PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

Co-Trimoxazole Pharma-Q Injection 5 ml solution for injection

COMPOSITION:

Each 5 ml contains:

80 mg trimethoprim and 400 mg sulphamethoxazole with ethanol 9,6 % *v/v*, benzyl alcohol 1 % *v/v*, and sodium metabisulphite 0,1 % *m/v*.

Excipients: propylene glycol, sodium hydroxide, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2 Anti-microbial agents other than antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Co-trimoxazole is a mixture of the sulphonamide sulphamethoxazole with trimethoprim in the proportions of 5 to 1. The two anti-biotics act synergistically to produce a bacteriostatic or bacteriocidal action against a wide range of Gram-positive and Gram-negative organisms and some protozoa.

Co-trimoxazole causes blockade of 2 consecutive steps in tetrahydrofolic acid synthesis:

i) Sulphamethoxazole causes inhibition of bacterial synthesis of dihydrofolic acid from para-aminobenzoic acid (PABA),

ii) Trimethoprim causes inhibition of the action of dihydrofolate reductase and thus the

prevention of synthesis of tetrahydrofolic acid from dihydrofolic acid.

Antibacterial spectrum:

Certain strains of the following organisms are sensitive in vitro:

Strep. pneumoniae, *Staph. aureus*, *Epidermidis*, *Strep. pyrogens*, the viridans group of *Streptococci*, *E.coli*, *Pr. mirabilis*, *Pr. morganii*, *Pr. rettgeri*, *Enterobactcer species*. *Salmonella*, *Shigella*, *Pseud. pseudomallei*, *Serratia*, species are inhibited. Also sensitive are *Klebsiella* species, *Brucella abortus*, *Yersinia pseudotuberculosis*, *Y. enterocolitica* and *Nocardia asteroides*. Methicillin-resistant strains of *Staph. aureus*, although also resistant to trimethoprim or sulphamethoxazole alone, are susceptible to the combination. In vitro sensitivity does not necessarily imply *in vivo* efficacy.

A synergistic interaction between the components of the preparation is apparent even when micro-organisms are resistant to sulphonamides and moderately resistant to trimethoprim. However a maximal degree of synergism occurs when micro-organisms are sensitive to both components.

Bacterial resistance:

Pseudomonas aeruginosa, *Bacteroides fragillis* and *enterococci* are usually resistant.

The frequency of development of bacterial resistance to co-trimoxazole is lower than it is to either of the components alone. Resistance in gram-negative bacteria is associated with the presence of R-factors, which can be transferred to susceptible micro-organisms by conjugation. Resistance to high concentrations of sulphonamides and to moderate concentrations of Trimethoprim may be transferred in this manner. Resistance to trimethoprim in *Staph. Aureus* appears to be determined by a chromosomal gene rather than by a plasmid. *E. coli* resistant to Trimethoprim and *H. influenza* resistant to Co-trimoxazole may also occur.

Pharmacokinetic properties:

Absorption, distribution and excretion:

The concurrent administration of sulphamethoxazole and trimethoprim appears to slow the absorption of sulphamethoxazole. The half-lives of trimethoprim and sulphamethoxazole are 16 and 10 hours, respectively. When 400 mg of sulpamethoxazole is given with 80 mg of trimethoprim (the conventional 5:1 ratio), three times daily, the mean minimal steady-state concentrations of the medicines are approximately 20 µg/ml and 1 µg/ml, respectively-the optimal ratio that is sought.

Peak concentrations are similar after intravenous infusions of the same dose over a period of one hour.

Trimethoprim is rapidly distributed and concentrated in tissues, and about 40 % is bound to plasma protein in the presence of sulphamethoxazole. Co-trimoxazole enters the cerebrospinal fluid and sputum readily. High concentrations of each component of the mixture are also found in bile. About 65 % of sulphamethoxazole is bound to plasma protein. Up to 60 % of administered trimethoprim and from 25 % to 50 % of sulphonamide are excreted in the urine in 24 hours. The rates of excretion and the urine concentrations of both compounds are significantly reduced in patients with uraemia.

INDICATIONS:

Co-Trimoxazole Pharma-Q Injection 5 ml is indicated in:

- Genito-urinary tract infections,
- Respiratory tract infections; including pneumonia and pneumocystis carinii pneumonitis,
- Gastro-intestinal tract infections including shigellosis and typhoid fever,
- Other bacterial infections caused by sensitive organisms: Brucellosis, septicaemia.

CONTRAINDICATIONS:

Co-Trimoxazole Pharma-Q Injection 5 ml is contraindicated in:

- Patients with a history of hypersensitivity to co-trimoxazole, the sulphonamides or trimethoprim.
- Patients who suffer from severe renal or hepatic failure; without monitoring of plasma concentrations of the medicines.
- Patients who suffer from blood disorders or impairments; without monitoring of plasma concentrations of the medicines.
- Patients who suffer from jaundice.
- Patients who suffer from megaloblastic anaemia.
- Patients who suffer from acute porphyria as the sulphamethoxazole component may cause exacerbations of the disease.
- Infants within 1 to 2 months of birth because of the risk of producing kernicterus.
- Patients who are pregnant or lactating (see **PREGNANCY AND LACTATION**).

WARNINGS and SPECIAL PRECAUTIONS:

Co-Trimoxazole Pharma-Q Injection 5 ml:

- Should be avoided in patients who have glucose 6 phosphate dehydrogenase deficiency.
- Should be used with caution in patients with impaired renal function and dosage adjustments may be necessary.
- An adequate fluid intake should be maintained to reduce the risk of crystalluria.
- Alkalinisation of the urine increases urinary excretion of the sulphamethoxazole component, but decreases urinary excretion of trimethoprim.

- Regular blood counts, urinalyses and renal function tests should be carried out in patients receiving prolonged treatment with **Co-Trimoxazole Pharma-Q Injection 5 ml**.
- Elderly patients may be more susceptible to the occurrence of adverse effects.
- Folate supplementation may be necessary in patients predisposed to folate deficiency, such as the elderly and patients on high doses of therapy over prolonged periods of time.

Special precautions:

The sulphamethoxazole component:

- Treatment with sulphonamides should be discontinued immediately if a rash appears because of the danger of severe allergic reactions such as the Stevens-Johnson syndrome.
- The risk of crystalluria can be reduced by the administration of fluids to maintain a high urine output. If necessary, alkalinization of the urine by administration of sodium bicarbonate may increase solubility and aid the elimination of sulphonamides.
- Care is generally advisable in patients with a history of allergy or asthma.
- Caution is also needed in the elderly.

The trimethoprim component:

- Trimethoprim should not be given to patients with a history of hypersensitivity to the medicine.
- It should be discontinued if a skin rash appears.
- Care is necessary in administering trimethoprim to patients with impaired renal function to avoid accumulation and toxicity.
- It should not be given in severe renal impairment unless blood concentrations can be monitored.

- It should be used with caution in patients with severe hepatic damage.
- It is suggested that regular haematological examination should be made during prolonged courses of treatment.
- Trimethoprim should not usually be given to patients with serious haematological disorders and particularly not in megaloblastic anaemia secondary to folate depletion.

Co-trimoxazole:

An extraordinarily, higher frequency of adverse reactions to co-trimoxazole may occur in patients who have AIDS (Acquired Immune Deficiency Syndrome).

Effects on the ability to drive and use machines:

Co-Trimoxazole Pharma-Q Injection 5 ml may cause dizziness, drowsiness and fatigue. Patients should be advised not to drive or operate hazardous machinery because loss of concentration could lead to serious accidents.

INTERACTIONS:

Co-Trimoxazole Pharma-Q Injection 5 ml may interact with other medicines:

The sulphamethoxazole component:

- Sulphonamides may potentiate the effects of some agents, such as oral anticoagulants, methotrexate, and phenytoin.
- High doses of sulphonamides may have a hypoglycaemic effect; the antidiabetic effect of the sulphonylurea compounds may be enhanced by the concomitant administration of sulphonamides.
- The action of sulphonamides may be antagonised by para-aminobenzoic acid and compounds derived from it, particularly the procaine group of local anaesthetics.

- Sulphonamides may interfere with some diagnostic tests including those for urea, creatinine, and urinary glucose and urobilinogen.

The trimethoprim component:

- In elderly patients, trimethoprim may increase serum concentrations and potentiate the effect of a number of medicines, including phenytoin, digoxin and procainamide.
- Trimethoprim and dapsone increase each other's serum concentrations when given concomitantly, whereas rifampicin may decrease trimethoprim concentrations.
- The use of trimethoprim concomitantly with diuretics may cause hyponatraemia.
- Administration of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors such as pyrimethamine or methotrexate.
- Trimethoprim may interfere with some diagnostic tests, including serum methotrexate assay where dihydrofolate reductase is used and the Jaffe reaction for creatinine.

Co-trimoxazole (both components together):

- An increased risk of nephrotoxicity may occur with the administration of trimethoprim or co-trimoxazole concomitantly with ciclosporin.
- Intravenous administration of trimethoprim and sulphonamides may reduce cyclosporin concentrations in blood.
- An increased risk of thrombocytopenia may occur in elderly patients when co-trimoxazole is given concomitantly with diuretics.

PREGNANCY AND LACTATION:

Co-Trimoxazole Pharma-Q Injection 5 ml is contra-indicated for use in pregnancy and lactation (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE:

Co-Trimoxazole Pharma-Q Injection 5 ml:

- **TO BE GIVEN BY INTRAVENOUS INFUSION ONLY.**
- **DILUTE BEFORE USE.**

Co-Trimoxazole Pharma-Q Injection 5 ml:

- Prepare infusion immediately before use, using dextrose 5 % or sodium chloride 0,9 % solution.
- The usual diluent is 5 % glucose.
- Ringers lactate solution, including 0,9 % sodium chloride, have been stated to be compatible for adequate periods.
- The following dilution scheme must be followed (*DO NOT USE UNDILUTED*):
    - 5 ml added to 125 ml infusion solution.
    - 10 ml added to 250 ml infusion solution.
    - 15 ml added to 500 ml infusion solution.
- Dosage to be infused over 60 to 90 minutes.
- Infusion solutions must be used within 6 hours of preparation.
- Must not be injected intramuscularly or subcutaneously.

Co-Trimoxazole Pharma-Q Injection 5 ml:

Dosages:

Adults and children over 12 years:

- **Standard dosage:** 960 mg (10 ml) twice daily, morning and evening.
- **Minimum dosage:** For long term treatment (more than 14 days):

5 ml twice daily, mornings and evenings.

- **Maximum dosage:** For particularly severe cases: 1,44 g (15 ml) twice daily, morning and evening. The maximum dosage should not be given for more than three days.

Children up to 12 years:

- 2 ml per 5 kg bodymass daily in two divided doses.
- The recommended basis for dosage in children under the age of 12 years is 6 mg trimethoprim and 30 mg sulphamethoxazole per kg body mass daily, divided into two equal doses, given morning and evening.
- In acute infections, it should be given for at least 5 days or until the patient has been symptom free for 2 days.
- As soon as oral treatment becomes possible, the intravenous administration must be discontinued.

Recommendation:

- 6 weeks to 5 months: 1,25 ml twice daily, morning and evening.
- 6 months to 5 years: 2,5 ml twice daily, morning and evening.
- 6 to 12 years: 5,0 ml twice daily, morning and evening.

Typhoid fever:

Adult dosage: 5 ml twice daily, morning and evening for 15 days.

SIDE EFFECTS

Co-Trimoxazole Pharma-Q Injection 5 ml may have side-effects:

Sulphamethoxazole:

The sulphamethoxazole component may cause side effects but the frequencies are unknown:

Blood and the lymphatic system disorders:

Frequency unknown: Agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, hypoprothrombinaemia and eosinophilia. Acute haemolytic anaemia is a complication which may be associated with glucose-6-phosphate dehydrogenase deficiency.

Endocrine disorders:

Frequency unknown: Hypoglycaemia and hypothyroidism.

Nervous system disorders:

Frequency unknown: Aseptic meningitis, ataxia, benign intracranial hypertension, convulsions, dizziness, drowsiness, fatigue, headache, insomnia, mental depression, peripheral or optic neuropathies, psychoses and vertigo.

Gastro-intestinal disorders:

Frequency unknown: Nausea, vomiting, anorexia and diarrhea.

Hepato-biliary disorders:

Frequency unknown: Sulphonamides may displace serum bound bilirubin, resulting in jaundice and kernicterus in premature neonates.

Skin and subcutaneous disorders:

Frequency unknown: Rashes, photosensitivity reactions, exfoliative dermatitis, toxic epidermal necrolysis (Lyell's syndrome) and erythema nodosum.

A severe, potentially fatal, form of erythema multiform, associated with widespread lesions of the skin and mucous membranes, termed the Stevens-Johnson syndrome may occur.
Systemic lupus erythematosus, particularly exacerbations of pre-existing disease, may also occur, as well as anaphylaxis.

Renal and urinary disorders:

Frequency unknown: Nephrotoxic reactions including interstitial nephritis and tubular necrosis, which may result in kidney failure. Lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine of sulphamethoxazole or its less soluble acetylated metabolite.

General disorders and administrative site conditions:

Frequency unknown: Fever and a syndrome resembling serum sickness, live necrosis, hepatomegaly, jaundice, myocarditis, pancreatitis, pulmonary eosinophilia, fibrosing alveolitis and vasculitis including polyarteritis nodosa. Sulphonamides may also cause cyanosis due to methaemoglobinaemia.

Trimethoprim:

The Trimethoprim component may cause side effects but the frequencies are unknown:

Blood and the lymphatic system disorders:

Frequency unknown: Depression of haemopoiesis. This may manifest as megaloblastic anaemia or as thrombocytopenia and leucopenia. Methaemoglobinaemia may also occur.

Nervous system disorders:

Frequency unknown: Aseptic meningitis.

Gastro-intestinal disorders:

Frequency unknown: Mild gastro-intestinal disturbances including nausea, vomiting and sore mouth.

Skin and subcutaneous disorders:

Frequency unknown: Pruritus, skin rash, exfoliative dermatitis, erythema multiforme and toxic epidermal necrolysis. Occasionally, hypersensitivity reactions may be severe and manifest as anaphylaxis.

Hepato-biliary disorders:

Frequency unknown: Disturbances of liver enzyme values and cholestatic jaundice.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

For symptoms see **SIDE EFFECTS** and **WARNINGS AND SPECIAL PRECAUTIONS.**

Co-Trimoxazole Pharma-Q Injection 5 ml:

- High doses may cause diarrhoea, nausea, vomiting, skin rashes and other allergic reactions.
- It may cause a depression of haemopoiesis due to interference of the medicine in the metabolism of folic acid.
- Injections of calcium folinate may be given to counteract this interference.
- Blood counts should be performed frequently, particularly in patients undergoing prolonged treatment.
- Supportive measures i.e. cortisone, intravenous infusion, adrenaline etc. can be used if anaphylaxis occurs.
- Treatment should be symptomatic and supportive.

IDENTIFICATION:

A clear colourless, to slightly yellow solution, filled in 5 ml clear colourless ampoules.

PRESENTATION:

5 ml ampoules in boxes of 10's

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Protect from light.

Keep all medicine out of reach of children.

REGISTRATION NUMBER:

29/20.2/0665

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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