V-Artem

Artemether + Lumefantrine Tablets

COMPOSITION:
Each uncoated tablet contains:

Artemether	20 mg
Lumefantrine	120 mg
Excipients	qs

Artemether is a semi-synthetic chiral derivative of artemisinin acetal, a bicyclic sesquiterpene brass endoperoxide isolated from the plant Artemisia annua.
Lumefantrine is a racemic mixture of a synthetic fluorene derivative.

INDICATIONS: V-Artem is a fixed combination of Artemether and Lumefantrine that acts as a blood schizonticide.

Suitable For: Treatment, including emergency treatment of adults, children and infants with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum. Since V-Artem is effective against both drug-susceptible and drug-resistant P. falciparum, it is also recommended for malaria infections in areas where parasites may be resistant to other antimalarial agents.

Emergency Treatment (Standby): Many travelers and business travelers, considered non-immune, can obtain immediate medical attention if malaria is suspected. However, a minority at risk of infection may not be able to obtain such care within 24 hours of the onset of symptoms, especially if they are in an isolated location and far from medical services. In these cases, prescribers are advised to prescribe V-Artem to the traveler to wean off self-medication ("emergency standby treatment"). It is important to educate travelers regarding the appropriate dosage of antimalarial agents.

DOSAGE AND ADMINISTRATION: Tablets for oral administration.
The dose should be administered with food or drinks containing fat, such as milk. Patients with acute malaria often manifest aversion to food. Patients should be encouraged to resume normal eating once they can tolerate food, as it improves the absorption of Artemether and Lumefantrine. In case of vomiting during the first hour after administration, the additional dose should be taken.

Treatment and emergency (stand-by) treatment: Treatment should be administered at initial diagnosis or at the onset of symptoms. A standard 3-day treatment plan is recommended for a total of 6 doses, as shown below.

BODY WEIGHT	DAY 1	DAY 2	DAY 3
5 a < 15 kg	2 x 1 Tablet	2 x 1 Tablet	2 x 1 Tablet
15 a < 25 kg	2 x 2 Tablets	2 x 2 Tablets	2 x 2 Tablets
25 a < 35 kg	2 x 3 Tablets	2 x 3 Tablets	2 x 3 Tablets
Adults to Children 35 kg more	2 x 4 Tablets	2 x 4 Tablets	2 x 4 Tablets

Dosage in the elderly: Although no studies have been performed in the elderly, there are no evaluations of the dosage of products or services in these patients. Dosage in patients with mild to moderate renal or hepatic impairment. However, there has been no evidence of significant renal excretion of Artemether and Lumefantrine, DHA in human studies, therefore any dosage adjustment for the use of V-Artem should be made with renal impairment. No dosage adjustments are recommended for patients with hepatic impairment (for patients with severe renal and/or hepatic impairment see section 4.2).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Most patients with maize malaria have some degree of hepatic impairment. The adverse effect profile did not differ in patients without hepatic impairment. Furthermore, since the initial abnormalities in liver tests, pain and pain improved and almost disappeared after treatment with V-Artem.

New infections and recrudescent infections
The data refer to a limited period of medical treatment with the last collection of infections and recrudescent infections can be treated with a second treatment with a drug.

CONTRAINDICATIONS
V-Artem is contraindicated in:
1. Hypersensitivity to Artemether, Lumefantrine or any excipient of V-Artem.
2. Patients with severe malaria as defined by WHO.
3. The first trimester of pregnancy in situations containing other suitable and effective antimalarial elements see section (PREGNANCY AND SEXUAL FEEDING)
4. Patients have a family history of QTc prolongation or any other clinical condition known to be associated with prolonged QTc interval, such as cornstarch with symptomatic cardiologies, clinically relevant bradycardia or cardiac disease. 5. Patients taking medications known to prolong the QTc interval, such as:
   *Class IA and III antiarrhythmics,
   *Neuroleptics and antidepressant agents,
   *Antibiotics, including some agents belonging to the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungals.
   *Certain sedative antihistamine tablets (Terfenadine, Astemizole, Cisapride).
6. Patients with known disturbances of electrolyte balance, such as hypokalemia or hypomagnesemia.
7. Patients taking a CYP2DE drug (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE V-Artem has not been evaluated for prophylaxis and, consequently, is not indicated. V-Artem has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria, including pulmonary edema or renal failure. V-Artem is not indicated for and has not been evaluated for the treatment of malaria due to P viv. Malaria or P ovale, although some patients participating in certain clinical studies had a co-infection with P falciparum and P vivai at baseline. V-Artem is active against blood cycles of Plasmodium vivax, but is not active against hypozoic ones. (e.g., halofantrine, quinine, and quinidine), Arte-Lume has the potential to cause QTc prolongation, although it has not been reported as an adverse clinical agent attributed to QTc prolongation (e.g., syncope, Mod sobeit). It has not been studied for its safety efficacy in severe hepatic or renal impairment and consequently it is not possible to do so than for dental groups. The results indicate that the average is about 0 years of treatment and is closely monitored, since the risk of recrudescence may be higher. If a patient's condition worsens during treatment with V-Artem, they should be started on an alternative treatment for malaria. In such cases, it is recommended to monitor patients with ECG and measures should be taken to correct any electrolyte disturbances. A prolonged elimination half-life of lumefantrine should be considered when administering quinine to patients treated with V-Artem. Caution should be exercised when administering other antimalarial drugs concomitantly.

Safety and efficacy data are limited and therefore V-Artem cannot be administered with other contaminants and other chemicals. The prolonged elimination half-life of Lumefantrine should be taken into account when administering quinine to V-Artem treated patients. If this is not the case, then ECG (for quinine) is necessary. Regarding halofantrine treatment, V-Artem should receive the dose of halofantrine. With other medications: V-Artem should not be used with medications metabolized by CYP2D6 (see CONTRAINDICATIONS section) and recommended with the oil. With CYP3A4 substrates, inhibitors or inducers, the therapeutic effects of some drugs may change.

INTERACTIONS: Despite the likelihood of interactions between V-Artem and other medications, ketoconazole (a potent inhibitor of CVP3A4), mefloquine and quinine in healthy volunteers are minimal, taking into account the administration of the double curia and the broad ethics and pharmacodynamics of the pharmaceutical industry.

PREGNANCY AND BREASTFEEDING
Pregnancy
Treatment with V-Artem is contraindicated during the first trimester of pregnancy in situations where other effective antimalarials are available. However, it should be administered in life-threatening situations where other effective antimalarials are not available. During the second and third trimesters, treatment should only be considered if the expected benefit outweighs the risk to the foetus.

Women of childbearing potential
Since V-Artem is contraindicated during the first trimester of pregnancy, women should not become pregnant while receiving V-Artem treatment for malaria, including women who have been prescribed V-Artem for emergency (stand-by) treatment of malaria during their travel, in case they require treatment for malaria. Women of childbearing potential should be advised to use contraception during travel with emergency (stand-by) treatment, while taking V-Artem or until the start of their next menstrual period after treatment.

Breastfeeding
Women who are breastfeeding should not take V-Artem. Due to the prolonged elimination half-life of Lumefantrine (4 to 6 days), it is recommended that breastfeeding should not be resumed for a period of less than 28 days, unless the potential benefits to the mother and child outweigh the risks of treatment with V-Artem.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients receiving V-Artem should be warned that dizziness or fatigue/asthenia may occur, in which case they should not drive or operate machinery.

UNDESIRABLE EFFECTS
Artemether and Lumefantrine tablets appeared to be well tolerated in infants, children, and adults. A represents a pooled analysis of the safety of adverse reactions Anorexia, Sleep disorders, Headache, Dizziness, Somnolence, Hypoesthesia, Ataxia, Heart disease Palpitation, Cough, Vomiting, Abdominal pain, Nausea, Diarrhea, Skin, Pruritus, Arthralgia, Myalgia, Antonia, Fatigue

OVERDOSAGE
If overdose is suspected, supportive symptomatic therapy should be administered as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

PHARMACOKINETICS
Absorption
Artemether was absorbed very rapidly, with peak plasma concentrations achieved in overdose. Absorption of lumefantrine, a lipophilic salmeterol compound, began after a lag time of up to 2 hours, with peak plasma concentrations reached approximately 6 to 8 hours after administration. Food facilitates the absorption of artemether and lumefantrine in healthy volunteers; the relative bioavailability of artemether increased more than 2-fold and the bioavailability of lumefantrine increased 16-fold compared with fasting conditions when V-Artem was administered after a fat meal. Food was also found to lead to increased absorption of lumefantrine in malaria patients, although to a lesser extent (approximately 2-fold), most likely due to the fat-free content of the fed intakes of acutely ill patients. Food interaction data indicate that absorption of lumefantrine under fasting and very fasting conditions is poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasting conditions would be <10% of the dose). Consequently, patients should be encouraged to take their medication as prescribed* following a normal diet as soon as food is tolerated.

Distribution
Artemether and lumefantrine are capable of binding human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin also binds human serine proteins (47% to 76%). Ipecac, a linear protein-binding agent for human plasma proteins.

Bio transformation:
Artemether rapidly and extensively metabolized (substantial first-pass metabolism). Human liver microsomes metabolize artemether to the major biologically active metabolite, dihydroartemisinin (demethylation), predominantly via the CYP3A4/5 enzyme. The pharmacokinetics of this metabolite have also been described in humans in vivo. The artemether/dihydroartemisinin ratio was 1:2 at the 0.3 and 6 doses at 3 days. Artemether and DHA have been reported to produce a mild inducing effect on CYP3A4 activity; What is expected to be a problem in the general patient population

Lumefantrine undergoes N-unbuffering primarily by CYP3A4 in human liver microsomes. In vivo in animals (dogs and rats), lumefantrine glucuronidase occurs directly and is linked to oxidative biotransformation.

In humans, systemic exposure to the challenge metabolite lumefantrine, for which the antiparasitic effect in vitro is between 5 and 8 times greater than that of lumefantrine, was less than 1% of exposure to the parent compound.

Lumefantrine in vitro significantly inhibits CYP2D6 activity at therapeutic plasma concentrations.

PRECLINICAL SAFETY DATA
General toxicity
Key observations in repeated-dose toxicity trials were assessed by expected pharmacology in erythrocytes, followed by responsive secondary hematopoiesis.

Mutagenicity
No evidence of mutagenicity was detected in in vivo tests with an artemether:lumefantrine combination (consisting of 1 part artemether:6 parts lumefantrine). In the microcycle test, myelotoxicity was observed at dose levels (500, 1000 and 2000 mg/kg), but recovery was almost achieved 48 hours after administration.

Carcinogenicity
Due to the limited duration of treatment, there are no carcinogenicity studies with an artemether-lumefantrine combination.

Cardiovascular pharmacology
At doses of 600 mg/kg/day). In dose-ranging toxicity studies, there was some evidence of prolongation of the interval. In vitro numbers of stably expressed HERG channels in HE.93 cells, a major metabolite of lumefantrine desbutyl-lumefantrine showed some inhibitory potential and on the chains responsible for cardiac vasopressin. This potency was lower than the potency of the other amphoteric drugs used. (2.5 micromolar)>lumefantrine challenge (5.5 micromolar), from the calculated ICE values, an order of HERG blockade for halofantrine) IC = 0.04 micromolar, 5 micromolar)>lumefantrine (8.1 micromolar) A prolongation of the QTcF interval may occur With a dose of V-Artem.

INCOMPATIBILITIES: Unknown

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
For the treatment of children and infants, a package of 6, 12, 24 tablets can be prescribed. The prescription must comply with the expiration date of the full day expiration date. In fact, the treatments are successful and the remaining tablets should be discarded or returned to the pharmacist (see DOSAGE AND ADMINISTRATION section).

Keep medicines out of reach of children.

Manufactured by:

US Pharma®
(INDIA) Private Limited
Pioneering Excellence. Redefining Quality.
www.uspharma.in