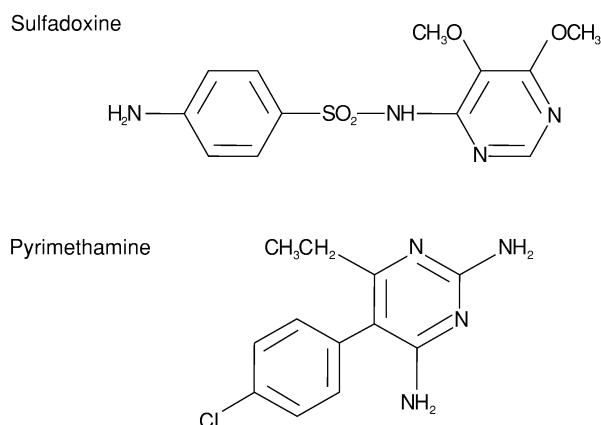


NAME OF THE DRUG

FANSIDAR[®]

(sulfadoxine and pyrimethamine)



CAS sulfadoxine 2447-57-6

CAS pyrimethamine 58-14-0

FANSIDAR contains the active ingredients sulfadoxine and pyrimethamine. The chemical name for sulfadoxine is N¹-(5,6-dimethoxy-4-pyrimidinyl)-sulfanilamide. It has an empirical formula of C₁₂H₁₄N₄O₄S and a molecular weight of 310.34. The chemical name for pyrimethamine is 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine. It has an empirical formula of C₁₂H₁₃ClN₄ and a molecular weight of 248.72.

DESCRIPTION

FANSIDAR is available as cross scored tablets containing 500 mg sulfadoxine and 25 mg pyrimethamine with the excipients maize starch, lactose, gelatin, talc, and magnesium stearate.

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 folic acid in the parasites. With FANSIDAR the risk of resistance development is reduced by this means. FANSIDAR acts on the asexual intraerythrocytic forms of the human malarial parasites.

FANSIDAR is effective against strains of *Plasmodium falciparum* resistant to chloroquine. However, *P. falciparum* resistant to both chloroquine and FANSIDAR have been reported with increasing frequency in parts of South East Asia and South America and East and Central Africa. Therefore, FANSIDAR should be used with caution in these areas.

FANSIDAR attacks the different development stages of the parasite. It is long-acting, and effective concentrations are obtained with a single dose. Trophozoites and schizonts are rapidly eliminated from the blood.

The pre-erythrocytic stages are also affected, and the gametocytes are rendered noninfective in the mosquito. The protective effect of a single dose lasts for approximately four weeks.

Pharmacokinetics

Absorption

After oral administration of a single tablet containing 500 mg of sulfadoxine and 25 mg of pyrimethamine the following pharmacokinetic parameters were reported. Peak plasma levels of sulfadoxine ranging from 51 -76 mg/L are reached in approximately 4 hours (range 1.5 to 8 hours). Sulfadoxine has a half-life of approximately 200 hours (range 100 – 250 hours). Peak plasma levels of pyrimethamine ranging from 0.13 to 0.4 mg/L are achieved within 2.1 – 7.7 hours and it has a plasma half-life of approximately 100 hours (range 54 to 148 hours).

Distribution

The volume of distribution for sulfadoxine and pyrimethamine is 0.14 L/kg (range 0.12 – 0.18 L/kg) and 3 L/kg (range 2.3 – 3.69 L/kg), respectively.

Patients taking 1 tablet a week (recommended adult dose for malaria prophylaxis) can be expected to have mean steady state plasma concentrations of about 98 mg/L for sulfadoxine after about seven weeks and about 0.15 mg/L for pyrimethamine after about four weeks.

Plasma protein binding is about 90% for both sulfadoxine and pyrimethamine.

Both sulfadoxine and pyrimethamine cross the placental barrier and pass into breast milk.

Metabolism

Approximately 5% of the sulfadoxine in plasma is present in N-acetylated form and 2 to 3% in the glucuronide form, leaving 92 to 93% as unchanged sulfadoxine.

However, in urine approximately 60% is present as the acetyl derivative and 10% as the glucuronide. Pyrimethamine is concentrated in kidneys, lungs, liver and spleen and is excreted as metabolites and intact drug.

Elimination

A relatively long elimination half-life is characteristic of both components. Both sulfadoxine and pyrimethamine are eliminated mainly by the kidneys.

INDICATIONS

FANSIDAR is indicated for the treatment and short-term prophylaxis of chloroquine-resistant *P. falciparum* malaria.

CONTRAINDICATIONS

FANSIDAR should not be used in premature or newborn infants in the first two months of life because of the immaturity of their enzyme systems.

FANSIDAR is contraindicated in patients who are hypersensitive to sulfonamides, pyrimethamine, or the combination, or any other ingredient in FANSIDAR. Pyrimethamine is also contraindicated in patients with documented megaloblastic anaemia due to folate deficiency.

If skin reactions are observed, the drug must be withdrawn **immediately**, as these may be indicative of a life-threatening reaction to the drug.

Prophylactic use of FANSIDAR is also contraindicated in patients with renal or hepatic failure, or with blood dyscrasias.

PRECAUTIONS

Long-acting sulfonamides have been reported to cause erythema multiforme. FANSIDAR contains sulfadoxine, a long-acting sulfonamide.

Patients should be advised that sore throat, fever, cough, dyspnoea or purpura may be the first signs of serious side effects. The intake of FANSIDAR must be stopped **immediately** at the first signs of skin eruptions, a significant decrease of blood cells, or a bacterial or fungal superinfection.

Because of the long half-lives of sulfadoxine and pyrimethamine the possibility of accumulation should be borne in mind. Care should be exercised in patients with hepatic and particularly renal impairment and dosage adjustments made if necessary. The renal clearance of sulfadoxine varies with pH. A decrease of urinary pH from 7.5 to 5.5 decreased renal clearance by a factor of 2.

Excessive exposure to the sun must be strictly avoided.

Regular blood counts are indicated whenever FANSIDAR is administered for more than three months.

During prolonged administration of high doses, urinalysis and complete blood cell counts (CBCs), including platelet counts, should be performed periodically. Signs of folic acid deficiency can be prevented by administration of folinic acid.

Pyrimethamine has been reported to cause aplastic anaemia if used between courses of antineoplastic agents. This should be borne in mind when using FANSIDAR.

Carcinogenicity

Pyrimethamine was not 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. Long-term carcinogenicity studies have not been conducted with sulfadoxine alone, or with sulfadoxine/pyrimethamine combined.

Mutagenicity/Genotoxicity

Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test in *Salmonella typhimurium*. No genotoxicity studies have been conducted with sulfadoxine alone or with sulfadoxine/pyrimethamine combined.

Effects on Fertility

Fertility of male rats and the ability of male or female rats to mate were not adversely affected at doses of up to 210 mg/kg/day of FANSIDAR. The pregnancy rate of rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at doses of 31.5 mg/kg/day or higher, a dose approximately 30 times the weekly human prophylactic dose or higher. A 3-month gavage study rats showed delayed sperm maturation with 100/5 mg/kg/day of FANSIDAR and 15 mg/kg/day of pyrimethamine alone.

Use in Pregnancy - Category C

FANSIDAR has been shown to be teratogenic in rats when given in weekly doses approximately 12 times weekly human prophylactic dose. A teratology study in rats showed the minimum oral teratogenic dose to be approximately 18/0.9 mg/kg/day sulfadoxine/pyrimethamine. In rabbits, no teratogenic effects were noted at oral doses as high as 400/20 mg/kg/day sulfadoxine/pyrimethamine.

The use of antimalarials in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus. Prophylaxis in high risk situations is also justified.

In pregnant women, limited prophylactic and therapeutic use of FANSIDAR did not indicate a risk of foetal damage. Nevertheless, FANSIDAR should be used in pregnancy only if it is absolutely essential, and only after the expected benefit has been weighed against the potential risk to the foetus.

However, women of child bearing potential who are travelling to areas where malaria is endemic should be advised against becoming pregnant. In addition, they should be advised to practise contraception during treatment with FANSIDAR and for three months after the last dose.

Pyrimethamine may interfere with folic acid metabolism and if pyrimethamine is given during pregnancy, folic acid supplementation may be required. Sulfadoxine may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulfadoxine should therefore be avoided during the last month of pregnancy.

Use in Lactation

Sulfadoxine and pyrimethamine is excreted in breast milk. Sulfonamides may cause jaundice and haemolytic anaemia in the newborn. FANSIDAR should not be given to pregnant women at term or breast feeding mothers. If FANSIDAR administration is considered essential, alternate arrangements should be made for feeding the infant.

Interactions with Other Medicines

The hypoglycaemic effect of some sulfonylureas is enhanced by sulfonamides. Long acting sulfonamides may displace protein bound drugs, such as phenytoin, coumarin derivatives etc., and thus, enhance their toxicity. The urinary excretion of sulfonamides is pH dependent and can significantly influence their plasma half-life. Drugs containing the para-aminobenzoic acid nucleus (e.g. some local anaesthetics) competitively antagonise the effects of sulfonamides.

Pyrimethamine may displace quinine from its protein binding site in the plasma. It can also potentiate the effects of folic acid antagonists e.g. methotrexate.

Concomitant administration of FANSIDAR and trimethoprim or trimethoprim-sulfonamide combinations may intensify the impairment of folic acid metabolism and the related haematological side effects, and should therefore be avoided.

There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with FANSIDAR as compared with the use of FANSIDAR alone.

ADVERSE EFFECTS

At the recommended dose, FANSIDAR is generally very well tolerated. It is however, potentially capable of producing all the adverse effects known for sulfonamides and for pyrimethamine. Skin reactions or gastrointestinal disorders may occasionally occur.

Skin reactions: rash, pruritus, urticaria, photosensitisation and slight hair loss have been observed. These reactions are usually mild and regress spontaneously on withdrawal of the drug. In very rare cases, particularly in hypersensitive patients, severe, possibly life-threatening skin reactions such as erythema multiforme, Stevens-Johnson syndrome and Lyell's syndrome may occur. The drug should be withdrawn immediately if skin reactions are observed.

Hepatic reactions: there have been isolated reports of a transient rise of liver enzymes as well as hepatitis occurring conjointly with administration of FANSIDAR.

Gastrointestinal reactions: feeling of fullness, nausea, infrequently vomiting, diarrhoea, stomatitis. Gastrointestinal disorders appear to be the most commonly reported side effect with the oral formulation.

Haematological changes: in infrequent cases, thrombocytopenia, megaloblastic anaemia and leucopenia have been observed, though these usually have been asymptomatic. In isolated cases they take the form of agranulocytosis or purpura. As a rule, all these changes regress after withdrawal of the drug.

Other side effects: fatigue, headache, dizziness, fever, and polyneuritis may occasionally occur. Pulmonary infiltrates resembling eosinophilic or allergic alveolitis have been reported in isolated instances. If symptoms such as cough or shortness of breath should occur, treatment with FANSIDAR should be discontinued. Isolated cases of serum sickness as well as allergic pericarditis have also been reported.

DOSAGE AND ADMINISTRATION

The tablets should be swallowed whole with plenty of fluid after a meal.

The recommended dose of FANSIDAR is as follows:

a) Curative treatment of uncomplicated malaria with a single dose

	Dose	Corresponds to	
		Sulfadoxine	Pyrimethamine
Adults According to body weight 50–70 kg	2 or 3 tablets	1000-1500 mg	50-75 mg
Children under 4 years	½ tablet	250 mg	12.5 mg
4-8 years	1 tablet	500 mg	25 mg
9-14 years	2 tablets	1000 mg	50 mg

b) Prophylaxis of malaria

FANSIDAR is not routinely recommended for malaria prophylaxis. Prophylaxis with FANSIDAR can only be considered for areas where *P. falciparum* malaria is endemic and sensitive to FANSIDAR, and when alternative drugs are not available or contraindicated. (see CONTRAINDICATIONS).

The malaria risk must be carefully weighed against the risk of serious adverse drug reactions. If FANSIDAR is prescribed for prophylaxis, it is important that the physician inquires about sulfonamide intolerance and points out the risk and the need for immediate drug withdrawal if skin reactions do occur (see PRECAUTIONS).

The dose given below should be taken at one time:

Semi-immune subjects		Sulfadoxine	Pyrimethamine
Once every four weeks			
Adults (according to body weight)	50-70 kg 2 or 3 tablets	= 1000-1500 mg	+50-75 mg
Children under 4 years	½ tablet	= 250 mg	+ 12.5mg
4-8 years	1 tablet	= 500 mg	+25 mg
9-14 years	2 tablets	= 1000 mg	+ 50 mg
Non-immune subjects		Sulfadoxine	Pyrimethamine

Once every two weeks

Adults (according to body weight)	50-70 kg		
	2 tablets*	= 1000 mg	+ 50 mg
Children under 4 years	½ tablet	= 250 mg	+ 12.5 mg
4-8 years	1 tablet	= 500 mg	+25 mg
9-14 years	1½ tablet	= 750 mg	+ 37.5 mg

* When convenient, a dosage of one tablet weekly may be given.

For malaria prophylaxis in travellers, the first dose of FANSIDAR should be taken 1 to 2 weeks before departure for an endemic area; administration should be continued in the above dosage during the stay and also for the first 4 weeks after returning. The malaria risk must be carefully weighed against the risk of serious adverse drug reactions.

FANSIDAR is approved for short term prophylaxis only.

OVERDOSAGE

Possible symptoms include headache, anorexia, nausea, vomiting, skin rashes, pruritus, symptoms of folic acid deficiency, signs of excitation, and haematological changes (megaloblastic anaemia, leucopenia, thrombocytopenia).

Convulsions and respiratory failure may occur. Symptomatic treatment should be instituted as necessary.

Monitoring of hepatic and renal function and repeated blood counts for up to four weeks after overdosage is advised. Haemodialysis may be of use. If hematological changes are found, folinic acid may be administered intramuscularly to treat the folic acid deprivation.

PRESENTATION

FANSIDAR is available as cross scored tablets containing 500 mg sulfadoxine and 25 mg pyrimethamine in packs of 3 tablets.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
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Dee Why NSW 2099

Date of TGA Approval: 24 February 2005

Date of amendment: 17 April 2008