Lecotrim®

Co-trimoxazole Preparations

COMPOSITION:

Lecotrim® Paediatric Tablets :**Each tablet contains:** 100mg Sulphamethoxazole BP and 20mg Trimethoprim BP (120mg COTRIMOXAZOLE)

Lecotrim® Tablets :**Each tablet contains:** 400mg Sulphamethoxazole BP and 80mg Trimethoprim BP (480mg COTRIMOXAZOLE)

Lecotrim® Forte Tablets :**Each tablet contains:** 800mg Sulphamethoxazole BP and 160mg Trimethoprim BP (960mg COTRIMOXAZOLE)

Lecotrim® Paediatric Suspension :**Each 5ml contains:** 200mg Sulphamethoxazole BP and 40mg Trimethoprim BP (240mg COTRIMOXAZOLE)

PHARMACEUTICAL FORM:

Lecotrim® Paediatric Tablets: White Flat Faced Bevel Edged scored on one side and plain on the reverse. **Lecotrim® Tablets:** White, circular FFBE tablets embossed "**LECOTRIM**" on one side and plain on the reverse. **Lecotrim® Forte Tablets:** White oblong shaped, scored on one side and plain on reverse. **Lecotrim® Paediatric Suspension:** Pink, viscous, sweet suspension.

CLINICAL PARTICULARS:

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 urahtritis.
- Acute exacerbations of chronic bronchitis
- Gastrointestinal infections notably travellers' diarrhea 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.

DOSAGE AND ADMINISTRATION:

Usual dosage in adult is 960mg every 12hours which may be increased to 1.44mg 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 the treatment of gonorrhea, 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 12hours and as follows in accordance with age.

6 weeks to 5 month : 2.5ml or one Paediatric tablets
6 months to 5 years : 5ml or two Paediatric tablets
6 to 12 years : 10ml or four Paediatric tablets

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

SIDE-EFFECTS:

Gastrointestinal disturbances, glossitis, rashes, erythema multiforme, epidermal necrolysis, blood dyscrasias, pneudomembranous colitis, jaundice, aplastic anaemia and hepatic necrosis.

CONTRA-INDICATIONS:

- Hypersensitivity to the active substances, to sulfonamides or trimethoprim, or to any of the constituent excipients.
- Marked parenchymal liver disease.
- Severe renal impairment (Creatinine clearance <15 ml/min) unless Trimethoprim and Sulphamethoxazole plasma concentrations can be determined repeatedly.
- Megaloblastic anemia due to folic acid deficiency.
- Use in premature infants or neonates during the first 6 weeks of life, as this may increase the risk of kernicterus.
- Use in the last trimester of pregnancy (see Pregnancy and lactation).
- Combination with dofetilide (see Interactions).

WARNINGS AND PRECAUTIONS:

Lecotrim® should be used with caution in patients with a history of allergy or bronchial asthma.

Depending on dosage and duration of treatment, there is an increased risk of severe adverse reactions in elderly patients, in patients with complicating 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 systemic symptoms and fulminant liver necrosis.

Other than in exceptional cases, **Lecotrim®** 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 leukemia, without evidence of any adverse effect on the bone marrow or peripheral blood.

Lecotrim® should be as short as possible, particularly in elderly patients.

Severe persistent diarrhea during or after treatment may be indicative of pseudomembranous colitis, which requires immediate treatment. In such cases, **Lecotrim®** should be discontinued, and appropriate diagnostic and therapeutic measures initiated (e.g. oral vancomycin 250 mg four times daily).

Antiperistaltic drugs are contraindicated. If **Lecotrim®** is given over a prolonged period, regular blood counts are required. If a significant reduction in the count of any formed blood element to below normal levels is noted, **Lecotrim®** should be discontinued.

Urine and renal function 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 contraceptive measures during **Lecotrim®** treatment.

Prolonged treatment with **Lecotrim®** can lead to overgrowth of non-sensitive organisms and fungi. Appropriate treatment should be initiated immediately in the event of superinfection.

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 folinic acid therapy.

Caution is indicated in patients with 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 (see Interactions).

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.

INTERACTIONS:

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 dosages. 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, primarily 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 (see Warnings and precautions). 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 hematopoiesis (rescue).

PREGNANCY AND LACTATION:

Pregnancy

Lecotrim® should not be used in pregnancy unless it is clearly necessary, since both Trimethoprim and Sulphamethoxazole cross the placental 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 (5 mg/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 Sulphamethoxazole 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) (see Contraindications).

Effects on ability to drive and use machine

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 (see Undesirable effects).

Undesirable effects

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

OVERDOSAGE

Symptoms

In acute overdosage the following signs and symptoms may occur: nausea, vomiting, headache, vertigo, dizziness, mental and visual disturbances; crystalluria, hematuria 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, 3–6 mg i.m. for 5–7 days, may be given to counteract the effect of TM on hematopoiesis.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic Properties

The ingredients of Co-trimoxazole (**Lecotrim®**); Sulphamethoxazole 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.

Sulphamethoxazole 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 other hand inhibits dihydrofolic acid to tetrahydrofolate reductase, the enzyme that converts bacterial dihydrofolic acid to tetrahydofolic acid.

Tetrahydofolic acid is necessary for the synthesis of certain aminoacids, purines, thymidine and ultimately DNA synthesis.

Antimicrobial spectrum:

Lecotrim® tablets are active against a-wide range of organisms. Among these are the Gram-positive and Gram-negative bacteria, Actinomyces and Nocardia species, *Clamydia trachomatis*, and some fungi including Pneumocystis carinii, some protozoa of which the Plasmodium species and T*oxoplasma* gondii are included. Among the Gram-negativeorganisms, strains of most Enterbacteriaceae are sensitive and these include *E.coli, haemophilus ducreyi, H.influenzae*, enterrobacter, klebsiella, and shigella. Proteus and Salmonella species. *Neisseria gonorrhoea, Morganella morganii. N.meningitidis* and *Vibrio cholera*,

Among the Gram-positive organisms are Listeria *monocytogenes, Clostridium perfringeni* and some of Staphylococci and Streptococcus.

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 160 mg Trimethoprim,+ 800 mg Sulfamethoxazole, peak plasma concentrations of 1.5–3 mg/l for Trimethoprim and 40–80 mg/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 1.2–1.5 l/kg and 0.15–0.36 l/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 bloodstream 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 placental barrier. As a rule, fetal Trimethoprim concentrations are similar to those in the maternal circulation, while fetal levels of Sulfamethoxazole are lower. Both substances are excreted in breast milk. Concentrations in breast milk 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 100 ml/min for Trimethoprim and 20 ml/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 20–80 ml/min for trimethoprim and 1–5 ml/min for Sulfamethoxazole. Both substances are detected to a slight extent in the feaces.

LEGAL CATEGORY: Prescription Only Medicines (POM).

THERAPEUTIC CATEGORY: ATC J03B (Systemic Chemotherapeutics – Sulfonamide and anti- infective combination).

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

SHELF LIFE: As per the product label.

PRESENTATION:

Lecotrim® Paediatric Tablets	: Available in blister packs of 10 x 10's and in polythene bags packed in high density plastic containers of 1000's
Lecotrim® Tablets	: Available in blister packs of 10 x 10's and in polythene bags packed in high density plastic containers of 500's and 1000's
Lecotrim® Forte Tablets	: Available in blister packs of 10 x 10's and in polythene bags packed in high density plastic containers of 1000's
Lecotrim® Paediatric Suspension	: Available in 50ml and 100ml amber coloured bottles and in plastic containers of 5 litres

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LICENSE HOLDER: LABORATORY & ALLIED LTD.

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