Summary of Product Characteristics

1. Name of the medicinal product

ARTEMETHER & LUMEFANTRINE TABLETS Ph Intl 80/480 mg

2. Qualitative and quantitative composition

Each film coated tablet contains

Artemether Ph Intl 80 mg

Lumefantrine Ph Intl 480mg

Excipients q. s.

Colour : Tartrazine

3. Pharmaceutical form

Film Coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

Artemether and Lumefantrine Tablets is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults, children and infants of 5 kg and above.

4.2 Posology and method of administration

Tablet for oral administration

Number of Artemether and Lumefantrine Tablets for treatment according to weight bands

Weight range	**1st day of treatment**	**2nd day of treatment**	**3rd day of treatment**
≥ 5kg to < 15kg	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)
15kg to <25kg	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)
25kg to <35kg	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L)

≥ 35kg (or ≥ 12 years of age	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration.

The first dose should be followed by a second dose after 8 hours. The following two days the doses of Artemether and Lumefantrine Tablets should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, Artemether and Lumefantrine Tablets should be taken with food or a milky drink. If a patient is unable to tolerate food, Artemether and Lumefantrine Tablets should still be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose. The tablets can also be crushed and administered with food or a milky drink.

Renal or hepatic impairment

No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Artemether and Lumefantrine Tablets to patients with severe renal or hepatic problems.

Elderly

No special precautions or dosage adjustments are necessary in such patients.

4.3 Contraindications

Artemether & Lumefantrine Tablet is contraindicated in:

• patients with known hypersensitivity to the active substances or to any of the excipients.

• 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 non-sedating antihistamines (terfenadine, astemizole),
- cisapride.
- flecainide

• patients with a history of symptomatic cardiac arrythmias 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.

• 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

Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

Artemether & Lumefantrine Tablet must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Artemether & Lumefantrine Tablet 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, Artemether & Lumefantrine Tablet should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Artemether & Lumefantrine Tablet, 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 Artemether & Lumefantrine Tablet.

If quinine is given after Artemether & Lumefantrine Tablet, close monitoring of the ECG is advised.

If Artemether & Lumefantrine Tablet is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Artemether & Lumefantrine Tablet should not be administered earlier than one month after the last halofantrine dose.

Artemether & Lumefantrine Tablet is not indicated and has not been evaluated for prophylaxis.

Artemether & Lumefantrine Tablet should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether & Lumefantrine Tablet.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether & Lumefantrine Tablet has the potential to cause QT prolongation.

Caution is recommended when combining Artemether & Lumefantrine Tablet 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 anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Artemether & Lumefantrine Tablet.

Caution is recommended when combining Artemether & Lumefantrine Tablet with hormonal contraceptives. Artemether & Lumefantrine Tablet 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.

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.

Renal impairment

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 Artemether & Lumefantrine Tablet in patients with renal impairment is recommended. Caution is advised when administering Artemether & Lumefantrine Tablet 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. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution is advised when administering Artemether & Lumefantrine Tablet to patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.

Elderly

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 Artemether & Lumefantrine Tablet. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether & Lumefantrine Tablet cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Artemether & Lumefantrine Tablet is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Artemether & Lumefantrine Tablet with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemether & Lumefantrine Tablet (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Artemether & Lumefantrine Tablet alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether & Lumefantrine Tablet.

Inducers should not be administered at least one month after Artemether & Lumefantrine Tablet administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Artemether & Lumefantrine Tablet should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If Artemether & Lumefantrine Tablet 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 & Lumefantrine Tablet. In patients previously treated with halofantrine, Artemether & Lumefantrine Tablet should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Artemether & Lumefantrine Tablet 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 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 & Lumefantrine Tablet (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 & Lumefantrine Tablet 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 & Lumefantrine Tablet 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 & Lumefantrine Tablet..

Concomitant use requiring caution

Interactions affecting the use of Artemether & Lumefantrine Tablet

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole:

The concurrent oral administration of ketoconazole with Artemether & Lumefantrine Tablet led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Artemether & Lumefantrine Tablet is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Artemether & Lumefantrine Tablet should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Grapefruit juice

Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug. Grapefruit juice should be used cautiously during Artemether & Lumefantrine Tablet treatment.

Interaction with weak to moderate inducers of CYP3A4

When Artemether & Lumefantrine Tablet is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Artemether & Lumefantrine Tablet should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether & Lumefantrine Tablet, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ ritonavir:

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Artemether & Lumefantrine Tablet.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of Artemether & Lumefantrine Tablet.

Interactions resulting in effects of Artemether & Lumefantrine Tablet on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether & Lumefantrine Tablet is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and

CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised by these enzymes.

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Artemether & Lumefantrine Tablet may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control for about one month.

Drug-food/drink interactions

Artemether & Lumefantrine Tablet should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased.

Grapefruit juice should be used cautiously during Artemether & Lumefantrine Tablet treatment.

4.6 Fertility, pregnancy and lactation

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Artemether & Lumefantrine Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether artemether or lumefantrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Artemether & Lumefantrine Tablets are administered to a nursing woman. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether & Lumefantrine Tablet should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines..

4.8 Undesirable effects

Very common: Palpitations, Headache, Dizziness, Vomiting, Abdominal pain, Nausea, Anorexia, Arthralgia, Myalgia, Asthenia, Fatigue, Sleep disorders

Common: Electrocardiogram QT prolonged, Paraesthesia, Gait disturbance, Cough, Rash, Pruritus, Insomnia.

Uncommon: Liver function tests increased, Ataxia, hypoaesthesia, Clonic movements, somnolence

Rare: Hypersensitivity

4.9 Overdose

There is no information on overdoses of Artemether & Lumefantrine Tablets higher than the doses recommended for treatment.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, Artemisinin and derivatives, combinations,
ATC code: P01BF01

Artemether & Lumefantrine 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 antimalarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine exerts its antimalarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of β-hematin by forming a complex with hemin. Both artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis.

5.2 Pharmacokinetic properties

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. Mean Cmax and AUC values of artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of Artemether & Lumefantrine Tablet (80mg/480mg). Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/mL. 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 Artemether & Lumefantrine Tablet (80mg/480mg) 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. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

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%).

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. Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of Artemether & Lumefantrine Tablet (80mg/480mg), plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In humans, the exposure to lumefantrine increases with repeated administration of Artemether & Lumefantrine Tablet over the 3-day treatment period, consistent with the slow elimination of the compound. Systemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days.

Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether & Lumefantrine Tablet.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether & Lumefantrine Tablet, and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant 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.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, Maize starch, Croscarmellose sodium, Sodium starch glycolate, Purified talc, Colloidal anhydrous silica, Magnesium stearate, Film coat universal white (FC0015), Colour tartrazine lake, Isopropyl alcohol, Dichloromethane and Purified water

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children

6.5 Nature and contents of container

10X1X6 ALU-PVC Blister Pack

6.6 Special precautions for disposal and other handling

Any product remaining at the end of treatment should be discarded.

7. Marketing authorisation holder

Not Applicable

8. Marketing authorisation number(s)

Not Applicable

9. Date of first authorisation/renewal of the authorisation

Not Applicable

10. Date of revision of the text

Not Applicable