

The safe & effective
first line antimalarial

Laridox



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Sulphadoxine and pyrimethamine - Laridox

DESCRIPTION

This is a combination of N¹-(5,6-dimethoxypyrimidin-4-yl)-sulphanilamide (sulphadoxine) and 5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diyldiamine (pyrimethamine).

Sulphadoxine is an ultra-long-acting sulphonamide. Pyrimethamine, an aminopyrimidine derivative, is an antimalarial agent that is structurally related to trimethoprim.

COMPOSITION

Laridox-Forte

Each uncoated tablet contains:
Sulphadoxine IP750mg
Pyrimethamine IP ...37.5mg

Laridox

Each uncoated tablet contains:
Sulphadoxine IP500mg
Pyrimethamine IP ...25mg

Laridox Suspension

Each 5ml contains:
Sulphadoxine IP250mg
Pyrimethamine IP ...12.5mg

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sulphadoxine and pyrimethamine combination 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 within the parasites.

Sulphadoxine, like other sulphonamides, is a structural analog of p-aminobenzoic acid (PABA) and competitively inhibits dihydrofolic acid synthesis by inhibiting dihydropteroate synthetase, which is necessary for the conversion of PABA to folic acid.

Pyrimethamine is a folic acid antagonist and has a mechanism of action similar to that of trimethoprim. By binding to and reversibly inhibiting dihydrofolate reductase, pyrimethamine inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid (folic acid). Pyrimethamine interferes with the synthesis of tetrahydrofolic acid in malarial parasites at a point immediately succeeding that where sulphonamides act.

The combination of sulphadoxine and pyrimethamine results in a synergistic action against susceptible plasmodia.

Sulphadoxine and pyrimethamine are blood schizonticidal agents and are active against the asexual erythrocytic forms of susceptible plasmodia

It is effective against certain strains of *Plasmodium falciparum* that are resistant to chloroquine.

The risk of resistance development is reduced by this means. This 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 non-infective in the mosquito. The protective effect of a single dose lasts for approximately four weeks.

PHARMACOKINETICS

Both sulphadoxine and pyrimethamine are well absorbed from the GI tract. Like other sulphonamides, sulphadoxine is widely distributed in the body. Pyrimethamine is distributed mainly to the kidneys, lungs, liver and spleen. Plasma protein binding is about 90% for both pyrimethamine and sulphadoxine. About 5% of sulphadoxine appears in the blood as acetylated metabolite, about 2-3% as the glucuronide. Pyrimethamine is transformed to several metabolites. Both sulphadoxine and the pyrimethamine are excreted mainly by the kidneys. The apparent elimination half life of sulphadoxine 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.

INDICATIONS

The combination is indicated for the treatment of *Plasmodium falciparum* malaria in those patients in whom chloroquine resistance is suspected.

The fixed combination of sulphadoxine and pyrimethamine is no longer recommended for routine prophylaxis.

CONTRAINDICATIONS

The drug is contraindicated in patients with severe renal insufficiency, marked liver parenchymal damage or blood dyscrasias, hypersensitivity to pyrimethamine or sulphonamides, patients with documented megaloblastic anemia due to folate deficiency, infants < 2 months of age, pregnancy at term and during the nursing period.

Treatment must be immediately discontinued upon the appearance of any skin reactions or mucocutaneous signs or symptoms such as pruritus, erythema, rash, urogenital lesions or pharyngitis, and a medical practitioner consulted as these may be indicative of a life-threatening reaction to the drug. The possibility of an adverse drug reaction should be considered in patients developing a rash, jaundice, fever or severe generalized malaise during treatment with sulphadoxine-pyrimethamine.

This combination should not be used in premature or newborn infants in the first two months of life because of the immaturity of their enzyme systems. Pyrimethamine has been reported to cause aplastic anaemia if used between courses of antineoplastic agents. This should be borne in mind when using sulphadoxine-pyrimethamine combination.

WARNINGS

Fatalities associated with the administration of sulphadoxine and pyrimethamine have occurred due to severe reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Discontinue sulphadoxine and pyrimethamine prophylaxis 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.

PRECAUTIONS

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

Excessive exposure to the sun must be strictly avoided.

Administer 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 sulphonamide drugs, in glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. Perform a urinalysis with microscopic examination and renal function test during therapy for patients who have impaired renal function.

Because sulphadoxine and pyrimethamine contains a sulphonamide, the drug shares the toxic potentials of the sulfonamides, and the usual precautions and contraindications to sulphonamide therapy should be observed, including maintenance of an adequate fluid intake to prevent crystalluria.

Patients who develop signs suggestive of sulphonamide or pyrimethamine sensitivity should never receive drugs containing these substances again. These signs include skin rashes, evidence of haemolysis including dark urine and purpura and presumptive signs of bone marrow depression such as sore throat and mouth ulcers.

Effect on ability to drive and use machines - None known

Laboratory test abnormalities

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

Long-acting sulfonamides have been reported to cause erythema multiforme. This combination contains sulphadoxine, a long-acting sulphonamide. Because of the long half lives of sulphadoxine 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. Excessive exposure to the sun must be strictly avoided. Regular blood counts are indicated whenever this combination is administered for more than three months.

Usage in pregnancy and lactation

Sulphadoxine and pyrimethamine therapy is contraindicated during pregnancy at term as there is possibility that use of sulphadoxine plus pyrimethamine may produce kernicterus in the neonate.

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

Sulphadoxine and pyrimethamine therapy is contraindicated in the nursing period because sulphonamides cross the placenta and are excreted in breast milk, which may result in kernicterus.

Usage in paediatrics

Do not give to infants < 2 months of age because of inadequate development of the glucuronide-forming enzyme system.

Patients should be warned to keep sulphadoxine pyrimethamine combination out of the reach of children, since children are extremely susceptible to adverse effects from an overdosage of pyrimethamine and accidental ingestion of pyrimethamine has been fatal in children.

Usage in geriatrics

Although no specific studies have been performed to establish the use of sulphadoxine and pyrimethamine in the elderly, it has been used extensively and the dosage requirements and side-effects appear to be similar to those of younger adults.

Drug interactions

Chloroquine - There have been reports that may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with sulphadoxine and pyrimethamine tablets as compared with the use of the sulphadoxine and pyrimethamine tablets alone.

Quinine - The tablets are compatible with quinine and with antibiotics

Antifolic drugs - Do not use antifolic drugs (e.g. sulfonamides or trimethoprim-sulfamethoxazole combinations, methotrexate, anticonvulsants) while the patient is receiving sulphadoxine and pyrimethamine tablets for antimalarial prophylaxis. It can result in increased impairment of folic acid metabolism which leads to haematological side effects.

Antidiabetic agents - The tablets have not been reported to interfere with antidiabetic agents.

Goitrogens, diuretics, hypoglycemic agents - 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.

PABA - Although the clinical importance is unclear, p-aminobenzoic acid (PABA) reportedly interferes with the action of pyrimethamine and probably should not be used in patients receiving pyrimethamine.

Lorazepam - Mild hepatotoxicity has been reported in some patients receiving pyrimethamine and lorazepam concomitantly.

ADVERSE EFFECTS

Sulphadoxine and pyrimethamine generally is well tolerated.

CNS - Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness, nervousness

GI - Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhoea, pancreatitis

Hematologic - Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia, eosinophilia

Hypersensitivity - 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, allergic myocarditis

Hepatic - Adverse hepatic effects, possibly secondary to sulphonamide hypersensitivity, have been reported in patients receiving sulphadoxine and pyrimethamine. In some patients adverse hepatic effects have been associated with severe cutaneous reactions to the combination. Abnormal liver function tests, jaundice, hepatomegaly, and hepatitis which can be fatal, have been reported with the combination.

Miscellaneous - Pulmonary infiltrates, drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa, LE phenomenon.

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

DOSAGE AND ADMINISTRATION

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

If anorexia or vomiting occur during the therapy, these adverse effects may be minimized by taking the drug with meals.

Instruct the patient to seek medical attention and discontinue prophylactic therapy if sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura, jaundice or glossitis develop.

Laridox/ Laridox Forte tablets

Adults : The combination is recommended as single adult doses of 1500 mg of sulphadoxine drug plus 75 mg pyrimethamine (25 mg of the sulfa component per kg as a single dose). This comprises 3 tablets of Laridox and 2 tablets of Laridox Forte.

Children :

Age	Body Weight	Dosage of Laridox Tablets (Number of tablets)
2 - 11 months	5 - 10 Kg	0.50
1 - 2 years	10.1 - 14 Kg	0.75
3 - 5 years	14.1 - 20 Kg	1.00
6 - 8 years	20.1 - 30 Kg	1.50
9 - 11 years	30.1 - 40 Kg	2.00
12 - 13 years	40.1 - 50 Kg	2.50
14+ years	> 50 Kg	3.00

Laridox Suspension :

Age	Body Weight	Dosage
2 - 11 months	5 - 10 Kg	5.0 ml
1 - 2 years	10.1 - 14 Kg	7.5 ml
3 - 5 years	14.1 - 20 Kg	10 ml
6 - 8 years	20.1 - 30 Kg	15 ml

OVERDOSAGE

Symptoms

Acute intoxication may be manifested by anorexia, vomiting and CNS stimulation (including convulsions), followed by megaloblastic anemia, leukopenia, thrombocytopenia, glossitis and crystalluria.

Treatment

In acute intoxication, emesis and gastric lavage followed by purges may be of benefit. Adequately hydrate the patient to prevent renal damage. Monitor the renal and hematopoietic systems for > 1 month after overdose. If the patient is having convulsions, the use of a parenteral barbiturate is indicated. Administer folic acid (leucovorin) 5 to 15mg IM daily for > 3 days for depressed platelet or white blood cell counts.

Storage

Store in cool dry dark place.

Presentation

Laridox Tablets - 10 x 2's

Laridox Forte - 10 x 2's

Laridox Suspension - 30 x 10ml

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