

1. NAME OF THE MEDICINAL PRODUCT:**IBUMARTEM 80/480**

(Artemether 80 mg & Lumefantrine 480 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Film Coated Tablet Contains:

Artemether Phl.....80 mg

Lumefantrine Phl..... 480 mg

Approved Colour used

Excipients (QS)

Sr. No.	Ingredients	Specification	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason For Function
a)	Dry Mixing					
1.	Artemether	Phl	80.000	NA	80.000	Medicament
2.	Lumefantrine	Phl	480.000	NA	480.000	Medicament
3.	Maize Starch	BP	NA	NA	182.730	Diluent
4.	Microcrystalline Cellulose	BP	NA	NA	65.000	Diluent
b)	Binder Preparation					
5.	Maize Starch	BP	NA	NA	25.000	Binder
6.	Gelatin (Gelling grade)	BP	NA	NA	5.000	Binder
7.	Povidone K-30	BP	NA	NA	5.000	Binder
8.	Methyl Hydroxybenzoate	BP	NA	NA	1.000	Preservative
9.	Propyl Hydroxybenzoate	BP	NA	NA	0.100	Preservative
10.	Polysorbate-80	BP	NA	NA	5.170	Wetting Agent
11.	Purified Water	BP	NA	NA	--	Vehicle
c)	Lubrication					
12.	Purified Talc	BP	NA	NA	17.000	Glidant
13.	Magnesium Stearate	BP	NA	NA	10.000	Lubricant
14.	Crospovidone (Type A)	BP	NA	NA	18.000	Disintegrant
15.	Colloidal Anhydrous Silica	BP	NA	NA	6.000	Glidant
	Average Weight of Uncoated Tablet (In mg)				900.000	
d)	Pre-Coating					
16.	Povidone K-30	BP	NA	NA	3.330	Coating agent
17.	Isopropyl Alcohol	BP	NA	NA	--	Vehicle
e)	Film Coating					
18.	Hypromellose (15 CPS)	BP	NA	NA	11.000	Film Former
19.	Purified Talc	BP	NA	NA	3.720	Antiadherent
20.	Macrogol-6000	BP	NA	NA	1.170	Plasticizer
21.	Titanium Dioxide	BP	NA	NA	2.400	Opacifier
22.	Tartrazine (Lake)	IH	NA	NA	1.720	Colour
23.	Isopropyl Alcohol	BP	NA	NA	-	Vehicle
24.	Dichloromethane	BP	NA	NA	-	Vehicle
	Average Weight of Film Coated Tablet (In mg)				920.000	

3. PHARMACEUTICAL FORM: Film Coated Tablet**Description:** Yellow coloured, round shaped, biconvex, film coated tablet, plain on both sides.**4. CLINICAL PARTICULARS****4.1 Therapeutic indications:****IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets) are indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults of 35 kg and above.The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with **IBUMARTEM 80/480**.

4.2 Posology and method of administration

Method of Administration

Weight in (kg) (Age in years)	Total Tablets	Dosage regimen					
		Day 1		Day 2		Day 3	
		0 Hr	8 Hrs	24 Hrs	36 Hrs	48 Hrs	60 Hrs
>35 kg (15 yrs and above)	6	1	1 Tablet	1 Tablet	1 Tablet	1 Tablet	1 Tablet

Second dose to be taken strictly after 8 hours of first dose.

Better taken with high fat food or drink such as milk.

4.3 Contraindications

IBUMARTEM 80/480 (Artemether 80mg & Lumefantrine 480mg Tablets) are contraindicated in:

- Known hypersensitivity to artemether, lumefantrine, or to any of the excipients of Artemether and Lumefantrine Tablets.
- patients with a personal or 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, clinically relevant bradycardia or severe cardiac diseases.
- patients taking drugs that are known to prolong QTc 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
 - certain non-sedating antihistamines (terfenadine, astemizole)
 - cisapride
- patients with known disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia
- patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine)
- patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John's wort.

4.4 Special warnings and precautions for use

IBUMARTEM 80/480 (Artemether 80mg & Lumefantrine 480mg Tablets) must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

IBUMARTEM 80/480 (Artemether 80mg & Lumefantrine 480mg 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, **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets) should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg 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 Artemether and Lumefantrine Tablets.

If quinine is given after **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets), close monitoring of the ECG is advised.

If **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets) is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets) should not be administered earlier than one month after the last halofantrine dose.

IBUMARTEM 80/480 (Artemether 80mg & Lumefantrine 480mg Tablets) is not indicated and has not been evaluated for prophylaxis of malaria.

IBUMARTEM 80/480 (Artemether 80mg & Lumefantrine 480mg Tablets) 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 **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets).

Like other antimalarials (e.g. halofantrine, quinine and quinidine) **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets) has the potential to cause QT prolongation.

Caution is recommended when combining **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg 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 **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets).

Caution is recommended when combining **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg Tablets) with hormonal contraceptives. **IBUMARTEM 80/480** (Artemether 80mg & Lumefantrine 480mg 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.

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 Artemether and Lumefantrine Tablets in patients with renal impairment is recommended. Caution is advised when administering Artemether and Lumefantrine 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. In patients with severe hepatic impairment, a clinically relevant 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. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

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

4.5 Interaction with other medicinal products and other forms of interaction

With other antimalarials: Data on safety and efficacy are limited, and Artemether 80 mg & Lumefantrine 480 mg Tablets should therefore not be given concurrently with other antimalarials unless there is no other treatment option. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with **IBUMARTEM 80/480** (Artemether 80 mg & Lumefantrine 480 mg Tablets).

Patients previously treated with other antimalarials: If Artemether 80 mg & Lumefantrine 480 mg Tablets is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. In patients previously treated with halofantrine, Artemether 80 mg & Lumefantrine 480 mg Tablets should not be administered earlier than one month after the last halofantrine dose.

With other drugs: Caution is recommended when combining Artemether 80 mg & Lumefantrine 480 mg Tablets with substrates, inhibitors or weak to moderate inducers of 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 Artemether 80 mg & Lumefantrine 480 mg Tablets.

With hormonal contraceptives: Artemether 80 mg & Lumefantrine 480 mg Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients should be advised to use an additional non-hormonal method of birth control.

4.6 Pregnancy and Lactation

Pregnancy

Artemether-lumefantrine 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.

Lactation

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

4.7 Effects on the ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions reported are: Decreased appetite, Sleep disorders, Headache, Dizziness, Paraesthesia, Cardiac disorders, Cough, Vomiting, Abdominal pain, Nausea, Diarrhoea, Liver function tests increased, Rash, Pruritus, Arthralgia, Myalgia, Asthenia, Fatigue.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

IBUMARTEM 80/480 (Artemether 80 mg & Lumefantrine 480 mg 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.

The antimalarial activity of the combination of lumefantrine and artemether is greater than that of either substance alone. In a double-blind comparative study in adults in China (n=157), the 28-day cure rate of artemether/ lumefantrine when given at four doses was 94% compared with 90% for lumefantrine and 46% for artemether based on intent-to-treat (ITT) population, when given as monotherapy.

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 to 8 hours after administration. 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 and 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 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 (DHA) is also bound to human serum proteins (47% to 76%). Protein binding to human plasma protein is linear.

Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). 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 also 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. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity, which is not expected to present a problem in the general patient population.

During repeated administration of Artemether and lumefantrine, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for the metabolism of artemether.

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 systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent compound.

In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours, while 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 artemether and lumefantrine.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of artemether and lumefantrine, and urinary excretion of DHA 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. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of both drug components were eliminated in bile/faeces and urine.

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.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions mainly in brainstem nuclei. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

Artemether and lumefantrine were not genotoxic/clastogenic based on in vitro and in vivo testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses >600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free C_{max}), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC₅₀ was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Microcrystalline Cellulose, Gelatin, Povidone K-30, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Polysorbate-80, Purified Talc, Magnesium Stearate, Crospovidone, Colloidal Anhydrous Silica, Hypromellose, Macrogol-6000, Titanium Dioxide, Tartrazine (Lake), Isopropyl Alcohol, Dichloromethane.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry & dark place.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Packing:

Primary packing: 6 Tablets in an ALU-PVC blister.

Secondary packing: 1 Blister is packed in an inner carton along with leaflet.

Tertiary packing: Such 10 inner cartons are packed in an outer carton. Shrink individual outer carton. Such 30 Shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

6.6 Special precautions for disposal and other handling

None.

7. APPLICANT / MANUFACTURER**Applicant**

Applicant name and address	M/s. IBU PHARMA NIGERIA LTD. No.: 1, Labiran Street, Ikenne Ogun State, Nigeria
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	M/s. ASTAMED HEALTHCARE (I) PVT. LTD. Plot No. 2 & 3, Phase II, Genesis Ind. Complex, Kolgaon, Dist. Thane, Tal. Palghar, 401404 Maharashtra State, India
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