SUMMARY OF PRODUCT CHARACTERISTICS OF FALCIDIN 500:25 MG TABLET

1. Name of the medicinal product

Falcidin 500:25 mg Tablet

2. Qualitative and quantitative composition

Each tablet contains 500 mg of Sulfadoxine and 25 mg of Pyrimethamine.

3. Pharmaceutical form

Uncoated Tablet

White, circular, flat bevellededge tablet, embossed “FALCIDIN ▲” on one side and two breaklines on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Falcidin is indicated for Intermittent Preventive Treatment in pregnant women along with other prevention and control measures of malaria in pregnant women. Intermittent Preventive Treatment in pregnant women with Falcidin is restricted to areas with high or moderate stable transmission level of uncomplicated P. Falciparum malaria.

4.2 Posology and method of administration

Treatment should start at the beginning of the high transmission period and is given in 3-day courses as follows: The 3-day course is repeated after 1 month, for a maximum 4 doses during the high-transmission period.

4.3 Contraindications

- Repeated prophylactic use of Falcidin Tablet is contraindicated in patients with renal or hepatic failure or with blood dyscrasias;
- Hypersensitivity to Pyrimethamine, sulfonamides, or any other ingredient of Falcidin;
- Patients with documented megaloblastic anemia due to folate deficiency;
- Infants less than 2 months of age;
- Prophylactic use of Falcidin in pregnancy at term and during the nursing period.

4.4 Special warnings and precautions for use

WARNINGS

Fatalities associated with the administration of Falcidin have occurred due to severe reactions, including stevens-johnson syndrome and toxic epidermal necrolysis. Falcidin prophylaxis must 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. Falcidin 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

Oral Falcidin has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including hyperparasitemia, pulmonary edema or renal failure. Patients with severe malaria are not candidates for oral therapy. In the event of recrudescent P. falciparum infections after treatment with Falcidin or failure of chemoprophylaxis with Falcidin, patients should be treated with a different blood schizonticide. Falcidin 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 dehydrogenasedeficient 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. Excessive sun exposure should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of these tablets with trimethoprim, or sulfonamide/trimethoprim, or another sulfonamide can increase antifolate effect and haematological side effects, and should be avoided. The risk of hepatic and haematological adverse effects may increase if Sulfadoxine /Pyrimethamine tablets + Amodiaquine dispersible tablets are given with other drugs with hepatic or haematological toxicity.

4.6 Pregnancy and lactation

Teratogenic Effects: Pregnancy Category C.

Falcidin 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, Falcidin 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, and should be advised to practice contraception during prophylaxis with Falcidin and for three months after the last dose.

4.7 Effects on ability to drive and use machines

These tablets are indicated for children aged up to 59 months and effects on driving and use of machines are not relevant. Side effects are not expected to affect attention or reduce co-ordination but care should be taken if the child feels dizzy or balance is affected.

4.8 Undesirable effects

• Nervous system disorders Very common: weakness, headache, dizziness Rare: neuromyopathy

• Gastrointestinal disorders Very common: anorexia, nausea, vomiting, abdominal pain, diarrhoea

• Skin and subcutaneous disorders Slate-grey pigmentation, notably of the fingers and mucous membranes (usually Associated with malaria treatment rather than seasonal chemoprophylaxis) Common: pruritus • General disorders and administration site conditions Common: fever

• Eye disorders Treatment rather than seasonal chemoprophylaxis) which reverses on stopping treatment Very rare: irreversible retinopathy requiring care from eye specialist

• Blood and lymphatic disorders Leucopoenia and neutropenia (agranulocytosis)—but see notes above • Hepato-biliary disorders Severe and sometimes fatal hepatitis but see notes above—development of hepatic Disorders may be delayed Sulfadoxine / Pyrimethamine

• Gastrointestinal reactions Glossitis, stomatitis, nausea, emesis, abdominal pain, diarrhoea, feeling of fullness

• Skin and subcutaneous tissue disorders Photosensensitivity, urticaria, pruritus, exfoliative dermatitis, slight hair loss, Lyell's Syndrome, erythema multiforme, Stevens-Johnson syndrome, generalized skin Eruptions, toxic epidermal necrolysis

• General disorders Fever, chills, periarteritis nodosa and lupus erythematosus phenomenon

• Nervous system disorders Headache, peripheral neuritis, convulsions, ataxia, hallucinations, insomnia, fatigue, muscle weakness, polyneuritis

• Psychiatric disorders Depression, nervousness, apathy

- Blood and lymphatic disorders Agranulocytosis, aplastic anemia, megaloblastic anaemia, thrombocytopenia, Leucopoenia, haemolytic anaemia, purpura, hypoprothrombinaemia, Methaemoglobinaemia, and eosinophilia
- Cardiac disorders Allergic myocarditis/pericarditis
- Ear and labyrinth disorders Tinnitus, vertigo
- Endocrine disorders Sulfadoxine, a sulphonamide is similar to some diuretics (acetazolamide and the thiazides), and sulfonylurea hypoglycaemics. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulphonamide.
- Eye disorders

4.9 Overdose

Amodiaquine Symptoms: headache, dizziness, visual disorders, cardiovascular collapse and convulsions, followed by early respiratory and cardiac arrest. Treatment: the patient should be urgently transferred to a specialized unit for close monitoring and supportive therapy. Sulfadoxine / Pyrimethamine Symptoms: headache, anorexia, nausea, vomiting, agitation, convulsions, haematologic changes (megaloblastic anaemia, leucopoenia, thrombocytopenia), glossitis, crystalluria. Treatment: the patient should be urgently transferred to a specialised unit for close monitoring and supportive therapy including, where appropriate, activated charcoal and fluid administration; a parenteral benzodiazepine, phenytoin or a barbiturate can be given for convulsions,. Liver and renal function should be monitored and blood counts checked repeatedly for up to four weeks after the overdose. Should blood dyscrasia occur, folinic acid (leucovorin) may be used.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Amodiaquine is a synthetic 4-aminoquinoline antimalarial. It has schizonticidal action on Plasmodium falciparum, P. vivax, and P. ovale by destroying intraerythrocytic forms. The mechanism of action of 4-aminoquinoline derivatives like amodiaquine against plasmodium is not yet completely known. It is nonetheless accepted that these derivatives penetrate the infected red blood cells and prevent the parasite from polymerizing haeme into an insoluble product called haemozoin, leading to parasite death. Page 7 of 9 Pyrimethamine is a diaminopyrimidine.

It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizonticide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It has in vitro activity against the four long-established human malaria parasites. There has been rapid emergence of clinical resistance. Sulfadoxine is a sulfonamide. Sulfonamides are competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the enzyme in P. falciparum, which is responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid. Therefore, by acting at a different step in folate synthesis, Sulfadoxine increases the effect of Pyrimethamine. Strains of P. falciparum resistant to 4-aminoquinolines (chloroquine, Amodiaquine) are present in many areas, and their geographical distribution is constantly changing. However, Amodiaquine remains active against some chloroquine-resistant P. falciparum strains. P. falciparum can also become resistant to the effects of Pyrimethamine / Sulfadoxine

5.2 Pharmacokinetic properties

Sulfadoxine / Pyrimethamine

Absorption Following single-dose administration of the Sulfadoxine / Pyrimethamine tablet in healthy volunteers (n = 46), the mean (± SD) Cmax value for Sulfadoxine was 183 ± 18 μg/ml, and the corresponding value for AUC0-72hour was 11037 ± 1142 μg·hour/ml. The median (range) Sulfadoxine tmax value was 5.5 hours (range 4–48 hours).

Distribution The volume of distribution for Pyrimethamine and Sulfadoxine is 2.3 l/kg and 0.14 l/kg, respectively. Plasma protein binding is about 90% for both Pyrimethamine and Sulfadoxine. Both cross the placental barrier and pass into breast milk.

Elimination

Pyrimethamine and Sulfadoxine both have long elimination half-lives: about 100 hours for Pyrimethamine and about 200 hours for Sulfadoxine. Both are eliminated mainly through the kidneys

5.3 Preclinical safety data

Pyrimethamine/Sulfadoxine

Genotoxicity

Pyrimethamine was not found mutagenic in the Ames test.

Carcinogenesis

Pyrimethamine was not found carcinogenic in female mice or in male and female rats. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totaling 200–300 mg.

Reproductive toxicity

Testicular changes have been observed in rats treated with Pyrimethamine/Sulfadoxine 5/100 mg/kg daily 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 Pyrimethamine/Sulfadoxine doses of up to 10/200 mg/kg daily.

6. Pharmaceutical particulars

6.1 List of excipients

Maize starch BP

Microcrystalline cellulose BP

Aerosil BP

Docusate sodium BP

Povidone BP

Sodium starch glycolate BP

Purified talc BP

Stearic acid BP

Sodium lauryl sulphate BP

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a dry place below 30°C. Protect from Light.

6.5 Nature and contents of container

PVC/Alu

6.6 Special precautions for disposal and other handling

No special requirements.

7 Registrant

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8 Manufacturer

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