1. Name of the medicinal product

AGWOIBA 80/480 (ARTEMETHER 80 MG AND LUMEFANTRINE 480 MG TABLETS PH. INT.)

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each film-coated tablet contains:
-Artemether Ph. Int. 80 mg
-Lumefantrine Ph. Int. 480 mg
-Excipients: q.s.

Sr. No.	Name of Ingredient	Spec.	Qty. in mg/ Tab	Ovg.	Reason for Inclusion
1.	Lumefantrine	Ph. Int	480.000	--	Active
2.	Microcrystalline Cellulose	BP	20.000	--	Diluent
3.	Maize Starch	BP	24.000	--	Binder
4.	Maize Starch (Paste)	BP	11.400	--	Binder
5.	Polysorbate 80 (Tween 80)	BP	5.000	--	Solubilizer
6.	**Purified Water	Inhouse	Q.S.	--	Solvent
Lubrication					
7.	Artemether	Ph. Int.	80.000	--	Active
8.	Colloidal Anhydrous Silica	BP	6.000	--	Glidant
9.	Magnesium Stearate	BP	10.000	--	Lubricant
10.	Purified talc	BP	8.000	--	Glidant
11.	Croscarmellose sodium	BP	28.000	--	Disintegrant
12.	*Maize Starch (additional)	BP	3.540	--	Binder
	TOTAL		**673.00**		
Film Coating					
13.	H.P.M.C (E-15)	Inhouse	10.000	--	Film-forming agent
14.	Purified Talc	BP	1.500	--	Glidant
15.	Propylene Glycol	BP	1.100	--	Plasticizer
16.	PEG-6000	BP	1.100		Plasticizer
17.	Quinoline Yellow Lake	Inhouse	5.000		Coloring agent
18.	**Isopropyl alcohol	BP	105.450		Solvent
19.	**Methylene Chloride	BP	158.400		Solvent
	TOTAL		**692.000**		

*Includes additional maize starch to compensate the loss on drying.
BP: British Pharmacopoeia
Ph. Int. : International Pharmacopoeia
Average weight of coated tablet: 692.00 mg ± 5.0 %

3. Pharmaceutical form

Film-coated Tablets
Yellow coloured, circular shaped, biconvex, film coated tablet having breakline on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

AGWOIBA is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above.

4.2 Posology and method of administration

Posology

Posology Adults and children weighing 35 kg 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.

Infants weighing less than 5 kg.
The safety and efficacy of AGWOIBA tablets have not been established in infants weighing less than 5 kg and no dosing recommendations can be made. Method of administration Tablets for oral administration.

4.3 Contraindications

AGWOIBA 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 IAand 111
-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).

4.4 Special warnings and precautions for use

AGWOIBA is not recommended during the first trimester of pregnancy. AGWOIBA 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.
AGWOIBA should not be given concurrently with any other antimalarial agent unless there is no other treatment option.
If a patient deteriorates whilst taking AGWOIBA, alternative treatment for malaria should be started without delay. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with AGWOIBA.
If quinine is given after AGWOIBA, close monitoring of the ECG is advised. If AGWOIBA is given after mefloquine, close monitoring of food intake is advised.
In patients previously treated with halofantrine, AGWOIBA should not be administered earlier than one month after the last halofantrine dose. AGWOIBA is not indicated and has not been evaluated for prophylaxis of malaria.
AGWOIBA 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 AGWOIBA Caution is recommended when combining AGWOIBA with hormonal contraceptives. AGWOIBA 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.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

AGWOIBA is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes).
Co-administration of AGWOIBA with drugs that are metabolised by this iso-enzyme is contraindicated.
Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with AGWOIBA .
Inducers should not be administered at least one month after AGWOIBA administration, unless critical to use as judged by the prescriber.

AGWOIBA should not be given concurrently with other antimalarials unless there is no other treatment option.
If AGWOIBA is given following administration of mefloquine or quinine, close monitoring of food intake (for meftoquine) 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 AGWOIBA. In patients previously treated with halofantrine, AGWOIBA should not be administered earlier than one month after the last halofantrine dose.
Concomitant use requiring caution.
Interactions affecting the use of AGWOIBA 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 AGWOIBA led to a modest increase (S2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. Interaction with weak to moderate inducers of CYP3A4: When AGWOIBA is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Lopinavir/ ritonavir: Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of AGWOIBA. Nevi rapine: Artemether/lumefantrine reduced the median Cmax and AUC of nevi rapine 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 the concomitant use of Artemether 20 Mg and Lumefantrine 120 Mg Tablets.

Interactions resulting in effects of AGWOIBA on other drugs.

Interaction with drugs metabolized by CYP450 enzymes: When AGWOIBA is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy.

Interaction with hormonal contraceptives: AGWOIBA 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
AGWOIBA 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 AGWOIBA treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug.

4.1 Pregnancy and lactation
Pregnancy: AGWOIBA treatment is not recommended 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, AGWOIBA treatment should be considered if the expected benefit to the mother outweighs the risk to the foetus.
Lactation: It is recommended that breast-feeding should not resume until at least one week after the last dose of AGWOIBA unless potential benefits to the mother and child outweigh the risks of AGWOIBA treatment.

4.7 Effects on ability to drive and use machines
Patients receiving AGWOIBA should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects
Like all medicines, this medicine 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.

Rare (may affect up to 1 in 1,000 people) 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.

Other side effects are:
Very common (may affect more than 1 in 10 people) Fast heartbeat, headache, dizziness, cough, being sick (vomiting), stomach pain, feeling sick (nausea), joints or muscles aching, loss of appetite, general weakness, tiredness, trouble with sleeping.

Common (may affect up to 1 in 10 people) Involuntary muscle contractions (sometimes in rapid spasms), heart rhythm disturbances (called QTc prolongation), Symptoms such as unexplained persistent nausea, stomach problems, loss of appetite or unusual tiredness or weakness (signs of liver problems), diarrhoea, abnormal walking), tingling or numbness of the hands and feet), a rash or itching on the skin, insomnia.

Uncommon (may affect up to 1 in 100 patients) inability to coordinate movements), decreased skin sensitivity), sleepiness, itching rash) These side effects have been reported in adults and adolescents above 12 years of age.

Not known (frequency cannot be estimated from the available data) Anaemia due to breakdown of red blood cells, which has been reported up to a few weeks after treatment has been stopped (delayed haemolytic anaemia). These side effects have been reported in adults and adolescents above 12 years of age.

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

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01BF01.

AGWOIBA 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. AGWOIBA has been reported to have potent activity in terms of clearing gametocytes.

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.

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%).

Biotransformation: 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. Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT287. Dihydroartemisinin is further converted to inactive metabolites.

Elimination: 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.

5.3 Preclinical safety data

Not Applicable

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Ingredients	Spec.
1.	Microcrystalline cellulose	BP
2.	Maize Starch	BP

3.	Maize Starch (Paste)	BP
4.	Crospovidone XL -10	BP
6.	Purified Talc	BP
7.	Calcium Stearate	BP
8.	Colloidal Anhydrous Silica	BP
9.	Maize Starch (Additional)	BP
10.	Microcrystalline cellulose (pH 102)	BP
11.	H.P.M.C (E-15)	BP
12.	Propylene Glycol	BP
13.	PEG-6000	BP
14.	Quinoline Yellow Lake	In-house
15.	**Isopropyl alcohol	BP
16.	**Methylene Chloride	BP

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
3 years

6.4 Special precautions for storage
Store in a cool and dry place below 30°C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container
ALU/ PVC Blister of 1 x 24 Tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.
No special requirements.

7. APPLICANT/MANUFACTURER

Fredun Pharmaceuticals Limited
14, 15, 16 Zorabian Industrial Complex, Village Vevoor,
Palghar (E) - 401 404, India.