# SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) FOR DRUG PRODUCTS IN NIGERIA

## FYNALE

(Artemether & Lumefantrine Tablets)

## 1 NAME OF MEDICINAL PRODUCT

**FYNALE TABLETS**

Artemether & Lumefantrine Tablets

**Strength**

Artemether 20 mg & Lumefantrine 120 mg.

**Dosage Form**

Tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Artemether ……20 mg
Lumefantrine…… 120 mg
Excipients Q.S.

## 3. PHARMACEUTICAL FORM

Uncoated tablet

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**FYNALE TABLETS** tablets are 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

**Method of administration:** Oral

**Posology:**

The tablets composing 1 dose should be completely dispersed in a small amount of water (approximately 10 ml per tablet). Stir gently and administer immediately to the patient. Rinse the glass with an additional small amount of water (approximately 10 ml) and give immediately to the patient.

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

tablet should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

| **Body Weight** | **Total** | **Dosage Regimen** | | | | | |
|---|---|---|---|---|---|---|---|
| In kg | Tablets | Day 1 | | Day 2 | | Day 3 | |
| | | 0 Hr | 8 Hrs | 24 Hrs | 36 Hrs | 48 Hrs | 60 Hrs |
| 5 to < 14 kg | 6 | 1 | 1 | 1 | 1 | 1 | 1 |
| 15 to < 24 kg | 2 x 6 | 2 | 2 | 2 | 2 | 2 | 2 |
| 25 to < 34 kg | 3 x 6 | 3 | 3 | 3 | 3 | 3 | 3 |
| 35 kg and above | 4 x 6 | 4 | 4 | 4 | 4 | 4 | 4 |

**Dosage in elderly patients**

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

**Dosage in patients with renal or hepatic impairment**

Caution is advised when administering tablets to patients with severe renal or hepatic problems. In these patients ECG and blood potassium monitoring is advised.

## 4.3 CONTRAINDICATIONS

**FYNALE TABLETS** are contraindicated:

In those with hypersensitivity to the active substances or any of the excipients.

In cases of severe malaria.

**In the first trimester of pregnancy**.

Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, patients with clinically relevant bradycardia or with severe cardiac disease, family history of sudden death, disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia. Concomitant use of drugs that are known to be metabolised by cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

Patients taking drugs that are known to prolong the QTc interval such as antiarrhythmics of classes IA and III, neuroleptics, 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.
Artemether and lumefantrine tablets are contraindicated for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary oedema or renal failure. It is also not indicated for and has not been evaluated in, the treatment of malaria due to P. vivax, P. malariae *or* P. ovale

## 4.4 WARNING AND PRECAUTIONS

### Warnings

Artemether and Lumefantrine tablets should be taken with or after food. If the patient can't tolerate food the tablets should still be taken, but they may be less effective. The tablets can be crushed for small children or infants.
If you are sick within one hour of taking a dose of this medicine you should consult your doctor or pharmacist, as you may need to take another dose.
It is very important that you complete the prescribed course of this medicine, unless otherwise directed by your doctor, as the medicine may not be fully effective if you don't.

Unless your doctor or pharmacist tells you otherwise, you should avoid drinking grapefruit juice while taking this medicine, as it may affect the level of this medicine in your blood.
This medicine may cause fatigue and dizziness. You should take care when performing potentially hazardous activites, such as driving or operating machinery, until you know how this medicine affects you and are sure you can perform such activities safely.
If you have kidney, liver or heart problems you should be regularly monitored while you are taking this medicine, to check the level of potassium in your blood (blood test), and your heart function (ECG).

### Precautions

Use with caution in patients with severe hepatic or renal insufficiency and patients refusing food intake. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The sequential oral administration of mefloquine prior to artemether and lumefantrine combination had no effect on plasma concentrations of artemether or the artemether / dihydroartemisinin (DHA) ratio but there was a significant (around 30-40%) reduction in plasma levels (Cmax and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Such patients should therefore be encouraged to eat at dosing times to compensate for this decrease in bioavailability.

Quinine alone caused a transient prolongation of the QTc interval, which was consistent with its known cardiotoxicity. This effect was slightly but significantly greater when quinine was infused after artemether and lumefantrine combination. Thus, prior administration of artemether and lumefantrine combination appears to enhance the inherent risk of QTc-prolongation from IV quinine.

Hence when artemether and lumefantrine combination is given to patients following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or the ECG (for quinine) should be carried out.

In patients previously treated with halofantrine, artemether and lumefantrine tablets should be administered atleast one month after the last halofantrine dose.

Due to limited data on safety and efficacy, the combination should not be given concurrently with other antimalarials unless there is no other treatment option. However, if a patient deteriorates while taking the combination, alternative treatments for malaria should be commenced without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct electrolyte disturbances.

Whereas in vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisnins have some capacity to induce the production of the cytochrome enzyme CYP2C19 and perhaps also CYP3A4. It is possible that iso-enzyme induction could alter the therapeutic effects of drugs that are predominantly metabolized 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 artemether and

lumefantrine tablets with drugs that are metabolized by this iso-enzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated.

## 4.6 PREGNANCY AND LACTATION

**Pregnancy**

There is insufficient data from the use of artemether & lumefantrine in pregnant woman. Based on animal data; FYNALE TABLETS is suspected to cause serious birth defects when administered durinf the first trimester of pregency. Reproductive studies with artemether have shown evidence of post implantation losses and teratogenicity in rats and rabbits. Other atremisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation. FYNALE TABLET Streatment 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 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 FYNALE TABLETS 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 FYNALE TABLETS unless potential benefits to the mother and child outweighs the risk of FYNALE TABLETS treatment.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Driving and use of machinery is not recommended due to risk of dizziness and fatigue or asthenia.

## 4.8 UNDESIRABLE EFFECTS

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

Undesirable Effects are ranked under headings of frequency using the Med DRA 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 values were taken from the summary tables submitted to the MHRA during the assessment of three parallel type II variation applications (UK/H/035/001/II/042-044)

** 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**

Experience of over dosage with artemether and lumefantrine is limited. In cases of suspected over dosage symptomatic and supportive therapy should be given as appropriate, which include monitoring of ECG and serum electrolytes.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Antimalarials

**ATC code:** P01BF01.

**Mechanism of action**

FYNALE TABLETS 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.

### 5.2 Pharmacokinetic properties

PHARMACOKINETICS: Pharmacokinetic Characterisation of FYNALE TABLETS is limited by the lack of an intravenous formulation ,and the very high inter-and intra-subject variability of artemether and Lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC,$C_{max}$)

**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 6-8hours 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 FYNALE TABLETS 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 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 been couraged to take the medication with 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). Dihydroartemisinin is also bound to human serum proteins ( 47%-76% Protein binding to human plasma is linear.

**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 enzyme CYP3A4/5 The pharmacokinetics of this metabolite has been described in humans in vivo. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days In-vivo date indicate that artemisinins have some capacity to induce cytochrome isoenzymesCYP2C19 and CYP3A4.
Lumefantrine is N-debutylated, mainly by CYP3A4,in human liver microsomes. In vivo in animals (dogs and rats) glucuronidation of lumefantrine tasks place directly and after oxidative biotransformation.
In vitro lumefantrine significantly inhibits the activity of CYP206 at the rapeutic plasma concentrations.

**ELIMINATION:** Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is 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 rat sand dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

**5.3 Preclinical safety data**

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the

expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Mutagenicity

No evidence of Artemether and lumefantrine tablet mutagenicity was detected in in vitro or in vivo tests. In the micronucleus test myelotoxicity was seen at all dose levels (500, 1000 and 2000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with Artemether and lumefantrine tablet were not conducted.

Reproductive toxicity studies

Reproductive toxicity studies with Artemether and lumefantrine tablet in rats showed both materno- and embryotoxic effects at doses of 60 to a 100 mg/kg but without evidence of teratogenicity. In rabbits, materno- and embryo toxicity were seen at 175 mg/kg, but not foetotoxicity or teratogenicity. A dose of 105 mg/kg was free of treatment-induced effects.

Lumefantrine doses up to 1000 mg/kg showed no evidence to suggest materno-, embryo- or foetotoxicity or teratogenicity in rats and rabbits. Artemisinins are known to be embryotoxic in animals. Artemether showed no effects in rabbits at doses up to 25 mg/kg, but at 30 mg/kg, materno-, embryo- and foetotoxicity were observed. In rats materno-, embryo- and foetotoxicity were all noted at 10 mg/kg, but without evidence of teratogenicity at any dose level. Artemether and lumefantrine tablet was not embryotoxic in rats at doses of ≤25 mg/kg.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

| |
|---|
| Microcrystalline Cellulose Phosphate BP |
| Lactose BP |
| Starch BP |
| Cross carmellose sodium BP |
| Crospovidone XL-10 BP |
| Polyvinyl Pyrrolidone K-30 BP |
| Sodium Methyl paraben BP |
| Sodium Propyl paraben BP |

| |
|---|
| Bronopol BP |
| Isopropyl alcohol BP |
| Sodium Lauryl Sulphate BP |
| Sodium starch Glycolate BP |
| Fumed silica BP |
| Magnesium stearate BP |
| Purified Talc BP |

**6.1 Incompatibilities**

Not applicable.

**6.2 Shelf life**

Three years.

**6.3 Special precautions for storage**

Store below 30°C. Protected from light.

**6.4 Nature and contents of container**

Available as blister of 1 x 24 tablets in carton with pack insert.

**6.5 Special precautions for disposal and other Special handling**

None

**7. Marketed by:**

**AQUATIX PHARMACEUTICALS LIMITED**
No.7, Sapara Williams Street, Industrial

Estate, lkeja, Lagos, Nigeria.

**8. Manufactured by:**

**SWISS PHARMA PVT. LTD.**
3709, G.I.D.C., Phase IV,
Vatva, Ahmedabad –382445, India

**9. NAFDAC REGISTRATION NUMBER(S):** A4-9924