1.5 Product Information: RENETRIM TABLETS

1.5.1 Prescribing information (Summary of products characteristics):

1. Name of the Medicinal Product: RENETRIM TABLETS

Strength: Sulfamethoxazole 400mg and Trimethoprim 80mg

Pharmaceutical form: Tablet

2. Qualitative and Quantitative composition:

Qualitative composition:

Sr. No.	Ingredient	Specification	Uses
1.	Sulfamethoxazole	BP	Active
2.	Trimethoprim	BP	Active
3.	Maize Starch	BP	Diluent
4.	Maize Starch	BP	Binder
5.	Sodium Methyl Paraben	BP	Antimicrobial preservative
6.	Sodium Propyl Paraben	BP	Antimicrobial preservative
7.	Sodium Starch Glycollate	BP	Disintegrant
8.	Magnesium Stearate	BP	Lubricant

CTD MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION	
Product Name :	**RENETRIM TABLETS** **(Co-trimoxazole Tablets 480mg)**

Quantitative composition:

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**			
		Each tablet contains Sulfamethoxazole 400mg and Trimethoprim 80mg			
		Quantity in mg per tablet	**%**	**Quantity in Kg Per 800,000 Tablets**	**%**
Contents of **RENETRIM TABLETS**					
Sulfamethoxazole BP	Active	400.00	68.02	320.000	68.02
Trimethoprim BP	Active	80.00	13.60	64.000	13.60
Maize Starch BP	Diluent	75.00	12.75	60.000	12.75
Maize Starch BP	Binder	25.00	4.25	20.000	4.25
Sodium Methyl Paraben BP	Antimicrobial preservative	1.00	0.17	0.800	0.17
Sodium Propyl Paraben BP	Antimicrobial preservative	0.580	0.10	0.464	0.10
Sodium Starch Glycollate BP	Disintegrant	5.00	0.85	4.000	0.85
Magnesium Stearate BP	Lubricant	1.50	0.26	1.200	0.26
Total	NA	588.08	100.00	470.464	100.00

3. Pharmaceutical form: Tablet

4. Clinical particular's:

4.1 Therapeutic indication:

Renetrim is an antibacterial agent, effective against a wide range of gram positive and gram negative organisms. It is indicated for the treatment of respiratory tract, genito-urinary tract, gastrointestinal tract, skin and other bacterial infections.

4.2 Posology and method of administration:

Adults including the elderly:
Renetrim should be taken preferably after food, to minimize the possibilities of gastro-intestinal disturbances. Treatment in all acute infections should be continued for a minimum of 5 days or until you are symptom-free for two days or whichever is the longer.

Children:
Children (6 to 12 years): 1 tablet twice daily (or 4 pediatric tablets twice daily)
Children (2 to 5 years): 2 pediatric tablets twice daily.

Method of Administration: Oral.

4.3 Contraindication:

Co-trimoxazole is contraindicated in patients with a known hypersensitivity to Trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. It is also contraindicated in pregnant patients at term and in nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. It is contraindicated in pediatric patients less than 2 months of age

4.4 Special warning and precaution 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) and drug reaction with eosinophilia and systemic symptoms (DRESS) 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, TEN or DRESS is within the first weeks of treatment.

- If symptoms or signs of SJS, TEN or DRESS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Co-trimoxazole treatment should be discontinued.

- The best results in managing SJS, TEN and DRESS 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 Co-trimoxazole, Co-trimoxazole must not be re-started in this patient at any time.

Particular 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 sulfonamide 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 when Co-trimoxazole is given 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.

Co-trimoxazole should be given with caution to patients with severe allergy or bronchial asthma.

Co-trimoxazole 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.

The administration of Co-trimoxazole to patients known or suspected to be at risk of acute porphyria should be avoided. Both Trimethoprim and sulfonamides (although not specifically Sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

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

Except under careful supervision Co-trimoxazole should not be given to patients with serious haematological disorders. Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

The combination of antibiotics in Co-trimoxazole should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

4.5 Interactions with other medicinal products and other forms of interactions:

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 Co-trimoxazole 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 with Co-trimoxazole 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 160 mg/800 mg (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 sulfonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia.

If Co-trimoxazole is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered.

Additional information on special populations:

Not Applicable

Pediatric population:

Not Applicable

4.6 Fertility, pregnancy and lactation:
Pregnancy

There are not any adequate data from the use of Co-trimoxazole in pregnant women. 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 hyperbilirubinaemia, 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 hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

Lactation

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, 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:

There have been no studies to investigate the effect of Co-trimoxazole on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless the clinical status of the patient and the adverse events profile of Co-trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects:

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency.

The following convention has been used for the classification of adverse events in terms of frequency:- Very common ≥1/10, common ≥1/100 and 01/10, uncommon ≥1/1000 and 01/100, rare ≥1/10,000 and 01/1000, very rare 01/10,000.

Infections and Infestations

Common:	Monilial overgrowth

Blood and lymphatic system disorders

Very rare	Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients

The majority of haematological changes are mild and reversible when treatment is stopped. Most of the changes cause no clinical symptoms although they may become severe in

isolated cases, especially in the elderly, in those with hepatic or renal dysfunction or in those with poor folate status. Fatalities have been recorded in at-risk patients and these patients should be observed carefully.

Immune system disorders

Very rare:	Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenleinpurpura, periarteritisnodosa, systemic lupus erythematosus

Metabolism and nutrition disorders

Very common:	Hyperkalaemia
Very rare:	Hypoglycaemia, hyponatraemia, anorexia

Close supervision is recommended when Co-trimoxazole is used in elderly patients or in patients taking high doses of Co-trimoxazole as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

Psychiatric disorders

Very rare:	Depression, hallucinations

Nervous system disorders

Common:	Headache
Very rare:	Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either Co-trimoxazole or to Trimethoprim alone.

Respiratory, thoracic and mediastinal disorders

Very rare:	Cough, shortness of breath, pulmonary infiltrates

Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Gastrointestinal disorders

Common:	Nausea, diarrhoea
Uncommon:	Vomiting
Very rare:	Glossitis, stomatitis, pseudomembranous colitis, pancreatitis

Eye Disorders

Very rare:	Uveitis

Hepatobiliary disorders

Very rare:	Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders

Common:	Skin rashes
Very rare:	Photosensitivity, exfoliative dermatitis, fixed drug eruption,erythemamultiforme, severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported
Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders

Very rare:	Arthralgia, myalgia

Renal and urinary disorders

Very rare:	Impaired renal function (sometimes reported as renal failure), interstitial nephritis

Effects associated with *Pneumocystis jiroveci* Pneumonitis (PCP) management.

Very rare:	Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia, hyponatraemia

At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10 mg/day). Severe hypersensitivity reactions have been reported in PCP patients on re-exposure to Co-trimoxazole, sometimes after a dosage interval of a few days.

4.9 Overdose and Treatment:

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

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 dialysable 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

Mode of Action

Co-trimoxazole is an antibacterial drug composed of two active principles, Sulfamethoxazole and Sulfamethoxazole. Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim binds to and reversibly inhibits bacterial dihydrofolate reductase (DHFR) and blocks the production of 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.

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 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 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. 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 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 elderly patients there is a reduced renal clearance of Sulfamethoxazole.

Paediatric population

The pharmacokinetics in the pediatric population with normal renal function of both components of Co-trimoxazole, Trimethoprim and Sulfamethoxazole are age dependent. Elimination of Trimethoprim and Sulfamethoxazole is reduced in neonates, during the first two months of life; thereafter both Trimethoprim and Sulfamethoxazole 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.

5.3 Preclinical safety data:

Reproductive toxicology: At doses in excess of recommended human therapeutic dose, Trimethoprim and Sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with Trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of Trimethoprim in excess of human therapeutic doses.

6. Pharmaceutical Particulars:

6.1 List of excipients

Renetrim tablets contain the following excipients:

Maize starch, Sodium methyl paraben, sodium propyl paraben, Sodium starch glycollate, Magnesium stearate.

6.2 Incompatibilities

None known

6.3 Shelf life

36Months

6.4 Special precaution for storage

Store in cool & dry place, below 30°C. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

10 tablets are packed in Aluminium/PVC blister; such 10 blisters are packed in a unit carton along with literature insert.
1000 tablets packed in polythene bag and contained in HDPE Container with leaflet.

6.6 Special precautions for disposal

No special precaution.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Marketing Authorization Holder:
Rene Industries Ltd
Address : PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

Manufactured by:
Rene Industries Ltd
Address : PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

8. MARKETING AUTHORISATION NUMBER:
Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION:
Not Applicable

10. DATE OF REVISION OF THE TEXT:
Not Applicable

11. DOSIMETRY (IF APPLICABLE):
Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):
Not Applicable