8SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

INN Name: **Artemether and Lumefantrine tablets**

Trade mark name: SUMETHER 80/480

2. Qualitative and quantitative composition

Each tablet contains: Artemether 80mg and Lumefantrin 480mg

3. Pharmaceutical form

Yellow, round tablet

4. Clinical particulars

4.1 Therapeutic indications

Sumether 80/480 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

Sumether 80/480 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 in Adult Patients (>14 years of age)

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Body Weight (in kg)	Age (in years)	Day-1		Day-2		Day-3	
		0 Hour	8 Hours	Morning	Night	Morning	Night
>34	>14	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet

DOSAGE IN CHILDREN FOR SUMETHER PLUS SUSPENSION.

Weight (Age)	Day-1		Day-2		Day-3	
	0 Hour	8 Hours	Morning	Night	Morning	Night
5 – 14 kg < 3 yrs	5ml	5ml	5ml	5ml	5ml	5ml
15 - 24kg ≥3 -8 yrs	10ml	10ml	10ml	10ml	10ml	10ml

4.3 Contraindication

Sumether 80/480 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, amitryptyline, clomipramine).

• Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.

• Patients taking drugs that are known to prolong the QTc interval. These drugs include:

- Antiarrhythmic of classes IA and III,

- Neuroleptics, antidepressive agents,

- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,

- Certain non-sedating antihistamines (terfenadine, astemizole),

- Cisapride.

• Patients with a history of symptomatic cardiac arythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

• Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

4.4 Special warnings and precautions for use

Sumether 80/480 must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

Sumether 80/480 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, Sumether 80/480 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 Sumether 80/480, 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 Sumether 80/480.

If quinine is given after Sumether 80/480, close monitoring of the ECG is advised (see section 4.5).

If Sumether 80/480 is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, Sumether 80/480 should not be administered earlier than one month after the last halofantrine dose.

Sumether 80/480 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. Sumether 80/480 is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

Sumether 80/480 is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Sumether 80/480 has the potential to cause QT prolongation.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480 were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a

significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Sumether 80/480 (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 Sumether 80/480 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 Sumether 80/480 in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of Sumether 80/480.

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 Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480, requires clinical surveillance and monitoring of clinical response/undesirable effects.

Other interactions

Administration of Sumether 80/480 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, Sumether 80/480 should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, Sumether 80/480 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 Sumether 80/480 to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy and lactation

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Sumether 80/480 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). Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480 unless potential benefits to the mother and child outweigh the risks of Sumether 80/480 treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Sumether 80/480 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 Sumether 80/480 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 Sumether 80/480 in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects

	Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below (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, hypoaesthesia	Uncommon	--
Clonus, somnolence	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)

Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria, angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
Metabolism and nutrition disorders		
Anorexia	Very common	Very common (16.8 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--
Immune system disorders		
Hypersensitivity	Not known	Rare
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon

*: These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Pharmacodynamic effects

Both components of Sumether ® 20/120, Sumether ® 80/480 and Sumether ® for Powder Suspension have their own action site in the malarial parasite. The presence of the endoperioxide bridge is 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, Sumether ® 20/120, Sumether ® 80/480 and Sumether ® for Powder Suspension did clear gametocytes in comparative clinical trials.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Sumether is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject

variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Orally administered Artemether is rapidly absorbed reaching therapeutic levels within 60-90 minutes. Artemether is metabolized in the liver to the demethylated derivate 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, lumefrantrine 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 Sumether Plus (see sections 4.3, 4.4 and 5.1).

6. Pharmaceutical particulars

6.1 List of excipients

Polysorbate 80, hypromellose, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep container well closed. Store below 30°C. Protect from freezing.

6.5 Nature and contents of container

Blister (Aluminum foil-PVC).
Packs of 6 tablets per blister, 1 blisters per packs.
No specific pack for the treatment of children and infants is available. The 6-tablets pack should be used for this patient population and the parent or care giver should be given the necessary information (see section 6.6).

6.6 Special precautions for disposal and other handing

For the treatment of children and infants, the 6-tablets pack should be prescribed. The prescriber and pharmacist should instruct the parent or care giver on the posology for their child and that a variable number of tablets (depending on the child's body weight) will be requested for the full treatment. Therefore, the whole pack may not be used. After successful treatment the remaining tablets should be discarded or returned to the pharmacist.

7. Registrant

Applicant: SUPERIOR PHARMA LTD.

Address: 9B, Robinson Gbagi Street, Ajao Estate, Lagos, Nigeria

E-mail: superiorpharmang@gmail.com

Contact person: Ike Okeke

Tel: +2348127678822

8. Manufacturer

Manufacturer name: Front Pharmaceutical PLC

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

Tel: 86-0563-2625199

Fax: 86-0563-2625199

E-mail: export@frontpharma.com

9. Date of revision of the text

March 2021

10. DOSIMETRY (IF APPLICABLE)

N/A

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

N/A