**1.3 Summary of product characteristics, labelling and package leaflet.**

**1.3.1 Summary of product characteristics (SPC)**

**AFEMART**

Artemether and Lumefantrine Tablets

## 1. NAME OF THE MEDICINAL PRODUCT

AFEMART Film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

| | | |
|---|---|---|
| Artemether | : | 80 mg |
| Lumefantrine | : | 480 mg |
| Excipients | : | Q.S. |
| Colour | : | Quinoline Yellow |

## 3. PHARMACEUTICAL FORM

Tablet.
For oral administration.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

AFEMART is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adult, children and infants of 5 kg and above.
Consideration should be given to official guidance regarding the appropriate use of anti malarial agents.

### 4.2 Posology and method of administration

Adults and children weighing 35 kg and above
For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

### 4.3 Contraindications

**Hypersensitivity**
Patients hypersensitive to Artemether, Lumefantrine, or to any of the excipients of AFEMART.

## 4.4 Special warnings and precautions for use

AFEMART Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

AFEMART has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.
Due to limited data on safety and efficacy, AFEMART should not be given concurrently with any other anti malarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking AFEMART, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.
The long elimination half-life of Lumefantrine must be taken into account when administering quinine in patients previously treated with AFEMART.

If quinine is given after AFEMART, close monitoring of the ECG is advised.
AFEMART is given after mefloquine, close monitoring of food intake is advised.
In patients previously treated with halofantrine, AFEMART should not be administered earlier than one month after the last halofantrine dose.

AFEMART is not indicated for, and has not been evaluated in, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. AFEMART is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

AFEMART is not indicated and has not been evaluated for prophylaxis.
Like other antimalarials (e.g. halofantrine, quinine and quinidine) AFEMART has the potential to cause QT prolongation.
Caution is advised when administering AFEMART to patients with severe renal, hepatic or cardiac problems.

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other antimalarials
A drug interaction study with AFEMART in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of AFEMART were not affected compared with a group which received mefloquine followed by placebo.
Pre-treatment with mefloquine had no effect on plasma concentrations of Artemether or the Artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of Lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

## 4.6 Pregnancy and lactation

**Pregnancy**
There is insufficient data from the use of Artemether and Lumefantrine in pregnant women. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

**Lactation**
Women taking AFEMART should not breast-feed during their treatment. 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 AFEMART unless potential benefits to the mother and child outweigh the risks of AFEMART treatment.

## 4.7 Undesirable effects

**Blood and lymphatic system disorders:** eosinophilia
**Ear and labyrinth disorders**: tinnitus
**Eye disorders**: conjunctivitis
**Gastrointestinal disorders**: constipation, dyspepsia, dysphagia, peptic ulcer
**General disorders:** gait disturbance
**Infections and infestations**: abscess, acrodermatitis, bronchitis, ear infection, gastroenteritis, helminthic infection, hookworm infection, impetigo, influenza, lower respiratory tract infection, malaria, nasopharyngitis, oral herpes, pneumonia, respiratory tract infection, subcutaneous abscess, upper respiratory tract infection, urinary tract infection
**Investigations**: alanine aminotransferase increased, aspartate aminotransferase increased hematocrit decreased, lymphocyte morphology abnormal, platelet count decreased, platelet count increased, white blood cell count decreased, white blood cell count increased
**Metabolism and nutrition disorders**: hypokalemia
**Musculoskeletal and connective tissue disorders**: back pain
**Nervous system disorders**: ataxia, clonus, fine motor delay, hyperreflexia, hypoaesthesia, nystagmus, tremor
**Psychiatric disorders**: agitation, mood swings
**Renal and urinary disorders**: hematuria, proteinuria
**Respiratory, thoracic and mediastinal disorders**: asthma, pharyngo-laryngeal pain
**Skin and subcutaneous tissue disorders:** urticaria

## 4.8 Overdose

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutical Category:** Antimalarial Agent
**ATC code:** P01BF01

AFEMART(Artemether Lumefantrine tablets) Tablets, a fixed ratio of 1:6 parts of Artemether and Lumefantrine, respectively, is an antimalarial agent. Artemether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). The anti-malarial activity of Artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which Lumefantrine exerts its anti-malarial effect is not well defined. Available data suggest Lumefantrine inhibits the formation of [3-hematin by forming a complex with hemin. Both Artemether and Lumefantrine were shown to inhibit nucleic acid and protein synthesis.

## 5.2 Pharmacokinetic properties

**Absorption**
Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of Artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Food enhances the absorption of both Artemether and Lumefantrine: in healthy volunteers the relative bioavailability of Artemether was increased more than two-fold, and that of Lumefantrine sixteen-fold compared with fasted conditions when AFEMART was taken after a high-fat meal. Food has also been shown to increase the absorption of Lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients.

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

**Metabolism**
Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolise Artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*. Dihydroartemisinin is further converted to inactive metabolites.
Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes.

**Elimination**
Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 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 ALIVE-LART.
No urinary excretion data are available for humans.

# 6. PHARMACEUTICAL PARTICULARS

### 6.1 Special precaution for storage

Store below 30°C.
KEEP OUT OF REACH OF CHILDREN.

## 7. MARKETING AUTHORISATION HOLDER

Ahmedabad
Gujarat, India.
E-mail: info@sagalabs.com
URL: www.sagalabs.com

## 8. MARKETING AUTHORISATION NUMBER(S)

G/25/1877