

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Product name: AKSOAL Tablets

Approved generic name: Artemether and Lumefantrin Tablets

Strength: Each tablet contains Artemether 20mg and Lumefantrin 120mg

Pharmaceutical form: Oral tablets

2. Qualitative and quantitative composition

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)	
		20mg + 120mg	
		Quant.	batch
Artemether , Ph.Int.	API	20mg	14.400kg
Lumefantrine , Ph.Int.	API	120mg	86.400kg
Silicon Dioxide USP	Filling agent	2mg	1.440kg
Croscarmellose Sodium USP	Filling agent	2mg	1.440kg
Magnesium stearate USP	Filling agent	2mg	1.440kg
Microcrystalline cellulose USP	Filling agent	74mg	53.280kg
Polysorbate-80	Disintegrator	0.3mg	0.220kg
9% HPMC 75% ethanol	Adhesive	7.5mg	5.400kg
Croscarmellose Sodium USP	Additional disintegrant	2.2%	2.2%
Silicon Dioxide USP	Additional lubricant	1.8%	1.8%
Magnesium stearate USP	Additional lubricant	2.6%	2.6%
Carboxymethyl starch sodium	Additional lubricant	2.0%	2.0%
Subtotal		247mg	177.120kg
HPMC USP	Coating material	0.984mg	0.710kg
Ethanol (95%) BP	Coating solvent	29.680mg	22.370kg

3. Pharmaceutical form

Yellow, roundness tablets.

4. Clinical particulars

4.1 Therapeutic indications

Artemether and Lumefantrin Tablets is used for the curative treatment of the mixed

infections of malaria, including plasmodium falciparum resistant to other classic antimalarials, particularly to adults and children more than 5 kg body weight in endemic area.

It is also recommended for the treatment of the apparent emergence of malaria.

4.2 Posology and method of administration

Artemether and Lumefantrine Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

Dosage and administration:

A 3-day treatment schedule with a total of 6 doses is recommended as below:

5 kg to less than 15 kg bodyweight: One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) for the following two days (total course of 6 tablets).

15 kg to less than 25 kg bodyweight: Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) for the following two days (total course of 12 tablets).

25 kg to less than 35 kg bodyweight: Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) for the following two days (total course of 18 tablets).

35 kg bodyweight and above: Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets).

Body Weight (in kg)	Age (in years)	Day-1		Day-2		Day-3	
		0 Hour	8 Hours	Mornin g	Night	Mornin g	Night
5-14	<3	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
15-24	≥3-8	2tablets	2tablets	2tablets	2tablets	2tablets	2tablets
25-34	≥9-14	3tablets	3tablets	3tablets	3tablets	3tablets	3tablets
>34	>14	4tablets	4tablets	4tablets	4tablets	4tablets	4tablets

4.3 Contraindication

It is contraindicated in:

- patients with known hypersensitivity to the active substances or to any of the excipients.
- 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, 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. 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 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. hypokalemia or hypomagnesemia.

4.4 Special warnings and precautions for use

Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets 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 and Lumefantrine Tablets, 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 Tablets.

If quinine is given after Artemether and Lumefantrine Tablets, close monitoring of the ECG is advised (see section 4.5).

If Artemether and Lumefantrine Tablets is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, Artemether and Lumefantrine Tablets should not be administered earlier than one month after the last halofantrine dose.

Artemether and Lumefantrine Tablets is not indicated for, and has not been evaluated in, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. Artemether and Lumefantrine Tablets is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Artemether and Lumefantrine Tablets is not indicated and has not been evaluated for prophylaxis.

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

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered (see sections 4.5 and 5.2).

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

Caution is advised when administering Artemether and Lumefantrine Tablets to patients with severe renal, hepatic or cardiac problems (see section 4.2).

4.5 Interaction with other medical products and other forms of interaction

Interaction with other antimalarials (see section 4.4)

A drug interaction study with Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets 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.

Interaction with CYP450 3A4 inhibitors (ketoconazole)

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

Interaction with CYP450 enzymes

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

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 Tablets with drugs that are metabolised by this

iso-enzyme is contraindicated (see section 4.3 and 5.2). In vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

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

Other interactions

Administration of Artemether and Lumefantrine Tablets is contra-indicated in patients taking drugs that are known to prolong the QTc interval (see section 4.3).

In patients previously treated with halofantrine, Artemether and Lumefantrine Tablets should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, Artemether and Lumefantrine Tablets should not be given concurrently with any other antimalarial agent.

In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Artemether and Lumefantrine Tablets to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy and lactation

Do not use this medicine to pregnant woman without medical advice. Concerning lactation, no data is available today about its excretion in the maternal milk.

Do not hesitate to seek the advice of your physician or your pharmacist.

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Artemether and Lumefantrine Tablets 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 and Lumefantrine Tablets treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are

available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Lactation

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

4.7 Effects on ability to drive and use machines

Patients should know that dizziness or fatigue may occur, and so should stop driving and operating machinery during the treatment.

4.8 Undesirable effects

The safety of Artemether and Lumefantrine Tablets has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received Artemether and Lumefantrine Tablets 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 ($\geq 1/10$)

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 1 Frequency of Undesirable effects

	Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below
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		(incidence estimates)
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, hypoesthesia	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
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*: 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 Pharmacotherapeutic group: Antimalarial

Pharmacotherapeutic group: antimalarials, blood schizonticide, ATC code: P01 BE52.

Pharmacodynamic effects

Both components of Artemether and Lumefantrine Tablets and Artemether and Lumefantrine Powder for Oral Suspension have their own action site in the malarial parasite. The presence of the endoperoxide bridge in Artemether (generating singlet oxygen and free radicals: those are very cytotoxic to the plasmodia). It appears to be essential for antimalarial activity. Morphological changes of the parasitic membranes induced by Artemether have been described, being the result of free-radical action.

Lumefantrine interferes more in the polymerization processes.

Other in-vitro tests suggest that both cause a marked diminution of nucleic acid synthesis. Inhibition of protein synthesis as the basic mechanism of action is suggested in the studies which showed morphological changes in ribosomes as well as in the endoplasmic reticulum, although Artemether acts essentially as a blood schizonticide, Artemether and Lumefantrine Tablets and Artemether and Lumefantrine Powder for Oral Suspension did clear gametocytes in comparative clinical trials.

5.2 Pharmacokinetic properties

Orally administered Artemether is rapidly absorbed reaching therapeutic levels within 60-90 minutes. Artemether is metabolized in the liver to the demethylated derivative dihydroartemisinin (DHA). The elimination is rapid, with a T_{1/2} of 2-4 hours. Dihydroartemisinin, being a potent antimalarial itself, has a T_{1/2} of 2-4 hours. The degree of binding to plasma proteins varies markedly according to the species studied.

The binding of Artemether with plasma protein in man is about 50%. Radioactivity distribution of Artemether was found to be equal between cells and plasma.

The absorption of Lumefantrine is highly influenced by lipids and food intake (from 10% by fasting to 100% at normal diet). Therefore patients should be encouraged to take the medication with some fatty food as soon as it can be tolerated.

Lumefantrine is N-debutylated in human liver microsomes . This metabolite has 5 to 8 fold higher antiparasitic effects than lumefantrine. Lumefantrine is found to be highly protein bound (95%). The elimination half life in malarial attaint patients will be 4 to 6 days. Lumefantrine and its metabolites are found in bile and faeces.

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 post-implantation 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 an in vitro assay of HERG channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyl-lumefantrine 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 IC₅₀ values, the order of potency of HERG current block was halofantrine (IC₅₀ = 0.04 µM) >chloroquine (2.5 µM) >mefloquine 2.6 µM >desbutyl-lumefantrine (5.5 µM) >lumefantrine (8.1 µM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of Artemether and Lumefantrine Tablets (see sections 4.3, 4.4 and 5.1).

6. Pharmaceutical particulars

6.1 List of excipients

Silicon Dioxide, Croscarmellose Sodium, Magnesium stearate, Microcrystalline cellulose, Tween 80, Ethanol, HPMC

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Blister(Aluminum foil-PVC).

Packs of 24 tablets per blister, 1 blisters per packs.

6.6 Marketing authorization holder

Manufacturer name: FRONT Pharmaceutical PLC

Physical address: Economic and Technical Development Zone, Xuancheng, China

Tel: 86-0563-2625199

Fax: 86-0563-2625199

E-mail: export@frontpharm.com

6.7 Marketing authorization numbers

6.8 Date of first authorization/renewal of the authorization

Date of first authorization: February 25, 2020

6.9 Date of revision of the text

February 25, 2020