SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lagatrim® Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of suspension contains Trimethoprim 40mg and Sulfamethoxazole 200 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Infections due to microorganisms sensitive to Lagatrim, in particular:

Infections of the upper and lower respiratory tract: acute and chronic bronchitis, bronchiectasis, pneumonia (pneumonia due to Pneumocystis carinii to a lesser degree). pharyngitis, tonsillitis (except when beta- hemolytic streptococci of group A are present results unsatisfactory), sinusitis, otitis media.

Infections of the urogenital tract: acute and chronic cystitis, pyelonephritis, urethritis including gonococcal urethritis, prostatitis.

Infections of the gastrointestinal tract, including typhoid and paratyphoid fevers (including permanent carriers): bacillary dysentery, cholera (in conjunction with electrolyte replacement therapy), shigellosis.

Infections of the skin and soft tissues: pyoderma, furunculosis, abscesses, and certain wound infections.

Other bacterial infections: acute or chronic osteomyelitis, acute brucellosis. septicemia due to sensitive microorganisms, nocardiosis, rnycetoma (except fungal mycetoma), South American blastomycosis, Toxoplasma.

Recommendations:

The current place of cotrimoxazole in therapy was reviewed by the UK Committee on Safety of Medicine in 1995. As a result they recommended that its use should be limited to: Pneumocystis carinii pneumonia, toxoplasmosis and nocardiosis; urinary- tract infections and acute exarcebations of chronic bronchitis. but only when there is bacteriological evidence of sensitivity of co-trimoxazole and good reason to prefer it to a single antibiotic; and acute otitis media in children, but again only when there is good reason to prefer the combination

4.2 Posology and method of administration

Dosage:

Lagatrim is administered at 12 hour intervals. Adults and children of 12 years and over are usually treated with Lagatrim Forte while children under 12 are treated with Lagatrim oral suspension which allows a more precise dosage.

Oral Dosage:

Children under 12 years: 2 ml of Lagatrim oral suspension per kg bodyweight per day, divided into equal doses twice daily. Lagatrim is usually taken after meal with a generous quantity of liquid.
Duration of treatment: The duration of treatment must be appropriate to the type of infection; as a general rule it should not exceed 5 days, except in chronic infections, where the treatment must be continued for at least 2 days after the symptoms have disappeared. In special high dosage administration, the maximum dosage should not be administered Longer than 3 successive days.

4.3 Contraindications

Lagatrim is not recommended in severe cases of liver parenchyma damage, and if the plasma concentration cannot be regularly determined in severe renal insufficiency (creatinine clearance < 15 ml/min).
Lagatrim is also contraindicated in cases of hypersensitivity to one or other of its components or to sulfonamides.
It is not recommended for patients with megaloblastic anemia due to folic acid deficiency. Lagatrim must on no account be administered to premature babies or to neonates during the first six weeks of life.

4.4 Special warnings and precautions for use

Precautions measures

To avoid any problems or complications during prolonged treatment with Lagatrim, we recommend regular monitoring of plasma levels, both of the active substances and blood cell count. If there is any significant change in the blood cell count, treatment should be discontinued immediately.
In common with other antibiotics, Lagatrim may reduce the effectiveness of oral contraceptives. It is therefore advisable to use supplementary mechanical contraceptive methods during treatment.
During prolonged treatment with Lagatrim, some microorganisms may develop resistance, and there is also a risk of fungal infection. In these cases, it is important to commence appropriate therapy immediately. The product must not be administered to patients suffering from G6PD-deficiency or to patients with certain types of hemoglobinosis (Hb-Zurich, Hb-Cologne). At the first sign of exanthema or other serious adverse reactions, Lagatrim therapy should be discontinued. In elderly patients and those with renal insufficiency, hematologic changes indicating a deficiency of folic acid may occur; these may be reduced by the administration of folic acid. Care is needed in patients being treated with folic acid antagonists (phenytoin and derivatives) or in a slate of malnutrition.
When treatment is prolonged, the urine and renal function should be monitored. During treatment with Lagatrim, it is also important to ensure that water intake and urinary output are sufficient to avoid crystalluria.

4.5 Interaction with other medicinal products and other forms of interaction

In elderly patients, with certain diuretics, particularly the thiazides, increasing the risk of thrombocytopenic purpura. With warfarin, inducing prolongation of the quick time. With phenytoin, by inhibiting its metabolism in the liver. With methotrexate and corresponding areas

of attachment to plasma proteins, by impeding renal transport, resulting in an increase in the free methotrexate level and potentiation of its activity. With hypoglycemics, diminishing or potentiating their effect. With pyrimethamine, favoring megaloblastic anemia. With cyclosporine, causing a reversible alteration of renal function.With oral contraceptives, reducing their effectiveness. With indomethacin, increasing the blood level of sulfamethoxazole.

4.6. Pregnancy & lactation

With high doses of Lagatrim, certain dysplasias directly related to folic acid antagonist may be observed. In view of the permeability of the placenta to the active substance and the associated reduction of folic acid, the administration of Lagatrim during pregnancy must be ruled out, unless the benefits of treatment outweigh these risks. Similarly, and for the same reasons, it is necessary to carefully weigh up the anticipated benefit to lactating mothers, as the risks of hypersensitivity to the chemotherapeutic agent are greater for nursing infants.

4.7Adverse effects:

Most frequent: nausea, with or without vomiting, stomatitis, diarrhea.

Rare: cholestatic hepatitis. pseudomembranous colitis, acute pancreatitis.

Very rare: liver necrosis.

The following may also be observed: mid, reversible rashes, sometimes severe cutaneous reactions such as erythema multiform Steven Johnson syndrome, or Lyell's syndrome. Renal failure or insufficiency and crystalluria; increased urinary output, especially in patients suffering from edema due to cardiac insufficiency. Changes in blood cell count as leukopenia, neutropenia or thrombocytopenia types; sometimes agranulocrtosis megaloblastic, hemolytic or splashy anemia, pancytopenia, or purpura. Reversible hypersensitivity or allergic reactions. Pulmonary infiltrations with associated symptoms such as cough and dyspnea. Aseptic meningitis or similar Hallucinations, headache and dizziness.Rarely, depression.
The side effects mentioned may be more frequent in immuno-depressives (AIDS sufferers). The risk of severe side effects is greater in elderly patients and those with renal or hepatic insufficiency, and when other drugs are being administered concurrently. The risk depends on the dosage and duration of treatment. In every case a limited duration of treatment is strongly recommended. Side effects such as blood dyscrasia, Stevens Johnson syndrome, bullous erythroderma with epidermolysis (Lyell's syndrome), and fulminating hepatitis, are extremely rare, as is death caused by treatment with Lagatrim.

4.9. Overdose:

In cases of acute overdosage, the following symptoms can be observed: nausea, vomiting, headache, dizziness, hallucinations, psychological disturbances and visual disturbances. Rarely, in severe cases, crystalluria, hematuria and anuria may occur. In cases of chronic Overdosage there may be medullary aplasia, including thrombocytopenia, leukopenia and blood dyscrasias, all due to folic acid deficiency. In cases of Overdosage, gastric lavage should be considered, vomiting should be induced and in cases of blood dyscrasias, the antidote should be

administered, namely 3 to 6 mg of calcium folinate intramuscularly for 5 to 7 days for blocking the effect of TM on hematopoiesis.
In cases of icterus treat the complications symptomatologically.

5. Pharmacokinetic properties

The combination of the two active ingredients, TMP and SMX, is known by the name of co trimoxazole.

TMP and SMX have a synergetic action. This is based on the blocking of two enzymes catalyzing successive reactions in the biosynthesis of folic acid in micro-organisms. Due to this mechanism of action, the effect is bactericidal, whereas taken separately, each of the active substances has only a bacteriostatic action for the same concentration of active substance. In addition, co-trimoxazole is often effective against organisms which are resistant to the two constituents taken separately. In vitro, Co- trimoxazole has a broad spectrum of activity encompassing many gram-positive and gram-negative organisms. Some of these are: Staphylococcus aureus, Staphylococcus spp., Enterococcus faecalis, non-hemolytic streptococci, beta-hemolytic streptococci of groups A and B; Moraxella catarrhalis. Neisseria gonorrhoeae, Haemophilus influenzae. Haemophilus parainfluenzae, Haemophilus ducreyi, Citrobacter, Klebsiella orytoca, Enterobacter, Serratia marcescens, Serratia liquefaciens, Serratia spp., Proteus mirabilis, Proteus vulgaris, various strains of Salmonella including those which cause enteritis, Shigella spp., Yersinia enterocolitica, Yersinia spp., Vibro cholerae, Acinetobacter, Alcaligenes Faecalis. Available results indicate that other organisms such as Brucetia, Chlamydia trachomatis, Nocardia asteroides, Toxoplasma gondii and Pneumocystis cannii are sensitive to Lagatrim. However, if these organisms are present, a sensitivity test is highly recommended as Lagatrim will not always be effective, particularly in a hospital environment. Some organisms are partially sensitive to co-trimoxazole. These are:
Penicillin resistant Streptococcus pneumoniae, E. coli, Klebsiella pneumoniae, other Klebsiella spp. other Providencia spp. and Pseudomonas cepacia. Other organisms are resistant to Co-trimoxazole. These are: most Pseudomonas, Xanthomonas maltophilia, anaerobic bacteria, Campylobacter fetus, Ureaplasma and Mycoplasma, Mycobacterium tuberculosis and Treponema pallidum. For infections due to organisms of intermediate sensitivity, it is advisable to carry out a sensitivity test to exclude resistant strains. Sensitivity to Lagatrim can be determined using standardized methods such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Cross resistance may occur when Lagatrim is used in combination with antibiotics of the same origin (sulfonamides), but no cross resistance is known at this time for combinations with other, unrelated antibiotics. There is a marked synergy between TMP and SMX and even when there is resistance to one or other of the constituents administered alone, it is rare to observe resistance to Lagatrim.

5.1 Pharmacokinetics

TMP and SMX are broadly similar in terms of their clinically significant pharmacokinetic properties.

a) Absorption

When administered orally, TMP and SMX are rapidly and almost totally absorbed (bioavailability 80-100%) in the upper part of the gastrointestinal tract. After administration of a single dose of 160 mg of TMP and 800 mg of SMX, the maximum plasma concentrations, reached between 1 and 4 hours, are 1.5-3 mcg/ml for TMP and 40-80 mcg/ml for SMX. When administration is repeated every 12 hours, the maximum plasma concentrations of TMP and SMX in a state of equilibrium are 50 to 100% higher than those recorded after a single oral dose. The plasma concentration evolves in proportion to the dose administered. The influence of food consumption on Lagatrim and on the kinetics of its active ingredients is not known. On the other hand, it is known that taking TMP with food reduces its absorption. It is therefore advisable to take Lagatrim.on an empty stomach to guarantee the maximum concentration of its active ingredients. As for the rate of absorption, this is not modified by a standard meal.

b) **Distribution**

The distribution volume is approximately 1.2-1.5 l/kg for TMP and approximately 0.15-0.36l/kg for SMX. The plasma protein binding level is 42-46% for TMP and 66% for SMX. The tissue diffusion of Lagatrim is good. TMP diffuses better than SMX, but both substances cross the placental barrier. Inflammatory tissue appears to contain increased concentrations of Lagatrim. Fetal concentrations are identical to those in the maternal blood, whereas in breast milk, TMP is found in a higher concentration than SMX.

c) **Metabolism**

TMP and SMX are eliminated unchanged to the extent of 50 -70% and 10 -30% respectively. The known metabolites of TMP are the 1-oxide and 3-oxide, together with the 3'-hydroxy and 4'-hydroxy derivatives; some metabolites are active. SMX is metabolized in the liver, essentially by N4 -acetylation and to a lesser extent, by glucuronization; its metabolites are inactive.

d) **Elimination**

If renal function is normal, the half-life of the two active ingredients is the same (10 hours on average for TMP and 10 to 11 hours for SMX). The total clearance rate is 100 ml/min for TMP and approximately 20 ml/min for SMX. In children, the total clearance rate is approximately half that recorded in adults, while that of SMX is unchanged. For the two substances and their metabolites, elimination is primarily renal. The urinary concentration of TMP is approximately 100 times greater than the plasma concentration, while that of SMX is approximately 5 times greater. The renal clearance rate of TMP is 20 - 80 ml/min and that of SMX is 1 - 5 ml/min. Small amounts of both substances are found in the feces. In elderly persons and those with renal insufficiency, elimination is slower, and it is therefore necessary to adjust the dosage. In hepatic insufficiency, the kinetics are unchanged in low doses; however, care is needed with high doses and prolonged treatment. In patients undergoing hemodialysis, the dosage must be adjusted.

5.2 Special Remarks

Influence on laboratory diagnostic procedures Co-trimoxazole, and particularly TMP, may falsify the results of tests for determining serum methotrexate. On the other hand, no influence has been observed on the determination of methotrexate by radioimmunology. Co-trimoxazole

may influence as well the results of the Jaffe-test (the reaction of picric acid with creatinine in basic milieu): for this reason normal values may be overestimated for about 10%.

Other remarks

Return any unused or partially used packaging to the pharmacist or physician.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Liquid Sorbitol (Non- crystallizing) , Glycerol , Saccharin Sodium , Sucralose , Methyl Hydroxybenzoate , Ethanol (96 per cent), Tragacanth , Banana Flavour , Citric Acid Monohydrate .

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 Months.

6.4. Special precautions for storage

Store at room temperature (15°C-25°C) in the original packaging.

6.5. Nature and contents of container

125 ml amber colored glass bottle sealed with child resistant cap placed in a printed carton along with a pack insert.
Pack size: 100ml Glass Bottle.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Lagap SA, UAE
Po. Box 46222
Abu Dhabi, UAE
(A division of Lagap Switzerland)

8. MARKETING AUTHORISATION NUMBER(S)

05377/07536/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Approval : 29-09-2020