SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artemether & Lumefantrine 20/120 tablets [Uncoated]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Artemether & Lumefantrine 20/120 tablets [Uncoated] is a fixed dose combination and each tablet contains artemether 20 mg and lumefantrine 120 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated Tablets

Yellow colored circular, flat, bevel edged tablet with break line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Artemether & Lumefantrine 20/120 tablets [Uncoated] is a fixed combination of Artemether and Lumefantrine, which acts as a blood schizontocide. It 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 antimalarial agents.

4.2 Posology and method of administration

Tablets for oral administration.

To increase absorption, Artemether & Lumefantrine 20/120 tablets [Uncoated] should be taken with food or a milky drink (see section 5.2). If patients are unable to tolerate food, Artemether & Lumefantrine 20/120 tablets [Uncoated] 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.

<u>Adults and children weighing 35 kg and above</u>

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

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.

Elderly

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

Renal or hepatic impairment

Caution is advised when administering Artemether & Lumefantrine 20/120 tablets [Uncoated] to patients with severe renal or hepatic problems. In these patients, ECG and blood potassium monitoring is advised.

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 20/120 tablets [Uncoated]. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether & Lumefantrine 20/120 tablets [Uncoated] cannot be recommended.

4.3 Contraindications

Artemether & Lumefantrine 20/120 tablets [Uncoated] is contraindicated in:

- Hypersensitivity to Artemether, Lumefantrine or to any of the excipients of Artemether & Lumefantrine 20/120 tablets [Uncoated].
- Patients with severe malaria according to WHO definition.
- First trimester of pregnancy in situations where other suitable and effective anti-malarials are available (see section Pregnancy and Lactation).
- Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- Patients taking drugs that are known to prolong the QTc interval 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.
  - Patients with known disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia.
  - Patients taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

4.4 Special warnings and precautions for use

Artemether & Lumefantrine 20/120 tablets [Uncoated] 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 20/120 mg 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 20/120 tablets [Uncoated] 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 20/120 mg, 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 20/120 tablets [Uncoated].

If quinine is given after Artemether & Lumefantrine 20/120 tablets [Uncoated] close monitoring of the ECG is advised (see section 4.5).

If Artemether & Lumefantrine 20/120 tablets [Uncoated] is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, Artemether & Lumefantrine 20/120 tablets [Uncoated] should not be administered earlier than one month after the last halofantrine dose.

Artemether & Lumefantrine 20/120 tablets [Uncoated] 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 20/120 tablets [Uncoated] is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Artemether & Lumefantrine 20/120 tablets [Uncoated] is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether & Lumefantrine 20/120 tablets [Uncoated]

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving Artemether & Lumefantrine 20/120 tablets [Uncoated] 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 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.

Caution is recommended when combining Artemether & Lumefantrine 20/120 tablets [Uncoated] with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered (see sections 4.5 and 5.2).

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Caution is advised when administering Artemether & Lumefantrine 20/120 tablets [Uncoated] to patients with severe renal, hepatic or cardiac problems (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other antimalarials (see section 4.4)

A drug interaction study with Artemether/Lumefantrine 20/120 mg 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 20/120 tablets [Uncoated] 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.

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 20/120 tablets [Uncoated] (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 20/120 tablets [Uncoated] 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 20/120 tablets [Uncoated] 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 20/120 mg.

Interaction with CYP450 3A4 inhibitors (ketoconazole)

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with Artemether & Lumefantrine 20/120 tablets [Uncoated] 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 20/120 tablets [Uncoated] is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Interaction with CYP450 enzymes

Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and zCYP1A2. 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).

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 20/120 tablets [Uncoated] with drugs that are metabolised by this iso-enzyme is contraindicated (see section 4.3 and 5.2). *In vitro* studies indicated that lumefantrine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with Artemether/Lumefantrine 20/120 mg, requires clinical surveillance and monitoring of clinical response/undesirable effects.

Other interactions

Administration of Artemether & Lumefantrine 20/120 tablets [Uncoated] is contra-indicated in patients taking drugs that are known to prolong the QTc interval (see section 4.3).

In patients previously treated with halofantrine, Artemether & Lumefantrine 20/120 tablets [Uncoated] should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, Artemether & Lumefantrine 20/120 tablets [Uncoated] should not be given concurrently with any other antimalarial agent.

In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Artemether & Lumefantrine 20/120 tablets [Uncoated] to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy and lactation

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Artemether/Lumefantrine 20/120 mg 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). Artemether & Lumefantrine 20/120 tablets [Uncoated] 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether & Lumefantrine 20/120 tablets [Uncoated] should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Artemether & Lumefantrine 20/120 tablets [Uncoated] unless potential benefits to the

mother and child outweigh the risks of Artemether & Lumefantrine 20/120 tablets [Uncoated] treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether & Lumefantrine 20/120 tablets [Uncoated] should be warned that dizziness or fatigue/asthenia might occur in which case they should not drive or use machines.

4.8 Undesirable effects

The frequency of adverse events reported during clinical trials with Artemether & Lumefantrine 20/120 tablets [Uncoated] was similar to or lower than that of other antimalarial drugs used as comparators.

Artemether & Lumefantrine 20/120 tablets [Uncoated] appeared to be well tolerated by infants, children and adults. Most of the reported events were of mild to moderate severity and duration, and likely related to the underlying malaria and/or to an unsatisfactory response to the treatment rather than to Artemether & Lumefantrine 20/120 tablets [Uncoated] although a causal relationship with the use of Artemether & Lumefantrine 20/120 tablets [Uncoated] could not be excluded for some reports. For other reports alternative factors were identified as the more likely cause of the events (e.g. concomitant drugs, concomitant infections) or the information provided was too scarce to draw any conclusion.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000), including isolated reports.

Table 1 represents a pooled safety analysis of adverse reactions from clinical trials in adults and adolescents >12 years of age or ≥35 kg body weight using the recommended 6-dose regimen.

Table 1

Metabolism and nutrition disorders	
Very common	anorexia
Psychiatric disorders	
Very common	Sleep disorders
Nervous system disorders	

Very common	Head ache, dizziness
Un common	Somnolence, hypoaesthesia, ataxia
Cardiac disorders	
Very common	Palpitation
Respiratory, thoracic and mediastinal disorders	
Common	cough
Gastrointestinal disorders	
Very common	Vomiting, abdominal pain, nausea
Common	diarrhoea
Skin and subcutaneous tissue disorders	
common	Rash, pruritus
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia
General disorders and administration site conditions	
Very common	Asthenia, fatigue
uncommon	Gait abnormal
Investigations	
common	Liver function tests increased
Uncommon	Electrocardiogram QT corrected interval prolonged

Table 2 is compiled from a pooled safety analysis of 4 studies in infants and children ≤12 years of age and ≥5 kg to <35 kg body weight receiving a 6-dose regimen of artemether/ lumefantrine.

Table 2

Immune system disorders	
Rare	Hypersensitivity
Metabolism and nutrition disorders	
Very common	anorexia
Psychiatric disorders	
uncommon	Sleep disorders
Nervous system disorders	
common	Head ache, dizziness
Un common	Somnolence,

Cardiac disorders	
uncommon	Palpitation
Respiratory, thoracic and mediastinal disorders	
Very common	cough
Gastrointestinal disorders	
Very common	Vomiting, abdominal pain, nausea
Common	diarrhoea
Skin and subcutaneous tissue disorders	
common	Rash
Uncommon	Pruritus
Musculoskeletal and connective tissue disorders	
common	Arthralgia, myalgia
General disorders and administration site conditions	
common	Asthenia, fatigue
Investigations	
common	Liver function tests increased
Rare	Electrocardiogram QT corrected interval prolonged

In this pooled safety analysis, mood swings have been reported in less than 1.2% of thepaediatric patients treated with Artemether & Lumefantrine 20/120 tablets [Uncoated], but they were not considered drug-related by the Investigators.

Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (1.2% of adolescents and adults, no cases in children); involuntary muscle contractions (1.3% of children).

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: antimalarial ATC code: P01 BE52

5.2 Pharmacokinetic properties

Pharmacodynamic effects

Artemether & Lumefantrine 20/120 tablets [Uncoated] tablet contains 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 non-toxic 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.

The antimalarial activity of the combination of lumefantrine and artemether in Artemether & Lumefantrine 20/120 tablets [Uncoated] is greater than that of either substance alone. In a double-blind comparative study in adults in China (n = 157), the 28-day cure rate of Artemether & Lumefantrine 20/120 tablets [Uncoated] when given as 4 doses was 94%, compared with 90% for lumefantrine and 46% for artemether based in intent-to-treat (ITT) population, when given as monotherapy. For the evaluable population, the 28-day cure rates were 100% for Artemether & Lumefantrine 20/120 tablets [Uncoated] compared with 92% for lumefantrine and 55% for artemether when given as monotherapy.

In areas where multi-drug-resistant strains of *P. falciparum* malaria are common and in the resident population, 28-day cure rates with the 6-dose regimen (given over 60 or 96 h) were 81% and 90% for Artemether & Lumefantrine 20/120 tablets [Uncoated] versus 94% and 96% for mefloquine/artesunate, based on the ITT population. For the evaluable population, 28-day cure rates were 97% and 95% for Artemether & Lumefantrine 20/120 tablets [Uncoated] and 100% for mefloquine/artesunate.

In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with Artemether & Lumefantrine 20/120 tablets [Uncoated] was 96 h. Artemether & Lumefantrine 20/120 tablets [Uncoated] was associated with more rapid gametocyte clearance than any comparator other than mefloquine/artesunate. Artemether & Lumefantrine 20/120 tablets [Uncoated] is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites (see section Special Warnings And Precautions For Use).

In non-immune adult patients living in regions free of malaria but with malaria acquired when travelling in endemic regions, a similar efficacy and safety profile was shown. In an open study

(n=165) in adults the 28-day cure rate for Artemether & Lumefantrine 20/120 tablets [Uncoated] given as the 6-dose regimen was 96% (119/124) for the evaluable and 74.1% (120/162) for the ITT population. The difference between evaluable and ITT population cure rates was due to 38 patients who were excluded from the evaluable population for the following reasons: 33 patients were lost to follow up, 19 of whom had no evaluation, 14 of whom had parasitic clearance at Day 7 but their efficacy status at Day 28 was unknown and 5 patients took concomitant medications that were not permitted by the protocol. All these patients were considered as treatment failures in the ITT analysis**.**

Children from non-endemic countries were not included in clinical trials.

QT/QTc Prolongation: 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 20/120 tablets [Uncoated] was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 h post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 h 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 h after the single dose with a maximal change at 1 h after dose of 14.1 msec.

No clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) has been reported

PHARMACOKINETICS

Artemether & Lumefantrine 20/120 tablets [Uncoated] tablet is bioequivalent to Coartem tablets. Pharmacokinetic characterization of Artemether & Lumefantrine 20/120 tablets [Uncoated] is limited by the lack of an intravenous formulation, and the very high inter- and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6 to 8 hours after administration. 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 20/120 tablets [Uncoated] 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% to 76%). Protein binding to human plasma protein is linear.

Biotransformation

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans *in vivo*. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. Arthemether and DHA were reported to have a mild inducing effect on CYP3A4 activity, which is not expected to present a problem in the general patient population (see sections Special Warnings And Precautions For Use And Interactions).

During repeated administration of Artemether & Lumefantrine 20/120 tablets [Uncoated], plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for the metabolism of artemether. The clinical evidence of induction is consistent with the *in vitro* data described in section Interactions.

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 systemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent compound.

In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see sections Contraindications and Interactions).

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2 to 3 days in healthy volunteers and 4 to 6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether & Lumefantrine 20/120 tablets [Uncoated].

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing to rats and dogs, metabolites (glucuronides of lumefantrine and of the des-butyl metabolite) were excreted with bile. Most of the dose was recovered in the form of the parent drug in faeces (including unabsorbed drug and drug released from glucuronide).

Pharmacokinetics in special patient populations

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of Artemether & Lumefantrine 20/120 tablets [Uncoated]) 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 20/120 tablets [Uncoated]) 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

]No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients.

Systemic exposure to artemether, DHA, and lumefantrine when dosed on a mg/kg body weight basis in paediatric malaria patients (≥5 to <35 kg body weight) is comparable to that of the recommended dosing regimen in adult malaria patients

5.3 Preclinical safety data

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Mutagenicity

No evidence of mutagenicity was detected in *in vitro* or *in vivo* tests with an artemether &lumefantrine combination (consisting of 1 part artemether:6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1000 and 2000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Due to the short time of treatment carcinogenicity studies with the artemether & lumefantrine combination were not conducted.

Reproductive toxicity studies

Reproductive oral toxicity studies in rats with the artemether &lumefantrine combination showed both maternal toxicity and increased post-implantation loss at doses □50 mg/kg (corresponding to approximately 7 mg/kg artemether). The artemether & lumefantrine combination was not embryotoxic in rats at a dose of 25 mg/kg (corresponding to 3.6 mg/kg artemether). In rabbits given orally the artemether & lumefantrine combination, maternal toxicity and increased post-implantation loss were seen at 175 mg/kg (corresponding to 25 mg/kg artemether), while the next lower dose level of 105 mg/kg (corresponding to 15 mg/kg artemether) was entirely free of treatment-induced effects.

Lumefantrine doses as high as 1000 mg/kg showed no evidence to suggest materno-, embryo- or foetotoxicity or teratogenicity in rats and rabbits.

Artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at a dose of 6 mg/kg artesunate and 19.4 mg/kg artemether. In rats, 3 mg/kg artemether was established as the non-toxic dose. In rabbits, artemether produced maternal toxicity and increased post-implantation loss at 30 mg/kg but no materno/embryo/foetotoxicity at doses up to 25 mg/kg. The artemisinin derivative artesunate produced a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose used.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Cardiovascular Pharmacology

In toxicity studies in dogs, only at higher doses than intended for use in man (600 mg/kg/day), there was some evidence of prolongation of the QTc interval. In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the currents responsible for cardiac repolarization. This potency was lower than that of the other antimalarial drugs tested. From the estimated IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 0.04 micromolar) > chloroquine (2.5 micromolar) > mefloquine (2.6 micromolar) > desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar).

A study in healthy adult volunteers indicates prolongation of QTcF can occur with standard dosing of Artemether/lumefantrine 20/120 mg (see sections Contraindications, Special Warnings And Precautions For Use And Pharmacodynamics).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Approved Name	***Purpose of inactive***
Microcrystalline Cellulose BP/Ph.Eur	Diluent
Hypromellose 2910 USP (5cp)	Binder
Croscarmellose Sodium BP/Ph.Eur/USNF (AC-DI-Sol, FMC)	Disintegrant
Colloidal Silicon Dioxide USNF	Glidant
Polysorbate 80 USNF/BP/Ph.Eur	Surfactant/Wetting agent
Magnesium Stearate USNF/Ph.Eur (Vegetable)	Lubricant

(Ferro)	
Purified Water BP/Ph.Eur	Granulating agent
Isopropyl Alcohol BP/Ph.Eur	Granulating agent

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

6.5 Nature and contents of container

PROPOSED PACKAGING CONFIGURATION

Artemether & Lumefantrine 20/120 tablets [Uncoated] is packed available in blister pack as follows:

Blister pack

4x6's tablets.

I. Primary Packaging component:

It is available in Blister pack

A. For Blister pack -

Plain Aluminium blister foil [208 mm] [25 micron foil with 3-6 GSM of HSL]
PVC – [PVC/PE/PVDC] [208 mm width] [clear colour less] [[0.337 mm] [250 microns PVC /25 microns pe/90 gsm PVDC] [total-453 gsm].

II. Functional Secondary Packaging component:

A. For Blister pack -

4 blisters of 6 tablets are packed in one carton

Plain carton – Reverse tuck [126 x 120 x 105 mm- ID] [Grey board] [300 gsm] [Lock Bottom]

III. Tertiary Packaging component:

A. For Blister pack -

Shipper - [5 ply] [515 x 370 x 440 mm ID] [180/150/150/150/180 GSM] [B.S. NLT 16 kg/cm.sq.min]

Bopp Tape- [72 mm] [Transparent][30 Micron]

It is expected that the stability of the drug product will not be affected by the proposed pack.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance of in accordance with local requirement

7. **MARKETING AUTHORISATION HOLDER**

Strides Arcolab Limited

'Strides House', Opp IIM-B, Bilekahalli,

Bannerghatta Road, Bangalore -560076,

INDIA.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

KTK/25/415/98

9. DATE OF FIRST <PREQUALIFICATION / RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

None