Summary of Product Characteristics

1. Name of the product:
Trimoxol Suspension.

2. Qualitative and quantitative composition:
Suspension.
Each 5 ml of oral suspension contains 40 mg trimethoprim BP and 200 mg sulphamethoxazole BP List of excipients see section 6.1.of the SmPC.

3. Pharmaceutical form:
Suspension for oral administration.
A pink coloured, viscous suspension free from any visible impurities.

4. Clinical particulars:
4.1 Therapeutic indications:
Trimoxol Suspension is indicated for the treatment of the following infections when owing to sensitive organisms
Urinary tract infection, respiratory, and gastrointestinal tracts, Pneumocystis carinii pneumonia, toxoplasmosis, and nocardiosis. Its other uses have included the treatment of acne, biliary-tract infections, brucellosis (generally in combination with other drugs), cat scratch disease, chancroid, Burkholderia cepacia(Pseudomonas cepacia) infections in cystic fibrosis, some forms of AIDS-associated diarrhoea such as the protozoal infection isosporiasis, gonorrhoea, granuloma inguinale, listeriosis, melioidosis, mycetoma, otitis media, pertussis, typhoid and paratyphoid fever, and Whipple's disease. It has also been used for the prophylaxis of infections in immunocompromised patients.

4.2 Posology and method of administration:
Method of administration: oral.
Adults and Children aged over 12 years: average dosage is 960 mg twice daily (morning and evening) after meals. For prolonged treatment (over 14 days) the dosage is 480 mg two to three times daily after meals.
Children aged 6 weeks-6 months: half 5ml spoonful (2.5 ml) of suspension twice daily after feeding.
Children aged 6 months-2 years: half to one 5ml spoonful (2.5-5 ml) of suspension twice daily after meals. Children aged 2 years-6 years: one 5ml spoonful (5 ml) of suspension twice daily after meals.
Children aged 6 years-12 years: two 5ml spoonfuls (10 ml) of suspension or 480 mg twice daily after meals.
Higher doses of up to 120 mg/kg daily given in 2 to 4 divided doses for 14 to 21 days are used in the treatment of Pneumocystis carinii pneumonia in adults and children over 4 weeks of age; serum concentrations should be monitored and folate supplementation possibly considered. For prophylaxis in adults with AIDS, the standard dose of 960 mg twice daily may be given, but has been associated with a high incidence of adverse effects. Alternatively the following dose regimens may be used: 960 mg daily (7 days each week); 960 mg daily on alternate days (3 days each week); or 960 mg twice daily on alternate days (3 days each week). Children may be given standard doses for prophylaxis; doses are given on 3 consecutive days per week or for 7 days per week.

4.3 Contraindications:
Should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, or any excipients
It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment.
It should be discontinued at the first appearance of skin rash, or if blood disorders develop.
The preparation should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations
An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion
Should not be given to premature babies nor to full-term infants during the first 6 weeks of life except for the treatment/prophylaxis of PCP in infants 4 weeks of age or greater.

Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses are given for a prolonged period.
Contra-indicated in patients with megaloblastic anaemia due to folate deficiency.
Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment

4.4 Special warnings and precautions for use:
Fatalities, although very rare, have occurred due to severe reactions including fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.
• Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Co -trimoxazole.
• 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 or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Septrin treatment should be discontinued
• The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
• If the patient has developed SJS or TEN with the use of Septrin, Septrin must not be re-started in this patient at any time.
-Care is always advisable when treating elderly 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 drugs.
An adequate urinary output should be maintained at all times. Evidence of crystalluria in vivo is rare, although sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.
Regular monthly blood counts are advisable for long periods, or to folate deficient patients or to the elderly, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. These changes may be reversed by administration of folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity.
-In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.
-Should be given with caution to patients with severe allergy or bronchial asthma.
-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.
Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.
Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.
Close monitoring of serum potassium and sodium is required in patients at risk of hyperkalaemia and hyopnatraemia. Except under careful supervision should not be given to patients with serious haematological disorders
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction:
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.
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.
Reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.
Concurrent use of rifampicin and Septrin 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 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.

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.
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.
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 is advisable.
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.
Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Co-trimoxazole may increase the free plasma levels of methotrexate.
Trimethoprim interferes with assays for serum methotrexate when dihydrofolate Reductase from Lactobacillus casei is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.
Administration of trimethoprim/sulfamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.
Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been
reported. Caution should be exercised in patients taking any other drugs that can cause
hyperkalaemia.
If Septrin is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered.

4.6 Pregnancy and Lactation:

Trimethoprim and sulfamethoxazole cross the placenta and their safety in human pregnancy has not been established. Trimethoprim is a folate antagonist and, in animal studies, both agents established have been shown to cause foetal abnormalities. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Therefore co-trimoxazole should be avoided in pregnancy, particularly in the first trimester, unless the potential benefit to the mother outweighs the potential risk to the foetus; folate supplementation should be considered if co-trimoxazole is used in pregnancy.
Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significant maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilrubinaemia, with an associated theoretical risk of kernicterus, when sulfamethoxazole-trimethoprim is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.
Trimethoprim and sulfamethoxazole are excreted in breast milk. Administration of co trimoxazole should be avoided in late pregnancy and in lactation mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of co-trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.7 Effects on ability to drive and use machines: None known

4.8 Side effects:

Very common: Hyperkalaemia
Common: Monilial overgrowth, Headache, Nausea, diarrhoea,Skin rashes
Uncommon: Vomiting
Very rare: Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients, Hypoglycaemia, hyponatraemia, anorexia, Depression, hallucinations, Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness, Cough, shortness of breath, pulmonary infiltrates, Glossitis, stomatitis, pseudomembranous colitis, pancreatitis, Uveitis, Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, severe cutaneous adverse reactions (SCARs):

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), Arthralgia, myalgia, Impaired renal function (sometimes reported as renal failure), interstitial nephritis.
Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia, hyponatraemia, rhabdomyolysis.

4.9 Overdose:

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.
If vomiting has not occurred, induction of 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 overdosage. Dependant 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 haemodialysis. Peritoneal dialysis is not effective.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives; ATC code: J01EE01
Sulfamethoxazole and other sulfonamides have a similar structure to p-aminobenzoic acid and interfere with the synthesis of nucleic acids in sensitive micro-organisms by blocking the conversion of p-aminobenzoic acid to the coenzyme dihydrofolic acid, a reduced form of folic acid; in man, dihydrofolic acid is obtained from dietary folic acid so sulfonamides do not affect human cells. Their action is primarily bacteriostatic, although they may be bactericidal where concentrations of thymine are low in the surrounding medium.
Trimethoprim is a dihydrofolate reductase inhibitor. It inhibits the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid which is necessary for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA. It acts in the same metabolic pathway as the sulfonamides. It exerts its selective action because of a far greater affinity for the bacterial than the mammalian enzyme. Because trimethoprim and Sulphamethoxazole act at different points of the folate metabolic pathway, a potent synergy exists between them with an increase of up to about 10-fold in antibacterial activity, and a frequently bactericidal action where the components individually are generally bacteriostatic. The spectrum of action includes Gram-negative and Gram-positive strains, such as: Escherichia coli, Klebsiella-Aerobacter, Proteus Vulgaris, Proteus mirabilis, Salmonella, Shigella, Vibrio cholerae, Brucella, Haemophylus influenzae, Streptococcus pneumoniae. The exception is Pseudomonas aeruginosa which is not affected by this drug.

5.2 Pharmacokinetic properties:

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.
Trimethoprim is a weak base with a pKa of 7.4. It is lipophilic. 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 humor, 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 50% of trimethoprim in the plasma is protein bound. The half-life 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 the elderly 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.

Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in a variety of body fluids is of the order of 20 to 50% of the plasma concentration.
Approximately 66% of sulfamethoxazole in the plasma is protein bound and the principal route of excretion of sulfamethoxazole is renal. The half-life 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 principle route of excretion of Sulphamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

5.3 Preclinical safety data:
No additional preclinical data of relevance.

6.0 Pharmaceutical particulars:
6.1 List of Excipients:
Sodium Saccharin
Xanthan gum
Sodium CMC
Tween 80
Simethicone 30%
Bronopol
Sodium methyl paraben
Sodium propyl paraben
Citric Acid
Strawberry flavour liquid Erythrosine
pink colour
Purified Water

6.2 Incompatibilities:
None

6.3 Shelf life:
3 years from the date of manufacture.

6.4 Special precautions for storage:
Store in a cool dry place, below 30^0C, protected from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container:
100ml packed in PET bottles and in a unit box along with a literature insert.

6.6 Special precautions for disposal:
No special requirements.

7. Marketing authorization holder
Dawa Limited,
Plot No. 7879/8, Baba Dogo Road, Ruaraka,
P.O. Box 16633 – 00620,
Nairobi, Kenya.

8. Marketing authorization number(s)
Kenya , Registration Number:3802
Uganda , Registration Number:7077/10/6

9.0 Legal category: Prescription only medicine, (POM)

10.0 Date of revision of the text: December 2019.