## 1.4 Product Information

### 1.4.1 Prescribing information (Summary of Product Characteristics)

1. **Name of the medicinal product**

Co-trimoxazole BP 480 mg Tablets

**2. Qualitative and quantitative composition**

Label claim:

Each uncoated Tablet Contains:

Sulfamethoxazole BP…..400 mg.

Trimethoprim BP…….80 mg

| S.No | Ingredients | Pharma copoeial Standard | Quantity per unit dose( mg/Tab) | Functions |
|---|---|---|---|---|
| **Active Substance:** | | | | |
| 1. | Trimethoprim | BP | 80.000 | API |
| 2. | Sulfamethoxazole | BP | 400.000 | API |
| **Excipients:** | | | | |
| 3. | Maize Starch | BP | 89.625 | Diluent |
| 4. | Povidone (PVP K30) | BP | 4.000 | Binder |
| 5. | Maize Starch | BP | 10.000 | Binder |
| 6. | Methyl Hydroxy benzoate | BP | 1.080 | Preservative |
| 7. | Propyl Hydroxy benzoate | BP | 0.120 | Preservative |
| 8. | Purified Water* | BP | Q.S | Solvent |
| 9. | Sodium Starch Glycollate | USP/NF | 12.925 | Disintegrant |
| 10. | Magnesium Stearate | BP | 2.250 | Lubricant |
| | Total | | 600.00 | |
| | | | | |

**3. Pharmaceutical form**

Tablet

White to off white flat circular bevel edged uncoated tablets with a break line on one side plain on other side.

**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.

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.

**4.2 Posology and method of administration**

*The standard dose for Adults and children 12 years and over:* 2 tablets twice daily.

*Children:* A more appropriate dosage formulation 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

**Special Population**

*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.

*Treatment of Pneumocytosis jiroveci (P. carinii) infection***-** the usual dosage is 20mg trimethoprim and 100mg sulfamethoxazole per kg body weight per day in 2 or more doses.

*Prophylaxis of Pneumocytosis jiroveci (P. carinii) infection*- the following regimines have been used:

Two tablets daily for seven days or

Two tablets daily three times a week on alternate days or

Two tablets twice a day three times a week on alternate days

*Treatment of Nocardiosis:* Six to eight tablets daily for up to 3 months.

*Treatment and prophylaxis of toxoplasmosis:* as prophylaxis of *Pneumocytosis jiroveci (P. carinii)*.

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 150µg/ml, then treatment should be interrupted until the value falls below 120µg/ml.
It may be preferable to take Co-trimoxazole with food or drink to minimise the possibility of gastrointestinal disturbances.

**Paediatric population :**
NA

### *4.3 Method of Administration*

For oral administration.

### 4.4 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 of *Pneumocytosis jiroveci (P. carinii)* in infants of four weeks of age or greater.

### 4.5 Special warnings and precautions 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.
*Sulfamethoxazole:*
Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported with the use of sulfamethoxazole. 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, sulfamethoxazole 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 sulfamethoxazole, sulfamethoxazole must not be re-started in this patient at any time.
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.

Patients on prolonged treatment should have blood counts at monthly intervals. As with all sulphonamides there is a possibility of blood dyscrasias more especially in elderly patients. Co-trimoxazole may induce haemolysis in certain susceptible glucose-6-phosphate dehydrogenase deficient patients. Serum potassium levels should be monitored closely in those patients at risk of hyperkalaemia.

In cases of renal impairment a modified dosage schedule is recommended coupled with plasma concentration measurements. Urine output must be maintained at all times, the risk of crystalluria is increased in patients suffering from malnutrition.

Folate supplementation may be necessary in patients predisposed to folate deficiency such as the elderly or when high doses of Co-trimoxazole are given for a prolonged period. Megaloblastic changes have been reported with long-term treatment, but have been reversed with folic acid therapy.

**4.6 Paediatric population**

NA

**4.7 Interactions 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 co-trimoxazole.

- 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.
- Immunosuppressants: reversible deterioration in renal function has been observed in patients treated with Co-trimoxazole and ciclosporin following renal transplantation.
- Potassium aminobenzoate: effects of sulphonamides inhibited.
- Labratory tests- trimethoprim and sulphonamides have been reported to interfere with diagnostic tests, including serum-methotrexate and serum-plasma creatinine levels, also urea, urinary glucose and urobilinogen tests.

**4.8 Additional information on special population.**

**4.9 Paediatric population:** Not applicable

**4.10 Fertility, pregnancy and lactation**

**4.10.1 General principles**

**4.10.2 Women of childbearing potential/Contraception in males and females.**

**4.10.3 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.

**4.10.4 Breastfeeding:**

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.

**4.10.5 Fertility:** Not applicable

**4.11 Effects on ability to drive and use machines**

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

**4.12Undesirable effects**

1 *Infections and infestations:* monilial growths are common.
2 *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.
3 *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.
4 *Metabolism and nutrition disorders* – electrolyte disturbances, metabolic acidosis, hyperkalaemia and hyponatraemia especially in the elderly and with high doses.
5 *Nervous system disorders* - few reports of subjective interference such as headache, depression, dizziness and hallucinations have occurred (although drug-relation remains unproven). Other neurological adverse effects include convulsions, peripheral neuritis, ataxia, drowsiness, fatigue, and insomnia.
6 *Ear and labyrinth disorders* - vertigo and tinnitus.
7 *Respiratory, thoracic and mediastinal disorders* - cough, dyspnoea, pulmonary infiltration; indicative of hypersensitivity
8 *Gastrointestinal disorders* - nausea, vomiting, diarrhoea, sore mouth, anorexia, glossitis, stomatitis, rarely pseudomembranous colitis.
9 *Hepato-biliary disorders* - jaundice, elevated hepatic transaminases, rarely hepatic necrosis and pancreatitis.
10 *Skin and subcutaneous tissue disorders* - skin rashes can occur and photosensitivity**,** fixed drug eruptions, Henoch-Schonlein purpura, and exfoliative dermatitis have also been reported. *Sulfamethoxazole*: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported very rarely.
11 *Musculoskeletal disorders* - arthralgia and myalgia.
12 *Renal and urinary disorders* - impaired renal function, rarely interstitial nephritis and crystalluria which can be avoided by adequate fluid intake.
13 *Other* – with the higher doses used for therapy of *Pneumocystis jiroveci (P. carinii)* in patients with AIDS if effects such as rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia and hyponatraemia occur stopping therapy may be necessary. If signs of bone marrow depression occur 5 to 10mg/day of calcium folinate should be given. Re-exposure of co-trimoxazole to HIV infected patients has caused severe hypersensitivity reactions, even after a dosage interval of a few days.

**4.13 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. Pharmacological Properties

### 5.1 Pharmacodynamic properties

**ATC code: J01E E01**

Trimethoprim is an antibacterial.

Sulfamethoxazole is a sulphonamide.

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacterio stasis. 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 mammmalian DHFR is some 50,000 times than for the corresponding bacterial enzyme.

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

Paediatric population:

Not applicable

### 5.2 Pharmacokinetic properties

*Trimethoprim* is readily absorbed from the gastrointestinal tract and peak concentrations in the circulation occur between 1 and 4 hours after a dose is taken. 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 kidney showing especially high concentrations. About 50% is bound to plasma proteins. The elimination half-life is in the range of 8.6 - 17 hours in the presence of normal of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10ml/min. There appears no significant difference in the elderly compared with the young patients. About 40 - 60% of a dose is excreted unchanged in the urine within 24 hours, together with metabolites. Trimethoprim is removed by haemodialysis to some extent.

*Sulfamethoxazole* is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached between 1 and 4 hours. 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. About 66% is bound to plasma albumin and the plasma half-life is in the range of 9 - 11 hours. It is prolonged in patients with severe renal impairment. About 15% of sulfamethoxazole in the blood is present as the acetyl derivative. Elimination in the urine is dependent on pH. In the region of 25% of a single 2g dose of sulfamethoxazole has been reported to be excreted in the urine within eight hours, around 60% being in the form of the acetyl derivative.

When Co-trimoxazole is administered, plasma concentrations of trimethoprim and sulfamethoxazole are generally in the ratio of 1:20; in urine this ratio may vary from 1:1 to 1:5. About 50% of each drug is excreted in the urine within 24 hours, but a larger proportion of sulfamethoxazole appears as inactive metabolite.

Paediatric population:

Not applicable

**5.3 Preclinical safety data**

There are no pre-clinical data of relevance

**6. Pharmaceutical Particulars**

**6.1 List of excipients**

| S. No | Ingredient | Monograph |
|---|---|---|
| 1. | Maize Starch | BP |
| 2. | Povidone (PVP K30) | BP |
| 3. | Maize Starch | BP |
| 4. | Methyl Hydroxy benzoate | BP |
| 5. | Propyl Hydroxy benzoate | BP |

| | | |
|---|---|---|
| 6. | Purified Water* | BP |
| 7. | Sodium Starch Glycollate | USP/NF |
| 8. | Magnesium Stearate | BP |

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

48 Months

**6.4 Special precautions for storage**

Store below $30^0$C.

**6.5 Nature and contents of container**

PVC/Al--Blister.
HDPE (Jar packing)

**Pack sizes**
10x10's Counts
1000's Counts

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. Marketing authorisation holder and manufacturing site address**

Bal Pharma Limited.
21 & 22 - Bommasandra Industrial Area
Bangalore - 560099 Karnataka, India.
Tel No : +91-080-41570811
Fax No: +91-080-41570820
E-mail: regulatory@balpharma.com

**8. Marketing authorisation number(s)**

Not applicable

**9. Date of first authorisation/renewal of the authorisation.**

Not applicable

**10. Date of revision of the text**

Not applicable