SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artemether/ Lumefantrine 20 mg/120 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 20 mg artemether and 120 mg lumefantrine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablets.

Yellow coloured, circular shaped, flat bevelled, uncoated tablets, debossed with 'CL' on one side

and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Artemether/ Lumefantrine dispersible tablet is indicated for the treatment of acute uncomplicated

Plasmodium falciparum malaria in infants and children weighing 5kg to less than 35 kg.

Consideration should be given to official guidance regarding the appropriate use of antimalarial

agents.

4.2 Posology and method of administration

Posology

Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 dispersible tablets per dose, depending on body

weight:

5 to less than 15 kg bodyweight

The first dose of one dispersible tablet, given at the time of initial diagnosis, should be followed

by five further doses of one dispersible tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight

The first dose of two dispersible tablets, given at the time of initial diagnosis, should be followed

by five further doses of two dispersible tablets given at 8, 24, 36, 48 and 60 hours thereafter.

25 to less than 35 kg bodyweight

The first dose of three dispersible tablets, given at the time of initial diagnosis, should be followed

by five further doses of three dispersible tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Renal or hepatic impairment
No specific studies have been carried out in these groups of patients. No specific dose adjustment
recommendations can be made for patients with renal or hepatic impairment.
Caution is advised when administering Artemether/ Lumefantrine dispersible tablet 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 dispersible tablet. In the absence of
carcinogenicity study data, and due to lack of clinical experience, more than two courses of
Artemether/ Lumefantrine dispersible tablet cannot be recommended.
Method of administration
Dispersible Tablets for oral administration
The dispersible tablet(s) composing 1 dose should be completely dispersed in a small amount of
water (approximately 10 mL per tablet). Stir gently and administer immediately to the patient.
Rinse the glass with an additional small amount of water (approximately 10 mL) and give immediately to the patient.
To increase absorption, Artemether/ Lumefantrine dispersible tablet should be taken with food or a
milky drink (see section 5.2). If patients are unable to tolerate food, Artemether/ Lumefantrine
dispersible tablet should be administered, but the systemic exposure may be reduced.
Patients who vomit within 1 hour of taking the medication should repeat the dose.

4.3 Contraindications

Artemether/ Lumefantrine dispersible tablet 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. flecainide, 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. 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.

· patients with a history of symptomatic cardiac arythmias 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 rifampicin, carbamazepine, phenytoin, St John's wort (*hyppericum perforatum*).

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 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 coinfection
with *P. falciparum* and *P. vivax* at baseline. Artemether/ Lumefantrine is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.
Artemether/ Lumefantrine is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether/ Lumefantrine has
the potential to cause QT prolongation.
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 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 with drugs exhibiting

variable patterns of inhibition, weak to 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 nonnucleoside
reverse transcriptase inhibitors should be used with caution in patients taking Artemether/ Lumefantrine dispersible (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 (see
sections 4.5).
Patients who remain averse to food during treatment should be closely monitored as the risk of
recrudescence may be greater.
In patients with severe hepatic impairment, a clinically relevant increase of exposure to 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).
Caution is advised when administering Artemether/ Lumefantrine 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

Contraindications of concomitant use

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 nonsedating
antihistaminics (terfenadine, astemizole), cisapride (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, flecainide,
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 rifampicin
Oral administration of rifampicin (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 rifampicin, carbamazepine,
phenytoin, St. John's wort is contraindicated with Artemether/ Lumefantrine (see section 4.3).
Concomitant use not recommended
Interaction with other antimalarials 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 CYP 3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme
CYP3A4, and 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. However,
due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Artemether/ Lumefantrine should be used cautiously with drugs that inhibit
CYP3A4.

Grapefruit juice

Administration of artemether with double concentrated grapefruit juice in healthy adult subjects
resulted in an approximately two fold increase in systemic exposure to the parent drug. Grapefruit
juice should be avoided during Artemether/ Lumefantrine treatment (see section 4.4).

Interaction with protease inhibitor anti-retroviral drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs (ARTs),

such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have
variable patterns of inhibition, induction or competition for CYP3A4. 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, and
efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%,
45%, and 20%, respectively. Exposures to lopinavir/ritonavir and efavirenz were not significantly
affected by concomitant use of Artemether/ Lumefantrine. 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).

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 non
hormonal method of birth control (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 avoided during Artemether/ Lumefantrine treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient data from the use of artemether and lumefantrine in pregnant women. 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). 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.
Women using oral, transdermal patch, or other systemic hormonal contraceptives should be
advised to use an additional non-hormonal method of birth control (see section 4.4).

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

38

The safety of Artemether/ Lumefantrine has been evaluated in 21 clinical trials with more than
3700 patients. A total of 1798 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**
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Clonus, somnolence	Uncommon	Uncommon
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 %)

Skin and subcutaneous tissue disorders

Rash Common Common (2.7 %)

Pruritus Common Uncommon

Urticaria, angioedema* Not known Not known

Musculoskeletal and connective tissue disorders

Arthralgia Very common Common (2.1 %)

Myalgia Very common Common (2.2 %)

Metabolism and nutrition disorders

Anorexia Very common Very common (16.8 %)

General disorders and administration site conditions

Asthenia Very common Common (5.2 %)

Fatigue Very common Common (9.2 %)

Gait disturbance Common --

Immune system disorders

Hypersensitivity Not known Rare

Hepatobiliary disorders

Liver function tests increased Uncommon Common (4.1 %)

Psychiatric disorders

Sleep disorders Very common Common (6.4 %)

Insomnia Common Uncommon

* 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, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BE52

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.
The antimalarial activity of the combination of lumefantrine and artemether in Artemether/
Lumefantrine 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 when given at 4 doses
was 94% compared with 90% for lumefantrine and 46% for artemether based on intent-to-treat
(ITT) population, when given as monotherapy. For the evaluable population, 28-day cure rates

were 100% for Artemether/ Lumefantrine, 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 60-96 h) were 81% and
90% for Artemether/ Lumefantrine 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 and 100% for mefloquine/artesunate.
In an open, multicenter clinical study conducted in Africa in 310 children weighing 5 kg to less

than 25 kg and receiving a 6-dose Artemether/ Lumefantrine according to their body weight range,
the mean 28-day parasitological cure rate (PCR-corrected) was 93.9% for the ITT population and
96.7% for the evaluable population.
In a randomised, investigator-blinded trial comparing the efficacy of Artemether/ Lumefantrine
dispersible tablets vs Artemether/ Lumefantrine (crushed) according to their body weight range
administered in children weighing 5 kg to less than 35 kg body weight with an age of 12 years or
less, the 28-day parasitological cure rate (PCR-corrected) for the primary analysis population was
97.8% and 98.5%, respectively, and for the ITT population was 95% and 96.2%, respectively.
In non-immune 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 given as the 6-dose regimen was 96%
(119/124) for the evaluable and 74.1% (120/162) for the ITT population. The main difference
between the evaluable and ITT cure rates was owing to 38 patients who were excluded from the
evaluable population for the following reasons: 33 patients were lost to follow up (19 of whom
were not evaluated at day 7 and 14 of whom had 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 of European origin were not included in clinical trials.
In comparative clinical trials Artemether/ Lumefantrine cleared gametocytes in less than one week

and more rapidly than non-artemisinin antimalarials.
Artemether/ Lumefantrine is active against blood stages of *Plasmodium vivax*, but is not active
against hypnozoites (see section 4.4).

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.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Artemether/ Lumefantrine is limited by the lack of an
intravenous formulation, and the large inter-and intra-subject variability of artemether and
lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).
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 to 3 hours after dosing. Mean C_{max} and AUC values of artemether ranged between

58.4-73.3 ng/mL and 208-263 ng·h/mL, respectively, in fed healthy adults after a single dose of
Artemether/ Lumefantrine dispersible tablet, 80 mg artemether/480 mg lumefantrine. Mean C_{max}
and AUC values of dihydroartemisinin ranged between 47.5-57.3 ng/mL and 171-206 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 8.81-10.2 μg/mL) reached about 8
hours after dosing. Mean AUC values of lumefantrine ranged between 257 and 295 μg·h/mL.
Food enhances the absorption of lumefantrine: The plasma concentration of lumefantrine
increased by about 50% and 65% when Artemether/ Lumefantrine dispersible tablet was taken
with meals or milk, respectively, in paediatric patients with malaria.
The food interaction data indicate that absorption of lumefantrine under fasted conditions is very
poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted
conditions would be <10% of the dose). Patients should therefore be encouraged to take the
medication with a normal diet as soon as food can be tolerated.
Distribution
Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and
99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).
Metabolism
Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro*
and in humans. Human liver microsomes metabolise artemether to the biologically active main
metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5.
This metabolite has also been detected in humans *in vivo*.

Dihydroartemisinin is further converted to inactive metabolites.
The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of
Artemether/ 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 2-6 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.
In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration
of Artemether/ Lumefantrine, and urinary excretion of DHA amounted to less than 0.01% of the
artemether dose.
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.
Pharmacokinetics in special patient populations
In paediatric malaria patients, mean C_{max} (CV %) of artemether (observed after first dose of

Artemether/ Lumefantrine) were 196 (104%), 150 (71%) and 134 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 C_{max} of DHA were 62.0 (105%), 66.5 (74%) and 73.9 ng/mL
(466%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of Artemether/ Lumefantrine) were 441,
704 and 1260 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.
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 in the same order of magnitude
than that of the recommended dosing regimen in adult malaria patients.
No specific pharmacokinetic studies have been performed either in patients with renal impairment
Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal
excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of Artemether/
Lumefantrine dispersible tablet in patients with renal impairment is advised.
No specific pharmacokinetic studies have been performed either in patients with hepatic or renal
insufficiency or elderly patients primary clearance mechanism of both artemether and lumefantrine and 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.

5.3 Preclinical safety data

General toxicity

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

Mutagenicity

No evidence of mutagenicity was detected in *in vitro* or *in vivo* tests with an artemether: lumefantrine combination (consisting of 1 part artemether: 6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but
recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with the artemether: lumefantrine combination were not conducted.

Reproductive toxicity studies

Reproductive toxicity studies performed with the artemether: lumefantrine combination caused
maternal toxicity and increased post-implantation loss in rats and rabbits at doses ≥50 mg/kg/day
(corresponding to approximately 7 mg/kg/day artemether) and 175 mg/kg/day (corresponding to
25 mg/kg/day artemether) respectively. These effects were not observed at lower doses. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000
mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with
artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic.
Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low
incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30
mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects

were observed at lower doses in rabbits. The no observed effect dose was 3 mg/kg/day in rats and
25 mg/kg/day in rabbits.
The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.
Artesunate, a structurally related compound, also caused increases in postimplantation loss and
teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and
in the lowest dose tested in the rabbits, 5 mg/kg/day.
Cardiovascular Pharmacology
In toxicity studies in dogs at doses >600 mg/kg/day only, there was some evidence of prolongation
of the QTc interval, at higher doses than intended for use in man. In *in vitro* assays of HERG
channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyllumefantrine
showed some inhibitory potential in one of the currents responsible for cardiac repolarization. The potency was lower than 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 μM)
>chloroquine (2.5 μM) >mefloquine 2.6 μM) >desbutyl-lumefantrine (5.5 μM) >lumefantrine (8.1
μM). Estimated IC_{50} values for artemether and DHA were > 100 μM and > 300 μM, respectively,
suggesting no increased QT prolongation liability for artemether or DHA. Clinical studies show
that prolongation of QTcF can occur with standard dosing of Artemether/ Lumefantrine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose,
Croscarmellose sodium,
Crospovidone,
Hydroxy Propyl Methyl Cellulose,
Polysorbate 80,
Saccharin sodium,
Cherry Flavour Permaseal (11035-31),

Magnesium stearate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

45

24 Months

6.4 Special precautions for storage

Do not store above 30° C.

6.5 Nature and contents of container

Alu-PVC/Aclar blister

Pack size: 6s, 12s and 18s.

Packed in 30x6s, 30x12s, 30x18s

6.6 Instructions for use, handling and disposal

Artemether and Lumefantrine 20/120mg dispersible tablets should not be disposed of via

wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer

required. These medicines will help to protect the environment