SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

GENERIC NAME: Co-trimoxazole Tablets BP 480 mg

BRAND NAME: COTRIKANT 480

2. QUALITY AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Trimethoprim BP …….80 mg

Sulfamethoxazole BP ……...400 mg

Excipients …….. q.s.

For complete list of excipients refer section 6.1

3. Pharmaceutical Form

Solid, Oral dosage form- Tablets

White coloured, circular flat faced beveled edge , uncoated tablet having central breakline on one side with COTRI & 480 debossed on it and other side plain.

4. Clinical Particulars

4.1 Therapeutic Indications

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.

The in vitro susceptibility of bacteria to antibiotics varies geographically and with time; the local situation should always be considered when selecting antibiotic therapy.

1) Treatment and prophylaxis (primary and secondary) of Pneumocytosis jiroveci (P. carinii) in adults and children.
2) Treatment and prophylaxis of toxoplasmosis, treatment of nocardiosis.
3) Treatment of urinary tract infections and acute exacerbations of chronic bronchitis, where there is bacterial evidence of sensitivity to Co-trimoxazole and good reason to prefer this combination to a single antibiotic.
4) Treatment of acute otitis media where there is good reason to prefer Co-trimoxazole to a single antibiotic.

4.2 Posology and method of administration

The standard dose for Adults and Children 12 years and over :

1) Treatment of Pneumocytosis jiroveci (P. carinii)

Trimethoprim 15-20 mg/kg day and Sulfamethoxazole 100 mg/kg/day, in divided doses at interval of 8 hours for 14 – 21 days.

2) Prophylaxis of Pneumocytosis jiroveci (P. carinii)

Trimethoprim 3-3.5 mg/kg day and Sulfamethoxazole 14-16 mg/kg/day daily for 7 days.

3) Treatment & Prophylaxis of Toxoplasmosis

Trimethoprim 3-3.5 mg/kg day and Sulfamethoxazole 14-16 mg/kg/day daily for 7 days.

4) Treatment of Nocardiosis

Trimethoprim 10-15 mg/kg day and Sulfamethoxazole 48 mg/kg/day daily in equally divided doses for upto 3 months.

5) Treatment of Urinary Tract Infection

Trimethoprim 6 mg/kg day and Sulfamethoxazole 32 mg/kg/day daily in equally divided doses at interval of 12 hours for 10 - 14 days.

6) Treatment of acute exacerbations of Chronic Bronchitis, where its bacterial evidence

Trimethoprim 6 mg/kg day and Sulfamethoxazole 32 mg/kg/day daily in equally divided doses at interval of 12 hours for 14 days.

7) Treatment of Acute Otitis media

Trimethoprim 8 mg/kg day and Sulfamethoxazole 40 mg/kg/day daily in equally divided doses at interval of 12 hours for 10 days.

Children below 12 years:
Co-trimoxazole is not advised for children below 12 years.
For Children below 12 years more appropriate Paediatric formulation should be prescribed.
A more appropriate low dosage formulation, Paediatric Suspension or Tablets should be used.
6 weeks - 5 months; 120mg twice daily
6 months – 5 years old; 240mg twice daily
6 years – 11 years; 480mg twice daily

Elderly:
Adult dosage.
Care must be taken since the elderly 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.

The following regimens are recommended in patients age 12 years or over with renal impairment:

Creatinine Clearance (ml/min)	Recommended dosage
> 30	Standard Dosage
15 to 30	Half the Standard Dosage
< 15	Not recommended

Measurements of plasma concentrations of sulfamethoxazole at intervals of two to three days are recommended in samples obtained 12 hours after administration. If the concentration of total sulfamethoxazole exceeds 150 μg/ml, then treatment should be interrupted until the value falls below 120 μg/ml. It may be preferable to take Co trimoxazole with food or drink to minimise the possibility of gastrointestinal disturbances.
OR
As directed by the physician.

MODE OF ADMINSTRATION: Oral.

4.3 Contraindications

Known hypersensitivity to trimethoprim, sulphonamides or any other ingredients in the tablet.
Pregnancy – especially in the period prior to birth.
Severe hepatic failure or marked liver parenchymal damage, jaundice.
Serious haematological disorders and porphyria.
Severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
Co-trimoxazole should not be given to neonates during the first 6 weeks, except for the treatment/prophylaxis ofPneumocytosis jiroveci (P. carinii) in infants of four weeks of age or greater.

4.4 Special warning and precaution for use

Fatalities have occurred, with severe skin, hepatic and blood disorders, aplastic anaemia and hypersensitivity of the respiratory tract. Co-trimoxazole should be discontinued immediately with first appearance of skin rash. Caution should be taken in patients with severe allergy and bronchial asthma. Co-trimoxazole should not be used to treat Group A beta-haemolytic streptococcia. Care must be taken since the elderly 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. Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be exercised when giving Co-trimoxazole to patients receiving:

- ACE Inhbitors: risk of severe hyperkalaemia.
- Anaesthetics: increased risk of methaemoglobinaemia when sulphonamides given with prilocaine.

Antiarrhythmics: increased risk of ventricular arrhythmias with amiodarone. Plasma levels of dofetilide increased markedly by co-administration with Co-trimoxazole resulting in the increase dofetilide-induced QT prolongation and the risk of arrhythmias.

- Antibacterials: serum levels of dapsone and Co-trimoxazole are possibly raised by the presence of the other. Be alert for dapsone toxicity causing methaemoglobinaemia. Increased risk of crystalluria when sulphonamides given with methenamine. Concomitant use of Co-

trimoxazole and rifampicin can result in increased rifampicin serum levels and reduced plasma half life of trimethoprim.

- Anticoagulants: effects of acenocoumarol and warfarin enhanced.
- Antidiabetics: effect of sulphonylureas enhanced.
- Antiepileptics: Co-trimoxazole prolongs the half life of phenytoin and co-administration could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.
- Antifolates: if considered appropriate therapy in patients receiving anti-folates , a folate supplement should be considered.
- Antimalarials: risk of megaloblastic anaemia with doses of pyrimethamine in excess of 25mg per week..
- Antivirals: plasma concentrations of lamivudine increased-avoid concomitant high dose co-trimoxazole. Concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to Co-trimoxazole. Zalcitabine plasma concentrations possibly increased by cotrimoxazole.
- Cations at physiological pH: plasma concentrations of trimethoprim and/or procainamide and/or amantadine can be increased unilaterally or bilaterally.
- Clozapine: avoid concomitatnt use; increased risk of fatal agranulocytosis.
- Cytotoxics: increased risk of haematological toxicity with mercaptopurine and azathioprine. Antifolate effects of methotrexate increased by Co-trimoxazole (avoid concomitant use).
- Digoxin: increase in digoxin levels in a proportion of elderly patients.
- Diuretics: elderly patients concurrently receiving diuretics, mainly thiazides, there is an increased risk of thrombocytopenia with or without purpura.

Potassium aminobenzoate: effects of sulphonamides inhibited.

4.6 Pregnancy and lactation

Pregnancy:
Co-trimoxazole should not be used in pregnancy as the safety in pregnancy has not been established. Co-trimoxazole interferes with folate metabolism and can cause teratogenic effects if given in the first trimester.
Co-trimoxazole can cause neonatal haemoylosis and methaemoglobinaemia when used in the third trimester, if given close to delivery kernicterus may occur due to displacement of bilirubin. Other toxicities that may be observed in the new born include jaundice and haemalytic anaemia. The risk of kernicterus is higher in infants at increased risk of hyperbilirubinaemia, such as if the infant is ill, stressed or premature or has glucose-6-phosphate dehydrogenase deficiency.
Lactation:
Co-Trimoxazole appears in breast milk in negligible amounts and the risk appears to be low.

However, there is a risk of kernicterus if the infant is at increased risk of hyperbilirubinaemia.

4.7 Effects on ability to drive and use machine

As Co-trimoxazole can cause dizziness, drowsiness, tinnitus, insomnia and hallucinations patients should make sure they are not affected before driving or operating machines.

4.8 Undesirable effects

Infections and infestations: monilial growths are common.
Blood and the lymphatic system disorders - blood dyscrasias may occur along with aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, megaloblastic anaemia, thrombocytopenia, purpura, leucopenia, eosinophilia, neutropenia, rarely agranulocytosis and bone marrow depression, especially in the elderly. These changes have been reversed on withdrawal of the drug. The elderly, patients with hepatic or renal failure or poor folate status are more susceptible to these effects. Co-trimoxazole may induce haemolysis in certain susceptible glucose-6-phosphate dehydrogenase deficient patients.
Immune system disorders – hypersensitivity effects have been reported, they include serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, peri-arteritis nodosa, systemic lupus erythematosus, aseptic meningitis (reversible on withdrawal), severe skin sensitivity reactions such as erythema multiforme bullosa (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) have occurred infrequently and rarely been associated with death. Treatment should be discontinued immediately.
Metabolism and nutrition disorders – electrolyte disturbances, metabolic acidosis, hyperkalaemia and hyponatraemia especially in the elderly and with high doses.

4.9 Overdose

Symptoms of overdosage may include dizziness, nausea, vomiting, rashes, headache, ataxia, drowsiness, dysuria, swelling of the face, weakness and confusion. Bone marrow depression has been reported in acute trimethoprim overdosage.
Treatment is symptomatic. Observe the patient for at least four hours and monitor U&Es and full blood count in symptomatic cases. Give fluids to maintain a good urine output, increased fluid intake will increase the elimination of sulfamethoxazole, but decrease that of trimethoprim. Calcium Leucovirin 5-10mg daily will counteract any adverse effects of trimethoprim on bone marrow or calcium folinate 3-6mg of 5-7 days by mouth or IM . Other measures as indicated by the patients clinical condition.

5.0 Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives

ATC code: J01EE01

Mechanism of Action

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. 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.

Mechanism of 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 in 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.

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

Many common pathogenic bacteria are susceptible *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antibiotics, however, *in vitro* activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

5.2 Pharmacokinetics

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

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 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 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.

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 (see section 4.2).

In elderly patients there is a reduced renal clearance of sulfamethoxazole.

Special patient population

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 10mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of co-trimoxazole should be reduced (see section 4.2).

Hepatic impairment

Caution should be exercised when treating patients with severe hepatic parenchymal damage as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.

Elderly patients

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

5.3 Preclinical Safety Data

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

Maize Starch , Docusate Sodium, Purified Talc, Sodium Starch Glycolate, Magnesium Stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 months

6.4 Special Precaution for Storage-

Store in a dry place below 30°C. Protect from light.

Keep all medicines away from children.

6.5 Nature and Contents of Container-

Alu-PVC blister of 10 tablets

7. Applicant/Manufacturer

Manufactured by:

S Kant
HEALTHCARE Ltd.

1802-1805, G.I.D.C., Phase III,

Vapi - 396 195. Gujarat, INDIA.