

# Crusade against Malaria

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## Amodiaquine Hydrochloride Tablets USP & Artesunate Tablets - Larimal

### DESCRIPTION

Drug - resistant Plasmodium falciparum malaria is a major contributor to the increasing malaria related morbidity and mortality. Combination of conventional antimalarial drugs with artemisinin derivatives is a treatment option for resistant P. falciparum. Amodiaquine-artesunate is a potential combination for inhibiting intensification of drug resistance and for decreasing malaria transmission levels. The combination shows improved treatment efficacy.

### DESCRIPTION

Amodiaquine is a 4-aminoquinoline antimalarial with a similar mode of action to chloroquine.

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. Artesunate is ideal for the treatment of severe malaria, including cerebral malaria. It is also active against chloroquine and mefloquine resistant strains of P. falciparum.

### COMPOSITION

Each tablet contains

|  |         |
|--|---------|
| Artesunate   | 50mg    |
| Amodiaquine hydrochloride USP equivalent to amodiaquine base | 153.1mg |

### CLINICAL PHARMACOLOGY

Amodiaquine is an antimalarial with schizonticidal activity. It is effective against the erythrocytic stages of all 4 species of plasmodium falciparum. It is as effective as chloroquine against chloroquine-sensitive strains of Plasmodium 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.

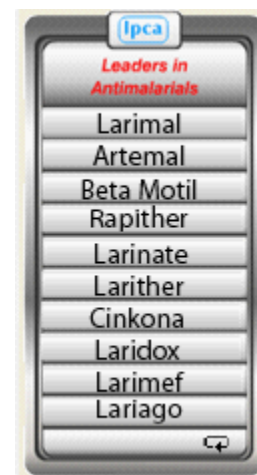
In general, 4-aminoquinoline derivatives appear to bind to nucleoproteins and inhibit DNA and RNA polymerase. High drug concentrations are found in the malaria parasite's digestive vacuoles.

Artesunate is a potent blood schizonticide agent for P. falciparum. 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.

### PHARMACOKINETICS

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.

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 hydrolyzed to the active metabolite dihydroartemisinin. 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.

## **INDICATIONS**

Amodiaquine - artesunate combination kit is indicated in the treatment of uncomplicated cases of malaria caused by *Plasmodium falciparum*.

## **CONTRAINDICATIONS**

Amodiaquine - artesunate combination kit is contraindicated in patients with known hypersensitivity to amodiaquine or 4-aminoquinolines and artesunate or artemisinin derivatives. Because of resistance and risk of major toxicity, amodiaquine is not recommended for the prophylaxis of malaria. Amodiaquine is also contraindicated in patients with hepatic disorders.

## **PRECAUTIONS**

They are mainly pertaining to amodiaquine in the amodiaquine - artesunate combination kit.

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 hepatic disease or 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.

### ***Usage in 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. Caution should be observed when the drug is administered during pregnancy.

Little experience has been gained with the use of artesunate in pregnancy. It should be used with extreme caution in pregnancy during the first trimester.

Therefore, risk benefit ratio should be considered before administering amodiaquine - artesunate combination kit in pregnancy as enough safety data is not available.

### ***Drug interactions***

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.

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.

## ADVERSE EFFECTS

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.

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.

## DOSAGE AND ADMINISTRATION

### Amodiaquine -Artesunate combination kit contains 2 types of co - packaged blister packs:

1. 12 tablets of amodiaquine and 12 tablets of artesunate.
2. 6 tablets of amodiaquine and 6 tablets of artesunate.

### Adults

12 tablets of amodiaquine and 12 tablets of artesunate is the total dose for treating an adult patient of Plasmodium falciparum malaria. This entire dose is to be given in equally divided doses over 3 days. Amodiaquine 2 tablets twice daily and artesunate 2 tablets twice daily are given for 3 days.

| Adult Tablet (Tab) Blister Pack  |                      |                              |
|--|----------------------|------------------------------|
|  | Artesunate<br>(50mg) | Amodiaquine<br>153.1mg(base) |
| <b>Blister Pack content</b><br>(To allow for equal daily divided doses for 3 days) | 12 tabs              | 12 tabs                      |

### Children

For children above 6 months of age and above 5Kg bodyweight, the dosage of artesunate is 4mg/Kg bodyweight and of amodiaquine is 10mg/Kg bodyweight for 3 consecutive days.

## OVERDOSAGE

This is mainly pertaining to amodiaquine in the amodiaquine - artesunate 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.

No data available for overdosage of artesunate.

### Treatment of overdose

Treatment of overdose 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

Keep in a cool, dry, dark place.

### Presentation

Blisters: 1x6+6 & 1x12+12 tablets

Blisters: 10x1x6+6 & 10x1x12+12 tablets.

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