SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Artemether 80 mg and Lumefantrine 480 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Artemether 80 mg and Lumefantrine 480 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated Tablet contains:

Artemether ……..…….. (80 mg)

Lumefantrine …….. (480 mg)

Excipients……(-- QS)

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Yellow, round concave shaped, uncoated tablets having emboss 80/480 on one side and plain on other sides.

4. Clinical particulars

4.1 Therapeutic indications

It is a combination of artemther and lumefantrine, which act as a blood schizontocide. It is indicated for the treatment of adults and children with acute, uncomplicated infections due to Plasmodium falciparum or mixed infection including P. Falciparium and strains from multi drug resistant areas. Artemether and Lumefantrine 80/480 is recommended for use as a standby emergency treatment for travellers to area where the Parasite is resistant to other drugs.

4.2 Posology and method of administration

For ORAL use only. Artemether/lumefantrine is administered as a 6-dose regimen over 3 days, based on body weight or age. The total course consists of 24 tablets (4 tablets per dose) in adults

Artemether and Lumefantrine 80/480 should be taken with high fat or drinks such as milk. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improve absorptions of Artemether and Lumefantrine. On the event of vomiting within 1 hour of administration, a repeat dose should be taken.

Weight in Kg Total Tablets	Total Tablets	Dosage Regimen					
35 kgs And above	6	Day 1		Day 2		Day 3	
		0h	8 h	20h	32h	44h	56h
	1	1	1	1	1	1	1

Second dose to be taken strictly after 8 hours of first dose. Better taken with high-fat food or drinks such as milk

Method of administration

1. Route: Oral
2. With Food: Administer with food, ideally fatty food or milk, to improve absorption — especially important for Lumefantrine.
3. Vomiting:
    - If the patient vomits within 1 hour of administration, repeat the full dose.
    - If vomiting occurs again, consider switching to parenteral antimalarial therapy (e.g., artesunate).

4.3 Contraindications

It is contraindicated in:

- patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- patients with severe malaria according to WHO definition.
- 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, 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
- 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 any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine.

4.4 Special warnings and precautions for use

- patients with known hypersensitivity to Artemether, Lumefantrine or to any of the excipients.
- patients with severe malaria according to WHO definition.

- 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.

4.5 Interaction with other medicinal products and other forms of interaction

Although the likelihood of the interactions with other drugs is minimal in view of its short duration of administration and wide therapeutic index, three specific pharmacokinetic and pharmacodynamic drug-drug interaction studies with ketoconzazole (a potent CYP3A4 inhibitor), mefloquine and quinine have been conducted in healthy volunteers.

It should not be used in patients taking drugs that are known to prolong the QTc interval (see section 4.3), as effects may be additive and increase the risk of cardiac arrhythmia. Interaction with other antimalarials Artemether and Lumefantrine 80/480 should not be given concurrently with any other antimalarial agent (see section 4.4).

In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Artemether and Lumefantrine 80/480 to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

Administration of a six-dose regimen of artemether/lumefantrine (over 60 hours) starting 12 hours after completion of a three-dose regimen of mefloquine or placebo in healthy volunteers showed no effect of mefloquine on plasma concentrations of artemether or the artemether/ dihydroartemisinin ratio, but a 30-40% reduction in plasma levels of lumefantrine.

These are possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients that have been pretreated with mefloquine should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Plasma mefloquine concentrations from the time of addition of artemether/lumefantrine were not affected compared with a group that received mefloquine followed by placebo.

In patients previously treated with halofantrine, Artemether and Lumefantrine 80/480 should be dosed at least one month after the last halofantrine dose due to the long elimination half-life of halofantrine and the potential additive/synergistic effects on the QT-interval. Interaction with CYP450 enzymes 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 or safety profile of drugs that are predominantly metabolised by these enzymes (see sections 4.3 and 5.2). Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index (see section 4.3).

Interaction with CYP450 3A4 inhibitors Ketoconazole: both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations.

The concurrent oral administration of ketoconazole with artemether/lumefantrine 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.

Dose adjustment of Artemether and Lumefantrine 80/480 is not considered necessary when administered concomitantly with ketoconazole or other azole antifungals, but such combinations should be used with caution.

HIV Treatment Medications HIV nucleoside and nucleotide reverse transcriptase inhibitors (NTRIs, e.g. abacavir, emtricitabine, lamivudine, tenofovir [TDF or TAF], zidovudine.) Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz:Co-administration of efavirenz and artemether/lumefantrine lead to decreases in artemether exposure (51% and 79%), dihydroartemisinin exposure (46% and 75%) and lumefantrine exposure by (21% and 56%).

Lumefantrine had no significant effect on efavirenz exposure in either study. Use with caution as decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy. Nevirapine:

Lumefantrine is metabolised predominantly by CYP3A4. Upon co-administration with artemether/lumefantrine with nevirapine decreased the AUCs of artemether and dihydroartemisinin.

In a crossover study lumefantrine exposure was decreased by 20% and lumefantrine reduced nevirapine exposure by 46%. Use with caution.

Rilpivirine: Co-administration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely. Rilpivirine should be used with caution when co-administered with a drug that has a potential risk to prolong the QT interval.

HIV Protease Inhibitors (PIs) Atazanavir: Co-administration may increase plasma levels of artemisinins and lumefantrine.

Both lumefantrine and atazanavir have been shown to prolong the QT interval.

Darunavir: Co-administration may increase plasma levels of artemisinins and lumefantrine. Lopinavir/ritonavir: Data from clinical studies and population modelling suggest that co-administration of lopinavir/ritonavir and artemether decreases exposure of dihydroartemisinin (the biologically active metabolite) by ~40-60%.

Lumefantrine AUC was significantly increased by 2.3-fold and there was trend towards increased Cmax (1.4-fold). The clinical meaning of these opposite effects on artemether and lumefantrine is not clear. Both lumefantrine and lopinavir have been shown to prolong the QT interval. Ritonavir: Co-administration may increase plasma levels of artemisinins and lumefantrine, as both are metabolised by CYP3A4. Caution is recommended.

HIV Integrase Strand-Transfer Inhibitors (INSTIs):

Dolutegravir, Raltegravir: Co-administration has not been studied but based on metabolism/elimination and toxicity profiles there is little potential for interaction. Elvitegravir/cobicistat: Co-administration has not been studied.

Artemether and lumefantrine are metabolized by CYP3A4. Elvitegravir/cobicistat may increase concentrations of artemisinins and lumefantrine.

Pharmacokinetic Enhancer Cobicistat: Co-administration has not been studied.

Cobicistat may increase concentrations of artemisinins and lumefantrine by inhibition of CYP3A4. Antivirals against Hepatitis B or C Co-administration has not been studied. In many instances a clinically significant interaction appears unlikely.

However, consult the summary of product characteristics of the desired medication.

4.6 Pregnancy and Lactation

A moderate amount of data on pregnant women in their first trimester (more than 500 pregnancy outcomes) is available for artemether/lumefantrine.

Data from a recent meta-analysis have shown that compared to quinine, artemether/lumefantrine treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth.

While the data are limited, they indicate no difference in the prevalence of major congenital anomalies between treatment groups (for animal data see section 5.3).

A large amount of data on pregnant women in their second and third trimester (more than 4000 documented pregnancy outcomes) is available for artemisinin derivatives including artemether/lumefantrine.

They indicate no fetal or neonatal toxicity. Artemether and Lumefantrine 80/480 can be used during pregnancy.

Breast-feeding the amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, breastfeeding women can receive artemisinin-based combination therapies (including Artemether and Lumefantrine 80/480) for malaria treatment.

There is no information on the effects of Artemether and Lumefantrine 80/480 on fertility in humans.

4.7 Effects on ability to drive and use machines

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There is no information on the effects of Artemether and Lumefantrine 80/480 on fertility in humans

4.8 Undesirable effects

The safety of artemether/lumefantrine has been evaluated in adults, adolescents and children in clinical trials with more than 3500 patients.
Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.
Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common (≥1/10) Common (≥1/100 to
Uncommon (≥1/1,000 to.
Rare (≥1/10,000 to

Not known (cannot be estimated from available data)

Table 1 Frequency of Undesirable effects

Cardiac disorders	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	Uncommon
Nervous system disorders		
Headache	Very common	Common
Dizziness	Very common	Common
Gait disturbance	uncommon	-
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorder		
Vomiting	Very common	Very common
Abdominal pain	Very common	Very common
Skin and subcutaneous tissue disorders	Very common	Very common
Rash	common	common

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 Pharmacodynamics properties Pharmacotherapeutic group: antimalarials, Artemisinin and derivatives, combination, ATC code: P01 BF01.

Pharmacotherapeutic group:

Pharmacotherapeuticgroup:antimalarial,Artemisinin

and derivatives, combination, ATC code: P01

BF01.

a. Mechanism of Action

Artemether:

- A derivative of artemisinin, acts rapidly against blood-stage *Plasmodium falciparum*.
- Works by generating reactive oxygen species (free radicals) in the parasite's food vacuole.
- These radicals damage parasite proteins, lipids, and membranes, leading to rapid parasite death.

Lumefantrine:

- Belongs to the arylaminoalcohol class (similar to mefloquine).
- Inhibits heme detoxification (heme polymerization into hemozoin), resulting in toxic heme accumulation and parasite death.
- Has a longer half-life, maintaining plasma levels to prevent recrudescence.

Combination rationale:

- Artemether clears early parasite burden rapidly.
- Lumefantrine clears residual parasites and reduces relapse and resistance.
- This synergistic action is crucial for treatment success

b) Pharmacodynamic effects:

Artemether and Lumefantrine 80/480 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.

c) Clinical efficacy and safety

Efficacy

- Artemether/lumefantrine is considered first-line treatment for uncomplicated ***P. falciparum*** malaria**,** especially in endemic areas.
- High cure rates (>95%) in both adults and children.
- Used successfully in Africa, Asia, and South America as part of WHO-recommended ACT (Artemisinin-based Combination Therapy)**.**

Clinical Trials:

- Multicenter trials have shown:
  - High parasite clearance rates within 48–72 hours.
  - Rapid resolution of symptoms (e.g., fever, anemia).
  - Low recrudescence due to lumefantrine's long half-life.

Safety Profile

- Generally well tolerated.

Common Adverse Effects:

- Headache, dizziness, anorexia, nausea, abdominal pain, fatigue.

Less common but serious:

- QT interval prolongation (lumefantrine)
- Hypersensitivity (rare)

Precautions:

- Avoid with other QT-prolonging drugs (e.g., halofantrine, erythromycin, fluoroquinolones).
- Use with caution in patients with hepatic dysfunction or electrolyte imbalance.

d) Resistance:

Artemisinin Resistance

- Partial resistance (slow clearance) reported in Southeast Asia.
- Associated with mutations in the ***PfKelch13*** gene.
- Artemether still rapidly reduces parasitemia, but efficacy is reduced in resistant regions.

b. Lumefantrine Resistance

- Linked to polymorphisms in ***pfmdr1*** gene (e.g., N86Y, D1246Y).
- Resistance develops more slowly than with monotherapy.
- Combination with artemether delays resistance emergence.

No widespread clinical resistance to the artemether-lumefantrine combo reported in Africa — but monitoring is essential.

e) Paediatric population

a. Indication

- Recommended for treatment of uncomplicated ***P. falciparum*** malaria in children.
- Suitable for infants and children ≥5 kg body weight.
- In younger children, dispersible formulations are often used (e.g., 20/120 mg per tablet).

b. Pharmacokinetics

- Children have faster metabolism and different drug absorption.
- Requires weight-based dosing to ensure therapeutic levels.
- Fat-containing food is essential to improve lumefantrine absorption, even in children.

c. Safety in Children

- Clinical trials confirm good safety and efficacy.
- Mild side effects similar to adults: vomiting, fever, cough, and diarrhea.

d. Dosing Schedule (based on weight)

(Example for dispersible form; adjust based on 80/480 mg availability)

Weight (kg)	**Doses per administration (20/120 mg tablets)**	**Total over 3 days**
5–14 kg	1 tablet per dose	6 tablets
15–24 kg	2 tablets per dose	12 tablets
25–34 kg	3 tablets per dose	18 tablets
≥35 kg	4 tablets per dose *(i.e., 80/480 mg)*	24 ablets

5.2 Pharmacokinetic properties

Absorption and Bioavailability:

Distribution: 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, 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 it 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

Metabolism:

Drug	Metabolizing Enzyme(s)	Active Metabolite
Artemether	**CYP3A4, CYP2B6, CYP2A6**	**Dihydroartemisinin (DHA)**
Lumefantrine	**CYP3A4** (slow metabolism)	Minor metabolites (less active)

- Artemether is rapidly converted to DHA, which is also a potent antimalarial.
- Lumefantrine is metabolized slowly, contributing to its long half-life and prolonged antimalarial activity

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 this medicine.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration, and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin 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, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

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

Special Population:

Pharmacokinetics in Special Populations

a. **Children**

- Faster clearance and different absorption; weight-based dosing is essential.
- Food still critical for lumefantrine absorption.
- Dispersible tablets often used in children <35 kg.

b. Pregnancy

- Mild decrease in drug exposure due to increased plasma volume and metabolism.
- Still effective and well tolerated in 2nd/3rd trimester.
- Limited data in the first trimester use only if benefits outweigh risks.

c. Hepatic Impairment

- Mild/moderate: no dose adjustment required.
- Severe: use with caution monitor clinical response.

d. Renal Impairment

- No significant change in pharmacokinetics.
- No dose adjustment typically need

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 mutagenicity was detected in in vitro or in vivo tests with an artemether:lumefantrine combination (consisting of 1 part artemether: 6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity: Carcinogenicity studies with the artemether/lumefantrine combination were not conducted**.**

Reproductive toxicology:

Reproductive toxicity studies performed with the artemether/lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits at doses 50 mg/kg/day (corresponding to approximately 7 mg/kg/day artemether) and 175 mg/kg/day (corresponding to 25 mg/kg/day artemether) respectively.

These effects were not observed at lower doses. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic in animals.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits

The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

he embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day (see section 4.6 for data in humans).

Cardiovascular Pharmacology In toxicity studies in dogs at doses > 600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man.

In an in vitro assay of HERG channels, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Micro Crystalline Cellulose, Sodium Starch Glycolate, Dibasic Calcium Phosphate, Maize Starch, PVPK-30, Methyl Paraben, Propyl Paraben, Purified Talcum, Magnesium Stearate, Aerosil.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C, Protect from moisture. Keep out of the reach of children

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

6 tablets packed in Alu / PVC Blister

1 blister of 6 tablet packed in carton with leaflet

Store the tablets in the blister in the provided cartons

6.6 Special precautions for disposal <and other handling>

Not Applicable

7.0 APPLICANT/MANUFACTURER

Manufacturer:
McCoy Pharma Pvt Ltd
Plot No:S-12/S-13 Tarapur Boisar
Dist-Palghar 401506
State-Maharashtra,
India.