Artheget™

آرتھیگیٹ

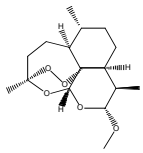
(Artemether + Lumefantrine)

20mg+120mg, 40mg+240mg, 80mg+480mg, 15mg+90mg/5mL Tablets, DS Tablets, EZ Tablets, Powder for Oral Suspension

DESCRIPTION

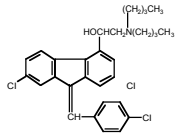
ARTHEGET is a fixed dose artemisinin-based combination therapy (ACT) combining artemether, an artemisinin derivative, and lumefantrine, a synthetic antimalarial drug.

Artemether, a sesquiterpene lactone derivative of naturally occurring substance, artemisinin. Chemically it 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. The molecular formula is $C_{16}H_{26}O_5$ and the structural formula is:



Artemether

Lumefantrine is a synthetic aryl-amino alcohol antimalarial (1R-S)-2-Dibutylamino-1-{2,7-dichloro-9-[(Z)(4-cholorobenzylidene)-9H-fluoren-4-yl}-ethanol. The molecular formula is $C_{30}H_{32}Cl_3NO$ and the structural formula is:



Lumefantrine

QUALITATIVE & QUANTITATIVE COMPOSITION

ARTHEGET (Artemether+Lumefantrine) is available for oral administration as:

ARTHEGET Tablets 20mg+120mg
Each tablet contains:
Artemether…20mg
Lumefantrine…120mg

ARTHEGET-DS Tablets 40mg+240mg
Each tablet contains:
Artemether…40mg
Lumefantrine…240mg

ARTHEGET-EZ Tablets 80mg+480mg
Each tablet contains:
Artemether…80mg
Lumefantrine…480mg

ARTHEGET Powder for Oral Suspension 15mg+90mg/5mL
Each 5mL contains:
Artemether...15mg
Lumefantrine...90mg

CLINICAL PHARMACOLOGY

Mechanism of Action

The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during hemoglobin breakdown, to the nontoxic hemozoin, malarial pigment. Lumefantrine is thought to interfere with the polymerization process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both Artemether and Lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis within the malarial parasite. The antimalarial activity of the combination of lumefantrine and artemether is greater than that of either substance alone.

Pharmacokinetics

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reaching about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. Food enhances the absorption of both Artemether+Lumefantrine. In order to improve bioavailability patients should be encouraged to take the drug with food.

Distribution

Artemether and Lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). The artemisinin metabolite dihydroartemisinin is also bound to human serum proteins (47% - 76%).

Metabolism

Artemether is rapidly and extensively metabolized (substantial first pass metabolism) by human liver microsomal enzyme mainly by CYP3A4/5 to the biologically active metabolite dihydroartemisinin. Lumefantrine is N-butylated, mainly by CYP3A4 in human liver microsomes.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy person and 4-6 days in patients with falciparum malaria.

THERAPEUTIC INDICATIONS

ARTHEGET (Artemether+Lumefantrine) is indicated for the treatment of uncomplicated infections with plasmodium falciparum, including multi-drug resistant strains in adult, children and infants of 5kg and above.

DOSAGE AND ADMINISTRATION

ARTHEGET (Artemether+Lumefantrine) should be taken with food or milk.

Artheget Tablets 20mg+120mg

Body Weight (Kg)	Each at 0 Hrs (Initial diagnosis), 8 Hrs, 24 Hrs, 36 Hrs, 48 Hrs, 60 Hrs
< 5	Not recommended at this time
5-14	1 Tablet
15-24	2 Tablets
25-34	3 Tablets
> 34	4 Tablets

Artheget-DS Tablets 40mg+240mg

Body Weight (Kg)	Each at 0 Hrs (Initial diagnosis), 8 Hrs, 24 Hrs 36 Hrs, 48 Hrs, 60 Hrs
15-24	1 Tablet
25-34	1.5 Tablets
> 34	2 Tablets

Artheget-EZ Tablets 80mg+480mg

Body Weight (Kg)	Each at 0 Hrs, (Initial diagnosis) 8 Hrs, 24 Hrs, 36 Hrs, 48 Hrs, 60 Hrs
> 34	1 Tablet

Artheget Powder for Oral Suspension 15mg+90mg/5mL

Body Weight (Kg)	Number of milliliters		
	1st Day	2nd Day	3rd Day
5	7	7	7
7.5	10	10	10
10	14	14	14
15	20	20	20

Patients who vomit within 1 hour of taking the medication should repeat the dose.

ADVERSE REACTIONS
Artemether+Lumefantrine is generally well tolerated. Many of the adverse experiences are due to the disease rather than to drug itself.

Very Common: Palpitations, headache, dizziness, abdominal pain, anorexia, vomiting, nausea, arthralgia, mylagia, asthenia, fatigue and sleep disorders.

Common: Amnesia, paraesthesia, diarrhea, pruritus, rash, cough, electrocardiogram QT prolongation, gait disturbances and insomia.

Uncommon: Liver function test increased, clonus, hypoesthesia and ataxia and somnolence.

Rare: Hypersensitivity.

CONTRAINDICATIONS
Artemether+Lumefantrine combination is contraindicated in:
- Patients with known hypersensitivity to the active substances or to any of the excipients.
- Patients who are taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g., flecainide, metoprolol, imipramine, amitryptyline, clomipramine).
- Patients with a family history of sudden death or congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval and those drugs which are known to prolong the QTc interval (e.g., antiarrhythmics of classes IA and III, narcoleptics, antidepressive agents, macrolides, fluoroquinolones, imidazole and triazole antifungal agents, non-sedating antihistamines like terfenadine, astemizole and cisapride).
- Patients with a history of symptomatic cardiac arythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- In patients previously treated with halofantrine, Artemether + Lumefantrine should not be administered earlier than one month after the last halofantrine dose.

Artemether+Lumefantrine tablets are not indicated for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary edema 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*.
Artemether+Lumefantrine combination tablets are contraindicated during the first trimester of pregnancy. However, it should not be withheld in life-threatening situations, where no other effective anti-malarials are available.
Women taking Artemether+Lumefantrine combination tablets should not breast-feed during their treatment.

PRECAUTIONS
- Due to limited data on safety and efficacy, Artemether+Lumefantrine should not be given concurrently with any other anti-malarial agent unless there is no other treatment option.
- Caution is advised when administering Artemether + Lumefantrine tablets to patients with severe renal, hepatic or cardiac problems. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.
- Caution is recommended when combining Artemether + Lumefantrine tablets with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered.
- If quinine is given after Artemether + Lumefantrine tablets then close monitoring of ECG is advised, while if Artemether + lumefantrine tablets are given after mefloquinine, then close monitoring of food intake is required.
- Patients receiving Artemether+Lumefantrine combination should be warned that dizziness or fatigue/asthenia might occur in which they should not drive or use machines.
- Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.
- The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether+Lumefantrine combination.
- Like other antimalarials (e.g., halofantrine, quinine and quinidine) Artemether+Lumefantrine combination has the potential to cause QT prolongation.

DRUG INTERACTIONS
Interaction with other antimalarials
Mefloquine
Pre-treatment with mefloquine has no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine:
Infusion of quinine alone caused a transient prolongation of the QTc interval, which was consistent with its known cardiotoxicity. Thus, prior administration of Artemether+Lumefantrine combination appears to enhance the inherent risk of QTc prolongation from IV quinine.

Interaction with CYP450 3A4 inhibitors (Ketoconazole):
The concurrent oral administration of ketoconazole with Artemether+Lumefantrine combination led to a modest increase ($\leq$ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy subjects. Dose adjustment of Artemether + Lumefantrine is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Halofantrine:
In vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine. In patients previously treated with halofantrine, Artemether+Lumefantrine combination should be dosed at least one month after the last halofantrine dose.

Pregnancy:
During the second and third trimester, treatment with Artemether+Lumefantrine combination tablets should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Nursing mothers:
Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of artemether and lumefantrine combination unless potential benefits to the mother and child outweigh the risks of artemether + lumefantrine combination treatment.

OVERDOSAGE
In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

STORAGE
Store at 25°C (Excursions permitted between 15°C-30°C). Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
ARTHEGET (Artemether+Lumefantrine) Tablets 20mg+120mg are available in blister packs of 16's.

ARTHEGET-DS (Artemether+Lumefantrine) Tablets 40mg+240mg are available in blister pack of 8's.

ARTHEGET-EZ (Artemether+Lumefantrine) Tablets 80mg+480mg are available in blister pack of 6's.

ARTHEGET (Artemether+Lumefantrine) Powder for Oral Suspension 15mg+90mg/5mL is available in 30mL bottle.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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