SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Product name: Paediatric Co-trimoxazole Oral Suspension BP 240mg/5ml

Brand Name: Cotrikant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:

Trimethoprim BP.....40 mg

Sulfamethoxazole BP.....200 mg

Sodium Methyl Hydroxybenzoate BP (As Preservative)….5.0 mg

Sodium Propyl Hydroxybenzoate BP (As Preservative)….1.5 mg

Bronopol BP (As Preservative)….1.0 mg

Sodium Benzoate BP (As Preservative)….5.0 mg

Flavoured Syrup Base…….....q.s

Colour: Tartrazine

3. PHARMACEUTICAL FORM:

Liquid Oral Dosage Form – Suspension.

Yellow coloured uniform suspension.

4.CLINICAL PARTICULARS

4.1 Therapeutic Indication:

Paediatric Co-Trimoxazole Oral Suspension is indicated for the treatment of the following infections when owing to sensitive organisms:

Treatment and prevention of *Pneumocystis jiroveci (P. carinii)* pneumonitis

Treatment and prophylaxis of toxoplasmosis

Treatment of nocardiosis

The following infections may be treated with Paediatric Co-Trimoxazole Oral Suspension where there is bacterial evidence of sensitivity to Paediatric Co-Trimoxazole Oral Suspension and good

reason to prefer the combination of antibiotics in Paediatric Co-Trimoxazole Oral Suspension 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:

Standard dosage recommendations for acute infections

Children aged 12 years and under:

This dosage approximates to 6 mg of Trimethoprim and 30 mg of Sulfamethoxazole per kilogram body weight per 24 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.

As an alternative to Standard Dosage for acute uncomplicated lower urinary tract infections, short-term therapy of 1 to 3 days' duration has been shown to be effective.

Special dosage recommendations

(Standard dosage applies unless otherwise specified)

Pneumocystis jiroveci pneumonitis:

Treatment: A higher dosage is recommended using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses for two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of grater than or equal to 5 microgram/ml(verified in patients receiving 1-hour infusions of intravenous Co-trimoxazole)

Method of administration: For oral administration only.

It may be preferable to take Paediatric Co-Trimoxazole Oral Suspension after some food or drink to minimize the possibility of gastrointestinal disturbances

4.3 Contraindications:

Paediatric Co-Trimoxazole Oral Suspension should not be given to patients with a history of hypersensitivity to Sulphonamides, Trimethoprim, Co-trimoxazole, or any excipients of Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/ 5ml.

Contra-indicated in patients showing marked liver parenchymal damage.

Contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.

Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/ 5ml 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.

4.4 Warning 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml.
- 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, Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/ 5ml 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml, Same 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 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 when Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml 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.

Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml should be given with caution to patients with severe allergy or bronchial asthma.

Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

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

Except under careful supervision Paediatric Co-Trimoxazole Oral Suspension should not be given to patients with serious haematological disorders. Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/ 5ml 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.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains methyl hydroxybenzoate, which may cause allergic reactions (possibly delayed).

4.5 Drug 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml 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 Paediatric Co-Trimoxazole Oral Suspension BP 240 mg/5ml is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered.

4.6 Fertility Pregnancy & Lactation

As it is indicated for paediatric use, effects on pregnancy and lactation are not relevant.

4.7 Effects on ability to drive and use machines:

As it is indicated for paediatric use, effects on ability to drive and use machines are not relevant.

4.8 Adverse Effects

As Co-trimoxazole contains Trimethoprim and Sulphonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience.

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. In addition, adverse events may vary in their incidence depending on the indication

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 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

Paediatric Co-Trimoxazole Oral Suspension BP 240mg/5ml is an antibacterial drug composed of two active principles, Sulfamethoxazole and Trimethoprim. 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.

5.1 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose Sodium (HVP), Xanthan gum, Glycerol, Polysorbate 80, Colloidal anhydrous silica, Sucrose (sugar S-30), Sorbitol Solution 70% (Non crystallizing), Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxybenzoate, Sodium Benzoate, Sodium Saccharine, Disodium EDTA, Citric acid (monohydrate), Bronopol, Colour Tartrazine Supra, Flavour Pineapple RS, Purified water.

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months

6.4 Special precautions for storage:

Store at a temperature not exceeding 30°C, in a dry place.

Protect from light.

Keep the medicine out of reach of children.

6.5 Nature and contents of container

100 ml Amber coloured Pet bottle with 25 mm cap in a carton along with insert.

7. APPLICANT

Manufactured by:

S Kant
HEALTHCARE Ltd.

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

Vapi - 396 195. Gujarat, INDIA.

8. NATIONAL REGISTRATION NUMBER

07917/08045/VAR/2022

9. DATE OF AUTHORISATION

09-10-2022

10. DATE OF REVISION OF THE TEXT

July 2023