NALIS® ARTEMETHER 80 mg + LUMEFANTRINE 480 mg TABLETS

(Magnesium Trisilicate 250mg, Light Magnesium Carbonate 250mg and Sodium Bicarbonate 250mg)

SUBMITTED BY: NALIS PHARMACEUTICALS LTD

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SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC).

1 NAME OF THE MEDICINAL PRODUCT:

Nalis® Artemether 80 mg + Lumefantrine 480 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yellow-coloured biconvex-shaped uncoated tablets.

Each Uncoated Tablet contains:
Artemether IP……..**80 mg**
Lumefantrine IP……..**480 mg**
Excipients……..**q.s**

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nalis Artemether 80 mg + Lumefantrine 480 mg Tablet is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above. Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

4.2 Posology and method of administration

Posology

Oral use
Table 1: Number of Artemether + Lumefantrine tablet for treatment according to weight bands

Weight range	1st day of treatment	2nd day of treatment	3rd day of treatment
≥ 5kg to < 15kg	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)
15kg to <25kg	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)
25kg to <35kg	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L))
≥ 35kg (or ≥ 12 years of age	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration.

The first dose should be followed by a second dose after 8 hours. The following two days the doses of Artemether + Lumefantrine tablet should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, Artemether + Lumefantrine tablet should be taken with food or a milky drink. If a patient is unable to tolerate food, Artemether + Lumefantrine tablet should still be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For very young children, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

Renal or hepatic impairment
No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Artemether + Lumefantrine tablet to patients with severe renal or hepatic problems.

Elderly

No special precautions or dosage adjustments are necessary in such patients.
The dispersible tablet(s) for one dose should be stirred in a small amount of water (approximately 10 ml per tablet) so that the active substance can be better dispersed before the suspension is drunk. Stir gently and administer immediately to the patient. Pour some more water (approximately 10 ml) into the glass and give immediately to the patient.

4.3 Contraindications

Artemether & Lumefantrine is contraindicated in:
• patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
• 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, amitrypt**yline, 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 cardia**c 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

Artemether & Lumefantrine must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).
Artemether & Lumefantrine 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, Artemether & Lumefantrine 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 Artemether & 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 & Lumefantrine.
If quinine is given after Artemether & Lumefantrine, close monitoring of the ECG is advised (see section 4.5).
If Artemether & Lumefantrine is given after mefloquine, close monitoring of food intake is advised (see section 4.5).
In patients previously treated with halofantrine, Artemether & Lumefantrine should not be administered earlier than one month after the last halofantrine dose.
Artemether & Lumefantrine is not indicated and has not been evaluated for prophylaxis of malaria.
Artemether & Lumefantrine 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 Artemether & Lumefantrine, (see section 4.5).
Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether & Lumefantrine has the potential to cause QT prolongation (see section 5.1).
Caution is recommended when combining Artemether & Lumefantrine 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 & Lumefantrine (see sections 4.5 and 5.2).
Caution is recommended when combining Artemether & Lumefantrine with hormonal contraceptives. Artemether & Lumefantrine 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 (see sections 4.5).
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 Artemether & Lumefantrine in patients with renal impairment is recommended. Caution is advised when administering Artemether & Lumefantrine 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 (see section 5.2). 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 Artemether & Lumefantrine. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether & Lumefantrine cannot be recommended.

4.5 Interaction with other medicinal products

Interaction with drugs that are known to prolong the QTc interval
Artemether & Lumefantrine 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 (see section 4.3)
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 Artemether & Lumefantrine 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 (see sections 4.3 and 5.2).
Interaction with strong inducers of CYP3A4 such as rifampin
Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemether & Lumefantrine Tablets (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 Artemether & Lumefantrine alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether & Lumefantrine (see section 4.3).
Inducers should not be administered at least one month after Artemether & Lumefantrine administration, unless critical to use as judged by the prescriber.
Concomitant use not recommended
Interaction with other antimalarial drugs (see section 4.4)
Data on safety and efficacy are limited, and Artemether & Lumefantrine should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section 4.4).
If Artemether & Lumefantrine 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 & Lumefantrine. In patients previously treated with halofantrine, Artemether & Lumefantrine should not be administered earlier than one month after the last halofantrine dose (see section 4.4).
Mefloquine
A drug interaction study with Artemether & Lumefantrine 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 Artemether & Lumefantrine 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 Artemether & Lumefantrine (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 Artemether & Lumefantrine 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 Artemether & Lumefantrine 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 & Lumefantrine.

Concomitant use requiring caution
Interactions affecting the use of Artemether & Lumefantrine

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 Artemether & Lumefantrine 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 Artemether & Lumefantrine is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.
Artemether & Lumefantrine 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 Artemether & Lumefantrine is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy (see section 4.4).

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. Artemether & Lumefantrine 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 & Lumefantrine, and increased lumefantrine concentrations may cause QT prolongation (see Section 4.4).

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 & 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
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 & Lumefantrine.

Interactions resulting in effects of Artemether & Lumefantrine on other drugs
Interaction with drugs metabolized by CYP450 enzymes
When Artemether & Lumefantrine 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 (see sections 4.4 and 5.2).
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, Artemether & Lumefantrine 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 (see sections 4.4 and 4.6).

Drug-food/drink interactions
Artemether & Lumefantrine should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see Section 4.2).
Grapefruit juice should be used cautiously during Artemether & Lumefantrine 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 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 (see section 4.4).

Pregnancy
Based on animal data, Artemether & Lumefantrine is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 4.4 and 5.3)
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 (see section 5.3).
Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether & Lumefantrine (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.
Artemether & Lumefantrine treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). 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 Artemether & Lumefantrine 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 Artemether & Lumefantrine unless potential benefits to the mother and child outweigh the risks of Artemether & Lumefantrine treatment.

Fertility
There is no information on the effects of Artemether & Lumefantrine on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients receiving Artemether & Lumefantrine 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 safety of Artemether & Lumefantrine 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 Artemether & Lumefantrine 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.

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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: antimalarials, blood schizontocide, ATC code: P01BF01.

Pharmacodynamic effects

Artemether & Lumefantrine 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 Artemether & Lumefantrine 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:

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, 75thpercentile]	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] –Artemether & Lumefantrine tablets administered as crushed tablets

[DT] –Artemether & Lumefantrine Dispersible tablets

Artemether & Lumefantrine 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. Artemether & Lumefantrine 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 tablets and dispersible tablets. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed tablets are reported in table 3 below.

Table 3 Clinical efficacy by weight for pediatric studies

Study No. Weight category	Median PCT[1] [25th, 75th percentile]	PCR-corrected 28-day cure 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] Artemether & Lumefantrine tablets administered as crushed tablets

QT/QTc Prolongation:

Adults and children with malaria

For information on the risk of QT/QTc prolongation in patients see section 4.4

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 Artemether & Lumefantrine 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 Artemether & Lumefantrine 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 Artemether & Lumefantrine 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 & Lumefantrine, 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 & Lumefantrine 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 Artemether & 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. 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 Artemether & Lumefantrine 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 Artemether & 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 & 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 Artemether & Lumefantrine dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies
Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Artemether & Lumefantrine as dispersible tablets and crushed tablets in healthy adults.
Systemic exposure to lumefantrine was similar following administration of Artemether & Lumefantrine dispersible 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 Artemether & Lumefantrine dispersible tablets was 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 Artemether & Lumefantrine) 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 Artemether & Lumefantrine) 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 Artemether & Lumefantrine 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate	BP
Microcrystalline Cellulose	BP

Sodium Starch Glycolate	BP
Povidone	BP
Tartrazine Yellow	In House
Magnesium Stearate	BP
Purified Talc	BP

6.2 Incompatibilities
None stated except as in 'Interactions with other medicaments'.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30°C.
Keep away from light

6.5 Nature and contents of container
6 tablets to be packed in a blister made up of rigid non toxic PVC and printed aluminum foil. Such a blister are packed in a carton along with a leaflet.

6.6 Special precautions for disposal and other handling
None

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

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9. NAFDAC REGISTRATION NUMBER(S)

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