SUMMARY OF PRODUCT CHARACTERISTICS.

1. Name of the medicinal product

Lecotrim Suspension.

2. Qualitative and quantitative composition

Each 5mL contains: Sulfamethoxazole BP 200mg & Trimethoprim BP 40mg.
For more information on excipients see section 6.1.

3.0 Pharmaceutical Form: Suspension for oral administration.

Pink, viscous, homogenous suspension, packed in 50mL/100mL amber pet/glass bottle and contained in a unit box along with literature insert.

4.0 Clinical Particulars

4.1 Therapeutic Indications

Lecotrim® preparations are indicated for the following infections and where the causative organism is sensitive to active components:

- Urinary tract infections such as urethritis, cystitis, pyelitis, chronic pyelonephritis, prostatitis and gonococcal urethritis.
- Acute exacerbations of chronic bronchitis.
- Gastrointestinal infections notably travellers' diarrhoea caused by enterotoxigenic strains of E. coli, shigellosis and salmonellosis.
- Pneumonia caused by pneumocystis carnii.
- Joint and bone infections and septicemias due to organisms resistant to other antibacterial agents.

4.2 Posology and method of administration:

Method of administration: Oral.

It is administered by oral route either with or after meals as follows:
Usual dosage in adult is 960mg every 12 hours which may be increased to 1.44g every 12 hours in case of severe infections. In treatment courses lasting more than 14 days, the dosage is 480mg every 12 hours. In prophylaxis of re-current urinary tract infections, dosage is 480mg every night. In treatment of gonorrhoea, 1920mg to be taken every 12 hours for 2 days or 3840mg as a single dose which is repeated after another 8 hours. Usual dosage for children is every 12 hours and as follows in accordance with age:

Age	**Recommended dosing schedule.**
6 weeks to 5 months.	2.5mL or one paediatric tablet.
6 months to 5 years.	5mL or two paediatric tablets.
6 years to 12 years.	10mL or four paediatric tablets.

In the treatment of pneumocystis carinii infection, the treatment course is 120mg for every kg body weight daily in divided doses for 14 days.

4.3 Contraindications

Hypersensitivity to the active substances, to sulfonamides or trimethoprim, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Lecotrim® preparation should be used with caution in patients with a history of allergy or bronchial asthma. Depending on dosages and duration of treatment, there is an increased risk of severe adverse reactions in elderly patients in patients with complicated conditions such as renal and/or hepatic impairment, and in patients concomitantly receiving other medicinal products. Fatal outcome, though rare, has been reported in connection with adverse reactions such as blood dyscrasias, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's Syndrome), drug rash with eosinophilia and systematic symptoms and fulminant liver necrosis. Other than in-exceptional cases, Lecotrim® preparations should not be given to patients with serious blood dyscrasias. The product has occasionally been administered to patients receiving cytotoxic agents for the treatment of leukaemia, without evidence of any adverse effect on the bone marrow or peripheral blood. Lecotrim® preparations course should be as short as possible, particularly in elderly patients. Severe persistent diarrhoea during or after treatment may be indicative of pseudomebraneous colitis, which requires immediate treatment. In such cases, Lecotrim® should be discontinued, and appropriate diagnostic and therapeutic measures initiated (e. g oral Vancomycin 250mg four times daily). Ant-peristaltic drugs are contraindicated. If Lecotrim® is given over prolonged period, regular blood counts are required. If a significant reduction in the count of any formed blood element is seen to be below normal levels, Lecotrim® should be discontinued.
Urine and renal functions should be monitored during long-term treatment, especially in patients with renal impairment. An adequate fluid intake and diuresis should be ensured during treatment in order to prevent crystalluria. Since Lecotrim® like other antibiotics, can reduce the effect of oral contraceptives, female patients should be advised to take additional contraceptives measures during Lecotrim® treatment. Prolonged treatment with Lecotrim® can lead overgrowth of non-sensitive organisms and fungi. Appropriate treatment should be initiated immediately in the event of super infection. Caution is indicated in patients

with porphyria or thyroid dysfunction. In elderly patients or patients with renal impairment, hematological changes indicative of folic acid deficiency may occur. These can be reversed by folic acid therapy. Caution is indicated in patients an additional risk factor for folic acid deficiency, e. g treatment with phenytoin or other folic acid antagonists, malnutrition. Cases of pancytopenia have been reported in patients given the combination of trimethoprim and methotrexate. Trimethoprim has been found to have an adverse effect on phenylalanine metabolism. However, this has no relevance to patients with phenylketonuria who adhere to an appropriate diet. "Slow acetylators" may be at increased risk for idiosyncratic reactions to sulfonamides.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic and pharmacodynamic interactions: Increased digoxin blood levels can occur with concomitant co-trimoxazole therapy, especially in elderly patients. Co-trimoxazole can inhibit the hepatic metabolism of phenytoin. A 39% increase in phenytoin half-life and a 27% decrease in the metabolic clearance rate of phenytoin have been observed following administration of co-trimoxazole at normal clinical doses. If the two drugs are given concurrently, the possibility of an undesirably increased phenytoin effect should be borne in mind. The efficacy of tricyclic antidepressants may be reduced if these are administered concurrently with co-trimoxazole.

Sulfonamides, including sulfamethoxazole can displace methotrexate from plasma protein binding sites and impair the renal transport of methotrexate, thus increasing free methotrexate concentration and effect. Co-trimoxazole may influence the required dose of oral antidiabetic agents.

Like other antibiotics, Lecotrim® can reduce the efficacy of oral contraceptives. Female patients should therefore be advised to take additional contraceptive measures during Lecotrim® treatment. Co-administration of indomethacin and co-trimoxazole can raise Sulfamethoxazole blood levels.

Observed interactions:

An increased incidence of thrombocytopenia with purpura has been observed in elderly patients concurrently receiving certain diuretics, primary thiazides.

It has been reported that co-trimoxazole may prolong prothrombin time in patients receiving the anticoagulant warfarin. This interaction should be borne in mind when Lecotrim® is given to patients already receiving anticoagulants. In such cases, the prothrombin time should be redetermined. Reversible deterioration of renal function, as detected by raised serum creatinine levels, has been observed in patients treated with co-trimoxazole and ciclosporin following renal transplantation. This interaction is thought to be due to the Trimethoprim component.

Cases of pancytopenia have been reported in patients given the combination of Trimethoprim and Methotrexate. Trimethoprim has a low affinity for human dihydrofolate reductase, but can potentiate the side effects of methotrexate and lead to undesirable hematological interactions with methotrexate, particularly in the presence of other risk factors such as advanced age, hypoalbuminemia, renal impairment and reduced bone marrow reserve. Such adverse drug reactions can occur in particular when high doses of methotrexate are administered. Such patients should be treated with folic acid or calcium folinate in order to counteract the effects on haematopoiesis (rescue).

4.6. Pregnancy and lactation

Pregnancy

Lecotrim® should not be used in pregnancy unless it is clearly necessary, since both Trimethoprim & Sulfamethoxazole cross the placenta barrier and may thus interfere with fetal folic acid metabolism. In animal experiments, very high doses of co-trimoxazole induced malformations typical of folic acid antagonism. On the basis of studies in pregnant women, literature reviews and spontaneous reports of malformations, co-trimoxazole appears to present no significant risk of teratogenicity in humans. Supplementary folic acid (5mg/day) is recommended for pregnant women who require Lecotrim® treatment. Lecotrim® should be avoided as far as possible during the last trimester, as it can increase the risk of kernicterus in the neonate.

Lactation

Both Trimethoprim and Sulfamethoxazole pass into breast milk. Although the amount of drug ingested by a breast-fed infant is extremely small, the benefit to the mother should be carefully weighed against the risk to the infant (kernicterus, hypersensitivity).

4.7 Effects on ability to drive and use machines

Lecotrim® has no direct effects on the ability to drive or operate machinery. However, undesirable effects are possible that could impair these abilities, in some cases severely.

4.8 Undesirable effects

The main undesirable effects are skin reactions and mild gastrointestinal upsets, which occurred in approximately 5% of treatment periods.

4.9 Overdose.

Symptoms

In acute overdosage, the following signs and symptoms may occur: nausea, vomiting, headache, vertigo, dizziness, mental and visual disturbances; crystalluria, haematuria and anuria can occur in severe cases. In chronic overdosage; bone marrow depression manifested as thrombocytopenia, leukopenia, or other blood dyscrasias due to folic acid deficiency.

Management
Depending on the signs and symptoms, the following measures should be considered: avoidance of further absorption, acceleration of renal elimination by forced diuresis, hemodialysis, monitoring of blood count and electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Calcium folinate, 3-6mg i.m for 5-7 days may be given to counteract the effects of Trimethoprim on haematopoiesis.

5. 0 Pharmacological Properties

5.1 Pharmacodynamic Properties.

Pharmacotherapeutic Group: Combinations of sulfonamides and trimethoprim, incl. derivatives, **ATC code: J01EE01.**
The ingredients of co-trimoxazole (Lecotrim®); Sulfamethoxazole and Trimethoprim affect their anti-microbial activity synergistically by interfering with the synthesis of nucleic acids. They cause blockade thought to be of sequential nature, of the metabolic pathway involving the synthesis of tetrahydrolic acid.
Sulfamethoxazole being similar structurally to p-aminobenzoic acid (PABA), blocks the conversion of PABA to the co-enzyme dihydrofolic acid which is the reduced form of folic acid. Trimethoprim on the other hand inhibits dihydrofolic acid to tetrahydrofolate reductase, the enzyme that converts bacterial dihydrofolic acid to tetrahydrofolic acid.
Tetrahydrofolic acid is necessary for the synthesis of certain aminoacids, purines, thymidine and ultimately DNA synthesis.
Antimicrobial spectrum:
Lecotrim® preparations is active against wide range of organisms. Among these are the Gram-positive and Gram-negative bacteria. Actinomyces and Nocardia species, chlamydia trachomatis and some fungi including pneumocystis carinii, some protozoa of which the plasmodium species and toxoplasma gondii are included.
Among the gram-negative organisms, strains of most Enterobacteriaceae are sensitive and these include E. coli, haemophilus ducreyi, H. influenzae, Enterobacter, klebsiella, and shigella. Proteus and salmonella species, Neisseria gonorrhoea, Morganella morganii, N. meningitidis and Vibrio chlorella.
Among the gram-positive organisms are listeria monocytogenes, clostridium perfringens and some of Staphylococci and streptococcus.

5.2 Pharmacokinetic properties

Absorption
Lecotrim® is absorbed rapidly and almost completely (bioavailability: 80-100%) in the upper gastrointestinal tract after oral administration. Following a single dose of 160mg Trimethoprim+ 800mg Sulfamethoxazole, peak plasma concentrations of 1.5-3mg/l for Trimethoprim and 40-80mg/l for Sulfamethoxazole are reached in 1-4 hours. If administration is repeated every 12 hours, the steady state peak plasma concentrations of Sulfamethoxazole and Trimethoprim are generally 50-100% higher than after a single oral dose. When a Trimethoprim suspension is taken on a full stomach, the extent of absorption is less than when taken on an empty stomach, though the rate of absorption was not affected by a standard meal.
Distribution
The volumes of distribution of Trimethoprim and Sulfamethoxazole are approximately 1.2-1.5l/kg and 0.15-0.36l/kg respectively. At the above concentrations 42-46% of Trimethoprim and 66% of Sulfamethoxazole are bound to plasma proteins. Studies in both animals and man have shown that diffusion of co-trimoxazole into the tissues is good. Large amounts of Trimethoprim and smaller amounts of Sulfamethoxazole pass from the blood stream into the interstitial fluid and other extravascular body fluids. The concentrations of Trimethoprim and Sulfamethoxazole may be increased in inflamed tissues. Trimethoprim and Sulfamethoxazole have been detected in the fetal placenta, cord blood, amniotic fluid and fetal tissues (liver, lungs), indicating that both substances cross the placenta barrier. As a rule, fetal Trimethoprim concentrations are similar to those in the material circulation, while fetal levels of Sulfamethoxazole are lower. Both substances are excreted in breast milk. Concentrations in breastmilk are similar to Trimethoprim or lower than Sulfamethoxazole those in the maternal plasma.
Metabolism
Some 50-70% of trimethoprim and 10-30% of Sulfamethoxazole are eliminated in the urine in unchanged form. The principal Trimethoprim metabolites are 1-and 3-oxides and 3'-and 4'-hydroxy derivatives; some of the metabolites are active. Sulfamethoxazole is metabolised in the liver, predominantly via N4-acetylation and to a lesser extent via glucuronidation; its metabolites are inactive.
Elimination
With normal renal function, the half-lives of the two components are very similar (mean of 10 hours for Trimethoprim and 11 hours for Sulfamethoxazole). Total clearance levels are around 100mL/min for Trimethoprim and 20ml/min for Sulfamethoxazole.
The elimination half-life of Trimethoprim in children is approximately half that in adults, while no corresponding significant difference applies to Sulfamethoxazole. Both substances and their metabolites are eliminated predominantly via the kidneys both by glomerular filtration and by tubular secretion. The concentrations of Trimethoprim and Sulfamethoxazole in the urine are some 100 and 5 times higher respectively than the corresponding plasma levels. Renal clearance levels are 20-80mL/min for Trimethoprim and 1-5mL/min for Sulfamethoxazole. Both substances are detected to a slight extent in the feaces.

5.3 Preclinical Safety Data

At doses in excess of the 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 co-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

Sodium Methyl Paraben, Sodium Propyl Paraben, Xanthan Gum 200 mesh, Polysorbate 80, Strawberry Flavour, Erythrosine Soluble colour, Sodium Saccharin, Citric acid, Sodium CMC & Purified water.

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months from the date of manufacture. (2 years).

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

50mL/100mL amber PET/glass bottles contained in unit box along with a literature insert.

6.6 Special precautions for disposal and other handling

None applicable.

7. Legal category

Prescription Only Medicine (POM).

8. Marketing authorization holder/Registrant.

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9. Manufacturer

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