



ARTIDOX

ANTI - MALARIAL

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Artesunate and Sulphadoxine - Pyrimethamine Tablets

A R T I D O X

DESCRIPTION

Artesunate is an antimalarial agent. It is a water-soluble hemisuccinate derivative of dihydroartemisinin. Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua*, a herb that has traditionally been used in China for the treatment of malaria.

Sulphadoxine-pyrimethamine 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

Each tablet contains:

Artesunate	50 mg
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Each tablet contains:

Sulfadoxine USP	500 mg
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Pyrimethamine USP	25 mg
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CLINICAL PHARMACOLOGY

Artesunate

Artesunate and its active metabolite dihydroartemisinin are potent blood schizonticides, active against the ring stage of the parasite. It is effective against *P. falciparum* resistant to all other antimalarial drugs. It does not have hypnozoiticidal activity. It reduces gametocyte carriage rate.

The functional group responsible for antimalarial activity of artesunate is endoperoxide bond. Release of an active oxygen species from this bond kills the parasite if accumulated in the erythrocytic cells.

It also suppresses the production or activity of antioxidant enzymes in the erythrocytes.

Sulphadoxine-Pyrimethamine

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. They are blood schizonticidal agents and are active against the asexual erythrocytic forms of susceptible plasmodia. 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.

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.

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.

The combination of sulphadoxine and pyrimethamine results in a synergistic action against susceptible plasmodia. The risk of resistance development is reduced by this means. This attacks the different development stages of the parasite.

Rationale for the co-package of artesunate tablets and sulphadoxine pyrimethamine tablets

Artemisinin and its derivatives are at present, the only effective drug against drug resistant malaria. However their use alone may result in development of resistance to these life saving drugs. According to the new WHO malaria treatment guidelines, uncomplicated falciparum malaria must be treated with artemisinin combination therapy (ACT) and not by artemisinin alone or any other monotherapy. Artemisinin when used correctly in combination with other anti-malarial drugs is not only effective in curing malaria, but also the parasite is highly unlikely to become drug resistant.

Artesunate achieve substantial and rapid decreases in parasite load but have a short half life, combination with a longer acting drug such as sulphadoxine- pyrimethamine, which acts on a different target, protects against the emergence of artemisinin resistant parasites and eliminates residual parasites. Combination of artesunate with sulphadoxine pyrimethamine reduces treatment failures, recrudescence, gametocyte carriage and prevents the emergence and spread of drug resistance.

PHARMACOKINETICS

Artesunate

Pharmacokinetic data in humans are sparse, with no data demonstrating the rate or extent of absorption or the systemic distribution of artesunate. The oral formulation is probably hydrolysed completely before entering the systemic circulation. Peak serum levels occur within one hour of an oral dose of artesunate and persist for up to 4 hours. Dihydroartemisinin has a plasma elimination half-life of less than 2 hours, which may slow the development of resistance to artesunate.

Sulphadoxine-Pyrimethamine

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 uncomplicated falciparum malaria in those patients in whom chloroquine resistance is suspected.

CONTRAINDICATIONS

The drug is contraindicated in patients with prior hypersensitivity to artesunate or artemisinin derivatives, pyrimethamine or sulphonamides. The drug is also contraindicated in patients with renal or hepatic impairment or blood dyscrasias, patients with documented megaloblastic anemia due to folate deficiency, infants < 2 months of age, pregnancy 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

Artesunate and sulphadoxine pyrimethamine combination should not be used for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary oedema or renal failure. It is also not indicated for and has not been evaluated in, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*.

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

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.

Administer with caution to patients with possible folate deficiency, including patients with malabsorption syndrome, alcoholism and those receiving other drugs that affect folate levels 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 sulphonamides, 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.

Laboratory test abnormalities

Folic acid deficiency – 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.

Effects on ability to drive and use machines - Driving and use of machinery is not recommended due to possible risk of dizziness and fatigue/asthenia.

Usage in pregnancy and lactation

The combination is contraindicated in pregnancy and lactation.

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 practice contraception during treatment with and for three months after the last dose.

Usage in paediatrics

Do not give this combination to infants < 5 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

Sulphadoxine pyrimethamine combination 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.

Drug interactions

Artesunate

Artesunate has a minimal effect on hepatic cytochrome P450 activity and does not appear to influence the metabolism of mefloquine, a drug likely to be used in combination with artesunate.

Artesunate does not inhibit the formation of carboxy-primaquine, a metabolite of primaquine.

The artemisinins have some capacity to induce the production of the cytochrome enzyme CYP2C19 and perhaps also CYP3A4. It is possible that iso-enzyme induction could alter the therapeutic effects of drugs that are predominantly metabolized by these enzymes.

Prolonged QT interval has been reported in some studies with high dosage of artemisinin derivatives. The cardiac effects of artemisinins are not very important from a clinical point of view, except that caution should be exercised against combinations with other drugs that prolong the QT interval, such as quinine and halofantrine.

Sulphadoxine-Pyrimethamine

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. sulphonamides 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. However, the hypoglycaemic effect of some sulfonylureas is enhanced by sulphonamides.

Local anaesthetics - Drugs containing the para-aminobenzoic acid nucleus (e.g. some local anaesthetics) competitively antagonize the effects of sulphonamides.

Goitrogens, diuretics, hypoglycemic agents - The sulphonamides 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 sulphonamides. 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

Artesunate

Artesunate and other related artemisinin derivatives have been widely used in China, with no reports of any serious adverse reactions.

Possible drug related adverse effects include dizziness, itching, vomiting, abdominal pain, flatulence, headache, bodyache, diarrhoea, tinnitus and increased hair loss, macular rash, reduction in neutrophil counts and convulsions. However, it is likely that many of these effects are disease-related rather than drug-induced.

In healthy volunteers, a reversible reduction in reticulocyte counts was the dose limiting adverse effect of artesunate, occurring with doses of 16.88mg/Kg.

Drug induced fever can occur. Neurotoxicity has been observed in animal studies but not in humans. In view of the uncertainty about toxic effects, caution should be exercised when more than one 3 day treatment is given. Cardiotoxicity has been observed following administration of high doses.

Occasional skin rash and pruritus has been observed with artesunate.

With intravenous artesunate, slight sinus bradycardia and transient first degree atrioventricular block was reported. Slight elevations in hepatic transaminases were also reported, but these were more likely to be related to the disease than to the treatment per se.

Sulphadoxine-Pyrimethamine

Sulphadoxine and pyrimethamine generally is well tolerated. Adverse effects include:

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, renal failure, interstitial nephritis, BUN and serum creatinine elevation.

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.

The recommended dose of artesunate is 4mg/Kg bodyweight once a day for 3 days.

The recommended dose of sulphadoxine-pyrimethamine is single dose of 25mg/Kg of sulphadoxine and 1.25mg/Kg of pyrimethamine.

Since it is not possible to give the exact dosage based on solid formulation, the dosage should be rounded off to the nearest strength of the tablet. Weight should be given precedence over age in paediatric dosing.

Suggested dosage guidelines by World Health Organisation for the co-package as per age group

Age	Artesunate Tablet			Sulphadoxine + Pyrimethamine (500mg/25mg) Tablet		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5 - 11 months	25 mg	25 mg	25 mg	250/12.5(1/2 tablet)	-	-
>1 - 6 years	50 mg	50 mg	50 mg	500/25 (1 tablet)	-	-
>7 - 13 years	100 mg	100 mg	100 mg	1000/50 (2 tablets)	-	-
>13 years	200 mg	200 mg	200 mg	1500/75 (3 tablets)	-	-

For additional information on paediatrics, please refer to Usage in paediatrics.

OVERDOSAGE

Artesunate

No data available for overdosage of artesunate.

Sulphadoxine-Pyrimethamine

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 overdosage. If the patient is having convulsions, the use of a parenteral barbiturate is indicated. Administer folic acid (leucovorin) 5 to 15mg IM daily for \geq 3 days for depressed platelet or white blood cell counts.

Storage

Store at a temperature not exceeding 25⁰ C.

Presentation

Adult pack	10x15's (12 tablets of Artesunate + 3 Tablets of Sulfadoxine & Pyrimethamine)
Adolescence Pack	10x8's (6 tablets of Artesunate + 2 tablets of Sulfadoxine & Pyrimethamine)
Child Pack	10x4's (3 tablets of Artesunate + 1 tablet of Sulfadoxine & Pyrimethamine)

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