SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME: Artemether 80 mg and Lumefantrine 480 mg Tablets

BRAND NAME: ESKAFAN FORTE

DESCRIPTION:

Yellow coloured, capsule shaped, uncoated biconvex tablets, having central break line on one side and plain on other side.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Artemether……. 80 mg

Lumefantrine……. 480 mg

Excipients…….. q.s.

For complete list of excipients refer section 6.1.

3. PHARMACEUTICAL FORM:

Solid Oral Dosage Form- Uncoated Tablet

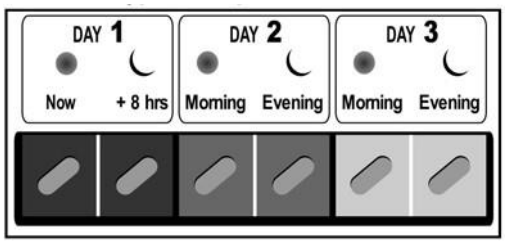
4. CLINICAL PARTICULARS

4.1 Therapeutic Indication:

It 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 antimalarial agents.

4.2 Posology and method of administration:



Tablets for oral administration.

To increase absorption, ESKAFAN FORTE should be taken with food or a milky drink. If patients are unable to tolerate food, ESKAFAN FORTE 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.

Elderly

Although no studies have been carried out in the elderly, no special precautions or dosage adjustments are considered necessary in such patients.

Renal impairment

No specific studies have been carried out in these groups of patients. However, there is no significant renal excretion of Lumefantrine, Artemether and Dihydroartemisinin in humans; therefore, no dose adjustment for the use of ESKAFAN FORTE in patients with renal impairment is advised.

Caution is advised when administering ESKAFAN FORTE 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 these groups of patients. Therefore, no specific dose adjustment recommendations can be made for patients with hepatic impairment.

Caution is advised when administering ESKAFAN FORTE to patients with severe hepatic impairment.

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 ESKAFAN FORTE . In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of ESKAFAN FORTE cannot be recommended.

4.3 Contraindications:

ESKAFAN FORTE 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. flecainide, 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. 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.

- 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

4.4 Special warning and precautions for use

ESKAFAN FORTE must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarial are available.

ESKAFAN FORTE 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, ESKAFAN FORTE should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking ESKAFAN FORTE , 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 ESKAFAN FORTE .

If quinine is given after ESKAFAN FORTE , close monitoring of the ECG is advised.

If ESKAFAN FORTE is given after mefloquine, close monitoring of food intake is advise.

In patients previously treated with halofantrine, ESKAFAN FORTE should not be administered earlier than one month after the last halofantrine dose.

ESKAFAN FORTE 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 coinfection with *P. falciparum* and *P. vivax* at baseline. ESKAFAN FORTE is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

ESKAFAN FORTE is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) ESKAFAN FORTE has the potential to cause QT prolongation.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving ESKAFAN FORTE experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

Caution is recommended when combining ESKAFAN FORTE with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered.

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

Caution is advised when administering ESKAFAN FORTE to patients with severe renal, hepatic or cardiac problems.

4.5 Drug Interactions

Interaction with other antimalarials

A drug interaction study with ESKAFAN FORTE 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 ESKAFAN FORTE 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.

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 ESKAFAN FORTE (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 ESKAFAN FORTE 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 ESKAFAN FORTE 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 ESKAFAN FORTE .

Interaction with CYP450 3A4 inhibitors (ketoconazole)

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with ESKAFAN FORTE 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 ESKAFAN FORTE is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Interaction with CYP450 enzymes

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.

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 ESKAFAN FORTE with drugs that are metabolised by this iso-enzyme is contraindicated. *In vitro* studies indicated that Lumefantrine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with ESKAFAN FORTE , requires clinical surveillance and monitoring of clinical response/undesirable effects.

Other interactions

Administration of ESKAFAN FORTE is contra-indicated in patients taking drugs that are known to prolong the QTc interval.

In patients previously treated with halofantrine, ESKAFAN FORTE should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, ESKAFAN FORTE should not be given concurrently with any other antimalarial agent.

In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering ESKAFAN FORTE to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy & Lactation

Pregnancy

There is insufficient data from the use of Artemether and Lumefantrine in pregnant women. Based on animal data, ESKAFAN FORTE 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 ESKAFAN FORTE treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarial 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking ESKAFAN FORTE 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 ESKAFAN FORTE unless potential benefits to the mother and child outweigh the risks of ESKAFAN FORTE treatment.

4.7 Effects on ability to drive and use machines:

Patients receiving ESKAFAN FORTE should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Adverse Effects

The safety of ESKAFAN FORTE has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received ESKAFAN FORTE in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates)**
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Clonus, somnolence	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)

Pruritus	Common	Uncommon
Urticaria, angioedema**	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
Metabolism and nutrition disorders		
Anorexia	Very common	Very common (16.8 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--
Immune system disorders		
Hypersensitivity	Not known	Rare
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon

**: These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

4.9 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:

Artemether involves an interaction with ferriprotoporphyrin IX ("heme"), or ferrous ions, in the acidic parasite food vacuole, which results in the generation of cytotoxic radical species. The generally accepted mechanism of action of peroxide antimalarials involves interaction of the peroxide-containing drug with heme, a hemoglobin degradation byproduct, derived from proteolysis of hemoglobin. This interaction is believed to result in the formation of a range of potentially toxic oxygen and carbon-centered radicals.

The exact mechanism by which lumefantrine exerts its antimalarial effect is unknown. However, available data suggest that lumefantrine inhibits the formation of β-hematin by forming a complex with hemin and inhibits 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. 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 ESKAFAN FORTE , 80 mg artemether/480 mg lumefantrine. 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 ESKAFAN FORTE was taken after a highfat 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.

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.

The pharmacokinetics of Artemether in adults is time-dependent. During repeated administration of ESKAFAN FORTE , 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. The clinical evidence of induction is consistent with the *in vitro* data.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of Lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to Lumefantrine increases with repeated administration of ESKAFAN FORTE 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.

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 ESKAFAN FORTE .

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

In animals (rats and dogs), no unchanged Artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of Lumefantrine were eliminated in bile/faeces.

Pharmacokinetics in special patient populations

In paediatric malaria patients, mean Cmax (CV%) of Artemether (observed after first dose of ESKAFAN FORTE) were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of Lumefantrine (population mean, covering the six doses of ESKAFAN FORTE) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of Artemether and Lumefantrine in children are unknown.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of Lumefantrine, Artemether and Dihydroartemisinin, no dose adjustment for the use of ESKAFAN FORTE in patients with renal impairment is advised.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Microcrystalline Cellulose powder BP
- Hydroxy Propyl methyl Cellulose E15 BP
- Polysorbate 80 BP
- Maize Starch for mixing BP
- Maize starch for paste BP
- Purified water BP
- Talcum BP

- Magnesium Stearate BP
- Crospovidone BP
- Maize starch (Additional)* BP
- Colloidal Anhydrous Silica BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

24 Months.

6.4 Special precautions for storage:

Store in a dry place below 30°C. Protect from light.
Keep the medicine out of reach of children.

6.5 Nature and contents of container

1 X 6Tablets in a blister pack

7. MARKETING AUTHORISATION HOLDER

Eskay Therapeutics Ltd.

42, South Industrial Area,

Accra, Ghana

Tel.: +233 30 2241509 / 2251725

8. MARKETING AUTHORISATION NUMBER(S)

FDA/SD.173-10833

9. DATE OF ~~FIRST AUTHORISATION~~/RENEWAL OF THE AUTHORISATION

1st-November 2020

10. DATE OF REVISION OF THE TEXT

July 2018