

1. Name of the Medical Product

1.1 Product Name:

Artefan Suspension (Artemether and Lumefantrine Powder for Oral Suspension)

1.2 Strength:

Each 60 mL of suspension on reconstitution contains:

Artemether Ph. Int. 180 mg

Lumefantrine 1080 mg

1.3 Pharmaceutical Dosage Form:

Reconstitution suspension for oral administration

2. Qualitative & Quantitative Composition:

Each 60 mL of suspension on reconstitution contains:

Artemether Ph. Int. 180 mg

Lumefantrine 1080 mg

For a full list of excipients, see section 6.1 of SmPC

3. Pharmaceutical Form:

Reconstitution suspension for oral administration

4. Clinical Particulars

Therapeutic Indications:

Artemether and Lumefantrine combination 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.

4.2 Posology and Method of administration:

Artemether and Lumefantrine combination is intended for pediatric use, but can also be used by adults.

The dose depends on the severity of the case and the clinical situation of the patient. 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 Artemether and Lumefantrine combination 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.

Special populations

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

Pediatric population

Artemether and Lumefantrine combination 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

Method of administration

Preparation of the Artemether and Lumefantrine combination 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.

4.3 Contraindications:

Artemether and Lumefantrine combination is contraindicated in:

- patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- patients with severe malaria according to WHO definition
- patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitriptyline, 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 (proarrhythmic): 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 arrhythmias 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 hypomagnesaemia;
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*).

Presence of one or more of the following clinical 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).

4.4 Special warning and precautions for use:

A. General information

- Artemether/Lumefantrine is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available
- 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, Artemether and Lumefantrine combination should not be given concurrently with any other antimalarial agent unless there is no other treatment option.
- If a patient deteriorates whilst taking Artemether and Lumefantrine combination, 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 and Lumefantrine combination.
- If quinine is given after Artemether and Lumefantrine combination, due to the potential of additive/synergistic QT prolongation, close monitoring of the ECG is advised.
- If Artemether and Lumefantrine combination is given after mefloquine, close monitoring of food intake is advised.
- In patients previously treated with halofantrine, Artemether and Lumefantrine combination should not be administered earlier than one month after the last halofantrine dose.
- Artemether and Lumefantrine combination is not indicated and has not been evaluated for prophylaxis of malaria.
- Artemether and Lumefantrine combination should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and Lumefantrine combination.
- Like other antimalarials (e.g. halofantrine, quinine and quinidine)

Artemether and Lumefantrine combination has the potential to cause QT prolongation.

Caution is recommended when combining Artemether and Lumefantrine combination 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 nonnucleoside reverse transcriptase inhibitors should be used with caution in patients taking Artemether and Lumefantrine combination.

- Caution is recommended when combining Artemether and Lumefantrine combination with hormonal contraceptives. Artemether and Lumefantrine combination may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.
- Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Renal impairment

No specific published studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in published studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of Artemether and Lumefantrine combination in patients with renal impairment is recommended. Caution is advised when administering Artemether and Lumefantrine combination to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific published 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 published carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether and Lumefantrine combination cannot be recommended.

Excipients with known effect

- Artemether and Lumefantrine combination contains 0.8 mg methyl Para hydroxybenzoate and 0.2 mg propyl Para hydroxybenzoate per ml of suspension. These substances may cause allergic reactions (possibly delayed).
- Artemether and Lumefantrine combination 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.

B. 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

4.5 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**

Artemether and Lumefantrine combination 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 antihistaminic (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Artemether and Lumefantrine combination 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

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 Artemether and Lumefantrine combination.

Inducers should not be administered at least one month after Artemether and Lumefantrine combination 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 Artemether and Lumefantrine combination should therefore not be given concurrently with other antimalarials unless there is no other treatment option. If Artemether and Lumefantrine combination 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 and Lumefantrine combination. In patients previously treated with halofantrine, Artemether and Lumefantrine combination should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A published 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 published 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 published 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 prior administration of artemether/lumefantrine.

Concomitant use requiring caution Interactions affecting the use of Artemether and Lumefantrine combination**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 published study, dose adjustment of Artemether and Lumefantrine combination is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Artemether and Lumefantrine combination should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, 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.

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Artemether and Lumefantrine combination 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 and Lumefantrine combination, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ritonavir

In a published 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 published clinical study in HIV-infected adults, nevirapine significantly reduced the median C_{max} and AUC of artemether by approximately 61% and 72%, respectively and reduced the median C_{max} and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine C_{max} and AUC were non-significantly reduced by nevirapine. Artemether/ lumefantrine reduced the median C_{max} and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of artemether/lumefantrine.

Interactions resulting in effects of Artemether and Lumefantrine combination 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 published in humans have demonstrated that artemisinin 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.

Interaction with hormonal contraceptives

Since Artemether and Lumefantrine combination has been designed for its use in children it is unlikely that this 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, Artemether and

Lumefantrine combination 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 for about one month.

Drug-food/drink interactions

Artemether and Lumefantrine combination should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased. Grapefruit juice should be used cautiously during Artemether and Lumefantrine combination treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug.

4.6 Fertility, pregnancy, and lactation:

Pregnancy

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

during early gestation.

Safety data from an published observational pregnancy study of approximately 500 pregnant women who were exposed to artemether/lumefantrine (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Artemether and Lumefantrine combination 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether and Lumefantrine combination should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that

breast-feeding should not resume until at least one week after the last dose of Artemether and Lumefantrine combination unless potential benefits to the mother and child outweigh the risks of Artemether and Lumefantrine combination treatment.

4.7 Effects on ability to drive and use machine:

Patients receiving Artemether and Lumefantrine combination should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable Effects:

The safety of artemether/lumefantrine has been evaluated in numerous published clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received artemether/lumefantrine in published clinical trials. Adverse reactions reported from published 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 ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ 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 QT 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	Uncommon	Common

increased		
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 age and 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.

Reporting of suspected adverse reactions: Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

4.9 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:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antimalarials, Artemisinin and derivatives, combinations.

ATC code: P01BF01

Artemether and Lumefantrine combination is an Artemether based Combination Therapy (ACT) which contains two substances active against malaria parasites. Artemether and Lumefantrine combination 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.

5.2 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 metabolized (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 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. 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 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.

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.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours.

Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether/lumefantrine.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of artemether/lumefantrine, and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose). In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

5.3 Preclinical safety data:

General toxicity

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

Neurotoxicity

Studies published in dogs and rat have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

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

Carcinogenicity

Carcinogenicity studies were not conducted

Reproductive toxicity studies

Embryotoxicity was observed in published rat and rabbit reproductive toxicity studies conducted with artemether. Artemisinin 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 published 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 published have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety

In published 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 C_{max}), 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 μ M for lumefantrine and 5.5 μ M for its desbutyl metabolite. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted.

6. Pharmaceutical particulars:

6.1 List of excipients

Sucrose, Sucralose, Microcrystalline Cellulose & Carboxymethyl Cellulose Sodium, Xanthan Gum, Hydrophobic Colloidal Silica, Anhydrous Citric Acid, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Capsaroma Pineapple DC 106 PH, Capsaroma Flavour Peppermint DC 117.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

6.4 Special Precautions for storage:

Store at a temperature below 30°C.

6.5 Nature and contents of container:

22.8 gms of Artefan Suspension powder is filled in 100 ml clear transparent PET Bottle sealed in gazette pouch is packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling:

Not applicable

7. Marketing authorization holder and manufacturing site addresses:

Marketing authorization holder:

Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
India

Manufacturing Site Address:

Ajanta Pharma Limited
Plot No. B-4/5/6, MIDC, Paithan,
Chhatrapati Sambhajinagar 431148
Maharashtra State, India.

8. Marketing authorization number: H2008/19342/668

9. Date of first registration/ renewal of the registration:

Date of first registration: Apr 07, 2009

Date of renewal of the registration: June 17, 2026

10. Date of revision of text: May, 2026