1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Loxaprim Suspension Co- trimoxazole 240 mg B.P

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml
contains:
Trimethoprim B.P 40 mg

Sulfamethoxazole B.P 200 mg

3. PHARMACEUTICAL FORM

Oral Suspension

4. Clinical particulars

4.1 Therapeutic indications

Co- trimoxazole Suspension 240 mg B.P is indicated in children aged 12 years and under (infants (>6 weeks to <2 years old) and children (>2 to <12 years old) for the treatment of the following infections;

Respiratory Tract Infections: Otitis media, acute exacerbations of chronic bronchitis, Pneumonitis Carinii (including prevention).

Urinary tract Infections: Acute uncomplicated urinary tract infection.

Gastro-intestinal tract infections: Bacillary Dysentery, cholera, as adjunct to fluid and electrolyte replacement, shigellosis, traveller's diarrhoea, nocardiosis, toxoplasmosis.

Protozoal Infections: Malaria due to P. Falciparum.

Skin and Soft Tissue: Furuncles, abscesses and infected wounds.

Genital Tract Infections: Chancroid, Salpingitis, Gonorrhoea,
Granuloma inguinale.

Other Bacterial Infections: Septicaemia due to sensitive organisms, mycetoma, acute and chronic osteomyelitis, brucellosis.

4.2 Posology and method of administration

Posology

The Dosage of Loxaprim Loxaprim Suspension Co- trimoxazole 240 mg B.P

AGE	STANDARD DOSE
Children 6 weeks – 5 months	2.5 ml (measure) every 12 hours
Children 6 months – 5 years	5 ml (measure) every 12 hours
Children 6 – 12 years	10 ml (measure) every 12 hours

Prevention

Adult

Standard dosage for the duration of the period at risk.

160mg trimethoprim/ 800mg Sulphamethoxazole for 7 days

320mg trimethoprim/ 1600mg Sulphamethoxazole per day in 2 divided doses 3 times on alternate days.

It may be preferable to take Co-Trimoxazole with some food or drink to minimize the possibility of gastrointestinal disturbances.

4.3 Contraindications

Co-trimoxazole is contra-indicated in infants under 6 weeks. It should not be given to patients with a history of sulphonamides or trimethoprim hypersensitivity. It is also contra-indicated in patients showing marked liver parenchymal damage, hepatic or renal failure. Caution is advised in folate deficient patients and patients receiving pyrimethamine or immunosuppressive therapy.

ADVERSE REACTION

Hypersensitivity reactions particularly involving the skin are among the most common adverse effects caused by Co-trimoxazole and are usually due to the sulphonamide component. The Steven Johnsons syndrome have been reported in patients receiving Co-trimoxazole. Hypersensitivity reactions also include rashes, photosensitivity reactions, exfoliative dermatitis and nephrotoxic reactions Lumbar pain, haematuria, oligouria and anuria may also occur due to crystallization in the urine of Sulphamethoxazole component of Co-trimoxazole or its less acetylated metabolite.

Blood disorders have occasionally occurred during co-trimoxazole administration and include agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia,

hypoprothrominaemia eosinophilia. Acute haemolytic anaemia is a rare complication which may be associated with glusose-6-phosphate dehydrogenase deficiency.
Other adverse effect include syndrome resembling serum sickness, hepatoxic reactions, myocarditis, pancreatitis, pulmonary eosinophilia and vasculitis including polyarteritis nodosa. Other adverse reactions include optic neupathy or transient myopia, fever, hypothyroidism and neuroplogical reactions including ataxia, dizziness, fatigue, headache, insomnia, peripheral neuritis and verigo. Pseudomembranous colitis can occur in prolong use of co-trimoxazole.

4.4 Special warnings and precautions for use

Loxaprim DS should be administered with food or drink. This is to reduce the possibilities of gastrointestinal disturbance.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use with rifampicin results in shortening of the plasma half-life of trimethoprim after a period of one week. Co-trimoxazole potentiates the anticoagulant effect of warfarin via stereo-selective inhibition of metabolism. Sulphamethoxazole may displace warfarin from plasma-albumin protein-binding sites in vitro.

Co-trimoxazole prolongs the half-life of phenytoin if administered concurrently so the physician should be alert for increased phenytoin effect. Patients treated with Co-trimoxazole and cyclosporin following transplantation could experience deterioration in renal function.

Patients receiving antifolate drugs such as methotrexate should receive folate supplement.

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.

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

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, 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 drugs.

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly 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 co-trimoxazole be prescribed concurrently.

Warfarin: co-trimoxazole 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 Co-Trimoxazole is advisable.

Phenytoin: co-trimoxazole 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 elderly patients.

Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate. If Co-Trimoxazole is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered Trimethoprim interferes with assays for serum methotrexate when dihydrofolate

reductase from Lactobacillus case is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

4.6 Pregnancy and Lactation

Pregnancy

Trimethoprim and sulfamethoxazole cross the placenta and their safety in pregnant women has not been established. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities. Co-trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if co-trimoxazole is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinemia, with an associated theoretical risk of kernicterus, when co-trimoxazole is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

Breast-feeding

The components of Co-Trimoxazole (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Co-Trimoxazole should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinemia. Additionally, administration of co-trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinemia.

4.7 Effects on ability to drive and use machines

No studies of the effect of Loxaprim Suspension on the ability to drive and use machines have been performed.

4.8 Preclinical safety data

The most commonly reported adverse drug reactions (ADRs) are blood and lymphatic system disorder, infections and infestations, immune system, nervous system, gastrointestinal, respiratory tract, skin, metabolism and nutrition disorders.

4.9 OVER DOSAGE:

An overdose is taking doses higher than the recommended dose. Symptoms in overdose consist of nausea, vomiting, dizziness and confusion. Bone marrow depression has been reported in acute trimethoprim over dosage. If vomiting has not occurred, induction vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross over dosage. Dependent on the status of renal function, administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are moderately dialyzable by hemodialysis. Peritoneal dialysis is not effective. Treatment and prevention: the appointment of folic acid (5-15 mg daily).

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibiotic (Antibacterial), ATC code: J01EE01

Mechanism of action:

Sulphamethoxazole competitively inhibits the utilization of para-amino benzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostatic. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions, the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents.

Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination that with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out- compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

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 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Distribution

Widely distributed into body tissues and fluids including sputum, aqueous humor, middle ear fluid, bronchial secretions, prostatic fluid, vaginal fluid, and bile. Both sulfamethoxazole and trimethoprim readily cross the placenta and are distributed into milk.

Sulfamethoxazole is approximately 70% and trimethoprim is approximately 44% bound to plasma proteins. Presence of sulfamethoxazole decreases protein binding of trimethoprim.

Metabolism

Both sulfamethoxazole and trimethoprim are metabolized in the liver. Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug 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 drug plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim in man is in the range 8.6 to 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 drug. 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.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ 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) and adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granulated Sugar BP
Sodium Carboxy Methylcellulose
Methyl Hydroxyl Benzoate
Propyl Hydroxybenzoate BP
Sorbitol
Tween 80
Aerosil 200
Witham Pineapple Flavour
Banana Flavour
Sunset Yellow
Purified Water BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C and protect from light. Shake suspension thoroughly before use

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

50 ml amber pet bottle. This is duly labelled.

6.6 Special precautions for disposal <and other handling>

To be destroyed by NAFDAC enforcement unit.

7. <APPLICANT/MANUFACTURER>

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