SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT :

1.1 Brand Name : L-Trim Oral Suspension

1.2 Generic Name : Paediatric Co-Trimoxazole Oral Suspension BP

1.3 Strength : 240mg/5ml.

1.4 Pharmaceutical Form: Oral Suspension

2. QUALITATIVE & QUANTITATIVE COMPOSITION :

Each 5 ml contains

Trimethoprim	BP	40 mg.
Sulfamethoxazole	BP	200 mg.
Flavoured base		q.s.
Colour:Ponceau 4R		

3. PHARMACEUTICAL FORM

Oral Suspention

Pink coloured, flavoured, palatable suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

(i) Renal and urinary tract infections and chronic cystitis, pyelonephritis, urethritis.
(ii) Upper and lower respiratory tract infections such as acute and chronic bronchitis, bronchiectasis, and bronchopneumonia, tonsilitis,sinusitis, pharyngitis and otitis media.
(iii) Genital infections in both sex, including gonococcal urethritis.
(iv) G. I. tract infection : Enteritis, typhoid and paratyphoid fever, cholera, bacillary dysentery.
(v) Skin infections : Pyoderma furuncles, abscesses and infected wounds some infections such as septicemia, osteomyelitis, other infections caused by sensitive organisms eg. brucellosis, hocardiosis, etc**.**

4.2 Posology and method of administration

L-Trim Suspension:

Children :

6 weeks to 6 months	½ teaspoonful (2.5ml)
6 months to 5 years	1 teaspoonful (5.0ml)
5 years to 12 years	2 teaspoonful (10 ml)

(Approximately the dose is equivalent to daily dose of 6 mg Trimethoprim & 30 mg Sulphamethoxazole per kg body weight) or as prescribed by the Physician.

4.3 Method of administration

Oral

4.4 Contraindications

The sulphonamides are contraindicated in patients with the history of sulpha hypersensitivity and advanced kidney diseases with elevated blood urea nitrogen. Caution is required inpatients with liver diseases, blood dyscrasias and impaired kidney function. Pregnant womanshould not receive sulphonamides because of possible placental transmission to the foetus and danger of kernicterus.

4.5 Special warnings and precautions for use

In patients with impaired renal function thedosage should be reduced and the interval between doses be prolonged in order toprevent cumulation in blood. The concentration of active ingredients in the plasmashould be determined in these patients. Indiscriminate use of Co-trimoxazole forcommon conditions may lead to serious blood disorders.

4.6 Paediatric population

The recommended dose for paediatric patients with urinary tract infections or acute otitis media is 8mg/kg trimethoprim and 40mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for five days in the treatment of shigellosis. For paediatric patients, the recommended dose is 150mg/m2/ day trimethoprim with 750mg/m2/day sulfamethoxazole given orally in

equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 320 mg trimethoprim and 1600mg sulfamethoxazole.

4.7 Interactionwithothermedicinalproductsandotherformsof interaction

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increasedincidence of thrombocytopenia with purpura has been reported. It has been reported that sulfamethoxazole; may prolong the prothrombin time in patients who are receiving theanticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole; trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed. Sulfamethoxazole; trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole; trimethoprim, given at a common clinical dosage, increased thephenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect. Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

4.8 Additional information on special populations

Geriatric Use: There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, (e.g. impaired kidney and /or liver function, or concomitant use of other drugs). Severe skin reactions, or generalized bone marrow suppression or a specific decrease in platelets with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function.

4.9 Paediatric population

None Known

4.10 Fertility, pregnancy and lactation

4.10.1 Women of childbearing potential / Contraception in males and females

None reported

4.10.2 Pregnancy

Contraindicated in pregnancy

4.10.3 Breastfeeding

Contraindicated

4.10.4 Fertility

None reported

4.11 Effects on ability to drive and use machines

None reported

4.12 Undesirable effects

At the recommended dosage Co-trimoxazole is welltolerated. Nausea, vomiting and skin rashes can occur. Purpura or agranulocytosis,may occur in isolated cases, both are reversible on withdrawal of the drug. Allergicreactions of the skin include urticaria, skin eruptions or acute hypersensitivity state.

4.13 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.

Treatment is symptomatic. Observe the patient for at least four hours and monitor U&Es and full blood count in symptomatic cases. Give fluids to maintain a good urine output, increased fluid intake will increase the elimination of sulfamethoxazole, but decrease that of trimethoprim. Calcium Leucovirin 5-10mg daily will counteract any adverse effects of trimethoprim on bone marrow or calcium folinate 3-6mg of 5-7 days by mouth or IM . Other measures as indicated by the patients clinical condition.

The amount of a single dose of sulfamethoxazole; trimethoprim that is either associated with symptoms of overdosage or is likely to be life threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic nausea, vomiting, dizziness, headache, drowsiness, and unconsciousness. Pyrexia, hematuria, and crystalluria may be noted. Blood dyscraslas and jaundice are potential late manifestations of overdosage. Signs of acute overdosage with trimethoprim include nausea, vomiting dizziness, headache, mental depression, confusion and bone marrow depression.

General principles of treatment include the institution of gastric cleavage or emesis; forcing oral fluids; and the administration of intravenous fluids if urine output is low & renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim.

The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyspraxia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating sulfamethoxazole; trimethoprim.

Chronic:Use of sulfamethoxazole; trimethoprim at high doses and / or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leucopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be

given leucovorin; 5 to 15mg leucovorin daily has been recommended by some investigators.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotic
ATC code: Trimethoprim: J01EE01 Sulphamethoxazole: J01EC01

Trimethoprim is a pyrimidine analogue that disrupts folate synthesis, an essential part of the thymidine synthesis pathway. Inhibition of the enzyme starves the bacteria of nucleotides necessary for DNA replication. The drug, therefore, exhibits bactericidal activity.

Sulfamethoxazole is a sulfonamide drug that inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA) for binding to dihydropteroate synthetase (dihydrofolate synthetase). Sulfamethoxazole is bacteriostatic in nature.

Inhibition of dihydrofolic acid synthesis decreases the synthesis of bacterial nucleotides and DNA. Sulfamethoxazole is normally given in combination with Trimethoprim, a dihydrofolate reductase inhibitor, which inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid. Studies have shown that bacterial resistance develops more slowly with the combination of the two drugs than with either Trimethoprim or Sulfamethoxazole alone.

5.2 Pharmacokinetic properties

Absorption: Sulfamethoxazole & Trimethoprim is rapidly absorbed following oral administration. Peak blood levels for the individual components occur 1 to 4 hours after oral administration.

Distribution: Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. Approximately 70% of sulfamethoxazole and 44% of trimethoprim are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Biotransformation: The metabolism of sulfamethoxazole occurs predominately by N4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms.

Elimination: Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethoxazole and trimethoprim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N4-acetylated metabolite. When

administered together as sulfamethoxazole & trimethoprim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Linearity/non-linearity: Trimethoprim follows linear pharmacokinetics.

Paediatricpopulation

Results of pharmacokinetic studies in the different pediatric age groups should be summarised, with a comparison to adults if available. If appropriate, the dose producing similar product exposure as in adults could be given. The pharmaceutical form(s) used for pharmacokinetic studies in children should be stated. Uncertainties due to limited experience should be stated.

5.3 Preclinical safety data

Reproductive toxicology: 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. PHARMACEUTICALPARTICULARS

6.1 List of Excipients:

SN	Ingredients	Spec.
1.	Citric Acid Monohydrate	BP
2.	Colloidal Anhydrous Silica	BP
3.	Essence Peppermint	IH
4.	Essence Pineapple	IH
5.	Ponceau 4R	IH
6.	Sodium Benzoate	BP
7.	Sodium Carboxymethylcellulose	BP
8.	Sod. Methyl Hydroxybenzoate	BP
9.	Sod. Propyl Hydroxybenzoate	BP
10.	Sorbitol	BP
11.	Sucrose	BP
12.	Tween 80	BP
13.	Purified Water	BP

6.2 Incompatibilities

None reported

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at a temperature not exceeding 30^{0}C. Protect from light. Keep away from moisture.

6.5 Nature and contents of container

a. 50 ml. in an amber coloured PET bottle in an inner carton.

b. 100 ml. in an amber coloured PET bottle in an inner carton.

6.6 Special precautions for disposal and other handling

Instructions for disposal should be included here, if appropriate for the product.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING
LEBEN LABORATORIES PVT. LTD.

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8. MARKETING AUTHORISATION NUMBER
06783/07399/REN/2020

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION
Nov 19, 2021

10. DATE OF REVISION OF THE TEXT
01/01/2023

11. DOSIMETRY (IF APPLICABLE)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OFRADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable