SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME: Artemether 40 mg and Lumefantrine 240 mg Tablets

BRAND NAME: ESKAFAN DS

DESCRIPTION:

Yellow coloured, circular, uncoated flat beveled edges tablet, having break line on one side and plain on other side.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Artemether……. 40 mg

Lumefantrine……. 240 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.

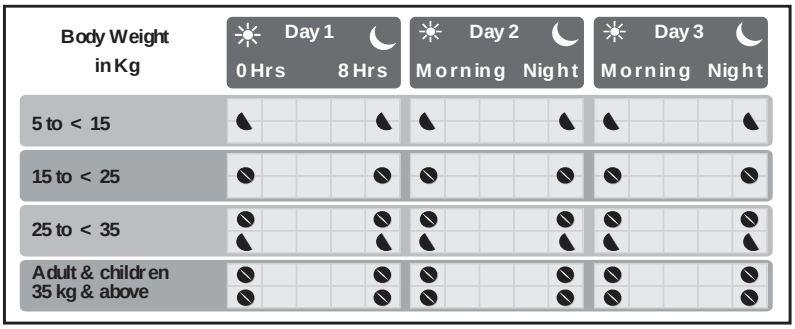
4.2 Posology and method of administration:

A six-dose regimen over 3 days is recommended, as described below:

Adults and adolescents weighing 35kg and above

1st dosage, at the time of initial diagnosis	2 Tablets
2nd dosage, at 8 hours after 1st dose	2 Tablets

3rd dosage, at 24 hours after 1st dose	2 Tablets
4th dosage, at 36 hours after 1st dose	2 Tablets
5th dosage, at 48 hours after 1st dose	2 Tablets
6th dosage, at 60 hours after 1st dose	2 Tablets



4.3 Contraindications:

Artemether & Lumefantrine Tablets are contraindicated in:

- patients with severe malaria.
- 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.

4.4 Special warning and precautions for use

How to take drug: Artemether + Lumefantrine Tablets should be taken with food or drinks rich in fat such as milk.

If any dose missed: Try to make sure that you do not miss any doses. However, if you do forget a dose of Artemether + Lumefantrine Tablets, take the missed dose as soon as you remember unless it is almost time for your next dose. Then take your next dose at the usual time.

Ask doctor for advice. Do not take a double dose to make up for a forgotten dose.

4.5 Drug Interactions

Rifampin: Oral administration of rifampin, a strong CYP3A4 inducer, with ESKAFAN Tablets/Suspension resulted in significant decreases in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether) and Lumefantrine by 89%, 85% and 68%, respectively, when compared to exposure values after ESKAFAN Tablets/Suspension alone.
Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin and St. John's wort are contraindicated with ESKAFAN Tablets/Suspension.
Ketoconazole: Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of ESKAFAN Tablets/Suspension resulted in a moderate increase in exposure to artemether, DHA, and lumefantrine in a study of 15 healthy subjects. No dose adjustment of ESKAFAN Tablets/Suspension necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, ESKAFAN Tablets/Suspension should be used cautiously with drugs that inhibit CYP3A4 .
Antiretroviral Drugs: Both artemether and lumefantrine are metabolized by CYP3A4. Antiretroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Therefore, the effects of antiretroviral drugs on the exposure to artemether, DHA, and lumefantrine are also variable. ESKAFAN Tablets/Suspension should be used cautiously in patients on antiretroviral drugs because decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of ESKAFAN Tablets / Suspension and increased lumefantrine concentrations may cause QT prolongation.
Prior Use of Meoquine: Administration of three doses of mefloquine followed 12 hours later by a 6 dose regimen of ESKAFAN Tablets/Suspension in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio.
However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of ESKAFAN Tablets/Suspension.
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, ESKAFAN Tablets/Suspension 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 non hormonal method of birth control.
CYP2D6 Substrates: Lumefantrine inhibits CYP2D6 in vitro. Administration of ESKAFAN Tablets/Suspension with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with ESKAFAN Tablets/Suspension due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine)
Sequential Use of Quinine: A single dose of intravenous quinine (10 mg/kg body weight) concurrent with the final dose of a 6-dose regimen of ESKAFAN Tablets/Suspension demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with ESKAFAN Tablets / Suspension due to the long elimination half-life of lumefantrine and the potential for additive QT effects; ECG monitoring is advised if use of drugs that prolong the QT interval is medically required.
Interaction with Drugs that are Known to Prolong the QT Interval ESKAFAN Tablets/Suspension are to be used with caution when co-administered with drugs that may cause prolonged QT interval 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.

4.6 Pregnancy & Lactation

Pregnancy - ESKAFAN Tablets/Suspension are suspected to cause serious birth defects when administered during the first trimester of pregnancy, so it must not be used during the first 3 months of pregnancy. If it is possible to use an alternative medicine first. However, it should not be withheld in life threatening their situations, where no other effective antimalarials are available. During the second and third trimester, treatment should't only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Lactation - Women taking ESKAFAN Tablets/Suspension 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 atleast one week after the last dose of ESKAFAN Tablets/Suspensionunless potential benefits to the mother and child outweigh the risks of Artemether and lumefantrine Tablets/Suspension treatment

4.7 Effects on ability to drive and use machines:

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

4.8 Adverse Effects

Like all medicines, ESKAFAN Tablets/Suspension can cause side effects although not everybody gets them. Most of the side effects are mild to moderate and generally disappear after a few days to a few weeks after treatment. Some

side effects are more commonly reported in children and others are more commonly reported in adults. In cases where there is a difference, the frequency listed below is the more common one. Some side effects could be serious and need immediate medical attention (affecting less than 1 in 1,000 patients). If you get a rash, swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing, tell your doctor straight away. These are signs of an allergic reaction.

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 with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 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 Artemether + Lumefantrine 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 twofold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food inter-action 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 (97.9%
- and 99.9%, respectively). Comparable binding values were observed in animals. Distribution has not been further investigated in humans, but in rats artemether is well distributed throughout the body, with some affinity for the brown fat and adrenal glands, while lumefantrine has an affinity for adipose and glandular tissue and to some extent for the lungs, spleen (due to slow elimination from lymphoid tissue) and bone marrow.

Metabolism

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolize artemether to the biologically active main metabolite dihydroartemisinin (demethy-lation), predominantly through the, enzyme CYP3A4/5. This metabolite has also been detected in humans in VIVO. 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 vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether is rapidly cleared from plasma with an elimination 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. No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Powder, Hydroxyl Propyl Methyl Cellulose, Polysorbate 80, Maize Starch, Purified water, Purified Talc, Magnesium Stearate, Crospovidone, Colloidal Anhydrous Silica.

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

12’s Tablets 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.173-10834

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

1st-Nov.-20

10. DATE OF REVISION OF THE TEXT

July 2018