

**SCHEDULING STATUS: S4****PROPRIETARY NAME (AND DOSAGE FORM):  
RESMED CO-TRIMOXAZOLE ORAL SUSPENSION****COMPOSITION:** Each 5ml contains:

Sulfamethoxazole BP 200mg + Trimethoprim BP 40mg

Preservatives: Methyl paraben 0,1% m/v  
Propyl paraben 0,025% m/v  
Sodium benzoate 0,15% m/v  
Sorbic acid 0,035% m/v**PHARMACOLOGICAL CLASSIFICATION:**

Category A, 20.20 – Anti-microbial agents other than antibiotics

**PHARMACOLOGICAL ACTION:**

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

- (i) Inhibition of bacterial synthesis of dihydrofolic acid from p-aminobenzoic acid.
- (ii) Inhibition of the action of dihydrofolate reductase and thus the prevention of the synthesis of tetrahydrofolic acid from dihydrofolic acid.

Co-trimoxazole is bactericidal at concentrations at which the active ingredients trimethoprim and sulfamethoxazole are usually bacteriostatic. It is therefore often active against organisms resistant to one of the active ingredients thereby minimizing the risk of bacterial resistance. Co-trimoxazole is effective in vitro against a range of gram-positive and gram-negative organisms. In vitro sensitivity does not necessarily imply clinical efficacy.

**Pharmacokinetics:** The pharmacokinetic properties of trimethoprim and sulfamethoxazole are similar.

**Absorption:** Following oral administration, trimethoprim and sulfamethoxazole are almost completely absorbed in the upper portion of the gastrointestinal tract. Following a single dose of 160mg trimethoprim + 800mg sulfamethoxazole, peak plasma concentrations of 1,5 – 3 µg/ml for trimethoprim and 40 – 80 µg/ml for sulfamethoxazole are reached after 1 to 4 hours. If administration is repeated every twelve hours, the concentration stabilizes at this level.

**Distribution:** The volume of distribution of trimethoprim is about 130 litres and that of sulfamethoxazole about 20 litres. At the above concentrations, 42 – 46% of trimethoprim and 66% of sulfamethoxazole is bound to plasma proteins. Studies in both animals and man have shown that large amounts of trimethoprim and smaller amounts of sulfamethoxazole pass through the bloodstream into the interstitial fluid and other extra-vascular body fluids. In humans, trimethoprim and sulfamethoxazole were detected in the fetal placenta, umbilical cord blood, amniotic fluid and fetal tissues (liver, lung), indicating placental transfer of both drugs. In general, fetal concentrations of trimethoprim are similar, those of sulfamethoxazole are lower than maternal concentrations. Both agents are excreted in breast milk. Concentrations in breast milk are similar (trimethoprim) or lower (sulfamethoxazole) than in maternal plasma.

**Metabolism:** Approximately 50 – 70% of the trimethoprim dose and 10 – 30% of the sulfamethoxazole dose are excreted unchanged. The principal trimethoprim metabolites are 1- and 3 oxides and the 3- and 4- hydroxy derivatives; some metabolites are active. Sulfamethoxazole is metabolised in the liver, predominantly by N<sup>4</sup>-acetylation and to a lesser extent by glucuronide conjugation; the metabolites are inactive.

**Elimination:** The elimination half-lives of the two components are similar (a mean of ten hours for trimethoprim and of eleven hours for sulfamethoxazole). Both substances, as well as their metabolites, are eliminated almost entirely by the kidneys through both glomerular filtration and tubular secretion, giving urine concentrations of both active substances considerably higher than the concentration in the blood. A small part is eliminated via the faeces.

Clinical situations with altered kinetics: In the elderly and in patients with severely impaired renal function the elimination half lives of both components are increased, requiring dosage regimen adjustment.

**Antibacterial spectrum:** (In Vitro) Strains of the following organisms are generally sensitive (MIC < 80 mg/l)

Gram-negative: Bordetella pertussis; Brucella spp.; Escherichia coli; Neisseria spp; Proteus spp; Salmonella typhi and paratyphi, other Salmonella spp; Shigella spp; Vibrio cholerae; Haemophilus influenzae.

Gram-positive: Staphylococcus aureus (including penicillin resistant);

Streptococcus pneumoniae, Streptococcus pyogenes.

Co-trimoxazole is also active against Nocardia spp; Pseudomonas pseudomallei,

Serratia, Yersinia spp, Pseudomonas cepacia and Pneumocystis carinii.

Mycobacteria and most Pseudomonas are not sensitive. Resistance developing during treatment of Haemophilus and Klebsiella infections has been reported.

Resistant organisms (MIC > 160 mg/l): Mycoplasma spp., Mycobacterium tuberculosis, Treponema pallidum.

In the case of a positive culture a sensitivity test is recommended to exclude any resistance. It is essential to note that recommended media (free from inhibitory substances especially thymidine and thymine) and methods must be used for satisfactory sensitivity testing.

**INDICATIONS:**

Infections due to sensitive strains or organisms such as:

**Respiratory tract infections:** Infections of the upper and lower respiratory tracts: acute and chronic bronchitis, bronchiectasis, sinusitis, otitis media, tonsillitis, pharyngitis, pneumonia and Pneumocystis carinii pneumonitis.

**Gastrointestinal tract infections:** Cholera (as an adjunct to fluid and electrolyte replacement), typhoid and paratyphoid fever, enteritis and bacillary dysentery.

**Urinary tract infections:** Acute and chronic cystitis, prostatitis, pyelitis, pyelonephritis, urethritis, cystopyelitis. May be effective in single dose treatment of acute uncomplicated lower urinary tract infections in adult non-pregnant women only.

**Genital infections:** In both sexes, including gonococcal urethritis and chancroid.

**Skin and soft tissue infections:** pyoderma, furuncles, abscesses and infected wounds.

**Other infections:** With bacteria sensitive to co-trimoxazole – acute brucellosis, mycetoma except those caused by true fungi, nocardiosis, acute and chronic osteomyelitis.

**CONTRA-INDICATIONS:** For safety reasons Co-trimoxazole is contra-indicated in pregnancy and during lactation. If pregnancy cannot be excluded, possible risks should be balanced against the therapeutic effect. Blood dyscrasias, sulphonamide or trimethoprim hypersensitivity (allergy to sulphonylurea antidiabetics and saluretic sulphonamide derivatives should also be considered), patients with marked liver parenchymal damage and severe renal insufficiency when repeated determinations of the plasma concentration cannot be made. Co-trimoxazole should not be given to patients with megaloblastic anaemia, or patients with serious haematological disorders. It should also be avoided in premature or newly born infants in the first six weeks of life, or in the presence of Vitamin B<sub>12</sub> and folic acid deficiency states.

**WARNINGS:** A high incidence of side effects occurs in immunocompromised patients, such as those suffering from Aids or patients receiving immunosuppressive therapy. The adverse effects include skin rash, recurrent fever, neutropenia, thrombocytopenia and raised liver enzyme values. Co-trimoxazole may cause the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis. Treatment should be discontinued immediately when a rash appears because of the danger of severe allergic reactions.

**DOSAGE AND DIRECTIONS FOR USE:**  
**Children 6 weeks to 5 months:** Half a medicine measure (2,5 ml) in the morning and half a medicine measure (2,5 ml) in the evening.  
**Children 6 months to 5 years:** One medicine measure (5 ml) in the morning and one medicine measure (5 ml) in the evening.  
**Children 6 years to 12 years:** Two medicine measures (10 ml) in the morning and two medicine measures (10 ml) in the evening.

Co-trimoxazole should be taken for the prescribed periods even though the symptoms may have been alleviated.

Dosage must be reduced in patients with renal insufficiency and the preparation should not be administered if creatinine clearance is less than 15 ml/minute

In acute infections Co-trimoxazole should be given for at least five days or until the patient has been symptom-free for two days. For severe infections the dosage shown for children may be increased by 50%.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS:** Nausea, vomiting, stomatitis and diarrhoea may occur. Rare cases of hepatitis and isolated cases of pseudomembranous enterocolitis have occurred. Cases of acute pancreatitis have been reported in patients with Co-trimoxazole, several of these patients were seriously ill, including those with AIDS. Allergic reactions may occur in patients who are hypersensitive to sulfamethoxazole and trimethoprim. Drug induced fever and angioneurotic oedema has rarely been noted. Tinnitus may occur. High dosage of trimethoprim as used in patients with Pneumocystis carinii pneumonia induces progressive but reversible increase of serum potassium concentration in a substantial number of patients. Even treatment with recommended doses may cause hyperkalaemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalaemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients. Cases of hypoglycaemia in non-diabetic patients treated with co-trimoxazole are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of co-trimoxazole are particularly at risk. Skin diseases e.g. reddening, exanthema and itch may occur. Photosensitivity, erythema multiforme, allergy, vasculitis, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported in rare cases. Haematological changes such as leukopenia, neutropenia, thrombocytopenia, agranulocytosis, purpura, anaemia (megaloblastic, haemolytic or aplastic) or pancytopenia may occur, particularly in elderly patients or after long-term treatment that regress after withdrawing the drug. Cyanosis due to methaemoglobinemia or sulphamoglobinemia may occur.

In elderly patients or patients with impaired renal or liver functions, dosage must be adjusted by reduction of the dose or increasing the dosage intervals.

For such patients measurements of plasma concentrations are advisable. Pulmonary infiltrates (as in eosinophilic or allergic alveolitis) could manifest with symptoms of cough or shortness of breath and treatment should therefore be re-evaluated or discontinued. Regular blood counts are advisable whenever Co-trimoxazole is given for prolonged periods. Rare cases of renal failure insufficiency (e.g. interstitial nephritis), and crystalluria have been reported. Sulfonamides, including Co-trimoxazole, may induce increased diuresis, particularly in patients with oedema of cardiac origin. Aseptic meningitis or meningitis-like symptoms and very rarely hallucinations have been reported to occur.

The incidence of side effects, particularly rash, fever, leukopenia and elevated transaminase values, with Co-trimoxazole therapy in AIDS patients who are being treated for pneumocystis carinii pneumonia are great compared with the incidence normally associated with the use of Co-trimoxazole in non-AIDS patients.

Owing to the possibility of haemolysis, Co-trimoxazole should not be given to patients with a G6PD deficiency unless absolutely essential, and then only in minimal doses.

In elderly patients, or in patients with pre-existing folic acid deficiency or kidney failure, haematological changes indicative of folic acid deficiency may occur. These are reversible by folic acid therapy. Patients undergoing long-term treatment with Co-trimoxazole (in particular, patients with kidney failure) should be examined regularly for urine values and kidney function. During treatment, adequate folic acid intake and urinary output should be ensured to prevent crystalluria.

Because both trimethoprim and sulfamethoxazole cross the placental barrier and may thus interfere with folic acid metabolism, Co-trimoxazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is recommended that pregnant women who are being treated with Co-trimoxazole should be given 5 to 10 mg of folic acid daily. During the last stage of pregnancy, Co-trimoxazole should be avoided as far as possible because of the risk of kernicterus in the neonate. Both trimethoprim and sulfamethoxazole pass into the breast milk. Although the quantity of Co-trimoxazole ingested by a breast fed infant is small, it is recommended that possible risks for the infant (kernicterus, hypersensitivity) should be weighed against the expected therapeutic benefit for the mother.

Previous or simultaneous administration of frusemide and thiazide diuretics with Co-trimoxazole may carry an increased risk of thrombocytopenia, especially in elderly patients with heart failure, death may occur.

**Drug interactions:** In elderly patients receiving certain diuretics, primarily thiazides with co-trimoxazole, an increased incidence of thrombocytopenia with purpura has been observed. Oral anticoagulants (e.g. warfarin, may prolong prothrombin time), phenytoin (inhibition of hepatic metabolism), oral anti-diabetics and pyrimethamine used in the prophylaxis of malaria. Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin. Sulfamethoxazole can compete with protein binding and also with the renal transport of methotrexate, thus increasing the free methotrexate fraction and the systemic exposure to methotrexate. Reversible deterioration of renal function, manifested by increased serum creatine, has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation. This combined effect is presumably due to the trimethoprim component.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Symptoms of acute overdosage may include nausea, vomiting, diarrhoea, headache, vertigo, dizziness, mental and visual disturbances, crystalluria, haematuria and anuria may occur in severe cases. The following treatment measures may be considered depending on the symptoms, gastric lavage within 3 hours of ingestion, emesis, promotion of renal excretion by forced diuresis (alkalinization of urine increases sulfamethoxazole elimination), haemodialysis (Note: peritoneal dialysis is not effective). Monitor blood picture and electrolytes. If significant blood dyscrasias or jaundice occurs, specific therapy should be instituted for these complications. Calcium folinate, 3 to 6mg intramuscularly for 5 to 7 days, may be given to counteract the effects of trimethoprim on haematopoiesis. Alternatively, folic acid and Vitamin B<sub>12</sub> i.m. can be given. In chronic overdosage bone marrow depression, manifested as thrombocytopenia or leukopenia, and other blood dyscrasias due to folic acid deficiency may occur.

**PRESENTATION:** Bottles of 100ml.

**STORAGE INSTRUCTIONS:** Store in a cool place (below 25°C).

**KEEP OUT OF REACH OF CHILDREN.**

**REFERENCE NUMBER:** H2369 (Act 101/1965).

**NAME AND BUSINESS ADDRESS OF APPLICANT:**

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