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RESPRIM®

SUSPENSION

Composition

Each teaspoonful (5 ml) contains

Active Ingredients

Trimethoprim	40 mg
Sulfamethoxazole	200 mg

Other Ingredients

Sucrose, glycerol, microcrystalline cellulose & sodium carboxymethylcellulose, ammonium glycyrrhizinate, carboxymethylcellulose sodium (cellulose gum), polysorbate 80, methylparaben, saccharin sodium, FD&C Red No.40, alcohol, vanilla flavour 407, anise oil, purified water.

Sucrose content: 2.5 g in one teaspoonful (5 ml).
Sodium content: 1.6-1.94 mg in one teaspoonful (5 ml)..

The combination of trimethoprim and sulfamethoxazole in the ratio of 1:5 is known generically as co-trimoxazole.

Mechanism of Action

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid.

Trimethoprim blocks the production of tetrahydrofolic acid by interference with the enzyme dihydrofolate reductase.

Thus, Resprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

Resprim has been shown to be effective against the following bacteria: *Escherichia coli*, indole-positive *Proteus species*, *Proteus mirabilis,* Klebsiella, Enterobacter, *Hemophilus influenzae*, *Streptococcus pneumoniae*, *Shigella flexneri, Shigella sonnei* and *Pneumocystis carinii.*

Indications

Treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, Klebsiella, Enterobacter, *Proteus mirabilis*, *Proteus vulgaris* and *Proteus morganii.*

Treatment of acute otitis media in children due to susceptible strains of *Hemophilus influenzae* or *Streptococcus pneumoniae.* To date, limited data is available on the safety of repeated use of Resprim in infants under 2 years of age. Resprim is not indicated for prophylactic or prolonged administration in otitis media at any age.

Treatment of acute exacerbations of chronic bronchitis due to susceptible strains of Hemophilus influenzae or *Streptococcus pneumoniae*.

Treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei.*

Treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications

Known hypersensitivity to trimethoprim or sulfonamides or to any other ingredient of the preparation.
Patients showing marked liver parenchymal damage.
Patients with severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
Cotrimoxazole is contraindicated in pregnancy at term, during nursing, in premature babies and during the first 2 months of life.
Documented megaloblastic anemia due to folate deficiency.

Warnings

Sulfonamide-associated deaths, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias and hypersensitivity of the respiratory tract..

The preparation should be discontinued at the first appearance of skin rash, or any sign of adverse reaction.

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 the product is given for long periods, or to folate deficient patients or to the elderly, since there exists a possibility of asymptomatic changes in hematological 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.

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

Close monitoring of serum potassium and sodium is warranted in patients at risk of hyperkalemia and hyponatremia.

The combination of antibiotics in Resprim 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

Streptococcal Pharyngitis

Do not use to treat streptococcal pharyngitis. Patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure with this combination than with penicillin.

Hematological Effects

Hematological hypersensitivity reactions have been reported with sulfonamides, and rarely with trimethoprim, especially when used in large doses and/or for prolonged periods. Clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. If any of these signs are noted, a complete blood count should be performed. If a significant reduction in the count of any formed blood element is found, the drug should be discontinued.

Except under careful supervision this product should not be given to patients with serious hematological disorders. Cotrimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Use in the Treatment of and Prophylaxis for Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS):

AIDS patients may not tolerate or respond to cotrimoxazole in the same manner as non-AIDS patients.The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with cotrimoxazole therapy in AIDS patients who are being treated for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of cotrimoxazole in non-AIDS patients.The incidence of hyperkalemia appears to be increased in AIDS patients receiving cotrimoxazole. Adverse effects are generally less severe in patients receiving cotrimoxazole for prophylaxis. A history of mild intolerance to cotrimoxazole in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis. However, if a patient develops skin rash or any sign of adverse reaction, therapy with cotrimoxazole should be reevaluated.

High dosage of trimethoprim, as used in patients with *Pneumocystis carinii* pneumonia, Induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

During treatment,adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

Use in Pregnancy

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, the drug should be used during pregnancy only if the potential benefits to the mother outweigh the possible risks to the fetus.

There are not any adequate data from the use of this product in pregnant women. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities . Resprim should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Resprim is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when this product is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

Use in Breastfeeding

See Contraindications.

Trimethoprim and sulfamethoxazole are excreted into breast milk. Administration of cotrimoxazole should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinemia. Additonally, administration of cotrimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia

Use in Pediatrics
The preparation is contraindicated for use in infants less than 2 months of age (see Contraindications).

Use in the Elderly
There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist (e.g. impaired kidney and/or liver function), or other drugs are being used concomitantly. Severe skin reactions, generalized bone marrow suppression, or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function.

Adverse Reactions

As cotrimoxazole contains trimethoprim and a 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.

The following convention has been used for the classification of adverse events in terms of frequency:- Very common ≥ 1/10, common ≥ 1/100 and <1/10, uncommon ≥ 1/1000 and <1/100, rare ≥ 1/10,000 and <1/1000, very rare <1/10,000.

Infections and Infestations
Common: Monilial overgrowth

Blood and lymphatic system disorders
Very rare: Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anemia, aplastic anemia, haemolytic anemia, methemoglobinemia, eosinophilia, purpura, hemolysis in certain susceptible G6PD deficient patients

Immune system disorders
Very rare: Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus

Metabolism and nutrition disorders
Very common: Hyperkalemia
Very rare: Hypoglycemia, hyponatremia, anorexia

Psychiatric disorders
Very rare: Depression, hallucinations

Nervous system disorders
Common: Headache
Very rare: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone.

Respiratory, thoracic and mediastinal disorders
Very rare: Cough, shortness of breath, pulmonary infiltrates
Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Gastrointestinal disorders
Common: Nausea, diarrhoea
Uncommon: Vomiting
Very rare: Glossitis, stomatitis, pseudomembranous colitis, pancreatitis

Eye Disorders
Very rare: Uveitis

Hepatobiliary disorders
Very rare: Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis
Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders
Common: Skin rashes
Very rare: Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis)
Lyell's syndrome carries a high mortality.

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia, myalgia

Renal and urinary disorders
Very rare: Impaired renal function (sometimes reported as renal failure), interstitial nephritis

Effects associated with Pneumocystis jiroveci (P.carinii) Pneumonitis (PCP) management
Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalemia, hyponatremia, rhabdomyolysis.
At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10 mg/day). Severe hypersensitivity reactions have been reported in PCP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days. Rhabdomyolysis has been reported in HIV positive patients receiving co-tromixazole for prophylaxis or treatment of PCP.

Precautions

Care must be taken in the use of the drug in patients with any degree of renal or hepatic impairment. In such cases, a reduced or more widely spaced dosage is indicated to avoid accumulation of the drug. Measurement of the plasma concentration of the drug is advisable. Urinalysis with careful microscopic examination and renal function tests should be performed during therapy.

Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Because of the trimethoprim component, cotrimoxazole should be given with caution to patients with possible folate deficiency e.g. the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states.

Care must be taken when this drug is given to patients with severe allergy or bronchial asthma.

In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is usually dose-related.

Patients should be warned against exposure to direct sunlight, bearing in mind that photosensitivity is an allergic reaction to cotrimoxazole.

The administration of Resprim 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.

Resprim Suspension contains 2.5 g sucrose in one teaspoonful (5ml). This should be taken into consideration when administered to diabetics. Resprim Suspension also contains methylparaben (methylhydroxybenzoate), which may cause allergic reactions (possibly delayed).

Drug Interactions

Sulfamethoxazole/ Warfarin: Cotrimoxazole 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. Thus cotrimoxazole may prolong the prothrombin time of patients who are receiving warfarin. This interaction should be kept in mind when the drug is given to patients on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole/ Sulfonylureas: The hypoglycemic response to sulfonylurea oral antidiabetic agents may be increased due to their displacement from protein binding sites.

Sulfamethoxazole/ Methenamine*:* In acid urine, methenamine breaks down into formaldehyde which may form an insoluble precipitate with sulfamethoxazole and may also increase the risk of crystalluria. Avoid concurrent use.

Sulfamethoxazole/ Methotrexate*:* Methotrexate may be displaced from protein binding sites, with increase in its free plasma levels, leading to megaloblastic changes. It is therefore recommended that caution be exercised if these agents are to be administered concurrently.

The hematological status of the patient should be closely monitored, and either or both agents may have to be discontinued if anemia occurs. The administration of folic acid may be considered.

Sulfamethoxazole/ Penicillins*:* Since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis, or in other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Sulfamethoxazole/ Zidovudine*:* Sulfonamides may completely inhibit the hepatic glucuronidation and decrease the clearance of zidovudine. Concurrent use should be avoided since the toxicity of zidovudine may be potentiated. Concomitant treatment may also increase the risk of hematological adverse reactions to cotrimoxazole.

Sulfamethoxazole/ Photosensitizing Medications: Caution in the concurrent use of these medicines with sulfonamides is recommended, because of the possible additive photosensitizing effects.

Sulfamethoxazole/Indomethacin: Increased sulfamethoxazole blood levels may occur in patients who are receiving indomethacin.
Trimethoprim/ Folate Antagonists*:* Concurrent use, or use of trimethoprim between courses of other folic acid antagonists, whether antineoplastics (e.g. methotrexate) or antimalarials (e.g. pyrimethamine), is not recommended because of the possibility of megaloblastic anemia. Occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anemia should cotrimoxazole be prescribed concurrently.
Trimethoprim/ Rifamipicin: Concurrent use may significantly increase the elimination and shorten the serum half-life of trimethoprim.
Trimethoprim/Drugs That Form Cations at Physiological pH: When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (eg. 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.
Trimethoprim/Digoxin: Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.
Cotrimoxazole/Diuretics: In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.
Cotrimoxazole/Lamivudine: Administration of trimethoprim/sulfamethoxazole 160mg/800mg causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.
Cotrimoxazole/Drugs That Cause Hyperkalemia: Caution should be exercised in patients taking any other drugs that can cause hyperkalemia.
Cotrimoxazole/ Phenytoin*:* Cotrimoxazole may inhibit phenytoin metabolism, resulting in a prolonged half-life and excessive phenytoin effect (increased incidence of nystagmus, ataxia or other toxic signs).
Cotrimoxazole/Cyclosporin: Reversible deterioration in renal function has been observed in patients treated with cotrimoxazole and cyclosporin following renal transplantation.
Cotrimoxazole/Tricyclic Antidepressants: The efficacy of tricyclic antidepressants can decrease when coadministered with cotrimoxazole.
Cotrimoxazole/Amantadine: In the literature,a single case of toxic delirium has been reported after concomitant intake of cotrimoxazole and amantadine.
Cotrimoxazole/Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors) In the literature, 3 cases of hyperkalemia in elderly patients have been reported after concomitant intake of cotrimoxazole and an angiotensin converting enzyme inhibitor.

Effects on ability to drive and use machines
There have been no studies to investigate the effect of cotimoxazole on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless the clinical status of the patient and the adverse events profile of the product should be borne in mind when considering the patients ability to operate machinery.

Diagnostic Interference
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.

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.

Information for Patients

Patients should be counseled that antibacterial drugs including cotrimoxazole should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cotrimoxazole is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cotrimoxazole or other antibacterial drugs in the future.

Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

Dosage and Administration

Resprim suspension is not recommended for use in infants less than 2 months of age.

Urinary Tract Infections and Shigellosis in Adults and Children, Acute Otitis Media in Children:

Adults

4 teaspoonfuls of Resprim Suspension, every 12 hours.

Treatment of shigellosis should be continued for 5 days. Treatment of urinary tract infections should be continued for 10-14 days.

Children

The recommended dosage is 8 mg/kg body weight/day trimethoprim and 40 mg/kg body weight/day sulfamethoxazole, administered in 2 divided doses.

The following table provides dosage guidelines for Resprim Suspension:

Weight kg	Dose-every 12 hours
	teaspoonful
10	1 (5 ml)
20	2 (10 ml)
30	3 (15 ml)
40	4 (20 ml)

Treatment of shigellosis should be continued for 5 days. Treatment of urinary tract infections or acute otitis media should be continued for 10 days.

Acute Exacerbations of Chronic Bronchitis in Adults

4 teaspoonfuls of Resprim Suspension every 12 hours, for 14 days.

Pneumocystis Carinii Pneumonitis in Children

The recommended dosage is 20 mg/kg body weight/day trimethoprim and 100 mg/kg body weight/day sulfamethoxazole, administered in equally divided doses every 6 hours for 14 days.

The following table provides dosage guidelines for Resprim Suspension

Weight kg	Dose-every 6 hours
	teaspoonful
8	1 (5 ml)
16	2 (10 ml)
24	3 (15 ml)
32	4 (20 ml)

Renal Impairment:

For patients with creatinine clearance greater than 30 ml/min the full recommended dosage may be administered. Dosage should be reduced to half the usual dose in patients with creatinine clearance between 30-15 ml/min. Resprim is not recommended in patients with creatinine clearance less than 15 ml/min.

Overdosage

Manifestations

Acute

Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage. Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

Chronic

Use of cotrimoxazole in high doses and/or for extended periods of time may cause bone marrow depression. This is manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia.

Treatment

Treatment includes the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If signs of bone marrow depression occur, the patient should be given leucovorin 5-15 mg daily, until normal hematopoiesis is restored. Specific therapy should be instituted if jaundice occurs.

Peritoneal dialysis is not effective, and hemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

Storage

Store in a dark and dry place below 25°C.
After first opening of the bottle, the product may be used within 30 days, but not later than the expiry date.

Registration Numbers

026 95 21177 00.

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