ARTEMETHER 80 MG AND LUMEFANTRINE 480 MG TABLETS

(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

ARTEMETHER 80 MG AND LUMEFANTRINE 480 MG TABLETS

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

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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 expecte 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.

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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).

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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.

6.1 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

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

Applicant MARCSON HEALTHCARE LIMITED, 9 ISAWO ROAD AGRIC BUSTOP

Manufacturer