1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

CETHAR 20/120 SOFTGEL CAPSULES

ARTEMETHER 20MG AND LUMEFANTRINE 120MG

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Each Soft Gelatin Capsule contains

Artemether……20 mg

Lumefantrine …….120 mg

Excipients ……..……. Q.S.

Qualitative & Quantitative Composition Formula:

Batch Size: 100000 Nos Soft gelatin Capsules

Name of Ingredient	Specification	Wt. per Capsules (mg)	O.A % per Caps	Qty. per Caps. With O.A % (mg)	Total Qty per Batch (kg)	Function
Active Ingredients						
Artemether Ph. Int	IH	20 mg	--	20 mg	2.0	**Active**
Lumefantrine Ph. Int	IH	120 mg	--	120 mg	12	**Active**
Excipients						
Soyabean Oil	USP	279.9 mg	--	279.9 mg	27.99	**Pharmaceutical Aid (Vehicle)**
White Bees Wax	BP	5 mg	--	5 mg	0.5	**Thickening agent**
Butylated Hydroxy Anisole	BP	0.08 mg	--	0.08 mg	0.008	**Antioxidant**
Butylated Hydroxy Toluene	BP	0.02 mg	--	0.02 mg	0.002	**Antioxidant**
Soya Lecithin	USP	45 mg	--	45 mg	4.5	**Emulsifying agent**
Total				**890 mg**	**89 kg**	

3. Pharmaceutical Form

Soft gelatin Capsules

Orange Opaque, Oval shaped soft gelatin capsule Containing Pale Yellow colored homogenous oily Paste.

4. Clinical Particulars

4.1. Therapeutic indications:

Artemether and Lumefantrine Softgel Capsules are indicated for the treatment of P. falciparum malaria cases resistant to both Chloroquine and Sulphadoxine-Pyrimethamine combination.

The combination is recommended for first line treatment of malaria.

4.2 Posology and method of administration

CETHAR 20/120

Weight in Kg	**Total SOFTGEL CAPSULES**	**Dosage Regimen**					
		Day – 1		Day – 2		Day – 3	
		0 Hour	8 Hours	24 Hours	36 Hours	48 Hours	60 Hours
5 - 14	6	1	1	1	1	1	1
15 – 24	12	2	2	2	2	2	2
25 – 34	18	3	3	3	3	3	3
35 - and More (Adults)	24	4	4	4	4	4	4

Artemether and Lumefantrine Softgel Capsules should be taken with high fat food or drinks such as milk. Note that patients with acute malaria 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 1 hour of administration a repeat dose should be taken.

For adults and children weighing 35 kg and above, a standard three days treatment schedule with a total of 6 doses is recommended as follows: four Softgel Capsule as a single dose at the time of initial diagnosis; again four Softgel Capsules after eight hours and then four Softgel Capsules

twice daily (morning and evening) on each of the following two days (total comprises 24 Softgel Capsules).

For infant and children weighing 5 to less than 35 kg, a six-dose regimen is recommended with 1 to 3 Softgel Capsules per dose, depending on bodyweight. With very small children, the Softgel Capsule should be crushed before giving.

Special population:

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 specific studies have been carried out in these groups of patients and no specific dose adjustment recommendations can be made for these patients. Most patients with acute malaria present with 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 adult, 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.

4.3 Contraindications

CETHAR 20/120 is contraindicated in:

• patients with known hypersensitivity to the active substances or to any of the excipients

• patients with severe malaria according to WHO definition*.

• patients who are taking any drug which is metabolised 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

• 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*).

(*Presence of one or more of the following clinical or laboratory features:

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

Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

CETHAR 20/120 must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

CETHAR 20/120 has 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, CETHAR 20/120 should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment option.

If a patient deteriorates whilst taking CETHAR 20/120, 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 CETHAR 20/120.

If quinine is given after CETHAR 20/120, close monitoring of the ECG is advised.

If CETHAR 20/120 is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, CETHAR 20/120 should not be administered earlier than one month after the last halofantrine dose.

CETHAR 20/120 is not indicated and has not been evaluated for prophylaxis of malaria.

CETHAR 20/120 should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of CETHAR 20/120.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) CETHAR 20/120 has the potential to cause QT prolongation.

Caution is recommended when combining CETHAR 20/120 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 CETHAR 20/120.

Caution is recommended when combining CETHAR 20/120 with hormonal contraceptives. CETHAR 20/120 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.

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 CETHAR 20/120 in patients with renal impairment is recommended. Caution is advised when administering CETHAR 20/120 to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

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 CETHAR 20/120. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of CETHAR 20/120 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

CETHAR 20/120 is 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 CETHAR 20/120 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 CETHAR 20/120 Softgel capsules(6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after CETHAR 20/120 alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with CETHAR 20/120.

Inducers should not be administered at least one month after CETHAR 20/120 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 CETHAR 20/120 should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If CETHAR 20/120 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 CETHAR 20/120. In patients previously treated with halofantrine, CETHAR 20/120 should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with CETHAR 20/120 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 CETHAR 20/120 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 CETHAR 20/120 (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 CETHAR 20/120 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 CETHAR20/120 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 CETHAR 20/120.

Concomitant use requiring caution

Interactions affecting the use of HAVAX 20/120

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine 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 CETHAR 20/120 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 CETHAR 20/120 is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

CETHAR 20/120 should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc (see Section 4.3 Contraindications), due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When CETHAR 20/120 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

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. CETHAR 20/120 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 CETHAR 20/120, 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 CETHAR 20/120.

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

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 CETHAR 20/120.

Interactions resulting in effects of CETHAR 20/120 on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When CETHAR 20/120 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, CETHAR 20/120 may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control for about one month.

Drug-food/drink interactions

CETHAR 20/120 should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased.

Grapefruit juice should be used cautiously during CETHAR 20/120 treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6. Use in pregnancy and lactation:

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.

Pregnancy

Based on animal data, CETHAR 20/120 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.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to CETHAR 20/120 (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.

CETHAR 20/120 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.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking CETHAR 20/120 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 CETHAR 20/120 unless potential benefits to the mother and child outweigh the risks of CETHAR 20/120 treatment.

Fertility

There is no information on the effects of CETHAR 20/120 on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

None anticipated.

4.8 Undesirable effects

The safety of CETHAR 20/120 has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received CETHAR 20/120 in clinical trials.

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 <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (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	Common (8.4 %)
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	--

*: These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

4.9. Overdose:

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01.

Pharmacodynamic effects

CETHAR 20/120 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.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of CETHAR 20/120 Softgel capsuleswas 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:

Table 2 Clinical efficacy results

Study No.	**Age**	**Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients**	**Median FCT[2] [25th, 75th percentile]**	**Median PCT[2] [25th, 75th percentile]**	**Year/ Study location**
A025[4]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries

					in Africa
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

[1] Efficacy cure rate based on blood smear microscopy

[2] mITT population

[3] For patients who had a body temperature >37.5°C at baseline only

[4]Only the 6-dose regimen over 60 hours group data is presented

[CT] –CETHAR 20/120 softgel capsulesadministered as crushed softgel capsules

[DT] –CETHAR 20/120 Dispersible softgel capsules

CETHAR 20/120 is not indicated for, and has not been evaluated in, the treatment of malaria due to *P. vivax, P. malariae* or *P. ovale,* although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. CETHAR 20/120 is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population

Two studies have been conducted

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5°C. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours. This study compared crushed softgel capsulesand dispersible softgel capsules. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed softgel capsulesare reported in table 3 below.

Table 3 Clinical efficacy by weight for pediatric studies

Study No.	**Median PCT[1]**	**PCR-corrected 28-day cure**

Weight category	**[25th, 75th percentile]**	**rate[2]n/N (%) in evaluable patients**
Study A2403		
5 - <10 kg	24 hours [24, 36]	145/149 (97.3)
10 - <15 kg	35 hours [24, 36]	103/107 (96.3)
15 -25 kg	24 hours [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 hours [24, 36]	65/69 (94.2)
10 - <15 kg	35 hours [24, 36]	174/179 (97.2)
15 -<25 kg	35 hours [24, 36]	134/140 (95.7)
25-35 kg	26 hours [24, 36]	30/31 (96.8)

[1] mITT population

2 Efficacy cure rate based on blood smear microscopy

[CT]CETHAR 20/120 softgel capsulesadministered as crushed softgel capsules

QT/QTc Prolongation:

Adults and children with malaria

For information on the risk of QT/QTc prolongation in patients

Healthy adults

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of CETHAR 20/120 was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving CETHAR 20/120 experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of CETHAR 20/120 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 CETHAR 20/120, 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 CETHAR 20/120 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%).

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 CETHAR 20/120, 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 described in section 4.5

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 CETHAR 20/120 over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). 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 (see sections 4.3 and 4.5).

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 CETHAR 20/120.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of CETHAR 20/120, 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 CETHAR 20/120 dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of CETHAR 20/120 as dispersible softgel capsulesand crushed softgel capsulesin healthy adults.

Systemic exposure to lumefantrine was similar following administration of CETHAR 20/120 dispersible softgel capsulesand intact softgel capsulesin 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 softgel capsulesin the paediatric population since adequate efficacy of CETHAR 20/120 dispersible softgel capsuleswas demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Older people

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.

Paediatric population

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of CETHAR 20/120) were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of CETHAR 20/120) were 577, 699 and 1150 μg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 μg•h/mL (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

Hepatic and Renal impairment

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine 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 CETHAR 20/120 in patients with renal impairment is advised.

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.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats

dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether:lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats . Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses ≥600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC_{50} was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite.

Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Soya bean oil	USP NF
White bees wax	BP
Butyl hydroxyl anisole	BP
Butylated hydroxyl toluene	BP
Soya lecithin	USP

6.2 Incompatibilities

None Known

6.3 Shelf life

24 years

6.4 Special precautions for storage

Store in a cool & dry Place, Protect from Light.

6.5 Nature and contents of container

CETHAR 20/120 is packed in an Alu-PVC Blister of 8 Capsules, such 3 Blister are packed in a primary carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7- Marketing Authorization Holder:

SUITLIFE PHARMACEUTICALS LIMITED

8- Marketing Authorization Number (s):

Product license / registration Number (s)

9- Manufacturer Name:

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