SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

Artemether 20 mg and Lumefantrine 120 mg Tablets

ANATOMIC THERAPEUTIC CHEMICAL CLASSIFICATION AND DISTRIBUTION CATEGORY

P01 B – Antimalarial

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Artemether Ph.Int 20 mg
Lumefantrine Ph.Int 120 mg

PHARMACEUTICAL FORM

Yellow coloured, circular, biconvex, uncoated, flat faced beveled edged matt finished tablets with breakline on one side and plain on the other side.

CLINICAL PARTICULARS

THERAPEUTICAL INDICATIONS

Artemether and lumefantrine tablets are indicated for the treatment of P. falciparum malaria cases resistant to both chloroquine and sulfadoxine pyrimethamine combination. The combination is not recommended for the first line treatment for malaria.

POSOLOGY AND METHOD OF ADMINISTRATION

Artemether and lumefantrine tablets should be taken with high fat food or drinks such as milk.Note that patient with are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine. In the event of vomiting within one hour of administration a repeat dose should be taken.

For adults and child weighing 35 kg and above a standard three day treatment schedule with a total of 6 doses is recommended as follow: four tablets as a single dose at the time of initial diagnosis again four tablets after eight hours and then four tablets twice daily (morning and evening) on each of the following two days (total comprises 24 tablets)

For infants and children weighing 5 kg and 35 kg, a six dose regimen is recommended with 1 to 3 tablets per dose, depending on body weight. With very small children the tablet should be crushed before giving.

Dosage schedule

Body weight	Day 1		Day 2		Day 3	
	0 hrs	8 hrs after	Morning	Evening	Morning	Evening
5 to less than 15 Kg	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
15 to less than 25 kg	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets
25 to less than 35 Kg	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets
Adults and children 35 kg and above	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets

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

Dosage in patients with renal or hepatic impairment
No studies have been carried out in these groups of patients and no specific dose adjustments recommendations can be made for these patients. Most patients with acute malaria present some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover baseline abnormalities in liver function tests improved in nearly all patients after treatment with artemether and lumefantrine combination.

New and recrudescent infections in adults, children and infants
Data for a limited number of patients show that new and recrudescent infections can be treated with a second course of artemether and lumefantrine combination.

CONTRAINDICATIONS

Artemether and lumefantrine tablets are contraindicated:

- In those with hypersensitivity to the active substances or any of the excipients.
- In cases of severe malaria.
- In the first trimester of pregnancy.

- Patients with a family history of congenital prolongation of the QTc interval such as patients with a history of symptomatic cardiac arrythmias, patients with a clinically relevant bradycardia or with severe cardiac disease, disturbances of electrolyte balance. e.g. Hypokalaemia or Hypomagnesaemia.

- Concomitant use of drugs that are known to be metabolized by cytochrome enzyme CYP2D6. (e.g. Flecainide, metoprolol, imipramine, amitryptiline, clomipramine)

- Patients taking drugs that are known to prolong the Qtc interval such as antiarrrythmias of classes IA and III, Neuroleptics, antidepressants agents, certain antibiotics including some agents of the following classes macrolides, fluoroquinolones , imidazole and triazole antifulgal agents, certain non-sedating antihistaminics (terfenadine, astemizole) cisapride.

- Artemether and lumefantrine tablets are not indicated for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary oedema or renal failure. It is also not indicated for and has not been evaluated in, the treatment of malaria due to P.vivax, P. malariae, or P.ovale.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The sequential oral administration of mefloquine prior to artemether and lumefantrine combination had no effect on plasma concentrations of artemether or the artemether / dihydroartemisinin (DHA) ratio but there was a significant (around 30-40%) reduction in plasma levels (Cmax and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Such patients should therefore be encouraged to eat at dosing times to compensate for this decrease in bioavailability.
Quinine alone caused a transient prolongation of the QTc interval, which was consistent with its known cardiotoxicity. This effect was slightly but significantly greater when quinine was infused after artemether and lumefantrine combination. Thus, prior administration of artemether and lumefantrine combination appears to enhance the inherent risk of QTc-prolongation from IV quinine.
Hence when artemether and lumefantrine combination is given to patients following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or the ECG (for quinine) should be carried out.
In patients previously treated with halofantrine, artemether and lumefantrine tablets should be administered atleast one month after the last halofantrine dose.

Due to limited data on safety and efficacy, the combination should not be given concurrently with other antimalarials unless there is no other treatment option. However, if a patient deteriorates while taking the combination, alternative treatments for malaria should be commenced without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct electrolyte disturbances.
Whereas in vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisnins have some capacity to induce the production of the cytochrome enzyme CYP2C19 and perhaps also CYP3A4. It is possible that iso-enzyme induction could alter the therapeutic effects of drugs that are predominantly metabolized by these enzymes.
Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of artemether and lumefantrine tablets with drugs that are metabolized by this iso-enzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated.

PREGNANCY AND LACTATION

Artemether and lumefantrine tablets are contraindicated during the first trimester of pregnancy. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.
As the drug is contraindicated during the first trimester of pregnancy, women of child-bearing potential should not conceive while on artemether and lumefantrine treatment for malaria. This includes women prescribed the combination for standby emergency treatment of malaria during their travel, in case they may require treatment for malaria.
Women of child-bearing potential should be advised to practice contraception during travel with standby emergency treatment, while on artemether and lumefantrine and until the start of next menstruation after the treatment.
Breast-feeding women should not take artemether and lumefantrine tablets. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume before 28th day after discontinuation of artemether + lumefantrine combination unless potential benefits to mother and child outweigh the risk of the combination treatment.

EFFECT ON ABILITY TO DRIVE AND USE MACHAINES

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

UNDESIRABLE EFFECTS

Artemether and Lumefantrine combination is well tolerated by children and adults with most adverse events being of mild to moderate severity and duration. Many of the reported events are likely to be related to the underlying malaria and/or to an unsatisfactory response to treatment rather than to the combination. Common adverse events reported with artemether and lumefantrine combination induced headache,

dizziness, sleep disorder, abdominal pain, anorexia, diarrhea, vomiting, nausea, fatigue. Somnolence, involuntary muscle contractions, paraesthesia, Hypoaesthesia, abdominal gait, ataxia were other adverse effects reported with artemether and lumefantrine combination. Rare adverse events include hypersensitivity.

Unspecified personality disorders have also been reported in children under 5 years treated with artemether and lumefantrine combination.

OVERDOSE

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

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Both Artemether and Lumefantrine act as blood schizontocides.

The site of antiparasitic action of both components of the combination 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 non-toxic haemozoin, malaria pigment.

Parasites in the infected erythrocytes ingest and degrade haemoglobin and concentrate the iron in a food vacuole in the form of toxic haem. Normally, the haem is then made harmless by conversion into haemozoin.

Artemether is concentrated in the food vacuole. It then splits its endoperoxide bridge as it interacts with haem, blocking conversion to haemozoin, destroying existing haemozoin and releasing haem and a cluster of free radicals into the parasite.

Lumefantrine is thought to interfere with the haem polymerisation process, a critical detoxifying pathway for the malaria parasite.

Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis within the malarial parasite.

Artemether and lumefantrine combination is active against the blood stages of *P. vivax*, but is not active against hypnozoites. Therefore, an 8- amino-quinoline derivative such as primaquine should be given sequentially after the combination in cases of mixed infections of *P. falciparum* and *P. vivax* to achieve hypnozoites eradication.

The combination is also associated with rapid gametocyte clearance.

Rationale for the combination of Artemether and Lumefantrine

Artemisinin and its derivatives are at present, the only effective drugs against drug resistant malaria. However their use alone may result in development of resistance to these life saving drugs. According to the new WHO malaria treatment guidelines, uncomplicated falciparum malaria must be treated with artemisinin combination therapy (ACT) and not by artemisinin alone or any other monotherapy. Artemisinin when used correctly in combination with other anti-malarial drugs is not only effective in curing malaria, but also the parasite is highly unlikely to become drug resistant.

Artemether is fast acting drug with a short half-life. Lumefantrine acts slowly and has a longer half-life. Artemether rapidly reduces parasite biomass and quickly resolves clinical symptoms, whilst the long-acting activity of lumefantrine is thought to prevent recrudescence. This dual effect also appears to reduce the selective pressure on the parasite to develop resistance. The antimalarial activity of the combination of lumefantrine and artemether is greater than that of either substance alone.

PHARMACOKINETIC PROPERTIES

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 period of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing.

Food enhances the absorption of both artemether and lumefantrine. 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 tablets were taken after a high fat meal. Likewise, in patients with

malaria, food increases the absorption of lumefantrine, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food eaten by acutely ill patients. Acutely ill patients are reluctant to eat and tend to avoid high-fat foods. In order to improve bioavailability, patients should be encouraged to take the drug with a normal diet as soon as food can be tolerated.

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). The artemisinin metabolite dihydroartemisinin is also bound to human serum proteins (47%-76%).
Artemether is rapidly and extensively metabolised by human liver microsomes (mostly through the enzyme CYP3A4/5) *in vitro* and *in vivo*, with a substantial first pass metabolism. The main active metabolite is dihydroartemisinin.

Lumefantrine is also metabolised predominantly by the enzyme CYP3A4 in human liver microsomes. At therapeutic plasma concentrations, lumefantrine significantly inhibits the enzyme CYP2D6 *in vitro*.

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of approximately 2-3 hours. Conversely, lumefantrine is

eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria.

No urinary excretion data are available for humans. In animal studies, unchanged artemether has not been detected in both faeces and urine due to its rapid and high first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs with excretion primarily in the faeces.

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
Due to the short time of treatment carcinogenicity studies with the Artemether: Lumefantrine combination was not conducted.

Reproductive toxicity studies
Reproductive oral toxicity studies in rats with the Artemether: Lumefantrine combination showed both maternal toxicity and increased post-implantation loss at doses ≥50 mg/kg (corresponding to approximately 7 mg/kg artemether). The artemether:lumefantrine combination was not embryotoxic in rats at a dose of 25 mg/kg (corresponding to 3.6 mg/kg artemether). In rabbits given orally the artemether:lumefantrine combination, maternal toxicity and increased post-implantation loss were seen at 175 mg/ kg (corresponding to 25 mg/kg artemether), while the next lower dose level of 105 mg/kg (corresponding to 15 mg/kg artemether) was entirely free of treatment-induced effects.
Lumefantrine doses as high as 1,000 mg/kg showed no evidence to suggest materno-, embryo- or foetotoxicity or teratogenicity in rats and rabbits. Artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at a dose of 6 mg/kg artesunate and 19.4 mg/kg artemether. In rats, 3 mg/kg artemether was established as the non-toxic dose. In rabbits, Artemether produced maternal toxicity and increased post-implantation loss at 30 mg/kg but no materno/embryo/foetotoxicity at doses up to 25 mg/kg. The artemisinin derivative Artesunate produced a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose used. The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemesinin exposures similar to those achieved in humans.

Cardiovascular pharmacology
In toxicity studies in dogs, only at higher doses than intended for use in man (≥600 mg/kg/day), there was some evidence of prolongation of the QTc interval. In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the currents
responsible for cardiac repolarization. This potency was lower than that of the other antimalarial drugs tested. From the estimated IC50 values, the order of potency of HERG
current block was halofantrine (IC50 = 0.04 micromolar) >chloroquine (2.5 micromolar) >mefloquine (2.6 micromolar) >desbutyl-lumefantrine (5.5 micromolar) >lumefantrine (8.1 micromolar). A study in healthy adult volunteers indicates prolongation of QTcF can occur with standard dosing of Coartem®/Riamet®

PHARMACEUTICAL PARTICULARS

INCOMPATABILITY

None known

SHELF LIFE

24 months

SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^0C, in a dry place.

Keep out of reach of children

NATURE AND CONTENTS OF CONTAINER

1. Blister of 6 tablets. 1 such Blister are packed in a printed monocarton along with a leaflet. 30 such monocartons in a printed showbox.

2. Blister of 6 tablets. 30 Such Blister are packed in a printed showbox along with a leaflet.

3. Blister of 12 tablets. 1 such Blister are packed in a printed monocarton along with a leaflet. 30 such monocartons in a printed showbox.

4. Blister of 12 tablets. 30 Such Blister are packed in a printed showbox along with a leaflet

5. Blister of 18 tablets. 1 such Blister are packed in a printed monocarton along with a leaflet. 30 such monocartons in a printed showbox.

6. Blister of 18 tablets. 30 Such Blister are packed in a printed showbox along with a leaflet

7. Blister of 24 tablets. 1 such Blister are packed in a printed monocarton along with a leaflet. 30 such monocartons in a printed showbox.

8. Blister of 24 tablets. 30 Such Blister are packed in a printed showbox along with a leaflet

SPECIAL PRECAUTIONS FOR DISPOSAL

After treatment the remaining tablets should be discarded or returned to the Pharmacist.

REGISTRANT

Name	:	Ipca Laboratories Limited
Business Address	:	48, Kandivli Industrial Estate Kandivli (west), Mumbai – 400 067 India
Postal Address	:	same as above
Country	:	India
Phone	:	91 –22- 66474444
Fax	:	91-22 – 28686613
Email	:	ipca@ipca.com