CARNARTEM 80/480

(Artemether 80 mg and Lumefantrine 480 mg Tablets Ph. Int.)

1.3 Product Information

1.3.1 Summary of product characteristics

SUMMARY OF PRODUCT CHARCTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

CARNARTEM 80/480
(Artemether 80 mg and Lumefantrine 480 mg Tablets Ph. Int.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each film coated tablet contains:
Artemether Ph. Int. 80 mg
Lumafantrine Ph. Int. 480 mg
Colour: Quinoline yellow
Excipients: q.s.

Sr. No.	Ingredients	Spec.	Qty mg/ Tab	Ovg.	Function
1.	Lumefantrine	Ph. Int	480.000	--	Active
2.	MCCP	BP	20.600	--	Binder
3.	Maize Starch	BP	24.000	--	Binder
4.	Maize Starch (Paste)	BP	11.400	--	Binder
5.	Tween 80	BP	5.000	--	Suspending agent
LUBRICANTS					
6.	Artemether	Ph.Int.	80.000	--	Active
7.	Colloidal Anhydrous Silica (Aerosil)	BP	6.000	--	Glidant
8.	Magnesium Stearate	BP	10.000	--	Lubricant
9.	Purified talc	BP	8.000	--	Glidant
10.	Croscarmellose sodium	BP	28.000	--	Disintegrant
11.	*Maize Starch (additional)	BP	3.5400	--	Binder
		Total	**673.00**		
FILM COATING					
12.	Hypromellose E- 15	BP	10.000	--	Film-former
13.	Purified Talc	BP	1.700	--	Glidant
14.	Propylene Glycol	BP	1.100	--	Plasticizer
15.	Macrogols (PEG 6000)	BP	1.200	--	Coating Agent
16.	Colour Quinoline Yellow Lake	IHS	5.000	--	Colouring Agent
17.	**Methylene Dichloride	BP	158.400	--	Solvent
18.	**Isopropyl alcohol	BP	105.450	--	Solvent
		Total	**692.000**		

* Additional quantity of Maize starch is added to compensate the loss on drying.
** Isopropyl alcohol & Methylene Dichloride are used as solvents so does not appear in the final product.

Int. Ph.: International Pharmacopoeia
BP : British Pharmacopoeia
HIS : IN- House specifications

Average weight of uncoated tablet : 673.000 mg ± 5.0 %

Average weight of film coated tablet: 692.000 mg ± 5.0 %

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

i) For the standby emergency treatment of adult and children with acute, uncomplicated infection due to P. falciparum or mixed infections including P. falciparaum.
ii) Highly effective against acute, uncomplicated malaria caused by Plasmodium failciparum in areas of multi-drug resistance. It eliminates parasites and symptoms significantly faster than most current anti-malerials.as it is a rapidly acting gametocytocidal,it helps in reducing transmission.

4.2 Posology and Method of Administration

Route of administration: Oral

Body weight (kg)	**Initial Dose**	**Following Doses**
35 and above (Adult and older children)	1 tablet at the time of initial diagnosis.	Then 1 tablet at 8, 24 and 4 hours thereafter.

Dosage in Adult Patients

35 kg bodyweight and above:

- One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice-daily (morning and evening) for the following 2 days (total course of 6 tablet).

Elderly

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

Hepatic and renal impairment

No specific studies have been carried out in these groups of patients. Therefore, no specific dose adjustment recommendations can be made for patients with hepatic impairment. Caution is advised when administering to patients with severe hepatic impairment.

4.3 Contraindications

i) Patients with Hypersensitivity to active sustances or to any of the excipients.

ii) Patients with severe malaria including cerebral malaria,or malaria with pulmonary edema or renal failure.

iii) First trimester of pregnancy.during the second and third trimester,treatment should

iv) 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.

v) patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

4.4 Special Warnings and Precautions for use

i) Administration of Artemether 80 mg and Lumefantrine 480 mg Tablets with drugs that are metabolized by the cytochrome enzyme CYP2D6 (Flecainide, metoprolol, imipramine, amitriptyline, clomipramine) should be avoided.

ii) Co-administration of Artemether 80 mg and Lumefantrine 480 mg Tablets should be with caution in patients taking drugs that are known to prolong the QTc interval such as anti-arrhythmics of classes IA and

III, neuroleptics, antidepressants, certain antibiotics including some agents of macrolides, fluoroquinolones imidazole, and trizole antifungal agents.

iii) Pregnant women (especially during 1st trimester) and nursing mothers should not be prescribed Artemether 80 mg and Lumefantrine 480 mg Tablets

iv) Driving vehicles and operating machinery should be avoided.

v) The dose should be taken with high fatty food or drinks such as milk to facilitate absorption and adequate bioavailability.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies in humans have been conducted with Artemether 80 mg and Lumefantrine 480 mg Tablets However, no safety issues that could be attributed to drug interactions arose during clinical studies with Artemether 80 mg and Lumefantrine 480 mg Tablets, in which most patients received antipyretic medication, anti-biotics and fluid and electrolyte replacement.

In-vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes.

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of clinical relevance for compounds with a low therapeutic index known to be meta-bolized by this enzyme (i.e. neuroleptics and tricyclic antidepressants).

The likelihood of adverse effects on the safety and efficacy of Artemether 80 mg and Lumefantrine 480 mg Tablets due to drug-drug interactions is minimal due to its short duration of administration and wide therapeutic index.

4.6 Pregnancy and Lactation

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, it 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. This 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 should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Artemether 80 mg and Lumefantrine 480 mg Tablets unless potential benefits to the mother and child outweigh the risks of treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether/Lumefantrine 80mg/480mg Tablets 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 frequency of adverse events reported in clinical trials of Artemether 80 mg and Lumefantrine 480 mg Tablets in the treatment of malaria was generally similar to or lower than that of other antimalarial drugs used in the clinical trials. Many of the adverse events observed during clinical testing are to the disease rather than to Artemether 80 mg and Lumefantrine 480 mg Tablets.

The most common adverse experiences (1 %) in patients treated with Artemether 80 mg and Lumefantrine 480 mg Tablets for which causality is suspected are:

Central nervous system: Sleep disorder, headache, dizziness

Cardiovascular system: Palpitation.

Gastrointestinal tract: Abdominal pain, anorexia, diarrhoea, vomiting, nausea

Respiratory tract: Cough.

Musculoskeletal system: Arthralgia, myalgia.

Others: Asthenia, fatigue

4.9 Overdose

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

5.1 Pharmacodynamic Properties

Therapeutic Category: Antimalarials, blood schizonticide.

Mechanism of action

Both components of **Artemether 80 mg and Lumefantrine 480 mg Tablets** have their own action site in the malarial parasite The presence of the endoperioxide bridge in Artemether (generating singlel oxygen and Tree radicals: those are very cytotoxic to the plasmodia) appears to be essential for antimalarial activity. Morphological changes of the parasitic membranes induced by Artemether have been described, being the result of free-radical action, Lumefantrine interferes more in the polymerization processes Other in vitro test suggest that both cause a marked diminution of nucleic acid synthesis Inhibition of protein synthesis as the basic mechanism of action is suggested in studies which showed morphological changes in ribosomes as well as in the endoplasmic reticulum.

5.2 Pharmacokinetic Properties

Pharmacokinetic characterisation of Artemether 80 mg and Lumefantrine 480 mg 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 Artemether 80 mg and Lumefantrine 480 mg 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 Artemether 80 mg and Lumefantrine 480 mg 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 metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. 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 Artemether 80 mg and Lumefantrine 480 mg 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 Artemether 80 mg and Lumefantrine 480 mg 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 a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether 80 mg and Lumefantrine 480 mg Tablets.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether 80 mg and Lumefantrine 480 mg Tablets, 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.

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.

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 toxicity studies

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

1	MCCP	BP
2	Maize Starch	BP
3	Tween 80	BP
4	Colloidal Anhydrous Silica (Aerosil)	BP
5	Magnesium Stearate	BP
6	Talcum	BP

7	Crosscarmellose Sodium	BP
8	Hypromellose E -15	BP
9	Propylene Glycol	BP
10	Macrogols (PEG 6000)	BP
11	Colour Quinoline Yellow Lake	IHS
12	Methylene Dichloride	BP
13	Isopropyl Alcohol	BP

6.2 Incompatibilities

None

6.3 Self Life

36 Months

6.4 Special Precautions for Storage

Store below 30°C.

Protect from direct sunlight, heat and moisture.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Blister Pack of 6 Tablets

6.6 Special precautions for disposal and other handling

No special requirement

CARNARTEM 80/480

(Artemether 80 mg and Lumefantrine 480 mg Tablets Ph. Int.)

7. Applicant/Manufacturer

7. Applicant/Manufacturer

MANUFACTURER BY:

Head Office Address:
FREDUN PHARMACEUTICALS LIMITED
26, Manoj Industrial Premises, G. D. Ambekar Marg,
Wadala, Mumbai- 400 031. India
Email: pravin.tari@fredungroup.com

Plant Address:
FREDUN PHARMACEUTICALS LIMITED
PLOT NO. 14,15,16, ZORABIAN INDUSTRIAL COMPLEX,
VILLAGE VEOOR, TAL. PALGHAR, THANE - 401404,
MAHARASHTRA STATE
Email: pravin.tari@fredungroup.com

APPLICANT NAME:
PART ONE PHARMACY LTD.
Carnauba Intergrated
Health Care Limited,
Block 3, FAAN Shopping Complex,
International Airport Road,
Ikeja, Lagos Nigeria.,