SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. **Name of the Medicinal Product**: **Artelumex Powder For Oral Suspension** (Artemether 20mg+Lumefantrine 120mg/5ml)

2. **Qualitative and Quantitative Composition**: Each bottle contains Artemether 240mg+ Lumefantrine 1440mg. For a full list of excipients, see section 6.1

3. **Pharmaceutical Form**: Powder for oral suspension

4. Clinical Particulars:

4.1 Therapeutic indications:

Artelumex 20/120 is a combination of artemether and lumefantrine which acts as blood schizontocides. It is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in children and infants of 5 kg and above.

4.2 Posology and method of administration:

Dosage and administration: Oral route of administration

Body Weight	**Dosage Regimen**		
	Day 1	**Day 2**	**Day 3**
5 kg	5 ml	5 ml	5 ml
7.5 kg	10 ml	10 ml	10 ml
10 kg	15 ml	15 ml	15 ml
15 kg	20 ml	20 ml	20 ml

Direction for preparation of suspension: Shake the bottle to loosen powder. Slowly add freshly boiled & cooled water upto the ring mark on the bottle and shake well. Add freshly boiled & cooled water if necessary to adjust the volume upto the ring mark, and shake again. Store the reconstituted suspension in a cool dry place, below 30^{o}C. Shake well before each use. Consume the content (reconstituted) of Artelumex

20/120 Powder for Oral Suspension within 7 days. Any extra portion left to be thrown away.

4.3. **Contraindications:** Artemether / Lumefantrine are contraindicated in patient hypersensitive to the active substances or to any of the excipients.

4.4 **Special warnings and precautions for use:**

Artelumex 20/120 Powder for Oral Suspension is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

Artelumex 20/120 Powder for Oral Suspension 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, Artelumex 20/120 Powder for Oral Suspension 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 Artelumex 20/120 Powder for Oral Suspension, 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.

4.5 **Interaction with other medicinal products and other forms of interaction:**

Although the likelihood of Artelumex 20/120 Powder for Oral Suspension interactions with other drugs is minimal in view of its short duration of administration and wide therapeutic index, three specific pharmacokinetic and pharmacodynamic drug - drug interaction studies with ketoconazole (a patient CYP3A4 inhibitor), mefloquine and quinine have been conducted in healthy volunteers.

Interaction with antimalaria: As patients to be treated with Artelumex 20/120 Powder for Oral Suspension may have recently been treated with other antimalarial, interactions with mefloquine and quinine were studied in healthy volunteers. The sequential oral administration of mefloquine prior to Artelumex 20/120 Powder for Oral Suspension had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin, but there was a significant (around 30-0%) reduction in plasma levels(Cmax and AUG) of lumefantrine, possibly due to lower absorption

secondary to a mefloquine-induced decrease in bile production. Based on this study, patients should be encouraged to eat at dosing times to compensate for this decrease in bioavailability.

The concurrent i.v. administration of quinine (10mg/kg BW) with Artelumex 20/120 Powder for Oral Suspension had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and DHA appeared to be lower in this study, administration of Artelumex 20/120 Powder for Oral Suspension to14 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 Artelumex 20/120 Powder for Oral Suspension 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 Artelumex 20/120 Powder for Oral Suspension. Artelumex 20/120 Powder for Oral Suspension should not be given concurrently with antimalarial other than mefloquine or quinine in patients previously treated with halofantrine. Artelumex 20/120 Powder for Oral Suspension should be administered at least one month after the last halofantrine dose. If a patient deteriorates while taking Artelumex 20/120 Powder for Oral Suspension, alternative treatment for malaria should be started without delay. In such cases, monitoring of the EGG is recommended and steps should be taken to correct any electrolyte disturbances.

Interaction with concomitant treatment other than antimalarias: No safety issues that could be attributed to drug interactions arose during clinical studies with Artelumex 20/120 Powder for Oral Suspension in which most patients received antipyretic medication, antibiotics and fluid electrolyte replacement.

Interaction with a cyp450 3a4 inhibitor (ketoconazole): The concurrent oral administration of ketoconazole with Artelumex 20/120 Powder for Oral Suspension led to a modest increase(<2-fold) in artemether, DHA, and lumefantrine exposure in healthy subjects. This increase in exposure to the antimalaria combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Artelumex 20/120 Powder for Oral Suspension is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Interaction with cyp450 enzymes: Whereas in-vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisinins have some capacity to induce the production of the cytochrome enzymeCYP2C19 and perhaps also CYP3A4.It is possible that iso-enzyme production could after the therapeutic effects of drugs that are predominantly metabolized

by these enzymes. 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 Artelumex 20/120 Powder for Oral Suspension with drugs that are metabolized by this iso-enzyme (e.g neuroleptics and tricylic antidepressant) is contraindicated.

4.6 Pregnancy and Lactation

4.6.1 *Pregnancy:*

Risk Summary

Published data from clinical studies and pharmacovigilance data have not established an association with artemether/lumefantrine use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations:

Disease-Associated Maternal and/or Embryo/Fetal Risk: Malaria during and after pregnancy increases the risk for adverse pregnancy and neonatal outcomes, including maternal anemia, severe malaria, spontaneous abortion, stillbirths, preterm delivery, low birth weight, intrauterine growth restriction, congenital malaria, and maternal and neonatal mortality.

Data

Human Data: While available studies cannot definitively establish the absence of risk, a meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy, data from observational, and open label studies including more than 1200 pregnant women in their second-or third trimester exposed to artemether-lumefantrine compared to other antimalarials, and pharmacovigilance data have not demonstrated an increase in major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published epidemiologic studies have important methodological limitations which hinder interpretation of data, including inability to control for confounders, such as underlying maternal disease, and maternal use of concomitant medications and missing information on the dose and duration of use.

Animal Data: Pregnant rats dosed orally during the period of organogenesis [gestational days (GD) 7 through 17] at 50 mg/kg/day

artemether-lumefantrine combination (corresponding to 7 mg/kg/day artemether or higher, a dose of less than half the maximum recommended human dose (MRHD) of 1120 mg artemether-lumefantrine per day (based on body surface area (BSA) comparisons), showed increases in fetal loss, early resorptions, and postimplantation loss. No adverse effects were observed in animals dosed at 25 mg/kg/day artemether-lumefantrine (corresponding to 3.6 mg/kg/day of artemether), about one-third the MRHD (based on BSA comparison). Similarly, oral dosing in pregnant rabbits during organogenesis (GD 7 through GD 19) at 175 mg/kg/day, (corresponding to 25 mg/kg/day artemether) about 3 times the MRHD (based on BSA comparisons) resulted in abortions, preimplantation loss, post implantation loss and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at 105 mg/kg/day artemether-lumefantrine (corresponding to 15 mg/kg/day artemether), about 2 times the MRHD. Artemether and other artemisinins are associated with maternal toxicity and embryotoxicity and malformations in animals at clinically relevant exposures; however, lumefantrine doses as high as 1000 mg/kg/day, showed no evidence to suggest maternal, embryo-or fetotoxicity or teratogenicity in rats and rabbits. The relevance of the findings from the animal reproductive studies to human risk is unclear.

4.6.2 Lactation Risk Summary:

There are no data on the presence of artemether or lumefantrine in human milk, the effects on the breastfed infant or the effects on milk production. Artemether and lumefantrine are transferred into rat milk. When a drug is transferred into animal milk, it is likely that the drug will also be transferred into human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Artelumex 20/120 and any potential adverse effects on the breastfed infant from Artelumex 20/120 or from the underlying maternal condition.

4.6.3 Fertility:

Contraception

Use of Artelumex 20/120 Powder for Oral Suspension may reduce the efficacy of hormonal contraceptives. Advise patients using hormonal contraceptives to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Artelumex 20/120 Powder for Oral Suspension.

Infertility

In animal fertility studies, administration of repeated doses of artemether-lumefantrine combination to female rats (for 2 to 4 weeks) resulted in

pregnancy rates that were reduced by one half. In male rats dosed for approximately 3 months with artemether-lumefantrine combination, abnormal sperm cells, decreased sperm motility, and increased testes weight were observed.

4.7 Effects on ability to drive and use machines:

Patients receiving Artelumex 20/120 Powder for Oral Suspension 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 following adverse effects have been reported, dizziness and fatigue, patients receiving Artelumex 20/120 Powder for Oral Suspension should not drive or use machines, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthragia, headache and rash.In children and adults treated with this combinations the frequency and degree of QTC prolongations was lower compared with other antimalarials. Stiches show no indication of cardiotoxicity.

4.9 **Overdose**

No case of overdose has been reported.

5. Pharmacological Properties

5.1 **Pharmacodynamics properties**: Artelumex 20/120 Powder for Oral Suspension comprises a fixed ratio of 1.6 parts of artemether and lumefantrine respectively. The site of antiparasitic action of both components is the food vacuole of the malaria parasite, where they are though to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerization process, while artemether generates reactive metabolites as a result of the interaction between the peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid, and protein synthesis within the malaria parasite. Data from in-vitro and in-vivo studies show that Artelumex 20/120 Powder for Oral Suspension did not induce resistance.

The antimalarial activity of the combination of lumefantrine and artemether in Artelumex 20/120 Powder for Oral Suspension is greater than that of either substance alone. In a double-blind comparative study in China (n=157), the 28-day cure rate of Artelumex 20/120 Powder for Oral

Suspension when given as 4 doses was 94%compared with 90% for lumefantrine and 46% for artemether when given as monotherapy (intention to treat analysis, ITT).

In areas where multi-drug-resistant strains of falciparum malaria are common and in the resident population, 28-day cure rates with the6-dose regimen (given over 60-96 h) were 87% and 90% for Artelumex 20/120 Powder for Oral Suspension versus 94% and 96% for mefloquine/artesunate (ITT). Patients of European origin were not included in trials with the six-dose regimen. However, as efficacy and safety were similar in European and Thai patients following a four-dose regimen, similar efficacy and safety profiles with the six-dose regimen would be expected in both populations. In 319 patients in whom gamelocytes were present, the median time to gamelocyte clearance with Artelumex 20/120 Powder for Oral Suspension was 96 h. Artelumex 20/120 Powder for Oral Suspension was associated with more rapid gamecolyte clearance than any comparator other than mefloquine/artesunate.

Artelumex 20/120 Powder for Oral Suspension is active against blood stages of Plasmodium vivax, but is not active against hypnozoites, therefore, sequential treatment with primaquine should be used to achieve hypnozoite eradication.

5.2 Pharmacokinetic properties:

Pharmacokinetics characterization of Artelumex 20/120 Powder for Oral Suspension 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 (AUG, Cmax).

Absorption:

Artemether is absorbed fairly rapidly with peak plasma concentrations 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 2 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 while Artelumex 20/120 Powder for Oral Suspension 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.

Metabolism

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism both in vitro and in humans). Human liver microsomes metabolized artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans in vivo. The artemether/dihydroartemisinin AUG ratio is 12 after a single dose and 0.3 after 6 doses given over 3 days. In vivo data indicate that artemisinins have omecapacity to inducecytochrome iso enzymes CYP2C19 and CYP3A4 (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND INTERACTIONS)

Lumefantrine is N-debutylated, mainly by CYP3M in human liver microsomes in vivo in animals (dogs and rats) glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND INTERACTIONS)

Elimination:

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria.

Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artelumex 20/120 Powder for Oral Suspension.

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine.

Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and gods, qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dole being recovered as parent drug.

5.3 **Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICALPARTICULARS

6.1 **List of excipients**:

Povidone K30, Aspartame, Sucrose.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

3years

6.4 Special precautions for storage:

Store in a cool and dry place below 30°C

6.5 **Nature and contents of container <and special equipment for use, administration or implantation>**

HDPE Bottles for Oral Liquid preparation with caps
Size of bottles: in mm
Total height: 110.0±3.0
Mouth OD: 27.0±0.3
Body diameter: 45.0±1.5

Size of caps: in mm
Total height: 17.0±0.3
Mouth ID: 28±0.2
Body diameter: 30.0±0.3

Measuring cups for Oral Liquid preparation
Size: in mm
Total height: 33.0±0.5
Mouth Diameter: 40.0±0.8
Bottom diameter: 35±0.3

Bottle is 60ml, 1 bottle per box.

6 **Special precautions for disposal <and otherhandling>**

No special requirements.

7. **Marketing authorisation holder:** :

ADLER PRODUCTS LIMITED.
28/32, ODUYEMI STREET, IKEJA,
LAGOS STATE, NIGERIA

8. Marketing authorisation number(s):

B4-6550

9. Date of first authorisation/renewal of the authorization

25 August, 2016

10. Date of revision of the text

04 December 2022