Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Co-Artesiane®
Artemether –Lumefantrine

1.1. Strength

Artemether 3 mg/ml
Lumefantrine 18 mg/ml

1.2. Pharmaceutical form

Powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration Artemether Lumefantrine

For a full list of excipients, see section 6.1.

2.2. Quantitative declaration

Co-Artesiane 60 ml
Bottle with 22, 8 g of powder containing 180 mg of Artemether and 1080 mg of Lumefantrine

Co-Artesiane 120 ml
Bottle with 45, 6 g of powder containing 360 mg of Artemether and 2160 mg of Lumefantrine.

Excipients with known effect:
Methyl parahydroxybenzoate 0,8 mg/ml
Propyl parahydroxybenzoate 0,2 mg/ml
Sucrose 328 mg/ml

3. PHARMACEUTICAL FORM

Powder for oral suspension.
Yellow powder
The reconstituted suspension has a yellow colour and a taste of coconut

4. CLINICAL PARTICULARS

1. Therapeutic indications

Co-Artesiane is indicated for the treatment of malaria in adults and children weighing 5 kg and above, due to Plasmodium *falciparum.*

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration for deciding on the appropriateness of therapy.

4.1. Posology and mode of administration

4.1.1. Posology

Co-Artesiane is intended for pediatric use (see posology 4.2.3), but can also be used by adults.

The dose depends on the severity of the case and the clinical situation of thepatient.

A standard 3-days-treatment schedule is recommended.

Full course therapy of three days is essential in order to avoid recrudescence.

Dosage scheme
The dose for each patient is calculated based on the body weight.
One (1) ml of the reconstituted suspension contains 3 mg Artemether and 18 mg Lumefantrine.

Additional information
A further course of Co-Artesiane may be necessary if the malaria infection returns (relapse) or if re-infection with a different strain of Plasmodium parasites occurs after having been cured.

2.Special populations
Artemether/lumefantrine has not been studied in patients with severe renal or hepatic impairment.

3.Pediatric population
Co-Artesiane suspension has been designed for use in children.
Daily dose schedule when calculated on 4 mg artemether per kg body weight:

Weight	**Daily dose schedule**		
	Day 1	**Day 2**	**Day 3**
5 kg	7 ml	7 ml	7 ml
6 kg	8 ml	8 ml	8 ml
7 kg -8 kg	10 ml	10 ml	10 ml
9 kg-10 kg	13 ml	13 ml	13 ml
Weight	**Daily dose schedule**		
	Day 1	**Day 2**	**Day 3**
11 kg-12 kg	15 ml	15 ml	15 ml
13 kg-14 kg	18 ml	18 ml	18 ml
15 kg-17 kg	22 ml	22 ml	22 ml
18 kg -20 kg	25 ml	25 ml	25 ml
21 kg -23 kg	29 ml	29 ml	29 ml
24 kg–26 kg	33 ml	33 ml	33 ml
27 kg-29 kg	37 ml	37 ml	37 ml
30 kg	40 ml	40 ml	40 ml

4. Method of administration

Preparation of the Co-Artesiane suspension

After opening the bottle (breaking the seal) tap water of good quality should be added up to the mark point indicating the 60 ml resp. 120 ml level.

After adding the water, the mixture needs to be shaken vigorously until all the powder has disappeared from the bottom and a yellow suspension is formed. It may be necessary to readjust the volume to the 60 ml/120 ml mark.

In-use shelf life of the suspension is maximum 28 days. It is advisable to shake the bottle before each use. Clear glass is chosen facilitating the control of suspension.

Method of administration

For oral administration.

To increase absorption, the medicine should be taken after food or a fat containing (milky) drink, particularly on the second and third day of treatment. In case of vomiting within 30 minutes after intake of the suspension, the full dose should be re-administered. Vomiting within 1 hour requires repeating half the dose.

2. Contraindications

Co-Artesiane 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 (1)

- patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitryptyline, clomipramine);

- patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval;

- patients taking drugs that are known to prolong the QTc interval (proarrythmic): these drugs include:
- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride,
- flecainide;
- patients with a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction;
- patients with disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesemia;
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

(1) Presence of one of more of the following clinical 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 oedema (radiological); abnormal bleeding; clinical jaundice; haemoglobinuria.

Laboratory tests: Severe normocytic anaemia; haemoglobinuria; hypoglycaemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia).

3. Special warning and precautions for use

1. General information

- Artemether/Lumefantrine is not recommended during 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 in 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, Co-Artesiane should not be given concurrently with any other antimalarial agent unless there is no other treatment option.
- If a patient deteriorates whilst taking Co-Artesiane, 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 Co-Artesiane.
- If quinine is given after Co-Artesiane, due to the potential of additive/synergistic QT-prolongation, close monitoring of the ECG is advised (see section 4.5).
- If Co-Artesiane is given after mefloquine, close monitoring of food intake is advised (see section 4.5).
- In patients previously treated with halofantrine, Co-Artesiane should not be administered earlier than one month after the last halofantrine dose.
- Co-Artesiane is not indicated and has not been evaluated for prophylaxis of malaria.
- Co-Artesiane 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 Co-Artesiane (see section 4.5).
- Like other antimalarials (e.g. halofantrine, quinine and quinidine) Co-Artesiane has the potential to cause QT prolongation (see section 5.1).
- Caution is recommended when combining Co-Artesiane 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 Co-Artesiane (see sections 4.5 and 5.2).
- Caution is recommended when combining Co-Artesiane with hormonal contraceptives. Co-Artesiane may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemichormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see section 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 doseadjustment for the use of Co-Artesiane in patients with renal impairment is recommended. Caution is advised when administering Co-Artesiane to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

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

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 Co-Artesiane cannot be recommended.

Excipients with known effect
- Co-Artesiane contains 0.8 mg methyl parahydroxybenzoate and 0.2 mg propyl parahydroxybenzoate per ml of suspension. These substances may cause allergic reactions (possibly delayed).
- Co-Artesiane contains 328 mg sucrose per ml of suspension. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

2. Pediatric population

Children remaining averse to food during treatment should be closely monitored, as the risk of recrudescence may be greater. Interactions with other medicinal products and other forms of interactions

Contraindications of concomitant use

- **Interaction with drugs that are known to prolong the QTc interval**

Co-Artesiane 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 Co- Artesiane with drugs that are metabolized 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 co-infected 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 Co-Artesiane (see section 4.3)

Inducers should not be administered at least one month after Co-Artesiane administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Co-Artesiane should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section 4.4).

If Co-Artesiane 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 Co-Artesiane. In patients previously treated with halofantrine, Co-Artesiane 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 wascommenced 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 IV 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 IV quinine was enhanced by prioradministration of artemether/lumefantrine.

Concomitant use requiring caution Interactions affecting the use of Co-Artesiane
Interaction with CYP3A4 inhibitors
Both artemether and lumefantrine are metabolized 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 Co-Artesiane is considered unnecessary in falciparum malaria patients when administered in association withketoconazole or other potent CYP3A4 inhibitors.
Co-Artesiane 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. Co- Artesiane 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 Co-Artesiane, 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 Co-Artesiane 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 metabolized by these *enzymes (see sections 4.4 and 5.2).*

Interaction with hormonal contraceptives
Since Co-Artesiane has been designed for its use in children it is unlikely that thisthis situation problem arises. However, the following information should be considered. 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, Co-Artesiane may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemichormonal contraceptives should be advised to use an additional non hormonal method of birth control for about one month.

Drug-food/drink interactions
Co-Artesiane 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 Co-Artesiane 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. Fertility, pregnancy and lactation

4.1. Fertility
There is no information on the effects of artemether/lumefantrine on human fertility (see section 5.3).

4.2. Pregnancy
Based on animal data, artemether/lumefantrine is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemether have shown evidence of post- implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased riskduring early gestation.

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 ofanother 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.

Co-Artesiane treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

4.3. Lactation
Animal data suggest excretion into breast milk but no data are available in humans. Women taking Co-Artesiane should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it isrecommended that breast-feeding should not resume until at least one week after the last dose of Co-Artesiane unless potential benefits to the mother and child outweigh the risks of Co-Artesiane treatment.

4.4. Fertility

5. Effects on the ability to drive and use machines
Patients receiving Co-Artesiane should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

6. Undesirable effects
The safety of artemether/lumefantrine has been evaluated in numerous 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 receivedartemether/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 MedDRAfrequency 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: Frequency of Undesirable effects

System organ Class/Effect	**Adults and adolescents above 12 years of age**	**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
Psychiatric disorders		
Sleep disorders	Very common	Uncommon
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Common
Dizziness	Very common	Common
Paraesthesia	Common	--
Gait disturbance	Uncommon	--
Ataxia, hypoesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Uncommon
Electrocardiogram Q T prolonged	Common	Rare
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorders		
Vomiting	Very common	Very common
Abdominal pain	Very common	Common
Nausea	Very common	Common
Diarrheal	Common	Common
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common
Skin and subcutaneous tissue disorders		
Rash	Common	Common

Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common
Myalgia	Very common	Common
System organ Class/Effect	**Adults and adolescents above 12 years of age**	**Children of 12 years of ageand below (incidence estimates)**
Asthenia	Very common	Common
Fatigue	Very common	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.

7. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.3. Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, Artemisinin and derivatives, combinations.
ATC code: P01BF01

Co-Artesiane is an Artemether based Combination Therapy (ACT) which contains two substances active against malaria parasites. Co-Artesiane comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively.

In this combination, the drug Artemether kills the parasites very fast and potentiates the effects of the second drug Lumefantrine. This combination therapy permits a shorter duration of treatment, thereby improving compliance. The theoretical risk for drug resistance is significantly reduced by using combination therapy.

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 polymerization 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.

5.4. Pharmacokinetic properties

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin (DHA), the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing.

Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing.

Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when 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. Dihydroartemisinin is also bound to human serum proteins.

Biotransformation
Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolize artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humansin 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. 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.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivoin 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.

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% ofthe exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination
Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours.
Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether/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 urinedue 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.

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 ofboth 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 Co-Artesiane in patients with renal impairment is advised.

5.5. 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 theno 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 oralartemether administration to dogs at a dose of about 29 times the highest artemetherclinical 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. 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 (characterized 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 IC50 was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human see sections 4.3, 4.4 and 5.1.

6. PHARMACEUTICAL PARTICULARS

1. List of excipients
- sucrose,
- microcrystalline cellulose and carmellose sodium
- citric acid,
- xanthan gum,
- methyl parahydroxybenzoate,
- propyl parahydroxybenzoate,
- colloidal silica, anhydrous,
- coconut flavour.

2. Incompatibilities
None known.

3. Shelf life
24 months.
In-use shelf life of the reconstituted suspension: 28 days

4. Special precautions for storage
Store below 30°C, in original packaging to protect from light and humidity.

In-use: Store the bottle in a dark place to protect from light. Shake the bottle well beforeeach use.

5. Nature and contents of container
Co-Artesiane 60 ml: cardboard box with one bottle (Type III clear glass) which is marked with a 60 ml level indication and contains 22, 8 g of yellow powder, closed witha plastic screw-cap.
Co-Artesiane 120 ml: cardboard box with one bottle (Type III clear glass) which is marked with a 120 ml level indication and contains 45, 6 g yellow powder, closed witha plastic screw-cap.

Each packaging contains a graded transparent plastic beaker with marks at 1 ml intervals and 5 ml intervals.

6. Special precautions for disposal and other handlings
Any unused medicinal product or waste material should be disposed of in accordancewith local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS
Marketing Authorisation Holder
Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel,
Switzerland.

Manufacturer
S Kant Healthcare Limited, Plot N° 1802-1805, GIDC – Phase III, Vapi - 396 195, Gujarat,
India.

8. MARKETING AUHORISATION NUMBER

TAN 22 HM 0097

9. DATE OF FIRST REGISTRATION
11/04/2022

10. DATE OF REVISION OF TEXT