1. NAME OF THE MEDICINAL PRODUCT

ARTEPREF 80/480 TABLETS

(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

Lumafantrine Ph. Int. 480 mg

Colour: Quinoline yellow

Excipients: q.s.

Batch Size: 10,000 Tablets

S.N.	Ingredients	Spec.	Qty/ Tab mg	Ovg.	Std. batch qty (kg)
1.	Lumefantrine	Ph. Int.	480.00	--	4.800
2.	Micro crystalline cellulose	BP	20.60	--	0.206
3.	Maize starch	BP	24.00	--	0.240
4.	Maize starch (for paste)	BP	11.40	--	0.114
5.	Polysorbate 80	BP	5.00	--	0.050
	Lubricants				
6.	Artemether	Ph. Int.	80.00	--	0.800
7.	Colloidal anhydrous silica	BP	6.00	--	0.060
8.	Magnesium stearate	BP	10.00	--	0.100
9.	Purified talc	BP	8.00	--	0.080
10.	Croscarmellose sodium	BP	28.00	--	0.280
11.	*Maize starch (additional)	BP	3.54	--	0.035
	Total		**673.00**		
	Film coating				
12.	Hypromellose	BP	10.00	--	0.100
13.	Purified talc	BP	1.70	--	0.017
14.	Propylene glycol	BP	1.10	--	0.011

15.	Macrogols (PEG 6000)	BP	1.20	--	0.012
16.	Colour quinoline yellow	IHS	5.00	--	0.050
17.	**Dichloromethane	BP	158.40	--	1.584
18.	**Isopropyl alcohol	BP	105.45	--	1.054
	Total		**692.00**		

Ph. Int.: International Pharmacopoeia

BP: British Pharmacopoeia

IHS: IN- House specifications

Note: * Includes additional maize starch to compensate the loss on drying.

** Dichloromethane & Isopropyl alcohol used as solvents and are not found in the final product.

Average weight of uncoated tablet: 673.00 mg ± 5.0%

Average weight of film coated tablet: 692.00 mg ± 5.0%

3. PHARMACEUTICAL FORM: Film coated Tablets

4. Clinical particulars

4.1 Therapeutic Indication:

Artemether and Lumefantrine 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.

4.1 Posology and method of administration:

Method of administration: Tablets for oral administration

To increase absorption, ARTEPREF 80/480 Tablets should be taken with food or a milky drink. If patients are unable to tolerate food, ARTEPREF 80/480 Tablets 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.

4.2 Contraindications

• 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 metabolized 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, anti-depressive 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)

4.3 Special warnings and precautions for use

ARTEPREF 80/480 Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective anti-malarials are available.

ARTEPREF 80/480 Tablets 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, ARTEPREF 80/480 Tablets should not be given concurrently with any other antimalarial agent (unless there is no other treatment option)

If a patient deteriorates whilst taking ARTEPREF 80/480 Tablets , 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 ARTEPREF 80/480 Tablets

If quinine is given after ARTEPREF 80/480 Tablets close monitoring of the ECG is advised.

If ARTEPREF 80/480 Tablets is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, ARTEPREF 80/480 Tablets should not be administered earlier than one month after the last halofantrine dose.

ARTEPREF 80/480 Tablets is not indicated and has not been evaluated for prophylaxis.

ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) ARTEPREF 80/480 Tablets has the potential to cause QT prolongation.

Caution is recommended when combining ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets. Caution is recommended when combining ARTEPREF 80/480 Tablets with hormonal contraceptives. ARTEPREF 80/480 Tablets 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. Hence 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 ARTEPREF 80/480 Tablets in patients with renal impairment is recommended. Caution is advised when administering ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of ARTEPREF 80/480 Tablets cannot be recommended.

4.4 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

ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets with drugs that are metabolized 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 ARTEPREF 80/480 Tablets (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 ARTEPREF 80/480 Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with ARTEPREF 80/480 Tablets.

Inducers should not be administered at least one month after ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets should therefore not be given concurrently with other anti-malarials unless there is no other treatment option.

If ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets. In patients previously treated with halofantrine, ARTEPREF 80/480 Tablets should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets (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 ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets.

Concomitant use requiring caution

Interactions affecting the use of ARTEPREF 80/480 Tablets

Interaction with CYP3A4 inhibitors

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

Ketoconazole

The concurrent oral administration of ketoconazole with ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets treatment.

Interaction with weak to moderate inducers of CYP3A4

When ARTEPREF 80/480 Tablets 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. ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets.

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 ARTEPREF 80/480 Tablets.

Interactions resulting in effects of ARTEPREF 80/480 Tablets on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When ARTEPREF 80/480 Tablets 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 metabolized 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, ARTEPREF 80/480 Tablets 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

ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets treatment.

4.5 Pregnancy and Lactation

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, the drug 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.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to ARTEPREF 80/480 Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

ARTEPREF 80/480 Tablets treatment 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 the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Women of childbearing potential

Women 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking ARTEPREF 80/480 Tablets should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of ARTEPREF 80/480 Tablets unless potential benefits to the mother and child outweigh the risks of ARTEPREF 80/480 Tablets treatment.

Fertility

There is no information on the effects of ARTEPREF 80/480 Tablets on human fertility.

4.6 Effects on ability to drive and use machines:

Patients receiving ARTEPREF 80/480 Tablets should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.7 Undesirable effects

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).

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates)**
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		

Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
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 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

*: 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.

4.8 Overdose

In cases of suspected over dosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antimalarials, blood schizontocide

ATC CODE: P01 BF01.

Pharmacodynamic effects

ARTEPREF 80/480 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 polymerization 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.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of ARTEPREF 80/480 Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/μL - 200,000/μL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

• 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28

• parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours

• fever clearance time (FCT), defined as time from first dose until the first-time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are

all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28.

5.2 Pharmacokinetic properties

Pharmacokinetic characterization of ARTEPREF 80/480 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, Cmax).

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 ARTEPREF 80/480 Tablets, 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 ARTEPREF 80/480 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 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 metabolized (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolize 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 ARTEPREF 80/480 Tablets 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 ARTEPREF 80/480 Tablets 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 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 ARTEPREF 80/480 Tablets.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of ARTEPREF 80/480 Tablets and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the ARTEPREF 80/480 Tablets dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of ARTEPREF 80/480 Tablets as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of ARTEPREF 80/480 dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of ARTEPREF 80/480 dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Special populations

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.

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose) 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 ARTEPREF 80/480 Tablets) 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. 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. 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 ARTEPREF 80/480 Tablets in patients with renal impairment is advised.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S.N.	Excipients	Specification
1	Micro crystalline cellulose	As per BP
2	Maize starch	As per BP
3	Polysorbate 80	As per BP
4	Colloidal anhydrous silica	As per BP
5	Magnesium stearate	As per BP
6	Purified talc	As per BP
7	Croscarmellose sodium	As per BP
8	Hypromellose	As per BP
9	Macrogols	As per BP
10	Propylene glycol	As per BP
11	Colour quinoline yellow	As per IHS
12	Dichloromethane	As per BP
13	Isopropyl alcohol	As per BP

BP: British Pharmacopoeia IHS: IN- House specification

6.2 Incompatibilities

None such data reported.

6.3 Shelf life:

24 months (2 years)

6.4 Special precautions for storage

Store in a cool, dry place. Store below 25°C. Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Blister pack of 6 Tablets .

6.6 Special precautions for disposal <and other handling>

None such special precautions required for this product.

7 APPLICANT/MANUFACTURER

APPLICANT :

PREFFRRED DRUGD NIGERIA LTD.

Address: 20 Erhuvwa Club Street, Asaba Delta State, Nigeria &

Preferred Groups LLC, Maryland U.S.A

www.preferred-drugs.com

MANUFACTURER:

Fredun Pharmaceutical Ltd.

Address: 14,15,16,Zorabian Indl. Complex,

Vevoor, Palghar-401404, Maharashtra state, India.

Contact No.: Phone: 91-22-40318111

Email: business@fredungroup.com