ARCEVA™

Tablets / Dry Suspension

(Artemether + Lumefantrine)

DESCRIPTION:
ARCEVA™ is a new treatment of malaria. It is the fixed combination of artemether (Methyl-ether derivative of artemisinin) & lumefantrine (Fluorene derivative belonging to aminoalcohol class)

COMPOSITION:

ARCEVA™ 20/120mg Tablets
Each tablet contains:
Artemether Ph. Int.....20mg
Lumefantrine MS.....120mg

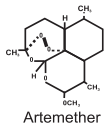
ARCEVA™ 40/240mg Tablets
Each tablet contains:
Artemether Ph. Int.....40mg
Lumefantrine MS.....240mg

ARCEVA™ 80/480mg Tablets
Each tablet contains:
Artemether Ph. Int.....80mg
Lumefantrine MS.....480mg

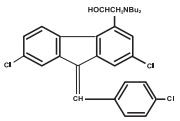
ARCEVA™ Dry Suspension
Each 5ml of reconstituted suspension contains:
Artemether Ph. Int.....15mg
Lumefantrine MS.....90mg

ARCEVA™ - DS Dry Suspension
Each 5ml of reconstituted suspension contains:
Artemether Ph. Int.....30mg
Lumefantrine MS.....180mg

CHEMICAL STRUCTURE:



Artemether



Lumefantrine

PHARMACODYNAMICS:
Artemether / lumefantrine comprises a fixed combination of 1 part of artemether and 6 parts of lumefantrine. Artemether has quick onset of action while lumefantrine has longer duration of action. Both exerts their anti-parasitic action at the blood stage of malarial parasite, where they convert the haem (A toxic metabolite produced during haemoglobin breakdown) to nontoxic haemozoin (Malaria pigment). Lumefantrine interfaces with the polymerization process, while artemether generates reactive metabolites as a result of interaction between its peroxide bridge & haem iron. Both components also have a secondary action involving inhibition of nucleic acid and protein synthesis within the malarial parasite

There is a synergism of independent actions of both artemether and lumefantrine, which has been shown to potentiate the blood schizontocidal effects. It is also effective against drug resistant strains of P. falciparum malaria. Comprehensive in vitro studies using laboratory maintained and fresh field parasite isolates from different malaria endemic areas have shown marked synergic effect of these two components

Results of comparative clinical trials indicate that this artemether and lumefantrine combination also clears gametocytes more rapidly than other conventional antimalarials

PHARMACOKINETICS:
ABSORPTION
Artemether is absorbed quickly with peak plasma concentrations reaching in about 2 hours after dosing, while absorption of lumefantrine is started after a lag-time of up to 2 hours, with peak plasma concentration in about 6-8 hours after dosing. Food enhances the absorption of artemether & lumefantrine. In healthy volunteers the relative bioavailability of lumefantrine increases sixteen fold compared with intake on empty stomach. High fat content is conducive for absorption. Food has also been shown to increase the absorption of lumefantrine in patients with malaria. Usually in acutely ill patients there is a tendency of consuming low fat diet. Absorption of lumefantrine under fasted conditions is very poor. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated

DISTRIBUTION:
Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.9%, respectively). Artemether is well distributed throughout the body with some affinity for the brown fat and adrenal glands, while lumefantrine has an affinity for adipose and glandular tissue and to some extent for the lungs, spleen (Due to slow elimination from lymphoid tissue) and bone marrow

METABOLISM:
Artemether is rapidly and extensively metabolized in human liver microsomes to the biologically active main metabolite dihydroartemisinin (Demethylation), predominantly through the enzyme system CYP3A4. Lumefantrine is also metabolized by CYP3A4 in human liver microsomes, where glucuronidation of lumefantrine takes place directly, after the oxidative biotransformation. However, lumefantrine inhibits the cytochrome enzyme CYP2D6

ELIMINATION:
Artemether is rapidly cleared from plasma with an elimination half-life of about 2 - 3 hours. Lumefantrine is eliminated very slowly with a elimination half-life of 4 - 6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether / lumefantrine. Unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (Unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in animals with excretion primarily in the faeces. After oral dosing in animals qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug

THERAPEUTIC INDICATION:
Artemether / lumefantrine is indicated for the treatment of uncomplicated P. falciparum malaria including multi-drug resistant strains of P. falciparum. Artemether / lumefantrine is also effective against the blood stage of P. vivax but not active against hypnozoites
Artemether / lumefantrine must be used for the malarial infections acquired in areas where the parasites may be resistant to other anti-malarial drugs

"World Health Organization recommends artemether / lumefantrine as a first line treatment for the acute uncomplicated P.falciparum malaria for both multi-drug resistant areas & drug sensitive areas"

DOSAGE & ADMINISTRATION:
Patients with acute malaria are frequently averse to food. The dose may be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine. In the event of vomiting within 1 hour of administration a repeat dose should be taken

6-Dose regimen should be given 3 days at oral treatment 1st dose as the time of initial diagnosis & than at 8, 24, 36, 48 & 60 hours

OR
As directed by the physician

Dosage according to body weight:
ARCEVA™ 20mg/120mg Tablets
5kg to 14kg: 1 B.I.D for 3 days

ARCEVA™ 40mg/240mg Tablets
Adults & over 35kg: 2 B.I.D for 3 days
25kg to 34kg: 1 1/2 B.I.D for 3 days
15kg to 24kg: 1 B.I.D for 3 days

ARCEVA™ 80mg/480mg Tablets
Adults & over 35kg: 1 B.I.D for 3 days

ARCEVA™ Dry Suspension

Once Daily for Three Days							
Strength	Body Weight (Kg)	5 - 7.4	7.5 - 9.9	10 - 12.4	12.5 - 14.9	15 - 17.4	17.5 - 19.9
15/90mg/5ml	Dosage	7ml	10ml	14ml	17ml	20ml	24ml
30/180mg/5ml		3.5ml	5ml	7ml	8.5ml	10ml	12ml

OR
As directed by the physician

SIDE EFFECTS:
Artemether / lumefantrine is well tolerated and there is no drug induced serious unwanted side effects. The most common adverse experiences (> 1%) in patients treated with artemether / lumefantrine combination are abdominal pain, diarrhoea, vomiting, nausea, palpitation, headache, dizziness, arthralgia, cough, myalgia, pruritis, rash, asthenia and fatigue

The predinical investigations and the clinical trial programmes revealed no cardiotoxicity with artemether / lumefantrine combination, and to date there have been no reports of adverse clinical cardiac events. Recent studies comparing artemether / lumefantrine with halofantrine in human showed a clear distinction between the two substances and confirmed no sign of cardiotoxicity with artemether / lumefantrine combination

CONTRAINDICATION:
Artemether / lumefantrine is contraindicated to those patients which have a history of hypersensitivity to artemether / lumefantrine

PRECAUTION:
Pregnancy
There are no adequate data from the use of artemether / lumefantrine in pregnant women. Artemether / lumefantrine treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus
Lactation
Artemether / lumefantrine excretes into breast milk. It should not be taken by breast-feeding women

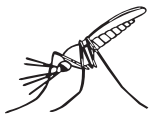
DRUG INTERACTION:
Patients who are taking any drug which inhibits the cytochrome enzyme CYP3A4 (e.g. Erythromycin, ketoconazole, itraconazole, cimetidine, HIV protease inhibitor, etc.)
Patients who are taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. Flecainide, metoprolol, imipramine, amitryptyline, clomipramine etc.)

DIRECTION FOR RECONSTITUTION:
ARCEVA™ 15/90mg Dry Suspension (30ml)
Shake bottle to loosen the mass. Add one time completely filled provided measuring cup (28ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension

ARCEVA™ 15/90mg Dry Suspension (60ml)
Shake bottle to loosen the mass. Add one time completely filled provided measuring cup (54ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension

ARCEVA™ - DS 30/180mg Dry Suspension (30ml)
Shake bottle to loosen the mass. Add one time completely filled provided measuring cup (24ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension

STABILITY:
See expiry on the pack



PRESENTATION:
ARCEVA™ 20/120 Tablets in pack of 16's
ARCEVA™ 40/240 Tablets in pack of 8's
ARCEVA™ 80/480 Tablets in pack of 6's
ARCEVA™ Dry Supension in pack of 30ml and 60ml
ARCEVA™ -DS Dry Supension in pack of 30ml

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine
The reconstituted suspension should be used within 7 days

آرسیوا™

ٹیبلٹ / سسپینشن

(آرٹیمیتھر+لومیفینٹرائن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

ہدایات: بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

تیار شدہ سسپینشن کو سات یوم کے اندر استعمال کرلیں

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

P001744/S R.N-04/HA/06/15

220 mm

71 mm

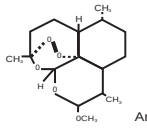
ARCEVA™
(Artemether)

80mg/ml Injection

DESCRIPTION:
Artemether is a lipid soluble methyl ether 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

Artemether 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

CHEMICAL STRUCTURE:



Artemether

COMPOSITION:
ARCEVA™ 80mg/ml Injection
Each ml contains:
Artemether Ph. Int.....80mg

PHARMACOKINETICS:
The drug is slowly absorbed from intramuscular injection. Peak plasma concentrations achieve in about 6 hours after intramascular 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. 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 is approximately 2 hours

INDICATIONS:
Artemether injection is used in the treatment of severe and complicated malaria caused by P. falciparum both in adults and children, in areas where there is multidrug resistance including the chloroquine resistant subtertian malaria. Treatment of uncomplicated malaria in situations where there is widespread prevalence of multi-drug resistant P. falciparum infection

DOSAGE AND ADMINISTRATION:
Artemether injection is for intramuscular use only. The recommended dose is as follows:
3.2mg/kg as a loading dose by intramuscular injection, followed by 1.6mg/kg daily until the patient is able to tolerate oral medication or for a maximum of 7 days

OR
As directed by the physician

DOSAGE IN HEPATIC & RENAL IMPAIRMENT:
No special precautions or dosage adjustments are considered in mild to moderate hepatic or renal impairment. Moreover the side effect profile did not differ in patients with or without hepatic impairment. Most patients with acute malaria present with some degree of relative hepatic impairment

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

SIDE EFFECTS:
Artemether has been remarkably well-tolerated, and appears less toxic than quinine or chloroquine; adverse effects include bradycardia, electrocardiogram abnormalities, 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

DRUG INTERACTION:
Patients who are taking any drug which inhibits the cytochrome enzyme CYP3A4 (e.g. erythromycin, ketoconazole, itraconazole, cimetidine, HIV protease inhibitor etc.). Patients who are taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitryptyline, clomipramine etc.)

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

Pregnancy: Artemether is not recommended in the first trimester of pregnancy because of limited data. Treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus

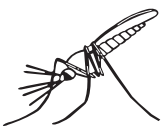
PRECAUTIONS:
Lactation: Artemether excretes into breast milk. It should not be taken by breastfeeding women

STABILITY:
See expiry on the pack

AVAILABILITY:
ARCEVA™ 80mg/ml injection in a pack of 5's

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and freezing
Store between 15 to 30°C
Improper storage may deteriorate the medicine

Injection should not be used if container is leaking, solution is coudly or it contains undissolved particle(s)



آرسیوا ۸۰ ملی گرام ملی لیٹر انجکشن
(آرٹیمیتھر)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی
انجکشن کے لیک ہونے، دھندلا ہونے یا اس میں
کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

R.N-03/HA/03/18

210mm

120mm