

Crusade against Malaria

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Larither

Prevents Complications, Saves Lives



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Artemether Injection

L A R I T H E R

COMPOSITION

Larither Injection

Each ml contains	Artemether...40mg
Each ml contains	Artemether...80mg

CHEMISTRY

Artemether is a lipid soluble methylether of dihydroartemisinin. Artemisinin is a novel sesquiterpene lactone, extracted from the leaves of the shrub *Artemisia annua* and possesses an endoperoxide bridge which is a rare feature in natural products. The endoperoxide bridge is essential for its antimalarial activity.

Its chemical formula is 3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin. Its molecular formula is $C_{16}H_{26}O_5$ and its molecular weight is 298.4.

CLINICAL PHARMACOLOGY

Artemether is active against all Plasmodia including those which may be resistant to other antimalarials.

Artemether has very rapid schizontocidal activity. The schizontocidal activity of artemether is mainly due to destruction of the asexual erythrocytic forms of *P. falciparum* and *P. vivax*.

Artemether is concentrated in the food vacuole. It then splits its endoperoxide bridge as it interacts with haem, blocking conversion to haemozoin, destroying existing haemozoin and releasing haem and a cluster of free radicals into the parasite. There is inhibition of protein synthesis during growth of trophozoites. There is no cross resistance with chloroquine.

Artemether is not active against hypnozoites. Therefore, an 8- amino-quinoline derivative such as primaquine should be given sequentially after the combination in cases of mixed infections of *P. falciparum* and *P. vivax* to achieve hypnozoites eradication.

Artemether reduces gametocyte carriage. There is no rationale at present for using artemether for chemoprophylaxis.

PHARMACOKINETICS

The drug is slowly absorbed from intramuscular injection. Peak plasma concentrations have been achieved in about 6 hours after intramuscular injection of artemether. Artemether is hydrolyzed after administration to a biologically active metabolite, dihydroartemisinin. Dihydroartemisinin accounts for most or all of clinical antimalarial activity.

Total protein binding is 95.4%. The drug is rapidly and extensively metabolised in the liver.

In animal studies, unchanged artemether has not been detected in both faeces and urine due to its rapid and high first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. The elimination half-life is approximately 1 hour, but following intramuscular administration the elimination phase is prolonged because of continued absorption. The elimination half life of dihydroartemisinin was approximately 2 hours.

Artemether has been reported to clear fever in severe falciparum malaria within 30 – 84 hours.

INDICATIONS

Artemether injection is indicated for treatment of severe and complicated malaria caused by *P. falciparum* both in adults and children in areas where there is multidrug resistance.

CONTRAINDICATIONS

Artemether is contraindicated in patients with hypersensitivity to artemether or other artemisinin compounds

Artemether is not recommended in the first trimester of pregnancy because of limited data.

PRECAUTIONS

1. Do not exceed the prescribed dose. In case of overdosage, urgent symptomatic treatment in a specialized unit is required.

2. Caution is required in patients with Cardiovascular disease , Hepatic impairment , Renal insufficiency.

Usage in pregnancy

As per information available from World Health Organisation, little experience has been gained with the use of this drug in pregnancy but it should not be withheld if it is considered life-saving to the mother.

Artemisinin and its derivatives can be used for treatment of uncomplicated malaria during the second and third trimester of pregnancy in areas of multidrug resistance. Owing to lack of data, use in the first trimester of pregnancy is not recommended.

Artemisinin and its derivatives have not been measured in the milk to 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.

Drug interactions

Since electrocardiographic QT prolongation has been reported in some patients treated with artemether, it is recommended to avoid prescription of medications known to produce a prolongation of QT interval or patients receiving such medication: erythromycin, terfenadine, astemizole, probucol, Class 1a anti-arrhythmic agents (quinidine, procainamide, disopyramide), Class III anti-arrhythmic agents (amiodarone, bretylium), bepridil, sotalol, tricyclic antidepressants, some neuroleptics and phenothiazines are to be monitored closely.

ADVERSE EFFECTS

Artemether has been remarkably well-tolerated, and appears less toxic than quinine or chloroquine; adverse effects include bradycardia, electrocardiogram abnormalities, gastrointestinal disturbances (nausea, abdominal pain, diarrhoea - oral therapy only), dizziness, injection site pain, skin reactions, and fever. Transient decreases in neutrophils and reticulocytes have been reported in some patients treated with artemether.

Drug induced fever has been observed with artemether. Mild reactions were seen in patients to whom artemether had been administered intramuscularly. These included nausea, hypotension, dizziness and tinnitus. These side effects were also reported: dark urine, sweating, somnolence, and jaundice. There were no deaths or any other side effects. No irreversible side effects were seen.

Slight rise of SGOT and SGPT may occur in individual cases. Neurological side effects have not yet been observed in clinical use but clinical trials suggest that coma may be prolonged in patients treated with artemether and there was an increased incidence of convulsions in one trial in cerebral malaria. Transient first degree heart block has been documented in three patients receiving artemether.

Neurotoxicity has been observed in animal studies but not in humans.

Cardiotoxicity has been observed following administration of high doses of Artemether.

DOSAGE AND ADMINISTRATION

Artemether Injection is for intramuscular use only.

The recommended dose is as follows :

3.2 mg/kg by the intramuscular route as a loading dose on the first day, followed by 1.6 mg/kg daily until the patient can take oral therapy to complete a 7-day course. The daily dose can be given as a single injection. In children, the use of a tuberculin syringe is advisable since the injection volume will be small.

OVERDOSAGE

There is no experience with overdosage with artemether. There is no specific antidote known for the artemisinin derivatives.

However, experimental toxicological results obtained with large doses of artemisinin on the cardiovascular system and the CNS should be considered. Overdosage could bring on cardiac irregularities. An ECG should be taken before initiating treatment in cardiac patients. Irregularities in the pulse should be looked for and cardiac monitoring carried out if necessary. The animal results on the CNS suggest that overdose could result in changes in brain stem function. Clinicians treating cases of overdosage should look for changes in gait, loss of balance, or changes in ocular movements and reflexes.

Storage

Store in a cool dry dark place.

Presentation

Larither Injection - 3 x 1ml

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