Indications

o-trimoxazole should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

Co-trimoxazole is an antibacterial agent. Co-trimoxazole is effective in vitro against a wide range of gram-positive and gram-negative organisms. It is not active against Mycobacterium tuberculosis, mycoplasma or Treponema pallidum, Pseudomonas aeruginosa is usually insensitive.

Co-trimoxazole is indicated for the treatment of adults, adolescents and children from 12-18 years of age.

Co-trimoxazole is indicated for the treatment of the following infections when owing to sensitive organisms (see section 5.1):

• Treatment and prophylaxis (primary and secondary) of Pneumocytosis jiroveci pneumonitis or PJP.

• Treatment and prophylaxis of toxoplasmosis

• Treatment of nocardoasis.

The following infections may be treated with co-trimoxazole where there is bacterial evidence of sensitivity to co-trimoxazole and good reason to prefer the combination of antibiotics in co-trimoxazole to a single antibiotic.

• Treatment of acute uncomplicated urinary tract infections

• Treatment of acute exacerbation of chronic bronchitis

• Treatment of acute otitis media

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

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4.2 Posology and Method of Administration

Posology

General dosage recommendations

Where dosage is expressed as "tablets" this refers to the adult Forte tablet, i.e 160 mg Trimethoprim BP and 800 mg Sulfamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Standard dosage recommendations for acute infections

Adults (>18 years old):

STANDARD DOSAGE	
Age	**Forte tablets**
>18 years old	1 tablet every 12 hours

Children over 12 years old (>12 to <18 years old):

The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day, given in two equally divided doses. The schedules for children are according to the child's age and provided in the table below:

Age	**Forte tablets**
>12 to <18 years old	1 tablet every 12 hours

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evident after 7 days of therapy, the patient should be reassessed.

As an alternative to Standard Dosage for acute uncomplicated lower urinary tract infections, short-term therapy of 1 to 3 days' duration has been shown to be effectiv

4.3 Contraindications

Hypersensitivity to the active substances sulphonamides, trimethoprim, co-trimoxazole or to any of the excipients Contra-indicated in patients with severe hepatic parenchymal damage. Contra-indicated in patients with severe renal insufficiency where repeated measurements of the plasma

concentration cannot be performed. Co-trimoxazole should not be given to infants during the first 6 weeks of life. Co-trimoxazole should not be given to patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides. Co-trimoxazole should not be given to patients with acute porphyria.

4.4 Special warnings and precautions for use

Fatalities although very rare have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of respiratory tract.

• Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of co-trimoxazole.

• Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

• If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, co-trimoxazole treatment should be discontinued (see section 4.8).

• The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

• If the patient has developed SJS or TEN with the use of co-trimoxazole, co-trimoxazole must not be re-started in this patient at any time.

• At the start of treatment, the occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of acute generalised exanthematous pustulosis (AGEP) (see section 4.8); it requires cessation of treatment and contraindicates any new administration of co-trimoxazole alone or in combination with other drugs.

Particular care is always advisable when treating elderly patients, because, as a group, they are

more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other drugs.

For patients with known renal impairment special measures should be adopted (see section 4.2).

An adequate urinary output should be maintained at all times. Evidence of crystalluria in vivo is rare, although sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

Regular monthly blood counts are advisable when co-trimoxazole is given for long periods, or to folate deficient patients or to the elderly, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. Supplementation with folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

In glucose-6-phosphatase dehydrogenase (G-6-PD) deficient patients, haemolysis may occur.

Co-trimoxazole should be given with caution to patients with severe atopy or bronchial asthma.

Co-trimoxazole should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci; eradication of these organisms from the oropharynx is less effective than with penicillin.

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

The administration of co-trimoxazole to patients known or suspected to be at risk of porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Close monitoring of serum potassium and sodium is warranted in patients at risk of

hyperkalaemia and hyponatraemia.

Co-trimoxazole has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Except under careful supervision co-trimoxazole should not be given to patients with serious haematological disorders (see section 4.8). Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

The combination of antibiotics in co-trimoxazole should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

4.5 Interactions with other medicinal products and other forms of interaction Contraindications of concomitant use

Interaction with laboratory tests: trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.

Rifampicin: concurrent use of rifampicin and co-trimoxazole results in a shortening of the

plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

When trimethoprim is administered simultaneously with drugs 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 drugs.

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co- trimoxazole be prescribed concurrently.

Warfarin: co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites in vitro. Careful control of the anticoagulant therapy during treatment with co-trimoxazole is advisable.

Phenytoin: co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable

4.6 Fertility, pregnancy and lactation

Trimethoprim and sulfamethoxazole cross the placenta and their safety in pregnant women has not been established. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see section 5.3). Co-trimoxazole should not be given during pregnancy, particularly in the first trimester, unless clearly necessary.

Folate supplementation should be considered if co-trimoxazole is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when co-trimoxazole is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm or those with glucose-6-phosphate dehydrogenase deficiency.

Breast-feeding:

The components of co-trimoxazole (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of co-trimoxazole should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of co-trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia

4.7 Effect on ability to drive and machines

There have been no studies to investigate the effect of co-trimoxazole on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless, the clinical status of the patient and the adverse events profile of co-trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable Effects

The following convention has been used for the classification of adverse events in terms of frequency: 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.

System Organ Class	Frequency	Side effects
Infections and infestations	Common	Overgrowth fungal.
	Very rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia,

		methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients.
Immune system disorders	Very rare	Serum sickness, anaphylactic reaction, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus. Severe hypersensitivity reactions associated with PJP*, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.
Metabolism and nutrition disorders	Very common	Hyperkalaemia.
	Very rare	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis
Psychiatric disorders	Very rare	Depression, hallucination.
	Not known	Psychotic disorder.
Nervous system disorders	Common	Headache.
	Very rare	Meningitis aseptic *, convulsions, neuropathy peripheral, ataxia, dizziness.
Ear and labrynth disorders	Very rare	Vertigo, tinnitus
Eye disorders	Very rare	Uveitis.
Respiratory, thoracic and mediastinal disorders	Very rare	Cough *, dyspnoea*, lung infiltration*.
Gastrointestinal disorders	Common	Nausea, diarrhoea.
	Uncommon	Vomiting.
	Very rare	Glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders*	Very rare	Jaundice cholestatic *, hepatic necrosis*. Transaminases increased, blood bilirubin increased.
Skin and subcutaneous tissue disorders*	Common	Rash.
	Very rare	Photosensitivity reaction, dermatitis exfoliative, angioedema, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) *, toxic epidermal necrolysis (TEN)*. Acute generalised exanthematous pustulosis (AGEP).
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome)
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia, myalgia.
Renal and urinary disorders	Very rare	Renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis

4.9 Overdose

Symptoms:

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment:

If vomiting has not occurred, induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. Dependant on the status of renal function administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Mechanism of Action

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoid acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus, trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents.

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.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase in the concentration of PABA and thereby out- compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

5.2 Pharmacokinetic Properties

Absorption

After oral administration trimethoprim and sulfamethoxazole are 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. 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 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Distribution

Approximately 50% of trimethoprim in the plasma is protein bound. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 66% of sulfamethoxazole in the plasma is protein bound. The concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluids is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72 hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim in man is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in elderly patients compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely.

The half-life of sulfamethoxazole in man is approximately 9 to 11 hours in the presence of normal renal function.

5.3 Preclinical Safety Data

General toxicity

At doses in excess of recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch,. Purified Talc , Magnesium Stearate, sodium starch glycolate, purified water , sodium hydroxyl propyl benzoate , sodium hydroxyl methyl benzoate

6.2 Incompatibilities

None known

6.3 Shelf Life

36 months

6.4 Special precautions for Storage

Store in a dry place, below 30ºC. Protect from light.

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6.5 Nature and Contents of Container

10 Tablets in Alu/PVC Blister packed in a carton along with Pack Insert and 10 such cartons are shrinked together

6.6 Special Precautions for disposal and other handling

Not applicable

7.0 Marketing Authorisation Holder

Sun Enterprises LTD.
BP 1952
Kigali, Rwanda
Email: Sanjay@sunenp.net

8.0 Marketing Authorisation Number

9.0 Date of First Authorisation

10.0 Date of revision of the Text: July 2022

1.4.2 Labeling

1. Product Name: Co-trimoxazole tablets BP 960 mg

2. Dosage Form: Tablet

3. Name of Active Ingredients:
Sulfamethoxazole BP
Trimethoprim BP

4. Strength of Active Ingredients
Sulfamethoxazole BP-800 mg
Trimethoprim BP- 160 mg

5. Batch Number

6. Manufacturing Date

7. Expiration Date

8. Route of Administration: Oral

9. Storage Condition:

Store in a dry place, below 30ºC. Protect from light.

10. Registration Number:

11. Name and Address of Marketing Authorisation Holder and/or Product Owner:

Sun Enterprises LTD.

Rwanda

12. Name and Address of the Manufacturer:

Aura Life Care Pvt Ltd

Survey No. 254/14/1, Jarod-Savli Road, P.O.: Karachiya.

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Gujarat State, India