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CIN NO: U24231GJ1992PLC018237

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product

1.1. Name of the medicinal product:

Generic Name/INN Name: Artemether & Lumefantrine Tablets

Trade Name: ARTEMEF-80/480 TABLETS

1.2 Strength:

Artemether .....80 mg

Lumefantrine ..... 480 mg

1.3 Pharmaceutical form: Solid Oral Dosage form (Tablet)

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specification	Qty. per Tablet (in mg)	% w/w	Function
Mixing & Binding (Part -I)					
1.	Artemether	In-House	80.000	11.834	Active
2.	Ethyl Cellulose	BP	1.595	0.236	Binder
3.	Isopropyl Alcohol	BP	15.000	----	Solvent
Mixing & Binding (Part -II)					
4.	Lumefantrine	In-House	480.000	71.006	Active
5.	Maize Starch	BP	34.405	5.089	Diluent
6.	PVP K-30	BP	6.00	0.888	Binder
7.	Isopropyl Alcohol	BP	115.435	-----	Solvent
Lubrication					
8.	Colloidal Silicon dioxide	BP	4.000	0.592	Glidant
9.	Magnesium Stearate	BP	9.000	1.331	Lubricant
10.	Sodium starch glycolate	BP	20.000	2.959	Disintegrant
11.	Purified Talc	BP	15.000	2.219	Lubricant
Total weight of uncoated Tablet			650.00 mg		
film coating					
12.	Isopropyl Alcohol	BP	217.390	----	Solvent
13.	Dichloromethane	BP	326.080	----	Solvent
14.	Di-Ethyl Phthalate	BP	3.260	0.482	Film- forming agent
15.	Polyethylene Glycol 6000	USP-NF	1.305	0.193	Plasticizer
16.	H.P.M.C. E-15	BP	10.045	[illegible]	Film- forming agent

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17.	Purified Talc	BP	7.045	1.042	Anti-tacking agent
18.	Titanium Dioxide	BP	2.175	0.322	Opacifier
19.	Col. Tartrazine Lake	In-House	2.17	0.321	Coloring agent
Net weight of film coated Tablet: 676.00 mg				100.00	

3. Pharmaceutical form:

Dosage Form: Tablets (Oral solid dosage form)

Visual & Physical characteristics of the product: A yellow coloured capsule shape, biconvex, film coated tablets having a embossed A/L on one side & 80/480 on other side & breakline on both side of tablets.

4. Clinical particulars

4.1. Therapeutic indications:

Artemef-80/480 Tablet is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adult, children and infants of 5 kg and above.

Consideration should be given to official guidance regarding the appropriate use of anti-malarial agents.

4.2. Posology and method of administration:

Posology:

Tablets for oral administration.

To increase absorption, Artemef-80/480 Tablets should be taken with food or a milky drink. If patients are unable to tolerate food, Artemef-80/480 Tablets should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For administration to small children and infants, the tablet/s may be crushed.

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

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A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:
5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.
15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.
25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Method of administration

Oral administration

4.3. Contraindications:

Artemef-80/480 Tablets are contraindicated in:

- Patients with known hypersensitivity to the active substances or to any of the excipients.
- Patients with severe malaria*.
- Patients who are taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitryptyline, clomipramine).
- Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- Patients taking drugs that are known to prolong the QTc interval (proarrythmic). These drugs include:

- Antiarrhythmics of classes IA and III,
- Neuroleptics, antidepressive agents,
- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- Certain non-sedating antihistamines (terfenadine, astemizole),
- Cisapride.
- Flecainide

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• 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.

• Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

• Patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

4.4. Special warnings and precautions for use:

Artemef-80/480 Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarial are available.

Artemether and Lumefantrine have 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, Artemef-80/480 Tablets should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Artemether and Lumefantrine, 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.

If quinine is given after Artemether and Lumefantrine, close monitoring of the ECG is advised.

If Artemef-80/480 Tablets is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Artemef-80/480 Tablets should not be administered earlier than one month after the last halofantrine dose.

Artemef-80/480 Tablets is not indicated and has not been evaluated for prophylaxis.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Artemef-80/480 Tablets should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and Lumefantrine.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemef-80/480 Tablets has the potential to cause QT prolongation.

Caution is recommended when combining Artemef-80/480 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 Artemether and Lumefantrine.

Caution is recommended when combining Artemef-80/480 Tablets with hormonal contraceptives. Artemef-80/480 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.

In patients with severe hepatic impairment, a clinically relevant increase of exposure to Artemef-80/480 Tablets and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment.

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 Artemef-80/480 Tablets in patients with renal impairment is recommended. Caution is advised when administering Artemef-80/480 Tablets to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

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No specific studies have been carried out in this group of patients. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution is advised when administering Artemef-80/480 Tablets to patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.

Elderly

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. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemef-80/480 Tablets cannot be recommended.

4.5. Interaction with other medicinal products and other forms of interaction:

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Artemef-80/480 Tablets are contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) 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 antihistaminics (terfenadine, astemizole), cisapride, flecainide

Interaction with drugs metabolized by CYP2D6

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 Artemef-80/480 Tablets Tablet with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemef-80/480 Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to [illegible]ether (89%), DHA

(85%) and lumefantrine (68%) when compared to exposure values after Artemef-80/480 Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether and lumefantrine.

Inducers should not be administered at least one month after Artemef-80/480 Tablets administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Artemef-80/480 Tablets should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If Artemef-80/480 Tablets is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether and lumefantrine. In patients previously treated with halofantrine, Artemef-80/480 Tablets should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Artemef-80/480 Tablets in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of Artemef-80/480 Tablets were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours)

was given sequentially 2 hours after the last (sixth) dose of Artemef-80/480 Tablets (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemef-80/480 Tablets to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemef-80/480 Tablets in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of Artemether and lumefantrine.

Concomitant use requiring caution

Interactions affecting the use of Artemether and lumefantrine

Interaction with CYP3A4 inhibitors

Artemef-80/480 Tablets are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with Artemef-80/480 Tablets 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. Based on this study, dose adjustment of Artemef-80/480 Tablets is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Artemef-80/480 Tablets should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Grapefruit juice

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Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug. Grapefruit juice should be used cautiously during Artemef-80/480 Tablets treatment.

Interaction with weak to moderate inducers of CYP3A4

When Artemef-80/480 Tablets is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Artemef-80/480 Tablets are metabolized by CYP3A4. Anti-retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Artemef-80/480 Tablets should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and lumefantrine, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Artemether and lumefantrine.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

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Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of Artemether and lumefantrine.

Interactions resulting in effects of Artemef-80/480 Tablets on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemef-480/480 Tablets is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. 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 of drugs that are predominantly metabolised by these enzymes.

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Artemef-80/480 Tablets may potentially reduces the effectiveness of hormonal contraceptives. 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.

Drug-food/drink interactions

Artemef-80/480 Tablets should be taken with food or drinks rich in fat such as milk as the absorption of Artemef-80/480 Tablets is increased.

Grapefruit juice should be used cautiously during Artemef-80/480 Tablets treatment.

4.6. Pregnancy and lactation:

Pregnancy

There is insufficient data from the use of Artemef-80/480 Tablets in pregnant women. Based on animal data, Artemef-80/480 Tablets 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.

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemef-80/480 Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Artemef-80/480 Tablets 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 fetus.

Women of childbearing potential

Women 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemef-80/480 Tablets 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 Artemef-80/480 Tablets unless potential benefits to the mother and child outweigh the risks of Artemef-80/480 Tablets treatment.

Fertility

There is no information on the effects of Artemef-80/480 Tablets on human fertility.

4.7. Effects on ability to drive and use machines:

Patients receiving Artemef-80/480 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:

	Adults and adolescents above 12 years of age	**Infants and children of 12 [illegible] age and below**

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

		(incidence estimates)
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Very common (8.4 %)

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

4.9. Overdose:

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

5. Pharmacological properties:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: Antimalarial

ATC code: P01 BF01

Pharmacodynamic effects:

Artemef-80/480 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

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artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both Artemef-80/480 Tablets have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of Artemef-80/480 Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µL - 200,000/µL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

• 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28

• Parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours

• fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

5.2. Pharmacokinetic properties:

Pharmacokinetic characterisation of Artemef-80/480 Tablets is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of Artemef-80/480 Tablets plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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 Absorption of lumefantrine, a highly lipophilic compound, and starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. 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 Artemef-80/480 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. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Artemef-80/480 Tablets 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%).

Biotransformation

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 and lumefantrine, 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.

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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 Artemef-80/480 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 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.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether and lumefantrine, 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 Artemef-80/480 Tablets dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of as tablets and crushed tablets in healthy adults.

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Systemic exposure to lumefantrine was similar following administration of Artemef-80/480 Tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of Artemef-80/480 Tablets was demonstrated in this population.

Special populations

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both Artemef-80/480 Tablets may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to Artemef-80/480 Tablets and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of Artemef-80/480 Tablets in patients with renal impairment is advised.

5.3. Preclinical safety data

No data available

6. Pharmaceutical particulars:

6.1. List of Excipients:

Ethyl Cellulose
Isopropyl Alcohol
Maize Starch
PVP K-30
Isopropyl Alcohol
Colloidal Silicon dioxide
Magnesium Stearate
Sodium starch glycolate

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Purified Talc
Isopropyl Alcohol
Dichloromethane
Di-Ethyl Phthalate
Polyethylene Glycol
H.P.M.C. E-15
Purified Talc
Titanium Dioxide
Col. Tartrazine Lake

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

24 months

6.4. Special precautions for storage:

Store below 30°C.

6.5. Nature and contents of container:

Pack Style: 1×6 Tablets

6 tablets are packed in 1 ALU - ALU Blister. Such 1 ALU-ALU blisters is packed in printed monocarton of Artemef-80/480 Tablets with patient information leaflet.

6.6. Special precautions for disposal:

No special requirement.

7. Applicant:

Name and Address of Applicant

Evans Therapeutics Limited

24 Abimbola Way,

Isolo Industrail Estate,

Isolo, Lagos, Nigeria

Name and Address of manufacturer:

M/s. Bharat Parenterals Limited

Survey No. 144 &146, Jarod Samlaya Road,

Village: Haripura, Ta. Savli, Dist. Vadodara – 391520

PARENTERALS LTD. VADODARA INDIA BHARAT

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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