FRONT SIDE

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 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 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 to 50% of the plasma concentration.
Biotransformation: Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolized 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 elderly 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.

5.3 Preclinical safety data
At doses in excess of recommended human therapeutic dose, trimethoprim and Sulphamethoxazole 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
Maize Starch
Sodium Lauryl Sulphate
Colloidal Anhydrous Silica
Magnesium Stearate
Sodium Starch Glycolate
Purified Talc

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 Months from the date of manufacture.

6.4. Special precautions for storage
Store at temperature not exceeding 30°C, protect from moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container
1000 Tablets are packed in a HDPE Jar.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Manufactured by :
ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India.

8. Marketing Authorization Number(S)
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
04 Jul 2019

*PB395/X/XX/XX

200 mm

COTRIZIM 480

Co-Trimoxazole Tablets BP 480 mg

1. Name of the Finished Pharmaceutical Product
1.1 Trade Name : COTRIZIM 480 (Co-Trimoxazole Tablets BP 480 mg)
1.2 Strength : 480 mg
1.3 Pharmaceutical Form : *"Uncoated Tablets"*

2. Qualitative And Quantitative Composition
Each uncoated tablet contains:
Trimethoprim BP 80 mg
Sulphamethoxazole BP 400 mg
For full list of excipients, see section 6.1

3. Pharmaceutical Form
Uncoated Tablet
White, circular, flat, beveled edge, uncoated tablets, having break ine on one side and plain on other side.

4. Clinical Particulars
4.1 Therapeutic indications
Co-Trimoxazole tablets are indicated in children (>12 to <18 years old) and adults (>18 years old) for the treatment of the following infections when owing to sensitive organisms:
- Treatment and prevention of *Pneumocystis jiroveci* pneumonitis or "PJP".
- Treatment and prophylaxis of toxoplasmosis.
- Treatment of nocardiosis.

The following infections may be treated with Co-Trimoxazole where there is bacterial evidence of sensitivity to Co-Trimoxazole and good reason to prefer the combination of antibiotics in Co-Trimoxazole to a single antibiotic:
- Acute uncomplicated urinary tract infection.
- Acute otitis media.
- Acute exacerbation of chronic bronchitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology:
Standard dosage recommendations for acute infections
Adults (>18 years old): 2 tablets every 12 hours
Children over 12 years old (>12 to <18 years old):
The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day, given in two equally divided doses. The schedules for children are according to the child's age and weight and provided in the table below:

Age	*Tablets*
>12 to <18 years old	2 tablets every 12 hours

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evident after 7 days therapy, the patient should be reassessed.
Impaired renal function:
Children (>12 to <18 years old) and adults (>18 years old):

Creatinine Clearance (ml/min)	Recommended Dosage
>30	2 tablets every 12 hours
15 to 30	Not recommended
<15	1 tablets every 12 hours

Pneumocystis jiroveci pneumonitis:
Adults (>18 years old):
The following dose schedules may be used:
160 mg trimethoprim/800 mg sulfamethoxazole daily 7 days per week.
160 mg trimethoprim/800 mg sulfamethoxazole three times per week on alternate days.
320 mg trimethoprim/1600 mg sulfamethoxazole per day in two divided doses three times per week on alternate days.
Children (>12 to <18 years old):
The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day, given in two equally divided doses. The following dose schedules may be used for the duration of the period at risk:

Age	Tablets
>12 to <18 years old	2 tablets every 12 hours, seven days per week
>12 to <18 years old	2 tablets every 12 hours, three times per week on alternative days
>12 to <18 years old	2 tablets every 12 hours, three times per week on consecutive days
>12 to <18 years old	4 tablets once a day, three times per week on consecutive days

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m^2/day and 750 mg sulfamethoxazole/m^2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

BACK SIDE

200 mm

Nocardiosis - Adults (>18 years old):
There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 tablets daily for up to 3 months have been used.
Toxoplasmosis:
There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition. The decision should be based on clinical experience. For prophylaxis, however, the dosages suggested for prevention of *Pneumocystis jiroveci* pneumonitis may be appropriate.

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

4.3 Contraindication
- Co-Trimoxazole is contra-indicated in patients with a known history of hypersensitivity to the active substance.
- Co-Trimoxazole should not be given to patients with severe hepatic parenchymal damage. Contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- Co-trimoxazole should not be given to infants during the first 6 weeks of life.
- Co-Trimoxazole should not be given to patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- Co-Trimoxazole should not be given to patients with acute porphyria.

4.4 Special warnings and special precautions for use
- Life-threatening cutaneousreactions 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, Co-Trimoxazole 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.
- 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.
- Co-Trimoxazole should be given with caution to patients with severe atopy 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.
- The administration of Co-Trimoxazole to patients known or suspected to be at risk of porphyria should be avoided.
- Close monitoring of serum potassium is warranted in patients at risk of hyperkalaemia and hyponatraemia.
- Co-Trimoxazole should not be given to patients with serious haematological disorders.
- 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 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 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.

4.6 Pregnancy and lactation
Co-Trimoxazole Should be avoided during pregnancy and lactation.
Influence on ability to drive or operate machinery:
Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

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 following adverse reaction observed while taking Co-Trimoxazole. The frequency grouping is defined using the following convention: Very common (> 1/10), Common (> 1/100 and <1/10), Uncommon (> 1/1000 and <1/100), Rare (> 1/10000 and <1/1000), Very rare (<1/10000) not known - cannot be estimated from the available data.
Very Common: Hyperkalaemia.
Common: Overgrowth fungal, headache, nausea, diarrhoea, rash.
Uncommon: Vomiting.
Very rare: Pseudomembranous colitis, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients, serum sickness, anaphylactic reaction, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus, severe hypersensitivity reactions associated with PJP, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis, hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis, depression, hallucination, meningitis aseptic, convulsions, neuropathy peripheral, ataxia, dizziness, vertigo, tinnitus, uveitis, cough, dyspnoea, lung infiltration, glossitis, stomatitis, pancreatitis, transaminases increased, blood bilirubin increased, cholestatic jaundice, hepatic necrosis, Photosensitivity reaction, angiodema, dermatitis exfoliative, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), arthralgia, myalgia, renal impairment, tubulointerstitial nephritis, uveitis syndrome and renal tubular acidosis.
Not known: Psychotic disorder

4.9 Overdose
Symptoms
Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.
Treatment
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
Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. 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.
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.

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 evels 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.