Approved Professional Information for Medicines for Human Use:

LAGATRIM AND LAGATRIM FORTE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LAGATRIM 80 mg/400 mg tablets

LAGATRIM FORTE 160 mg/800 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LAGATRIM 80 mg/400 mg tablet

Each tablet contains 80 mg trimethoprim and 400 mg sulphamethoxazole.

Contains 0,1 % *m/m* nipasept (preservative).

Sugar free.

LAGATRIM FORTE 160 mg/800 mg tablet

Each tablet contains 160 mg trimethoprim and 800 mg sulphamethoxazole.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

LAGATRIM 80 mg/400 mg tablets

A white scored biconvex tablet.

The tablet can be divided into equal halves.

Shanur Healthcare (Pty) Ltd, R20.2.1/241-2, Lagatrim and Lagatrim forte, Trimethoprim 80/160 mg; Sulphamethoxazole 400/800 mg, tablets

LAGATRIM FORTE 160 mg/800 mg tablets

A white scored capsule-shaped tablet.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bacterial infections, caused by susceptible micro-organisms, of the upper and lower respiratory tract, genitourinary tract, gastro-intestinal tract and skin infections.

4.2 Posology and method of administration

Posology

LAGATRIM**:**

Adults and children over 12 years:

Standard dosage: 2 tablets every 12 hours (preferably morning and evening after meals).

For severe infections maximum dosage: 3 tablets every 12 hours.

Maintenance dosage for long-term treatment (more than 14 days): 1 tablet every 12 hours.

Children:

6 - 12 years: ½ to 1 tablet every 12 hours.

LAGATRIM FORTE:

Adults and children over 12 years:

Standard dosage: 1 tablet every 12 hours (preferably morning and evening after meals).

For severe infections maximum dosage: 1½ tablets every 12 hours.

Maintenance dosage for long-term treatment (more than 14 days): ½ tablet every 12 hours.

In the treatment of acute infections LAGATRIM and LAGATRIM FORTE should be administered for at least 5 days or for at least 2 days after the symptoms have disappeared. If clinical improvement is not

evident after 7 days therapy, the patient should be reassessed.

Special populations

Renal impairment

If LAGATRIM OR LAGATRIM FORTE is indicated for patients with renal impairment, the following dosage scheme, based on creatinine clearance is suggested:

Above 25 mL/min: Standard dosage

15 – 25 mL/min: Standard dosage for a maximum of 3 days followed by half the standard daily dosage.

Below 15 mL/min: Not to be administered unless haemodialysis facilities are available when half the standard daily dosage may be given.

Measurements of plasma concentrations of sulfamethoxazole at intervals of 2 days are recommended in samples obtained 12 hours after administration of LAGATRIM OR LAGATRIM FORTE. If the concentration of total sulfamethoxazole exceeds 150 ug/mL then treatment should be interrupted until the value falls below 120 ug/mL.

No Information is available for children with renal failure.

Method of administration

LAGATRIM and LAGATRIM FORTE is for oral use.

It is preferable to administer LAGATRIM AND LAGATRIM FORTE morning and evening after meals.

The tablets must be swallowed with a drink of water.

4.3 Contraindications

- Hypersensitivity to sulphonamides, trimethoprim, sulphamethoxazole or any of the excipients listed in section 6.1.
- Patients with acute porphyria.

- Patients with renal or hepatic failure or with blood disorders.
- Patients with renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- Liver parenchymal damage.
- Megaloblastic anaemia due to folic acid deficiency.
- During pregnancy and lactation, and to women prior to delivery.
- Premature babies and infants during the first 6 weeks of life.

4.4 Special warnings and precautions for use

Life-threatening adverse reactions

- Erythema multiforme, toxic dermal necrolysis or allergic vasculitis may occur. Treatment should be discontinued immediately when a rash appears because of the danger of severe allergic reactions.
- Fatalities, although very rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.
- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
- If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, treatment should be discontinued (see section 4.8).
- The best results in managing SJS, TEN and DRESS come from early diagnosis and immediate discontinuation of any suspect medicine. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS, TEN and DRESS with the use of LAGATRIM or LAGATRIM FORTE, treatment with LAGATRIM or LAGATRIM FORTE must not be re-started in this patient

at any time.

- At the start of treatment, the occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of acute generalised exanthematous pustulosis (AGEP) (see section 4.8); it requires cessation of treatment and contraindicates any new administration of LAGATRIM and LAGATRIM FORTE alone or in combination with other medicines.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported very rarely in patients treated with ~~this medicine~~ LAGATRIM and LAGATRIM FORTE. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, treatment should be discontinued.

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS) have been reported during treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, LAGATRIM or LAGATRIM FORTE should be discontinued, and appropriate treatment given.

Elderly patients

Particular care is always advisable when treating older patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other medicines.

Adverse effects on the blood may be more severe in malnourished or elderly patients; there also appears to be an increased risk of thrombocytopenia in elderly patients concurrently receiving diuretics, mainly thiazides. All patients receiving prolonged treatment with LAGATRIM or LAGATRIM FORTE should be given regular blood examinations and urine analysis with microscopic examination.

Patients with renal impairment

LAGATRIM and LAGATRIM FORTE should be used cautiously and in reduced dosage in patients with impaired renal function (see section 4.2).

Urinary output

Because of the risk of crystalluria, and adequate fluid intake should be maintained, and the administration of alkalis may be necessary if large doses are used. In patients suffering from malnutrition the risk may be increased.

Folate

Regular monthly blood counts are advisable when LAGATRIM or LAGATRIM FORTE is given for long periods, or to folate deficient patients or to older patients, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. Supplementation with folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

Patients with glucose-6-phosphate dehydrogenase deficiency

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients, haemolysis may occur.

Patients with severe atopy or bronchial asthma

LAGATRIM and LAGATRIM FORTE should be used with caution in patients with severe atopy or bronchial asthma.

Treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci

LAGATRIM and LAGATRIM FORTE 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.

Phenylalanine metabolism

Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

Patients with or at risk of porphyria

The administration of LAGATRIM and LAGATRIM FORTE 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.

Patients with hyperkalaemia and hyponatraemia

Close monitoring of serum potassium and sodium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

Metabolic acidosis

Sulphamethoxazole and trimethoprim has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Patients with serious haematological disorders

Except under careful supervision LAGATRIM and LAGATRIM FORTE should not be given to patients with serious haematological disorders (see section 4.8). Sulphamethoxazole and trimethoprim has

been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

A high incidence of side-effects occurs in immunocompromised patients such as those suffering from AIDS or patients receiving immunosuppressive therapy. The adverse effects include skin rash, recurrent fever, neutropenia, thrombocytopenia and raised levels of liver enzymes.

LAGATRIM and LAGATRIM FORTE should also be used with caution in patients receiving pyrimethamine as they may develop megaloblastic anaemia due to the trimethoprim component.

The combination of antibiotics in LAGATRIM and LAGATRIM FORTE should only be used where, in the judgement of the medical practitioner, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

Excipient nipastat

LAGATRIM contains nipastat, a mixture of parahydroxybenzoate esters. It may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicines and other forms of interaction

Interaction with laboratory tests: Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10 %. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23 % to 9 % whilst the glomerular filtration remains unchanged.

Sulphamethoxazole may interfere with some diagnostic tests including those for urea, creatinine, urinary glucose and urobilinogen.

Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to sulphamethoxazole and trimethoprim. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Ciclosporin: Reversible deterioration in renal function has been reported in patients given trimethoprim and cyclosporin following renal transplantation.

Rifampicin: concurrent use of rifampicin and sulphamethoxazole and trimethoprim results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

When trimethoprim is administered simultaneously with medicines that form cations at physiological pH and are also partly excreted by active renal secretion (e.g. procainamide, tolbutamide and amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the medicines.

Diuretics (thiazides): in older patients concurrently receiving diuretics, mainly acetazolamide and thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should LAGATRIM or LAGATRIM FORTE be prescribed concurrently.

Warfarin: LAGATRIM and LAGATRIM FORTE has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with LAGATRIM or LAGATRIM FORTE is advisable.

Phenytoin: sulphamethoxazole and trimethoprim prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

Digoxin: concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of older patients.

Methotrexate: LAGATRIM and LAGATRIM FORTE may increase the free plasma levels of methotrexate. If LAGATRIM or LAGATRIM FORTE is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (see section 4.4).
Trimethoprim may interfere with some diagnostic tests including serum methotrexate assay where dihydrofolate reductase is used, and the Jaffe reaction for creatinine. No interference occurs if methotrexate is measured by radioimmuno assay.

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

High doses of sulphamethoxazole may have a hypoglycaemic effect; the antidiabetic effect of the sulphonylurea compounds may be enhanced by the concomitant administration of sulphamethoxazole.

Repaglinide: trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

Hyperkalaemia: caution should be exercised in patients taking any other medicines that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole may result in clinically relevant hyperkalaemia.

Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in *Pneumocystis jirovecii pneumonia* prophylaxis and treatment.

Contraceptives: oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive or choose another method of contraception.

Azathioprine: There are conflicting clinical reports of interactions between azathioprine and trimethoprim-sulfamethoxazole, resulting in serious haematological abnormalities.

Para-aminobenzoic acid and compounds: The action of sulphamethoxazole may be antagonised by para-aminonbenzoic acid and compound derived from it, particularly the procaine group of local anaesthetics.

Paraldehyde has been reported to increase the acetylation of sulphamethoxazole with subsequent increased risk of crystalluria.

4.6 Fertility, pregnancy and lactation

Pregnancy

Trimethoprim and sulfamethoxazole as in LAGATRIM and LAGTRIM FORTE cross the placenta and their safety in pregnant women has not been established. LAGATRIM and LAGTRIM FORTE should

not be used during pregnancy (see section 4.3).

Breastfeeding

The components of LAGATRIM and LAGTRIM FORTE (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of LAGATRIM and LAGTRIM FORTE should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinemia. LAGATRIM and LAGTRIM FORTE should not be given to the new-born infant during the first weeks of life (see section 4.3)

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

It is not always possible to predict to what extent LAGATRIM and LAGTRIM FORTE may interfere with the daily activities of a patient. LAGATRIM and LAGTRIM FORTE can cause hallucinations, headache, dizziness and vertigo (see section 4.8). Patients should ensure that they do not engage in the above activities until they are aware of the measure to which LAGATRIM and LAGTRIM FORTE affects them.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	Overgrowth fungal	Pseudomembranous colitis	
Blood and lymphatic system disorders		Leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplasticanaemia, haemolytic anaemia, methaemoglobinaemia (with cyanosis), eosinophilia, hypothrombinaemia, purpura, haemolysis in certain susceptible G-6-PD deficient patients	
Immune system disorders		Serum sickness, anaphylactic reaction, allergic myocarditis, 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	
Endocrine disorders		Hypothyroidism	
Metabolism and nutrition disorders	Hyperkalaemia	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis	
Psychiatric disorders		Depression, hallucinations	Psychotic disorder
Nervous system disorders	Headache	Meningitis aseptic*, convulsions, neuropathy peripheral, ataxia, dizziness, insomnia	
Eye disorders		Uveitis, optic neuropathy or transient myopia	
Ear and labyrinth disorders		Vertigo, tinnitus	
Vascular disorders		Polyarteritis nodosa	
Respiratory, thoracic and mediastinal disorders		Cough*, dyspnoea*, lung infiltration*	

Gastrointestinal disorders	Nausea, diarrhoea	Vomiting, glossitis, stomatitis, pancreatitis	
Hepatobiliary disorders		Transaminases increased, blood bilirubin increased, cholestatic jaundice*, hepatic necrosis*	
Skin and subcutaneous tissue disorders	Rash	Photosensitivity, dermatitis exfoliative, angioedema, toxic epidermal necrolysis (Lyell's syndrome), fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)*, acute generalised exanthematous pustulosis (AGEP).	Acute febrile neutrophilic dermatosis (Sweet's syndrome), Drug reaction with eosinophilia and systemic symptoms (DRESS)*
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, lumbar pain, haematuria, oliguria, anuria	

* See description of selected adverse reactions

b) Description of selected adverse reactions

Aseptic meningitis

Aseptic meningitis was rapidly reversible on withdrawal of LAGATRIM and LAGATRIM FORTE but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone.

Pulmonary hypersensitivity reactions

Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Hepatobiliary disorders

Jaundice cholestatic and hepatic necrosis may be fatal.

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life-threatening (see section 4.4).

As with any other medicine, allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of the medicine. Very rare cases of acute generalised exanthematous pustulosis (AGEP) have been observed (see section 4.4).

Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management

Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia and rhabdomyolysis.

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days.

Rhabdomyolysis has been reported in HIV positive patients receiving co-trimoxazole for prophylaxis or treatment of PJP.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@shanur.co.za.

4.9 Overdose

Signs and symptoms

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment

Treatment is supportive and symptomatic.

If vomiting has not occurred, induction of vomiting may be desirable.

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 Pharmacodynamic properties

Category and Class: A 20.2.1 Sulphonamides.

Pharmacotherapeutic group: Antibacterials for systemic use – Sulfonamides and trimethoprim, incl. derivatives

ATC code: J01EE01

Mechanism of action

LAGATRIM and LAGATRIM FORTE is a bactericidal agent based on trimethoprim and sulphamethoxazole. The combination of these components gives a synergistic effect and is active in vitro against susceptible micro-organisms which may be resistant to one of the components. The components of LAGATRIM and LAGATRIM FORTE both block folinic acid formation which is essential for bacterial development.

LAGATRIM and LAGATRIM FORTE is active against susceptible strains of Gram-positive and Gram-

negative organisms such as *Streptococci* (including Group A haemolytic *Streptococci*), *Staphylococci, Neisseria, Bordetella, Pneumococci, Klebsiella, Aerobacter, Vibrio cholera, Shigella, E. coli* and *Salmonella*. (In vitro efficacy does not necessarily imply in vivo efficacy).

5.2 Pharmacokinetic properties

Absorption

After oral administration trimethoprim and sulfamethoxazole 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 to 3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Distribution

Approximately 50 % of trimethoprim in the plasma is protein bound. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 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 – 50 % of the plasma concentration.

Biotransformation

Renal excretion of intact sulfamethoxazole accounts for 15 – 30 % of the dose. LAGATRIM and LAGATRIM FORTE is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72-hour period, approximately 85 % of the dose can be accounted for in the urine as unchanged medicine plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim in man is in the range 8,6 – 17 hours in the presence of normal renal function. It is increased by a factor of 1,5 to 3,0 when the creatinine clearance is less than 10 mL/minute. There appears to be no significant difference in older patients compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50 % of the dose is excreted in the urine within 24 hours as unchanged medicine. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely.

The half-life of sulfamethoxazole in man is approximately 9 to 11 hours in the presence of normal renal function. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 mL/minute.

The principal route of excretion of sulfamethoxazole is renal; between 15 % and 30 % of the dose recovered in the urine is in the active form. In older patients there is a reduced renal clearance of sulfamethoxazole.

Paediatric population

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, Trimethoprim and Sulphamethoxazole are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1,7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3,6 years), children (7,5 years and < 10 years).

Special patient population

Elderly patients

In elderly patients, a slight reduction in renal clearance of sulfamethoxazole but not trimethoprim has been observed.

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1,5 – 3,0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of LAGATRIM and LAGATRIM FORTE should be reduced (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LAGATRIM 80 mg/400 mg tablet:

Microcrystalline cellulose

Povidone

Maize starch

Magnesium stearate

Nipasept

LAGATRIM FORTE 160 mg/800 mg tablet:

Povidone

Sodium starch glycollate

Sodium lauryl sulphate

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C, in well-closed containers.

Protect from light.

6.5 Nature and contents of container

LAGATRIM 80 mg/400 mg tablet:

Packs of 28, 56, 100 & 1 000.

LAGATRIM FORTE 160 mg/800 mg tablet:

Packs of 1 000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Shanur Healthcare (Pty) Ltd

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8. REGISTRATION NUMBERS

LAGATRIM 80 mg/400 mg tablets: R/20.2.1/241

LAGATRIM FORTE 160 mg/800 mg tablets: R/20.2.1/242

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 July 1984

10. DATE OF REVISION OF THE TEXT

27 January 2025