1.3.3 PACKAGE LEAFLET

Enclosed

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Artesunate & Amodiaquine Tablets

DESCRIPTION

Artesunate is an antimalarial agent. It is a water-soluble hemisuccinate derivative of artemisinin. Artemisinin is a sesquiterpene lactone isolated from Artemisia annua, a herb that has traditionally been used in China for the treatment of malaria. Artesunate and its active metabolite dihydroartemisinin are potent blood schizonticides, active against the ring stage of the parasite. It is also active against chloroquine and mefloquine resistant strains of *P. falciparum*.
Amodiaquine is a 4-aminoquinoline antimalarial with a similar mode of action to chloroquine.

COMPOSITION

Artesunate & Amodiaquine Tablets (25mg/67.5mg)
Each bilayer tablet contains:
Artesunate Ph. Int.....25 mg
Amodiaquine Hydrochloride USP
equivalent to Amodiaquine Base..... 67.5 mg
Artesunate & Amodiaquine Tablets (50mg/135mg)
Each bilayer tablet contains:
Artesunate Ph. Int.....50 mg
Amodiaquine Hydrochloride USP
equivalent to Amodiaquine Base.....135 mg
Artesunate & Amodiaquine Tablets (100mg/270mg)
Each bilayer tablet contains:
Artesunate Ph. Int.....100 mg
Amodiaquine Hydrochloride USP
equivalent to Amodiaquine Base.....270 mg

PHARMACOLOGY

Artesunate

Artesunate is a potent blood schizonticide agent for *P. falciparum*. It is also effective for other types of malarial parasites like *P. vivax*. Artesunate binds tightly to parasitized erythrocyte membranes. 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, causing lysis of the parasitic cell due to the highly reactive free oxygen radicals. It reduces gametocyte carriage rate.

Amodiaquine

Amodiaquine is an antimalarial with schizonticidal activity. It is effective against the erythrocytic stages of all 4 species of plasmodium like *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. It is as effective as chloroquine against chloroquine-sensitive strains of *P. falciparum* and is also effective against some chloroquine-resistant strains. Amodiaquine accumulates in the lysosomes and brings about loss of function. The parasite is unable to digest haemoglobin on which it depends for its energy.
In general, 4-aminoquinoline derivatives appear to bind to nucleoproteins and inhibit DNA and RNA polymerase. High drug concentrations are found in the malaria parasite's digestive vacuoles.

Rationale for the fixed dose combination of artesunate and amodiaquine

Artemisinin and its derivatives are at present, the only effective drugs 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 is a fast acting drug with a short half-life. Amodiaquine acts slowly and has a longer half-life. Artesunate rapidly reduces parasite biomass and quickly resolves clinical symptoms, whilst the long-acting activity of amodiaquine is thought to prevent recrudescence. This dual effect also appears to reduce the selective pressure on the parasite to develop resistance. Being a fixed dose combination, it also reduces the number of tablets required and thus improves patient compliance.

PHARMACOKINETICS

Artesunate

Pharmacokinetic data for artesunate in humans are sparse, with no data demonstrating the rate or extent of absorption or the systemic distribution of artesunate. Artesunate is rapidly and completely hydrolysed to the active metabolite dihydroartemisinin 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.

Amodiaquine

Amodiaquine hydrochloride is readily absorbed from gastrointestinal tract. Amodiaquine is rapidly converted in the liver to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine is being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more. About 5% of the total administered dose is recovered in urine while the rest is metabolised in the body. Amodiaquine and desethylamodiaquine have been detected in the urine several months after administration.

INDICATIONS

Artesunate - amodiaquine fixed dose combination is indicated in the treatment of acute uncomplicated infection of malaria caused by *Plasmodium falciparum*.

CONTRAINDICATIONS

Artesunate - amodiaquine fixed dose combination is contraindicated in patients with known hypersensitivity to artesunate or artemisinin derivatives and amodiaquine or 4-aminoquinolines. Due to amodiaquine component, artesunate-amodiaquine combination is also contraindicated in patients with hepatic disorders.

PRECAUTIONS

The combination has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including pulmonary oedema or renal failure.
Safety and efficacy of the combination in patients with severe hepatic and renal impairment has not been evaluated.
Amodiaquine is no longer recommended for chemoprophylaxis of falciparum malaria because its use is associated with hepatic toxicity and agranulocytosis. Severe neutropenia can occur. Large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions and involuntary movements.
Amodiaquine may cause blood dyscrasias, hepatitis, peripheral neuropathy and haemolytic anaemia. If long term therapy is given, regular ophthalmic examination is recommended.
Because amodiaquine may concentrate in the liver, the drug should be used with caution in patients with alcoholism and in patients receiving hepatotoxic drugs.
Since hemolysis and acute renal failure has been reported to occur in a few patients with glucose 6-phosphate dehydrogenase deficiency receiving chloroquine, this should also be considered when using amodiaquine.
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
There are no safety data available on use of artemisinin derivatives during pregnancy and lactation. However, as per information, available from World Health Organisation, artemisinin and its derivatives including artesunate should not be used during the first trimester of pregnancy. Although no data are available for amodiaquine, chloroquine, a structurally similar 4-aminoquinoline with the same spectrum of activity and similar adverse reaction profile is known to cross the placental barrier. Hence, risk benefit ratio should be considered before administering artesunate - amodiaquine fixed dose combination in second and third trimester of pregnancy.
Artemisinin and its derivatives have not been measured in the milk of nursing mothers. It is very likely that these are present in milk and nursing mothers should not be given artemisinin if they are suffering from uncomplicated malaria either in multidrug resistance or drug sensitive situations. If the nursing mother is suffering from complicated and serious malaria induced by multidrug-resistant *P. falciparum* and artemisinin is indicated, breast feeding should be stopped.
Usage in paediatrics
Artemisinin derivatives are to be given to children over 6 months of age.

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Amodiaquine is to be given to children weighing more than 5kg. Hence the combination is indicated for children over 6 months of age and above 5kg body weight.

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.

Amodiaquine

The incidence of agranulocytosis is higher when amodiaquine is combined with other antimalarials. Idiosyncratic drug induced involuntary movements have occurred when amodiaquine is combined with chloroquine.

Since magnesium trisilicate and kaolin are known to decrease the gastrointestinal absorption of chloroquine when administered simultaneously, it is likely that this also follows for amodiaquine.

Concomitant administration of chloroquine at recommended doses for malaria chemoprophylaxis during pre-exposure prophylaxis of rabies with intradermally administered rabies vaccine may interfere with the antibody response to the vaccine. However, the clinical significance of this interaction remains to be clearly established but should be considered and may have relevance in the case of amodiaquine.

ADVERSE EFFECTS

Artesunate

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

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

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.

Occasional skin rash and pruritus has been observed with artesunate.

Amodiaquine

Agranulocytosis and other blood dyscrasias, hepatitis and peripheral neuropathy have been reported occasionally after amodiaquine usage alone. Administration of quinoline type drugs has been associated with hemolytic anaemia.

In therapeutic doses used for malaria. amodiaquine may occasionally cause nausea, vomiting, diarrhoea, vertigo and lethargy. Abdominal pain, headache and photosensitivity have been reported with amodiaquine. When given for long periods, it sometimes causes corneal deposits, visual disturbances and bluish - grey pigmentation of the finger nails, skin and hard palate. These reactions clear somewhat slowly, on stopping treatment. However, because of the occasional development of irreversible retinopathy, regular ophthalmic examinations should be carried out if the drug is used over a long period. The drug can also cause irregular heart beats and tremors.

Prophylactic use of amodiaquine is associated with an unacceptably high incidence of serious toxicity. Approximately 1 in 2000 patients develop agranulocytosis. Serious hepatotoxicity has also been reported. Minor adverse effects are similar to those of chloroquine, although pruritus is less of a problem.

DOSAGE AND ADMINISTRATION

The total recommended treatment is 4mg/kg bodyweight of artesunate and 10mg/kg bodyweight of amodiaquine given once a day for 3 days.

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.

Weight range (approx. Age range)	Strength of ASAQ Tablets	Day 1	Day 2	Day 3
≥ 4.5 to < 9kg (2-11 months)	25mg + 67.5mg	1 tablet	1 tablet	1 tablet
≥ 9 to < 18kg (1-5 years)	50mg + 135mg	1 tablet	1 tablet	1 tablet
≥ 18 to < 36kg (6-13 years)	100mg + 270mg	1 tablet	1 tablet	1 tablet
≥ 36kg (14 years & above)	100mg + 270mg	2 tablets	2 tablets	2 tablets
ASAQ - Artesunate & Amodiaquine				

OVERDOSAGE

No data is available for overdosage of artesunate.

It is mainly pertaining to amodiaquine in the artesunate - amodiaquine combination.

Intoxication with amodiaquine is far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions and involuntary movements.

The usual signs and symptoms of an overdose are headache, vertigo and vomiting; the more severe manifestations including cardiac arrhythmias, convulsions and coma. The most dramatic feature is visual disturbance, including sudden loss of vision, which is usually transitory.

Other symptoms include itching, cardiovascular abnormalities, dyskinesia, neuromuscular and haematological disorders and hearing loss.

Nausea, vomiting, diarrhoea, headache, drowsiness, blurred vision, blindness, convulsions, coma, hypotension, cardiac arrhythmias, cardiac arrest, and impaired respiration are the characteristic features of amodiaquine poisoning.

ECG may show inverted or flattened T waves, widening of QRS, ventricular tachycardia and fibrillation. Hypokalemia may be present.

Treatment of overdosage

Treatment of overdosage is supportive and must be prompt since acute toxicity can progress rapidly, possibly leading to vascular collapse and respiratory and cardiac arrest.

Early endotracheal intubation and mechanical ventilation may be necessary. Early gastric lavage followed by administration of activated charcoal may provide some benefit in reducing absorption of the drug. These should be preceded by measures to correct cardiac and severe cardiovascular disturbances, if present and by respiratory support. Diazepam IV may control seizures and other manifestations of CNS stimulation. Seizures caused by anoxia should be corrected by oxygen and other respiratory support. Defibrillators and cardiac pacemakers may be required.

STORAGE

Store below 30°C

Keep out of reach of children

PRESENTATION

Artesunate & Amodiaquine Tablets (25mg/67.5mg):
Blister of 3 tablets

Artesunate & Amodiaquine Tablets (50mg/135mg):
Blister of 3 tablets

Artesunate & Amodiaquine Tablets (100mg/270mg):
Blister of 3 & 6 tablets

Made in India by

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