1.4 Product Information

1.4.1. Summary of Product Characteristics (Product Data Sheet)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the medicinal product

ML-Cotri Suspension (Paediatric Co-trimoxazole Oral Suspension BP)

1.2 Strength

Each 5ml Contains:

Trimethoprim BP 40 mg

Sulfamethoxazole BP 200 mg

1.3 Pharmaceutical form

Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml Contains:

Trimethoprim BP 40 mg

Sulfamethoxazole BP 200 mg

Excipients: Sorbitol 70%, Carboxy methyl cellulose, Xanthan gum, Methyl Paraben, Propyl Paraben, Polysorbate-80, Glyserin, Disodium edetate, Saccharin sodium, Colour erythrosine supra, Essence Banana, Essence Banana, Essence BTM 7020, Menthol crystal .

3. PHARMACEUTICAL FORM

Light Pink coloured suspension having pleasant flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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. The *in vitro* susceptibility of bacteria to antibiotics varies geographically and with time; the local situation should always be considered when selecting antibiotic therapy.

1) Treatment and prophylaxis (primary and secondary) of *Pneumocytosis jiroveci (P. carinii)* in adults and children.

2) Treatment and prophylaxis of toxoplasmosis, treatment of nocardiosis.

3) Treatment of urinary tract infections and acute exacerbations of chronic bronchitis, where there is bacterial evidence of sensitivity to Co-trimoxazole and good reason to prefer this combination to a single antibiotic.

4) Treatment of acute otitis media where there is good reason to prefer Co-trimoxazole to a single antibiotic.

4.2 Posology and method of administration

The preparation is administered orally with a measuring cup.

It may be preferable to take Co-trimoxazole Suspension with some food or drink to minimize the possibility of gastrointestinal disturbances.

Co-trimoxazole should be administered twice daily after meals as follows:

	Dosage form	Average dose	Dose in prolonged treatment (more than 14 days)	Dose in severe infections
Adult	Suspension	4 teaspoonful (20 ml)	4 teaspoonful (20 ml)	i.d
Children from 6 to 12 years	Suspension (5-10 ml)	1-2 teaspoonful (5-10 ml)	1 teaspoonful (5 ml)	2-3 teaspoonful (10-15 ml)

Children from 6 months to 5 years	Suspension	½ to 1 teaspoonful (2.5 – 5 ml)	½ teaspoonful (2.5 ml)	1 teaspoonful (5 ml)
Babies from 6 weeks to 5 months	Suspension	½ teaspoonful (2.5 ml)	-	1 teaspoonful (5 ml)

4.3 Contraindications:

Co-trimoxazole is contraindicated in impaired hepatic functions, in blood dyscrasias, and in severely impaired renal function provided that during the treatment, the control of serum concentration of the preparation is not possible. Co-trimoxazole should not be given to patients sensitive to sulphonamides. It should also not be given in pregnancy and lactation and to premature and newborn infants in the first weeks of life. Hypersensitivity to Paracetamol or any of the constituents.

4.4 Special warnings and precautions for use

Fatalities, although very rare, have occurred due to severe reactions including fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the 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.

• 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.

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.

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. These changes may be reversed by administration of folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity.

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patient's haemolysis may occur.

Co-trimoxazole should be given with caution to patients with severe allergy 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 acute 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 hyopnatraemia.

Except under careful supervision Co-trimoxazole should not be given to patients with serious haematological disorders. 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 judgment 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 Interaction with other medicinal products and other forms of interaction

Care should be exercised when giving Co-trimoxazole to patients receiving**:**

• ACE Inhbitors: risk of severe hyperkalaemia.

• Anaesthetics: increased risk of methaemoglobinaemia when sulphonamides given with prilocaine.

• Antiarrhythmics: increased risk of ventricular arrhythmias with amiodarone. Plasma levels of dofetilide increased markedly by co-administration with Co-trimoxazole resulting in the increase dofetilide-induced QT prolongation and the risk of arrhythmias.

• Antibacterials: serum levels of dapsone and Co-trimoxazole are possibly raised by the presence of the other. Be alert for dapsone toxicity causing methaemoglobinaemia. Increased risk of crystalluria when sulphonamides given with methenamine. Concomitant use of Co-trimoxazole and rifampicin can result in increased rifampicin serum levels and reduced plasma half life of trimethoprim.

• Anticoagulants: effects of acenocoumarol and warfarin enhanced.

• Antidiabetics: effect of sulphonylureas enhanced.

• Antiepileptics: Co-trimoxazole prolongs the half life of phenytoin and co-administration could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

• Antifolates: if considered appropriate therapy in patients receiving anti-folates , a folate supplement should be considered.

• Antimalarials: risk of megaloblastic anaemia with doses of pyrimethamine in excess of 25mg per week..

• Antivirals: plasma concentrations of lamivudine increased-avoid concomitant high dose co-trimoxazole. Concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to Co-trimoxazole. Zalcitabine plasma concentrations possibly increased by co-trimoxazole.

• Cations at physiological pH: plasma concentrations of trimethoprim and/or procainamide and/or amantadine can be increased unilaterally or bilaterally.

• Clozapine: avoid concomitatnt use; increased risk of fatal agranulocytosis.

• Cytotoxics: increased risk of haematological toxicity with mercaptopurine and azathioprine. Antifolate effects of methotrexate increased by Co-trimoxazole (avoid concomitant use).

• Digoxin: increase in digoxin levels in a proportion of elderly patients.

• Diuretics: elderly patients concurrently receiving diuretics, mainly thiazides, there is an increased risk of thrombocytopenia with or without purpura.

• Immunosuppressants: reversible deterioration in renal function has been observed in patients treated with Co-trimoxazole and ciclosporin following renal transplantation.

• Potassium aminobenzoate: effects of sulphonamides inhibited.

• Labratory tests- trimethoprim and sulphonamides have been reported to interfere with diagnostic tests, including serum-methotrexate and serum-plasma creatinine levels, also urea, urinary glucose and urobilinogen tests.

4.6 Pregnancy and lactation

Pregnancy:

Co-trimoxazole should not be used in pregnancy as the safety in pregnancy has not been established. Co-trimoxazole interferes with folate metabolism and can cause teratogenic effects if given in the first trimester.

Co-trimoxazole can cause neonatal haemoylosis and methaemoglobinaemia when used in the third trimester, if given close to delivery kernicterus may occur due to displacement of bilirubin. Other toxicities that may be observed in the new born include jaundice and haemalytic anaemia. The risk of kernicterus is higher in infants at increased risk of hyperbilirubinaemia, such as if the infant is ill, stressed or premature or has glucose-6-phosphate dehydrogenase deficiency.

Lactation:

Co-Trimoxazole appears in breast milk in negligible amounts and the risk appears to be low. However, there is a risk of kernicterus if the infant is at increased risk of hyperbilirubinaemia.

4.7 Effects on ability to drive and use machines

As Co-trimoxazole can cause dizziness, drowsiness, tinnitus, insomnia and hallucinations patients should make sure they are not affected before driving or operating machines.

4.8 Undesirable effects

- *Infections and infestations:* monilial growths are common.
- *Blood and the lymphatic system disorders* - blood dyscrasias may occur along with aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, megaloblastic anaemia, thrombocytopenia, purpura, leucopenia, eosinophilia, neutropenia, rarely agranulocytosis and bone marrow depression, especially in the elderly. These changes have been reversed on withdrawal of the drug. The elderly, patients with hepatic or renal failure or poor folate status are more susceptible to these effects. Co-trimoxazole may induce haemolysis in certain susceptible glucose-6-phosphate dehydrogenase deficient patients.
- *Immune system disorders*– hypersensitivity effects have been reported, they include serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, peri-arteritis nodosa, systemic lupus erythematosus, aseptic meningitis (reversible on withdrawal), severe skin sensitivity reactions such as erythema multiforme bullosa (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) have occurred infrequently and rarely been associated with death. Treatment should be discontinued immediately.
- *Metabolism and nutrition disorders* – electrolyte disturbances, metabolic acidosis, hyperkalaemia and hyponatraemia especially in the elderly and with high doses.
- *Nervous system disorders* - few reports of subjective interference such as headache, depression, dizziness and hallucinations have occurred (although drug-relation remains unproven). Other neurological adverse effects include convulsions, peripheral neuritis, ataxia, drowsiness, fatigue, and insomnia.
- *Ear and labyrinth disorders* - vertigo and tinnitus.
- *Respiratory, thoracic and mediastinal disorders* - cough, dyspnoea, pulmonary infiltration; indicative of hypersensitivity
- *Gastrointestinal disorders* - nausea, vomiting, diarrhoea, sore mouth, anorexia, glossitis, stomatitis, rarely pseudomembranous colitis.
- *Hepato-biliary disorders* - jaundice, elevated hepatic transaminases, rarely hepatic necrosis and pancreatitis.

- *Skin and subcutaneous tissue disorders* - skin rashes can occur and photosensitivity**,** fixed drug eruptions, Henoch-Schonlein purpura, and exfoliative dermatitis have also been reported.
- *Musculoskeletal disorders* - arthralgia and myalgia.
- *Renal and urinary disorders* - impaired renal function, rarely interstitial nephritis and crystalluria which can be avoided by adequate fluid intake.
- *Other* – with the higher doses used for therapy of *Pneumocystis jiroveci (P. carinii)* in patients with AIDS if effects such as rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia and hyponatraemia occur stopping therapy may be necessary. If signs of bone marrow depression occur 5 to 10mg/day of calcium folinate should be given. Re-exposure of co-trimoxazole to HIV infected patients has caused severe hypersensitivity reactions, even after a dosage interval of a few days.

4.9 Overdose

Symptoms of overdosage may include dizziness, nausea, vomiting, rashes, headache, ataxia, drowsiness, dysuria, swelling of the face, weakness and confusion. Bone marrow depression has been reported in acute trimethoprim overdosage.

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

Pharmacotherapeutic group: Dihydrofolate reductase inhibitor + sulfonamide antibacterial.

ATC Code: J01EE01 sulfamethoxazole and trimethoprim

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacterio stasis. 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 mammmalian DHFR is some 50,000 times than for the corresponding bacterial enzyme.

Many of common pathogenic bacteria are sensitive *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after administration of recommended doses. In common with other antibiotic, however, *in vitro* activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

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 older 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. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 ml/minute.

The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In older patients there is a reduced renal clearance of sulfamethoxazole.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a

higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

5.3 Preclinical safety data

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

Sorbitol 70%, Carboxy methyl cellulose, Xanthan gum, Polysorbate-80, Glycerin, Disodium edetate, Saccharin sodium, Colour Erythrosine supra, Essence Banana, Essence BTM 7020, Menthol crystal.

Preservative: Methyl paraben, Propyl paraben

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precaution for storage

Store below 30°C.

6.5 Nature and contents of container

100 ml amber coloured glass bottle with PP cap and measuring cup packed in a unit printed carton along with its package insert.

6.6 Instructions for use and handling

Shake well before use. Keep all medicines out of reach of children.

7.REGISTRANT

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8. MANUFACTURER

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9. DATE OF REVISION OF THE TEXT

Not Applicable

10. DOSIMETRY

Not Applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not Applicable