Summary Product Characteristics

1. Name of the proprietary product: AMAKIN ARTEMETHER 20/120

Name of the nonproprietary International Product: Artemether & Lumefantrine Tablets

Route of Administration: Oral

2. Qualitative and Quantitative composition:

Batch size: 6, 40,000 Tablets

Sr. No.	Ingredient	Specification	Qty. in mg / Tab	Qty. / Batch (in kg)	Reason on inclusion
Active					
1.	Artemether	IH	20.00	12.800	Active
2.	Lumefantrine	USP	120.00	76.801	Active
Excipient					
3.	Magnesium Stearate	BP	4.6	2.944	Lubricant
4.	Purifid talc	BP	7.47	4.787	Lubricant
5.	Sodium starch Glycolate	BP	3.47	2.227	Disintegrant
6.	Croscarmellose sodium	BP	2.5	1.600	Disintegrant
7.	Sodium Lauryl Sulphate	BP	2.0	1.280	Wetting agent
8.	Collodial Anhydrous Silica	BP	3.35	2.150	Glidant
9.	M.C.C.P 102 (Microcel) Micro Crystalline Cellulose Powder	BP	135.60	86.785	Diluent
10.	Colour Tartrazine Supra	IH	1.00	0.640	Colouring agent

Where, USP: United State Pharmacopoeia, BP: British Pharmacopoeia, IH: In House, q.s: quantity sufficient

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3. Pharmaceutical Form: Uncoated Tablet
PLAIN YELLOW COLOURED ROUND TABLETS WITHOUT BREAKLINE

4. Clinical Particulars:

4.1 Therapeutic Indications:
Artemether and Lumefantrine is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adult, children and infants of 5 kg and above.

4.2 Posology and method of administration:
Dosage and administration: Tablets for oral administration.

To increase absorption, Artemether and Lumefantrine should be taken with food or a milky drink. If patients are unable to tolerate food, Artemether and Lumefantrine should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.
For administration to small children and infants, the tablet/s may be crushed.

Adults and children weighing 35 kg and above
For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg
A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:
5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.
15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.
25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

4.3 Contraindications
Artemether and Lumefantrine 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:
- 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 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

Artemether and Lumefantrine must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Artemether and Lumefantrine 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 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, 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.

If quinine is given after Artemether and Lumefantrine, close monitoring of the ECG is advised.

If Artemether and Lumefantrine is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Artemether and Lumefantrine should not be administered earlier than one month after the last halofantrinedose.Artemether and Lumefantrine 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 is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.Artemether and Lumefantrine is not indicated and has not been evaluated for prophylaxis.Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether and Lumefantrine has the potential to cause QT prolongation.In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving Artemether and Lumefantrine 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 with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered.

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 to patients with severe renal, hepatic or cardiac problems.

4.5 Interaction with other medicinal products and other forms of interaction:
Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Artemether and Lumefantrine tablet is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide

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 tablet with drugs that are metabolised 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 and Lumefantrine tablet Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Artemether and Lumefantrine tablet alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether and Lumefantrine tablet

Inducers should not be administered at least one month after Artemether and Lumefantrine tablet 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 tablet should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

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

Mefloquine

A drug interaction study with Artemether and Lumefantrine tablet 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 tablet were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in

bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine
A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Artemether and Lumefantrine tablet (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemether and Lumefantrine tablet 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 and Lumefantrine tablet 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 Artemether and Lumefantrine tablet.

Concomitant use requiring caution

Interactions affecting the use of Artemether and Lumefantrine tablet

Interaction with CYP3A4 inhibitors
Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole
The concurrent oral administration of ketoconazole with Artemether and Lumefantrine tablet 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 tablet is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.
Artemether and Lumefantrine tablet should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc (see Section 4.3 Contraindications), due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Grapefruit juice
Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug. Grapefruit juice should be used cautiously during Artemether and Lumefantrine tablet treatment.

Interaction with weak to moderate inducers of CYP3A4
When Artemether and Lumefantrine tablet 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. Anti-retroviral drugs (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 tablet 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 tablet, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Artemether and Lumefantrine tablet.

Nevirapine

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

Efavirenz

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

Interactions resulting in effects of Artemether and Lumefantrine tablet on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether and Lumefantrine tablet is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised by these enzymes

Interaction with hormonal contraceptives

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 tablet 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 nonhormonal method of birth control for about one month

Drug-food/drink interactions
Artemether and Lumefantrine tablet 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 tablet treatment.

4.6 Pregnancy and Lactation:
There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, artemether and lumefantrine is suspected to cause serious birth defects when administered during the first trimester of pregnancy .Reproductive studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation .artemether and lumefantrine 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 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 unless potential benefits to the mother and child outweigh the risks of artemether and lumefantrine treatment.

4.7 Effects on the ability to drive and use machines
Patients receiving artemether and lumefantrine 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 and Lumefantrine 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 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 Particulars:
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimalarials.
ATC code: P01BF01.

This medicine contains two active ingredients, artemether and lumefantrine, both of which are antimalarial medicines.

Malaria is caused by a protozoal parasite called Plasmodium, which is carried by mosquitoes. During a bite from an infected mosquito, the parasite passes into the body. Once inside, it lives and reproduces, resulting in the disease known as malaria.

The malaria parasites have various stages in their lifecycle within the body. After entering the bloodstream during a bite from an infected mosquito they are carried to the liver, where they reproduce. They are then released back into the bloodstream where they infect red blood cells.

In the red blood cells, the malaria parasites digest haemoglobin, the red protein within red blood cells that is responsible for carrying oxygen. When this happens, the haemoglobin is divided into two parts; hemoglobin. Haem is toxic to the malaria parasites, and they protect themselves from it by producing a substance that converts the toxic haem into a compound called haemozoin, which is not toxic to the parasites.

Artemether and lumefantrine work by interfering with the ability of the malaria parasites to convert haem into haemozoin. This causes the levels of the toxic haem to rise, which kills the blood stages of the malaria parasites and stops the infection from continuing.

This medicine is given as a three-day course of treatment, which minimises the length of time that the parasites are exposed to the active ingredients. This reduces the chances of the parasites becoming resistant to the medicine - something that is an increasing problem with antimalarial drugs.

5.2 Pharmacokinetic properties
Pharmacokinetic characterisation of Artemether and Lumefantrine is limited by the lack of an intravenous formulation, and the very high inter-and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).

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 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 and 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* (95.4 % and 99.9 %, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).

Metabolism
Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomesmetaboliseartemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. *In-vivo* data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4. Dihydroartemisinin is further converted to inactive metabolites.
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 kinetic profile of the metabolite desbutyl-lumefantrine, for which the in-vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, has not been documented. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

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 Artemether and Lumefantrine.
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 (unindentified) 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 dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

5.3 Pre-clinical Safety:
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 embryotoxicartemether 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 IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 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 –Lumefantrine 20/120 tablet

6. Pharmaceutical Particulars:

List of Excipients:

Magnesium Stearate	BP
Purifid talc	BP
Sodium starch Glycolate	BP
Croscarmellose sodium	BP
Sodium Lauryl Sulphate	BP
Collodial Anhydrous Silica	BP

M.C.C.P 102 (Microcel) Micro Crystalline Cellulose Powder	BP
Colour Tartrazine Supra	IH

6.2 Incompatibilities: Nil.

6.3 Shelf Life: 36 months.

6.4 Special Precautions for storage:
No special precautions for storage.

6.5 Nature and contents of container:
Blister of 1x24's tablets packed in a primary carton along with pack insert.
Also available in 3x8's, 1x6's, 1x12's,1x18's .

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing Authorization Holder: AMAKIN PHARMACEUTICALS NIG. LTD

8. Marketing Authorization Number: -

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: Feb. 2019