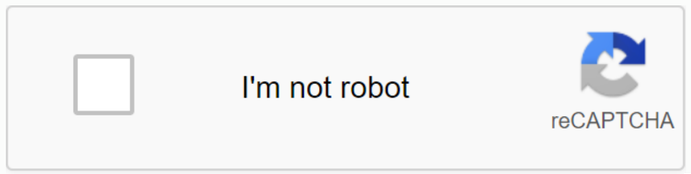

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Smz/tmp ds tab 800-160

Updated August 6, 2019 If you are a consumer or patient, please visit this version. SPL UKCLASSIFIED SECTION To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfametophazole and trimethoprim tablets and other antibacterial medicinal products, sulfamethoxazole and trimethoprim tablets should only be used to treat or prevent infections that have been proven or strongly suspected to be caused by bacteria. DESCRIPTION Sulfamethosazole and trimethoprim are a synthetic antibacterial combination product available in DS (double strength) tablets, each containing 800 mg sulfamethosazole, USP and 160 mg trimethoprim, USP; in tablets, each contains 400 mg sulfametoxazole, USP and 80 mg trimethoprim, USP for oral administration. Sulfamethoxazole, USP is N1-(5-methyl-3-isoxazoleyl) sulanilamide; the molecular formula is C 10H 11N 3O 3S. It is an almost white, odorless, tasteless compound with a molecular weight of 253.28 and the following structural formula: Trimethoprim, USP is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine; the molecular formula is C 14H 18N 4O 3. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3. It has the following structural formula: Inactive ingredients: Magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate. PHARMACOLOGY Sulfamethoxazole and trimethoprim are rapidly absorbed after oral administration. Both sulfamethosazole and trimethoprim are found in the blood as unbound, protein-bound and metabolized forms; sulfameoxazole also exists as a conjugated form. Sulfamethoxazole is metabolised in humans to at least 5 metabolites: N 4-acetyl-, N 4-hydroxy,5-methylhydroxy-, N 4-acetyl-5-methylhydroxy- sulfamethozole metabolites and an N-glukuronide conjugat. The formulation of N 4 hydroxymetabolite is mediated via CYP2C9. Trimethoprim is metabolized in vitro to 11 different metabolites, five of which are glutathione adducts and six are oxidative metabolites, including the major metabolites, 1- and 3-oxides and 3- and 4-hydroxy derivatives. The free forms of sulfamethosazole and trimethoprim are considered to be the therapeutically active forms. In vitro studies suggest that trimethoprim is a substrate of P-glycoprotein, OCT1 and OCT2, and that sulfamethosazole is not a substrate of P-glycoprotein. Approximately 70% of sulfamethozole and 44% of trimethoprim are bound to plasma proteins. The presence of 10 mg percent sulfamethoazole in plasma reduces the protein binding of trimethoprim to a negligible degree; trimethoprim does not affect the protein binding of sulfametoxazole. Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum halving of sulfamethoazole and trimethoprim is 10 and 8 to 10 hours, respectively. Patients with severe renal impairment an increase in half-life for both components, which require dose regimen adjustment (see section on DOSING AND ADMINISTRATION). Detectable amounts of sulfamethosazole and trimethoprim are present in the blood 24 hours after drug administration. During administration of 800 mg sulfamethoxazole and 160 mg trimethoprim b.i.d., the mean steady-state plasma concentration of trimethoprim was 1.72 micrograms/ml. Steady-state mean plasma levels of free and total sulfameoxazole were 57.4 µg/ml and 68 µg/ml, respectively. These steady-state levels were achieved after three days of drug administration on 1. Excretion of sulfamethosole and trimethoprim is mainly of the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are significantly higher than concentrations in the blood. The mean percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethozole and trimethoprim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remainder as N 4-acetylated metabolite 2. When administered together as sulfamethoxazole and trimethoprim, neither sulfamethosazole nor trimethoprim affect the urinary excretion pattern of the other. Both sulfamethosazole and trimethoprim distribute to sputum, vaginal fluid and middle ear fluid; Trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in human milk. Geriatric pharmacokinetics: The pharmacokinetics of sulfametoxazole 800 mg and trimethoprim 160 mg were studied in 6 geriatric subjects (mean age: 78.6 years) and 6 young healthy subjects (mean age: 29.3 years) using an unsonic formulation approved. Pharmacokinetic values for sulfametoxazole in geriatric subjects were similar to those observed in young adult subjects. The mean renal clearance of trimethoprim was significantly lower in geriatric subjects compared to young adult subjects (19 ml/h/kg vs. 55 ml/h/kg). However, after normalization by body weight, the apparent total body clearance of trimethoprim was on average 19% lower in geriatric subjects compared to young adult subjects 3. Microbiology Sulfamethoxazole inhibits the bacterial synthesis of dihydrofolic acid by competing with paraaminozoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversible inhibiting the necessary enzyme, dihydrofolate reductase. Thus, sulfamethosazole and trimethoprim block two consecutive steps in the biosynthesis of nucleic acids and proteins that are essential for many bacteria. In vitro studies have shown that bacteria resistance develops more slowly with both and trimethoprim in combination than with either sulfamethoxazole or or Alone. Sulfamethoxazole and trimethoprim have been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USE section. Aerobic Gram-Positive Microorganisms: Streptococcus pneumoniae Aerobic Gram-Negative Microorganisms: Escherichia coli (including exposed enterotogic strains implicated in traveler's diarrhea) Klebsiella species Enterobacter species Haemophilus influenzae Morganella morganii Proteus mirabili S Proteus vulgaris Shigella flexneri Shigella sonnei Other organisms: Pneumocystis jiroveci Susceptibility Testing For specific information on sensitivity test interpretive criteria and associated testing methods and quality control standards recognized by the FDA for this drug, please see: . INDICATIONS AND USE To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfamethozole and trimethoprim tablets and other antibacterial medicinal products, sulfamethozole and trimethoprim tablets should only be used to treat or prevent infections that have been proven or strongly suspected to be caused by sensitive bacteria. When cultural and susceptibility information is available, they should be considered when choosing or changing antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns can contribute to the empiric choice of therapy. Urinary tract infections: For the treatment of urinary tract infections due to sensitive strains of the following organisms: Escherichia coli, Klebsiella species, Enterobacter species, Morganella morganii, Proteus mirabilis and Proteus vulgaris. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a simple effective antibacterial agent instead of the combination. Acute Otitis Media: For the treatment of acute otitis media in pediatric patients due to sensitive strains of Streptococcus pneumoniae or Haemophilus influenzae when in the judgment of the doctor sulfamethosazole and trimethoprim gives some advantage over the use of other antimicrobials. To date, there are limited data on the safety of repeated use of sulfamethoazole and trimethoprim tablets in paediatric patients less than two years of age. Sulfamethoxazole and trimethoprim tablets are not indicated for prophylactic or prolonged administration in otitis media at any age. Acute exacerbations of chronic bronchitis in adults: For the treatment of acute exacerbations of chronic bronchitis due to sensitive strains of Streptococcus pneumoniae or Haemophilus influenzae when a doctor believes that sulfamethoxazole and trimethoprim can provide some benefit over the use of a single antimicrobial agent. Shigellosis: For the treatment of enteritis caused by sensitive strains of Shigella flexneri and Shigella sonnei antibacterial therapy is indicated. Pneumocystis jiroveci Pneumonia: For the treatment of documented pneumocystis jiroveci pneumonia and for prophylaxis against P. jiroveci pneumonia in people who are immunosuppressed and are considered to be at increased risk of developing P. jiroveci pneumonia. Traveler's diarrhea in adults: For the treatment of traveler's diarrhea due to susceptible strains of enterotoxigenic E. coli. CONTRAINDICATIONS Sulfamethoxazole and trimethoprim are contraindicated in patients with known hypersensitivity to trimethoprim or sulphonamides, in patients with a history of drug-induced immunotrothophytopenia using trimethoprim and/or sulphonamides, and in patients with documented megaloblastic anaemia due to folate deficiency. Sulfamethoxazole and trimethoprim are contraindicated in paediatric patients less than 2 months of age. Sulfamethoxazole and trimethoprim are also contraindicated in patients with marked liver damage or with severe renal impairment when renal function status cannot be monitored. WARNINGS Embryofetal toxicity Some epidemiological studies suggest that exposure to sulfamethosazole/trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, especially neural tube defects, cardiovascular malformations, urinary tract defects, oral ravines and club foot. If sulfamethozole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be informed of the potential dangers to the foetus. Hypersensitivity and other fatal reactions Deaths associated with administration of sulfonamides, although rare, have arisen due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyssasias. Sulfonamides, including sulfonamide-containing products such as sulfamethosazole/trimethoprim, should be discontinued at the first of the skin or signs of side effect. In rare cases, a skin rash can be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, liver necrosis and serious blood diseases (see PRECAUTIONS). Clinical signs, such as sore throat, fever, arthralgia, pallor, purpura or jaundice, may be early indications of severe reactions. Cough, shortness of breath and pulmonary infiltrates are hypersensitivity reactions in the respiratory tract reported in conjunction with sulphonamide therapy. Thrombocytopenia Sulfamethosazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life-threatening have been reported. Thrombocytopenia usually disappears within a week upon discontinuation of sulfametoxazole/trimethoprim. Streptococcal infections and Fever Sulfonamides should not be used to treat group A β-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococci, and therefore will not prevent sequels such as rheumatic fever. Clostridium hard-to-associate diarrhea Clostridium hard-associated diarrhea (CDAD) has been reported with the use of almost all antibacterial agents, including sulfamethozole and trimethoprim, and may vary in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents changes the normal flora of the large intestine leading to overgrowth of C. difficult. C. difficult produces toxins A and B that contribute to the development of CDAD. Hypertoxin that produces strains of C. hard causes increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colektomy. CDAD must be considered in all patients presenting with diarrhoea after antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use that is not aimed at C. may need to be discontinued. Proper fluid and electrolyte management, protein supplements, antibiotic treatment of C. difficult and surgical evaluation should be introduced as clinically indicated. Adjunctive therapy with Leucovorin for Pneumocystis jiroveci pneumonia Treatment failure and excess mortality were observed when trimethoprim sulfamethoxazole was used concomitantly with leucovorin to treat HIV-positive patients with Pneumocystis jiroveci pneumonia in a randomized placebo-controlled study 4. Co-administration of trimethoprim-sulfamethozole and leucovorin during the treatment of Pneumocystis jiroveci pneumonia should be avoided. PRECAUTIONS Development of resistant bacteria Prescribing sulfamethoxazole and trimethoprim tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to benefit the patient and increases the risk of developing drug-resistant bacteria. Folate deficiency Sulfamethoxazole and trimethoprim should be administered with caution to patients with renal or hepatic impairment, to those with possible folate deficiency (e.g. elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome and patients in malnutrition conditions) and to those with severe allergies or bronchial asthma. Haematological changes indicating folic acid deficiency may occur in elderly patients or in patients with existing folic acid deficiency or renal failure. These effects are reversible in folic acid therapy. Hemolysis In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is (see clinical pharmacology and DOSING AND ADMINISTRATION). Hypoglycaemia Cases of hypoglycaemia in non-diabetics treated with sulfamethoxazole and trimethoprim are rarely seen, usually occurring after a few days of treatment. Patients with renal impairment, liver disease, malnutrition or those receiving high doses of sulfamethozole and trimethoprim are particularly at risk. Phenylalanine metabolism Trimethoprim has been shown to impair phenylalanine metabolism, but this has no bearing in phenylketonuric patients on appropriate dietary restriction. Porphyroid and hypothyroidism As with all medicines containing sulfonamides, caution is advisable in patients with porphyia or thyroid dysfunction. Use in the treatment and prophylaxis of Pneumocystis jiroveci pneumonia in patients with acquired immunodeficiency syndrome (AIDS) AIDS patients cannot tolerate or respond to sulfamethoxazole and trimethoprim in the same way as non-AIDS patients. The incidence of adverse reactions, in particular, fever, leukopenia and elevated aminotransferase (transaminase), with sulfamethoxazole and trimethoprim therapy in AIDS patients treated for P. jiroveci pneumonia has been reported to be greatly increased compared to the incidence normally associated with sulfamethoxazole and trimethoprim patients. Adverse reactions are generally less severe in patients receiving sulfamethoazole and trimethoprim for prophylaxis. A history of mild intolerance to sulfamethozole and trimethoprim in AIDS patients does not seem to predict intolerance to subsequent secondary prophylaxis 5. If a patient develops skin rashes or signs of adverse reaction, treatment with sulfametosazole and trimethoprim should be reconsidered (see WARNINGS). Co-administration of sulfamethoxazole and trimethoprim and leucovorin should be avoided with P. jiroveci pneumonia (see WARNINGS). Electrolyte abnormalities High dose trimethoprim, used in patients with P. jiroveci pneumonia, induces a progressive but reversible increase in serum potassium concentrations in a significant number of patients. Even treatment with recommended doses can cause hyperkalaemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if medicinal products known to induce hyperkalaemia are given concurrently. Careful monitoring of serum potassium is justified in these patients. Severe and symptomatic hyponatraemia may occur in patients receiving sulfamethoxazole and trimethoprim, especially for the treatment of P. jiroveci pneumonia. Evaluation of hyponatraemia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications. During treatment, adequate fluid intake and urine effect should be ensured to prevent crystalluria. Patients who are acetylene may be more susceptible to idiosyncratic reactions to sulfonamides. Information for patients Patients should be advised that antibacterial drugs, including sulfamethoazole and trimethoprim tablets, should be used only to treat bacterial infections. They do not treat viral infections (e.g. colds). When sulfamethosazole and trimethoprim tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of treatment, the medication should be taken exactly as directed. Skipping doses or not completing the entire course of treatment can (1) reduce the effectiveness of immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treated by sulfamethozole and trimethoprim tablets or other antibacterial drugs in the future. Patients should be instructed to maintain an adequate fluid intake to prevent crystaluria and stone formation. Diarrhea is a common problem caused by antibiotics that usually end when antibiotics are discontinued. Sometimes after starting treatment with antibiotics, patients may develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after taking the last dose of antibiotics. If this happens, patients should contact their doctor as soon as possible. Laboratory tests Complete blood values should be done often in patients receiving sulfamethoxazole and trimethoprim; if a significant reduction in the number of formed blood cells is noted, sulfamethozole and trimethoprim

should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during treatment, especially for patients with renal impairment. Drug interactions Potential for Sulfamethoxazole and Trimethoprim to affect other medicinal products Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfameoxazole is an inhibitor of CYP2C9. Caution is recommended when sulfamethosole and trimethoprim are administered concomitantly with medicinal products that are substrates of CYP2C8 and 2C9 or OCT2. In elderly patients receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Sulfamethozole and trimethoprim have been reported to prolong prothrombin time in patients receiving anticoagulant warfarin (a CYP2C9 substrate). This interaction should be taken into account when sulfametoxazole and trimethoprim are given to patients already taking anticoagulant therapy and the coagulation time should be reconsidered. Sulfamethozole and trimethoprim may inhibit liver metabolism of phenytoin (a CYP2C9 substrate). Sulfamethoxazole and trimethoprim, given at a regular clinical dose, phenytoin increased half-life by 39% phenytoin metabolic clearance rate by 27%. When administering these drugs at the same time, one should pay attention to the possible excessive phenytoin effect. Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with renal transport of methotrexate, thereby increasing free methotrexate concentrations. There have been reports of marked but reversible nephrotoxicity with co-administration of sulfametoxazole and trimethoprim and cyclosporine in renal transplant recipients. Increased digoxin blood levels may occur with concomitant sulfametotoxazole and trimethoprim therapy, especially in elderly patients. Serumgrawaxin levels should be monitored. Increased sulfamethoxazole levels in the blood may occur in patients receiving indomethacin. Sporadic reports suggest that patients receiving pyrimethamine as malaria prophylaxis at doses above 25 mg weekly may develop megaloblastic anemia if sulfamethozole and trimethoprim are prescribed. The effect of tricyclic antidepressants may be reduced when administered concomitantly with sulfamethozole and trimethoprim. Sulfamethozole and trimethoprim enhance the effect of oral hypoglycaemics metabolised by CYP2C8 (e.g. pioglitazone, repaglinide and rosiglitazone) or CYP2C9 (e.g. glipizide and glycode) or eliminated renal al-C via OCT2 (e.g. metformin). Further monitoring of bloodsuckers may be justified. In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfametoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin have also been reported. In the literature, three cases of hyperkalaemia in elderly patients have been reported following concomitant intake of sulfametoxazole/trimethoprim and an angiotensin converting enzyme inhibitor 6.7. Drug/laboratory test Interactions Sulfamethoxazole and trimethoprim, especially the trimethoprim component, may interfere with a serum methotrexate analysis determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofola treductase is used as a binding protein. However, no interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of sulfamethoxazole and trimethoprim can also interfere with Jaffé alkaline picrate reaction analysis for creatinine, resulting in overestimates of about 10% in the range of normal values. Carcinogenicity, Mutagenese, Impaired fertility carcinogenicity: Sulfamethoxazole was not carcinogenic when assessed in a 26-week tumourogenic mouse (Tg-rasH2) study at doses up to 400 mg/kg/day sulfamethoxazole; equivalent to 2.4 times human systemic exposure (at a daily dose of 800 mg sulfametoxazole b.i.d.). Mutagesis: In vitro reverse mutation bacterial tests according to the standard protocol have not with sulfamethoxazole and trimethoprim in combination. An in vitro chromosomal lymphocyte test with sulfamethozole/trimethoprim was negative. In in vitro and in vivo tests in animal species, sulfamethozole/trimethoprim did not damage chromosomes. In vivo micronucleus analyses were positive following oral administration of sulfametoxazole/trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethosazole and trimethoprim showed no chromosomal abnormalities. Sulfamethozole alone was positive in an in vitro reverse mutation bacterial analysis and in vitro micronucleus assays using cultivated human lymphocytes. Trimethoprim alone was negative in in vitro reverse mutation bacterial analyses and in vitro chromosomal extraction analysis with Chinese Hamster ovary or lung cells with or without S9 activation. In in vitro Comet, micronucleus and chromosomal damage analyzes using cultivated human lymphocytes, trimethoprim was positive. In mice following oral administration of trimethoprim, no DNA damage was recorded in comet analyses of liver, kidney, lung, spleen or bone marrow. Decreased fertility: No adverse reactions to fertility or general reproductive capacity were observed in rats given oral doses as high as 350 mg/kg/day sulfamethoazole plus 70 mg/kg/day trimethoprim doses approximately twice the recommended human daily dose on a body surface surface area basis. Pregnancy Although there are no large, well-controlled studies on the use of sulfametoxazole and trimethoprim in pregnant women, Brumfitis and Pursell 8, reported in a retrospective study the outcome of 186 pregnancies in which the mother received either placebo or sulfamethozole and trimethoprim. The incidence of congenital abnormalities was 4.5% (3 of 66) in those receiving placebo and 3.3% (4 out of 120) in those receiving sulfametoxazole and trimethoprim. There were no abnormalities in the 10 children whose mothers were given the drug in the first trimester. In a separate study, Brumfitis and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral sulfamethosazole and trimethoprim at the time of conception or shortly afterwards. Because sulfamethozole and trimethoprim can interfere with folic acid metabolism, sulfamethozole and trimethoprim should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. Teratogenic Effects Pregnancy Category D. Human Data Although there are no large prospective, well-controlled studies in pregnant women and their babies, some retrospective epidemiological studies suggest a link between first trimester exposure to sulfamethoazole/trimethoprim with an increased risk of congenital malformations, especially neural tube defects, cardiovascular abnormalities, urinary tract defects, oral ravines and clubfoot. however, studies were limited by the small number of exposed cases and lack of adjustment for several statistical comparisons and confounders. These studies are further limited by recall, selection and information bias, and by the limited generalizability of their findings. Finally, performance measures varied between studies, limiting comparisons across studies. Alternatively, other epidemiological studies did not detect statistically significant relationships between sulfamethoxazole/trimethoprim exposure and specific malformations. Animal data In rats, oral doses of either 533 mg/kg sulfametoxazole or 200 mg/kg trimethoprim teralogical effects were mainly manifested as palates. These doses are approximately 5 and 6 times the recommended human total daily dose on a body surface surface surface. In two studies in rats, teratology was not observed when 512 mg/kg sulfametoxazole was used in combination with 128 mg/kg trimethoprim. In some rabbit studies, a general increase in fetal loss (dead and resorbed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose based on the body surface. Nonteratogene effects see section CONTRAINDICATIONS. Nursing mothers: Levels of trimethoprim/sulfamethosazole in breast milk are approximately 2% to 5% of the recommended daily dose for infants over 2 months of age. Caution should be exercised when sulfamethosole and trimethoprim are administered to a lactating woman, especially during breastfeeding, jaundice, sick, stressed or premature infants due to the potential risk of bilirubin displacement and kernicterus. Paediatric use: Sulfamethoxazole and trimethoprim are contraindicated for infants less than 2 months of age (see section on INDICATIONS and CONTRAINDICATIONS). Geriatric use: Clinical studies of sulfamethoazole and trimethoprim did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. There may be an increased risk of serious adverse reactions in elderly patients, especially when complicating conditions, such as renal and/or hepatic impairment, possible folate deficiency, or concomitant use of other medicinal products occur. Severe skin reactions, generalised bone marrow suppression (see sections WARNINGS and ADVERSE REACTIONS), a specific decrease in platelets (with or without purpura) and hyperkalaemia are the most frequently reported serious adverse reactions in elderly patients. In those who concomitantly receive certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels may occur with concomitant sulfametotoxazole and trimethoprim therapy, especially in elderly patients. Serumgrawaxin levels should be monitored. Haematological changes indicating folic acid deficiency may occur in elderly patients. These reversible in the treatment of folic acid. Appropriate dose adjustments should be made for patients with renal impairment and the duration of use should be as short as possible to minimize the risk of adverse reactions (see section on dosing and administration). The trimethoprim component of sulfamethozole and trimethoprim may cause hyperkaemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency or when administered concomitantly with medicinal products known to induce hyperkalaemia, such as angiotensin converting enzyme inhibitors. Careful monitoring of serum potassium is justified in these patients. Discontinuation of treatment with sulfamethoxazole and trimethoprim is recommended to help lower potassium serum levels. Sulfamethozole and Trimethoprim tablets contain 1.8 mg sodium (0.08 mEq) sodium per tablet. Sulfamethosazole and Trimethoprim double strength tablets contain 3.6 mg (0.16 mEq) sodium per tablet. Pharmacokinetic parameters of sulfameoxazole were similar for geriatric subjects and younger adult subjects. Mean maximum serum trims concentration was higher and mean renal clearance of trimethoprim was lower in geriatric subjects compared to younger subjects (see CLINICAL PHARMACOLOGY: Geriatric pharmacokinetics). ADVERSE REACTIONS The most common side effects are gastrointestinal disorders (nausea, vomiting, anorexia) and allergic skin reactions (such as and urticaria). DEATHS ASSOCIATED WITH ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT LIVER NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRATES (SEE WARNINGS). Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprotrombinmia, methemoglobinemia, eosinophilia. Allergic reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum disease-like syndrome, generalized allergic reactions, generalized skin outbreaks, photosensitivity, conjunctival and scleral injection, pruritus, urtikaria and. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported. Gastrointestinal: Hepatitis (including cholestatic jaundice and liver necrosis), increase of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emese, abdominal pain, diarrhoea, anorexia. Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystaluria and nephrotoxicity associated with cyclosporine. Metabolic and nutritional: hyponatraemia (see PRECAUTIONS: Electrolyte deviation). Neurological: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, dizziness, tinnitus, headache. Psychiatric: Hallucinations, depression, apathy, nervousness. Endocrine: Sulfonamides carry certain chemical similarities with some goitrogens, diuretics (acetazolamide and thiazides) and oral hypoglycemic agents. Cross-sensitivity can exist with these funds. Diuresis and hypoglycaemia have rarely occurred in patients receiving sulfonamides. Musculoskeletal and arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with sulfamethozole and trimethoprim, mainly in AIDS patients. Respiratory protection: Cough, shortness of breath and pulmonary infiltrate (see WARNINGS). Various: Weakness, fatigue, insomnia. Post-marketing Experience The following adverse reactions have been identified below after approval of trimethoprim-sulfamethozole. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure: Thrombotic thrombocytopenia purpura Idiopathic thrombocytopenic purpuric coppura QT prolongation resulting in ventricular tachycardia and torsade de pointes To report suspected side effects, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. OVERDOSAGE Acute: The amount of a single dose of sulfametoxazole and trimethoprim either associated with symptoms of overdose or likely to be life-threatening has not been reported. Signs and symptoms of overdose reported with sulphonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystaluria can be noted. Blood dyssasias and jaundice are potential late manifestations of overdose. Signs of acute overdose with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression. General principles of treatment include the institution of gastric lavation or emesis, forcing oral fluids and administration of intravenous fluids if urine production is low and kidney function is normal. Acidification of urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrat or jaundice occurs, specific therapy should be introduced for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating sulfamethosazole and trimethoprim. Chronic: Use of sulfamethosazole and trimethoprim at high doses and/or for prolonged periods may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anaemia. If signs of Marrow depression occurs, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored. DOSING AND ADMINISTRATION Sulfamethosazole and trimethoprim tablets are contraindicated in paediatric patients less than 2 months of age. Urinary tract infections and shigellosis in adult and paediatric patients, and acute otitis media in children adults: The usual adult dose in the treatment of urinary tract infections is 1 sulfamethozole and trimethoprim DS (double strength) tablet or 2 sulfamethosazole and trimethoprim tablets every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. Children: The recommended dose for children with urinary tract infections or acute otitis media is 40 mg/kg sulfametoxazole and 8 mg/kg trimethoprim per 24 hours, given in two divided doses every 12 hours. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for achieving this dose: Children 2 months or older: For patients with renal impairment When renal function is impaired, Reduced dosage should be used using the following table: Acute exacerbations of chronic bronchitis in adults The usual adult dose in the treatment of acute exacerbations of chronic bronchitis is 1 sulfamethoxazole and trimethoprim double strength tablet, or 2 sulfamethozole and trimethoprim single strength tablets, every 12 hours for 14 days. Pneumocystis Jiroveci Pneumonia Treatment: Adults and children The recommended dose for the treatment of patients with documented Pneumocystis jiroveci pneumonia is 75 to 100 mg/kg sulfamethozole and 15 to 20 mg/kg trimethoprim per 24 hours given in equally divided doses every 6 hours for 14 to 21 days 9. The following table is a guideline for the upper limit of this dose: For the lower limit dose (75 mg/kg sulfametoxazole and 15 mg/kg trimethoprim per 24 hours) administer 75% of the dose in the table above. Prophylaxis Adults The recommended dose for prophylaxis in adults is 1 sulfamethozole and trimethoprim DS (double strength) tablet daily 10. Children For children, the recommended dose is 750 mg/m 2/day sulfametoxazole with 150 mg/m 2/day trimethoprim given orally in equally divided doses twice daily, on 3 consecutive days per week. The total daily dose should not exceed 1600 mg sulfamethoxazole and 320 mg trimethoprim 11. The following table is a guideline for the achievement of this dose in children: Traveler's diarrhea in adults For the treatment of traveler's diarrhea, the usual adult dose is 1 sulfamethozole and trimethoprim DS (double strength) tablet or 2 sulfamethosazole and trimethoprim single strength tablets every 12 hours for 5 days. HOW TO SUPPLI Sulfamethoxazole and Trimethoprim Tablets, USP supplied as follows: Sulfamethoxazole and DS (double strength) Tablets USP, 800 mg, are supplied as white, oval, bisected tablets debossed IP bisect 272 on one side. They are available as follows: Bottles of 6: NDC 54348-625-06 Bottles of 10: NDC 54348-625-10 Bottles of 14: NDC 54348 -625-14 Bottles of 20: NDC 54348-625-20 Store at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature]. DISPENSER IN TIGHT, LIGHT CONTAINER. REFERENCES Kremers P, Duvivier J, Heusghem C. Pharmacokinetic studies of co-trimoxazole in male after single and repeated doses. J Clin Pharmacol. February-March 1974; 14:112-117. Kaplan SA, et al. Pharmacokinetic profile of Trimethoprim-Sulfamethoxazole in Man. J Infect Dis. Nov 1973; 19:00 128 (Suppl): S547-S555. Varoquaux O, et al Pharmacokinetics of the trimethoprim-sulfamethosazole combination in the elderly. Br J Clin Pharmacol. 1985;20:575-581. Safrin S, Lee BL, Sande MA. 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In 1992, a single j med was established. 327:1853-1880. Recommendations for prophylaxis against Pneumocystis cariniipneumonia for adults and adolescents infected with human immunodeficiency virus. - There's nothing to do with it. 1992; 41 (RR-4):1-11. CDC Guidelines for prophylaxis against Pneumocystis cariniipneumonia for children infected with human immunodeficiency virus. - There's nothing to do with it. 1991; 40 (RR-2):1-13. Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807 Fox. 04-2019-01 Package Marking: (54348-625-06) Package Marking: (54348-625-10) Package Marking (54348-625-14) Labelling of packages: (54348-625-20) (54348-625-20)