1. Name of the medicinal Product

Sulphatrim Oral Suspension

1.1 Strength

Trimethoprim BP 40 mg and Sulphamethoxazole BP 200 mg /5 ml

1.2 Pharmaceutical Form

Oral Suspension

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Sulfamethoxazole BP

Trimethoprim BP

2.2 Quantitative declaration

For full list of Excipients, see section 6.1.

3. Pharmaceutical Form

Distribution Category: Prescription Only Medicines (POM)

Oral Suspension

White to off-white colored suspension

4. Clinical Particulars

4.1 Therapeutic Indications

Co-Trimoxazole Pediatric Suspension is indicated in children aged 12 years and under (infants (>6 weeks to <2 years old) and children (>2 to <12 years old) for the treatment of the following infections when owing to sensitive organisms

- Treatment and prevention of Pneumocystis jirovecii pneumonitis (PJP).
- Treatment and prophylaxis of toxoplasmosis.
- Treatment of nocardiosis. it can affect the lungs, skin and brain

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

- Acute uncomplicated urinary tract infection.

- Acute otitis media
- Acute exacerbation of chronic bronchitis

4.2 Posology

Method of administration: oral

Posology:

Children aged 12 years and under (infants (>6 weeks to <2 years old) and children (>2 to <12 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 as per below:

- 6 to 12 years: 10 ml every 12 hours, seven days per week
- 6 months to 5 years: 5 ml every 12 hours, seven days per week
- 6 weeks to 5 months: 2.5 ml every 12 hours, seven days per week

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m2/day and 750 mg2 sulfamethoxazole/m2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Impaired renal function: Adults (>18 years old) and children over 12 years old (>12 to <18 years old):

Creatinine Clearance (ml/min)

> 30: 10 ml every 12 hours

15 to 30: 5 ml every 12 hours

<15: Not recommended.

Pneumocystis jirovecii pneumonitis: Treatment - Children aged 12 years and under (infants (>6 weeks to <2 years old) and children (>2 to <12 years old): A higher dosage is recommended, using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses for two weeks.

Nocardiosis: There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 tablets daily for up to 3 months have been used (one tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim).

Toxoplasmosis: There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition.. For prophylaxis, however, the dosages suggested for prevention of Pneumocystis jirovecii pneumonitis may be appropriate.

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 therapy, the patient should be reassessed. It may be preferable to take Co-Trimoxazole with some food or drink to minimize the possibility of gastrointestinal disturbance

Use the suspension within 28 days after opening the container.

4.3 Method of Administration

Oral Suspension

4.4 Contraindications

- Hypersensitivity to the active substance(s) sulphonamides, trimethoprim, co-trimoxazole or to any of the excipients listed Severe hepatic parenchymal damage.
- Patients with severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- 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.
- Co-Trimoxazole should not be given to infants during the first 6 weeks of life..

4.5 Special Warnings and Special 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 anemia, other blood dyscrasias and hypersensitivity of the respiratory tract.
- Cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis with the use of Co-Trimoxazole.
- Use with caution in Asthma Blood disorders, Decreased kidney function, Decreased liver function, Elderly people, Infants under 6 weeks of age, Lack of the enzyme G6PD in the blood.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions.If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, CoTrimoxazole consult to the physician.
- 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.
- 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. 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 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, and Patients with rare hereditary problems of fructose intolerance should not take this medicine This medicinal product contains Sodium methyl hydroxybenzoate, which may cause allergic reactions.

  Pregnancy: Co-Trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Co-Trimoxazole is used in pregnancy.

  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.

  The administration of Co-Trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

  Effects on ability to drive and use machines on driving performance or the ability to operate machinery co-trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.6 Pediatric Population

The schedules for children are according to the child's age and provided as per below:

- 6 to 12 years: 10 ml every 12 hours, seven days per week
- 6 months to 5 years: 5 ml every 12 hours, seven days per week
- 6 weeks to 5 months: 2.5 ml every 12 hours, seven days per week

4.7 Interaction with other medicinal products and other forms of interaction

Zidovudine: It may increase the risk of hematological adverse reactions to co-trimoxazole.

Cyclosporin: reversible deterioration in renal function for treated with co-trimoxazole and cyclosporin following renal transplantation,

Rifampicin: results in a shortening of the plasma half-life of trimethoprim after a period of about one week.

Diuretics (thiazides): there appears to be an increased risk of thrombocytopenia with or without purpura,

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

Warfarin: anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism.

Phenytoin: co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect.

Digoxin: increase plasma digoxin levels in a proportion of older patients.

Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate.

Lamivudine: administration of trimethoprim/sulfamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Sulphonylurea and hypoglycemic agents: Interaction is uncommon but potentiation has noted.

Hyperkalaemia: caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, ACE inhibitors angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone

Repaglinide: which may result in hypoglycemia.

Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprimsulfamethoxazole.

There are observe in Pneumocystis jirovecii pneumonia prophylaxis and treatment. Contraceptives, Azathioprine.

4.8 Additional information on special populations

No specific Information

4.9 Paediatric Population

No specific Information

4.10 Pregnancy and Lactation

4.10.1 Pregnancy

Co-Trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Co-Trimoxazole is used in pregnancy.

4.10.2 Lactation

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.

The administration of Co-Trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.11 Effects on ability to Drive and use Machines

Effects on ability to drive and use machines on driving performance or the ability to operate machinery co-trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.12 Undesirable Effects

As co-trimoxazole contains trimethoprim and a sulfonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience. Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency. In addition, adverse events may vary in their incidence depending on the indication.

The follow below table.

Frequency	System Organ Class	Side Effect
Very common	Metabolism and nutrition disorders	Hyperkalaemia
Common	Infections and infestations	Overgrowth fungal
	Nervous system disorders	Headache.
	Gastrointestinal disorders	Nausea, diarrhoea
	Skin and subcutaneous tissue disorders	Rash.
Uncommon	Gastrointestinal disorders	Vomiting.
Not known	Psychiatric disorders	Depression, hallucination.
Very rare	**Infections and infestations**	Pseudomembranous colitis
	Blood and lymphatic system disorders	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	Serum sickness, anaphylactic reaction,allergicmyocarditis,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:	Hypoglycaemia, hyponatraemia,

		decreased appetite, metabolic acidosis
	Psychiatric disorder	Depression, hallucination.
	Nervous system disorders	Meningitis aseptic, seizure, neuropathy peripheral, ataxia, dizziness
	Eye and Ear and labrynth disroders	Uveitis, Vertigo, tinnitus
	Gastrointestinal disorders:	Glossitis, stomatitis, pancreatitis.
	Hepatobiliary disorders	Jaundice cholestatic, hepatic necrosis, Transaminases increased, blood bilirubin increased
	Skin and subcutaneous tissue disorders	Photosensitivity, dermatitis exfoliative, angioedema, fixed drug eruption, erythema multiforme, Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
	Musculoskeletal and connective tissue disorders	Arthralgia, myalgia
	Renal and urinary disorders	Renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis

Description of selected adverse reactions: Aseptic meningitis, pulmonary hypersensitivity reactions, Hepatobiliary disorders, Jaundice cholestatic and hepatic necrosis, Severe cutaneous adverse reactions (SCARs), Very rare: Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia and rhabdomyolysis

4.13 Overdose

Signs/symptoms are likely Nausea, vomiting, dizziness and confusion, Bone marrow depression of over dosage

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 over dosage. 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 Pharmacodynamics Properties

Co-trimoxazole is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim. Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) 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. 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.

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

Antibacterial Spectrum: The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Trimethoprim/sulfamethoxazole susceptibilities against a number of bacteria are shown in the below:

Commonly susceptible species:

Gram-positive aerobes: Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus pyogenes

Gram-negative aerobes: Enterobacter cloacae, Haemophilus influenza, Klebsiella oxytoca, Moraxella catarrhalis, Salmonella spp, Stenotrophomonas maltophilia Yersinia spp.

Species for which acquired resistance may be a problem:

Gram-positive aerobes: Enterococcus faecalis, Enterococcus faecium, Nocardia spp. Staphylococcus epidermidis, Streptococcus pneumoniae

Gram-negative aerobes: Citrobacter spp. Enterobacter aerogenes Escherichia coli Klebsiella pneumoniae Klebsiella pneumonia, Proteus mirabilis, Proteus vulgaris, Providencia spp. Serratia marcesans

Inherently resistant organisms:

Gram-negative aerobes:

Pseudomonas aeruginosa Shigella spp. Vibrio cholera.

5.2 Pharmacokinetic Properties

Absorption: After oral administration co-trimoxazole 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: Trimethoprim passes into amniotic fluid and foetal tissues. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity concentrations distributes to in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions, amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluids. Approximately 50% of trimethoprim and 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.

Metabolism: Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolized than trimethoprim, biotransformation 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.

Excretion: 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. Sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form.

5.3 Preclinical Safety Data

Not Applicable

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium methyl hydroxybenzoate

Sodium propyl hydroxybenzoate

Disodium Edetate

Carmellose sodium HVP

Sucrose

Citric acid Monohydrate

Sodium citrate

Aspartame

Polysorbate 80 (Tween 80)

Ess. Mixed fruit

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from Light.

6.5 Nature and Contents of Container

100 ml amber PET bottle packed in printed carton with a packaging insert.

6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder and Manufacturing Site Addresses

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Tal.-Kalol,
Dist.- Gandhinagar, Gujarat State, India.
Telephone no.: +91-079-41078096
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Tal.-Kalol,
Dist.- Gandhinagar, Gujarat State, India.
Telephone no.: +91-079-41078096
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8. Marketing Authorization Number

Rwanda FDA-HMP-MA-0654

9. Date of First <Registration> / Renewal of The <Registration>

02/12/2023

10. Date of Revision of the Text

December, 2023

11. Dosimetry (If Applicable)

Not Applicable

12. Instructions for preparation of radiopharmaceuticals

Not Applicable