# SUMMARY OF PRODUCT CHARACTERISTICS
# (LIVETHER TABLETS)

## 1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each uncoated coated caplet contains:
Artemether PhI 80 mg
Lumefantrine 480 mg

## 3. PHARMACEUTICAL FORM
Uncoated Tablets

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications
Artemether and lumefantrine combination therapy is indicated for the treatment of acute uncomplicated malaria caused by Plasmodium falciparum, including malaria acquired in chloroquine-resistant areas. May also be used to treat uncomplicated malaria when the Plasmodium species has not been identified. Indicated for use in adults and children greater than 5 kg.

### 4.2 Posology and Method of Administration
Tablets for oral administration. To increase absorption, Artemether and lumefantrine should be taken with food or a milky drink. If patients are unable to tolerate food, should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose. For administration to small children and infants, the tablet/s may be crushed. 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. Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight: 5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter. 15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter. 25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

**Method of administration:** For oral use.

**4.3 Contraindications:**

- Patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Patients with severe malaria according to WHO definition*.
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitryptyline, clomipramine).
- Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- Patients taking drugs that are known to prolong the QTc interval (proarrythmic).
  These drugs include: - antiarrhythmics of classes IA and III, - neuroleptics, antidepressive agents, - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents, - certain nonsedating antihistamines (terfenadine, astemizole), - cisapride. - Flecainide
- Patients with a history of symptomatic cardiac arrhythmias 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. hypokalaemia or hypomagnesaemia.
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*). (*Presence of one or more of the following clinical or laboratory features: Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

**4.5 Special warnings and precautions for use:**

LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available

LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) 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, LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) should not be given concurrently with any other antimalarial agent unless there is no other treatment option. If a patient deteriorates whilst taking LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG), 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 LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG). If quinine is given after LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG), close monitoring of the ECG is

advised. If LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) is given after mefloquine, close monitoring of food intake is advised. In patients previously treated with halofantrine LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG /480 MG) should not be administered earlier than one month after the last halofantrine dose. LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) is not indicated and has not been evaluated for prophylaxis of malaria. LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG), Like other antimalarials (e.g. halofantrine, quinine and quinidine) LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) has the potential to cause QT prolongation

Caution is recommended when combining LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE

TABLETS 80 MG/480 MG) with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially antiretroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG)

Caution is recommended when combining LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) with hormonal contraceptives. MEFARTTABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

<u>Renal impairment</u>

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG /480 MG) in patients with renal impairment is recommended. Caution is advised when administering LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG /480 MG) to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG). In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of

LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) cannot be recommended.

**4.6 Paediatric Population:**

None stated

**4.7 Interaction with other Medicinal products and other forms of Interaction**

Interaction with other antimalarial drugs Data on safety and efficacy are limited, and Artemether and lumefantrine should therefore not be given concurrently with other antimalarials unless there is no other treatment option. If Artemether and lumefantrine is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether and lumefantrine. In patients previously treated with halofantrine, Artemether and lumefantrine should not be administered earlier than one month after the last halofantrine dose. Mefloquine A drug interaction study with Artemether and lumefantrine 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 Artemether and lumefantrine 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.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Artemether and lumefantrine (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemether and lumefantrine to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and lumefantrine in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of Artemether and lumefantrine.

**4.8 Additional information on special populations**

None stated

**4.9 Paediatric Population:**

None stated

**4.10 Fertility, Pregnancy and Lactation**

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Artemether and lumefantrine is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether and lumefantrine (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates. Artemether and lumefantrine treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breastfeeding should not resume until at least one week after the last dose of LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) unless potential benefits to the mother and child outweigh the risks LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) treatment.

Fertility

There is no information on the effects of LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) on human fertility

**4.11 Effects on Ability to Drive and Use Machines:**

Patients receiving LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

**4.12 Undesirable Effects** With Artemether virtually no side effects have been seen. Laboratory abnormalities such as slight rise in transaminases and a decrease in reticulocyte count are rare and transient. A lowering of sinus frequency without causing ECG changes has been noticed. At high doses transient abdominal pain, tinnitus and diarrhoea have been described but a causal relationship is unclear. Some antimalarials as halofantrine and quinine can influence the ECG pattern Attention should be made to patients previously treated with those antimalarials. A reasonable period should be taken in account before to start a treatment with lumefantrine combinations. For those patients physicians will be prescribed Artemisinin derivatives in mono therapy in cause of severe paludism. Sometimes it could be possible that the following common side effect occur; rash, check this with you doctor. Other common side effects may occur as trouble of sleeping, nausea, vomiting, diarrhoea, coughing. They need medical attention when persisting.

**4.13 Overdose & Treatment:**

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

## 5. PHARMACOLOGICAL PROPERTIES:

### 5.1 Pharmacodynamic Properties

**Pharmacotherapeutic group:** antimalarials, blood schizontocides, **ATC code:** P01 BF01. Pharmacodynamic effects Artemether and lumefantrine comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. 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 haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation 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. Treatment of Acute Uncomplicated P. falciparum Malaria The efficacy of Artemether and lumefantrine Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/μL - 200,000/μL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America. Efficacy endpoints consisted of:

- 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients:

Microcrystalline Cellulose BP, Maize Starch BP, Sodium lauryl Sulphate USP, Sodium Starch Glycolate USP, Colloidal Silicon Dioxide BP, Cross Carmellose sodium, Magnesium Stearate BP, Purified Water BP are used as excipients in the manufacturing process of LIVETHER TABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG)

### 6.2 Incompatibilities

None known.

### 6.3 Shelf-Life

24 months from the date of manufacture.

**6.4 Special Precautions for Storage**

Store below 30°C.

Keep Medicine Out of Reach of Children.

**6.5 Nature and Contents of Container**

1 X 6 TABLETS ALU - PVDC BLISTER PACK

**6.6 Special Precautions for Disposal and Other Handling**

No special requirements.

**7.0 Marketing Authorisation Holder:**

EVERLIVING PHARMACY LTD.

**8.0 Marketing Authorisation Numbers:**

NOT APPLICABLE

**9.0 Date of the First Authorisation or Renewal:**

NOT APPLICABLE

**10.0 Date of Revision of the Text:**

NOT APPLICABLE