Roche

FANSIDAR®

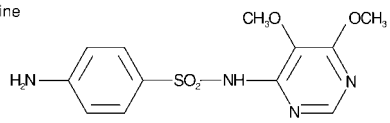
brand of
sulfadoxine and pyrimethamine
TABLETS

WARNING: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF FANSIDAR HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS. FANSIDAR PROPHYLAXIS SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH, IF A SIGNIFICANT REDUCTION IN THE COUNT OF ANY FORMED BLOOD ELEMENTS IS NOTED, OR UPON THE OCCURRENCE OF ACTIVE BACTERIAL OR FUNGAL INFECTIONS.

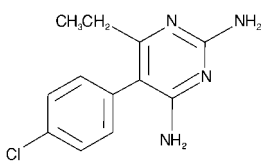
DESCRIPTION

Fansidar is an antimalarial agent, each tablet containing 500 mg N^1-(5,6-dimethoxy-4-pyrimidinyl) sulfanilamide (sulfadoxine) and 25 mg 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine (pyrimethamine). Each tablet also contains cornstarch, gelatin, lactose, magnesium stearate and talc.

Sulfadoxine



Pyrimethamine



CLINICAL PHARMACOLOGY

Fansidar is an antimalarial agent which acts by reciprocal potentiation of its two components, achieved by a sequential blockade of two enzymes involved in the biosynthesis of folinic acid within the parasites. Fansidar is effective against certain strains of *Plasmodium falciparum* that are resistant to chloroquine.

Both the sulfadoxine and the pyrimethamine of Fansidar are absorbed orally and are excreted mainly by the kidney. Following a single tablet administration, sulfadoxine peak plasma concentrations of 51 to 76 mcg/mL were achieved in 2.5 to 6 hours and the pyrimethamine peak plasma concentrations of 0.13 to 0.4 mcg/mL were achieved in 1.5 to 8 hours. The apparent half-life of elimination of sulfadoxine ranged from 100 to 231 hours with a mean of 169 hours, whereas pyrimethamine half-lives ranged from 54 to 148 hours with a mean of 111 hours. Both drugs appear in breast milk of nursing mothers.

INDICATIONS AND USAGE

Fansidar is indicated for the treatment of *P. falciparum* malaria for those patients in whom chloroquine resistance is suspected. Malaria prophylaxis with Fansidar is indicated for travelers to areas where chloroquine-resistant *P. falciparum* malaria is endemic. However, strains of *P. falciparum* may be encountered which have developed resistance to Fansidar.

CONTRAINDICATIONS

Prophylactic (repeated) use of Fansidar is contraindicated in patients with severe renal insufficiency, marked liver parenchymal damage or blood dyscrasias. Hypersensitivity to pyrimethamine or sulfonamides. Patients with documented megaloblastic anemia due to folate deficiency. Infants less than 2 months of age. Pregnancy at term and during the nursing period because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF FANSIDAR HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS. FANSIDAR PROPHYLAXIS SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH, IF A SIGNIFICANT REDUCTION IN THE COUNT OF ANY FORMED BLOOD ELEMENTS IS NOTED, OR UPON THE OCCURRENCE OF ACTIVE BACTERIAL OR FUNGAL INFECTIONS.

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Fansidar prophylactic regimen has been reported to cause leukopenia during a treatment of 2 months or longer. This leukopenia is generally mild and reversible.

PRECAUTIONS

General: Fansidar should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. As with some sulfonamide drugs, in glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. Urinalysis with microscopic examination and renal function tests should be performed during therapy of those patients who have impaired renal function.

Information for the Patient: Patients should be warned that at the first appearance of a skin rash, they should stop use of Fansidar and seek medical attention immediately. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Patients should also be warned that the appearance of sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura, jaundice or glossitis may be early indications of serious disorders which require prophylactic treatment to be stopped and medical treatment to be sought.

Females should be cautioned against becoming pregnant and should not breastfeed their infants during Fansidar therapy or prophylactic treatment.

Patients should be warned to keep Fansidar out of reach of children.

Laboratory Tests: Periodic blood counts and analysis of urine for crystalluria are desirable during prolonged prophylaxis.

Drug Interactions: There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with Fansidar as compared to the use of Fansidar alone. Fansidar is compatible with quinine and with antibiotics. However, antifolic drugs such as sulfonamides or trimethoprim-sulfamethoxazole combinations should not be used while the patient is receiving Fansidar for antimalarial prophylaxis. Fansidar has not been reported to interfere with antidiabetic agents.

If signs of folic acid deficiency develop, Fansidar should be discontinued. Folinic acid (leucovorin) may be administered in doses of 5 mg to 15 mg intramuscularly daily, for 3 days or longer, for depressed platelet or white blood cell counts in patients with drug-induced folic acid deficiency when recovery is too slow.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Pyrimethamine was not found carcinogenic in female mice or in male and female rats. The carcinogenic potential of pyrimethamine in male mice could not be assessed from the study because of markedly reduced life-span. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totaling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test. Testicular changes have been observed in rats treated with 105 mg/kg/day of Fansidar and with 15 mg/kg/day of pyrimethamine alone. Fertility of male rats and the ability of male or female rats to mate were not adversely affected at dosages of up to 210 mg/kg/day of Fansidar. The pregnancy rate of female rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at dosages of 31.5 mg/kg/day or higher, a dosage approximately 30 times the weekly human prophylactic dose or higher.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Fansidar has been shown to be teratogenic in rats when given in weekly doses approximately 12 times the weekly human prophylactic dose. Teratology studies with pyrimethamine plus sulfadoxine (1:20) in rats showed the minimum oral teratogenic dose to be approximately 0.9 mg/kg pyrimethamine plus 18 mg/kg sulfadoxine. In rabbits, no teratogenic effects were noted at oral doses as high as 20 mg/kg pyrimethamine plus 400 mg/kg sulfadoxine.

There are no adequate and well-controlled studies in pregnant women. However, due to the teratogenic effect shown in animals and because pyrimethamine plus sulfadoxine may interfere with folic acid metabolism, Fansidar therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant.

Nonteratogenic Effects: See CONTRAINDICATIONS.

Nursing Mothers: See CONTRAINDICATIONS.

Pediatric Use: Fansidar should not be given to infants less than 2 months of age because of inadequate development of the glucuronide-forming enzyme system.

Geriatric Use: Clinical studies of Fansidar did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually

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starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

For completeness, all major reactions to sulfonamides and to pyrimethamine are included below, even though they may not have been reported with Fansidar. See WARNINGS and PRECAUTIONS: *Information for the Patient.*

Blood Dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia, and eosinophilia.

Allergic Reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, toxic epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, and pancreatitis.

Central Nervous System Reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness, and nervousness.

Respiratory Reactions: Pulmonary infiltrates.

Miscellaneous Reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and LE phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

OVERDOSAGE

Acute intoxication may be manifested by anorexia, vomiting and central nervous system stimulation (including convulsions), followed by megaloblastic anemia, leukopenia, thrombocytopenia, glossitis and crystalluria. In acute intoxication, emesis and gastric lavage followed by purges may be of benefit. The patient should be adequately hydrated to prevent renal damage. The renal and hematopoietic systems should be monitored for at least 1 month

FANSIDAR® (sulfadoxine and pyrimethamine)

after an overdosage. If the patient is having convulsions, the use of a parenteral barbiturate is indicated. For depressed platelet or white blood cell counts, folinic acid (leucovorin) should be administered in a dosage of 5 mg to 15 mg intramuscularly daily for 3 days or longer.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE)

(a) *Treatment of Acute Attack of Malaria*

A single dose of the following number of Fansidar Tablets is used in sequence with quinine or alone:

Adults	2 to 3 tablets
9 to 14 years	2 tablets
4 to 8 years	1 tablet
Under 4 years	½ tablet

(b) *Malaria Prophylaxis*

The first dose of Fansidar should be taken 1 or 2 days before departure to an endemic area; administration should be continued during the stay and for 4 to 6 weeks after return.

	Once Weekly	Once Every 2 Weeks
Adults	1 tablet	2 tablets
9 to 14 years	¾ tablet	1½ tablets
4 to 8 years	½ tablet	1 tablet
Under 4 years	¼ tablet	½ tablet

HOW SUPPLIED

Scored tablets, containing 500 mg sulfadoxine and 25 mg pyrimethamine — unit dose packages of 25. (NDC-0004-0161-03). Imprint on tablets: FANSIDAR ((ROCHE LOGO)) ROCHE.

℞ only

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Roche Laboratories Inc.
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