1.3.1 Summary of product characteristics (SmPC)

(Attached)

1. Name of the medicinal product:
Artemether 20 mg and Lumefantrine 120 mg Tablets

2. Qualitative and quantitative composition
Yellow coloured, round, biconvex shape film coated tablets.

3. Pharmaceutical form
Coated Tablets

4. Clinical particulars
4.1 Therapeutic indications
Used 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

Posology

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.

Method of administration

Tablets for oral administration.

To increase absorption, Artemether 20 mg and Lumefantrine 120 mg Tablets should be taken with food or a milky drink. If patients are unable to tolerate food, Artemether 20 mg and Lumefantrine120 mg Tablets should be administered with water, 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.

4.3 Contraindications

Hypersensitivity

Known hypersensitivity to artemether, lumefantrine, or to any of the excipients of Artemether 20 mg and Lumefantrine 120 mg Tablets Strong CYP3A4 Inducers Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort with Artemether 20 mg and Lumefantrine 120 mg Tablets can result in decreased concentrations ofartemether and/or lumefantrine and loss of antimalarial efficacy

INTERACTION WITH OTHER MEDICAMENTS:

The absorption of posaconazole, clopidogrel, erlotinib, ketoconazol and itraconazol is significantly reduced when taken with Omeprazole capsule.

4.4 Special warnings and precautions for use

Artemether 20 mg and Lumefantrine 120 mg Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Artemether 20 mg and Lumefantrine 120 mg 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 20 mg and Lumefantrine 120 mg Tablets should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Artemether 20 mg and Lumefantrine 120 mg 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 20 mg and Lumefantrine 120 mg Tablets.
If quinine is given after Artemether 20 mg and Lumefantrine 120 mg Tablets, close monitoring of the ECG is advised.
If Artemether 20 mg and Lumefantrine 120 mg Tablets is given after mefloquine, close monitoring of food intake is advised .
In patients previously treated with halofantrine, Artemether 20 mg and Lumefantrine 120 mg Tablets should not be administered earlier than one month after the last halofantrine dose.

Artemether 20 mg and Lumefantrine 120 mg Tablets is not indicated and has not been evaluated for prophylaxis of malaria.

Artemether 20 mg and Lumefantrine 120 mg Tablets should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether 20 mg and Lumefantrine 120 mg Tablets,
Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether 20 mg and Lumefantrine 120 mg Tablets has the potential to cause QT prolongation.
Caution is recommended when combining Artemether 20 mg and Lumefantrine 120 mg Tablets with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Artemether 20 mg and Lumefantrine 120 mg Tablets.

Caution is recommended when combining Artemether 20 mg and Lumefantrine 120 mg Tablets with hormonal contraceptives. Artemether 20 mg and Lumefantrine 120 mg Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.
Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of Artemether 20 mg and Lumefantrine 120 mg Tablets in patients with renal impairment is recommended. Caution is advised when administering Artemether 20 mg and Lumefantrine 120 mg Tablets to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of Artemether 20 mg and Lumefantrine 120 mg Tablets. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether 20 mg and Lumefantrine 120 mg Tablets cannot be recommended.

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 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg 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 20 mg and Lumefantrine 120 mg Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether 20 mg and Lumefantrine 120 mg Tablets.

Inducers should not be administered at least one month after Artemether 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If Artemether 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets. In patients previously treated with halofantrine, Artemether 20 mg and Lumefantrine 120 mg Tablets should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Artemether 20 mg and Lumefantrine 120 mg 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 20 mg and Lumefantrine 120 mg 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.

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 20 mg and Lumefantrine 120 mg Tablets (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 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets.

Concomitant use requiring caution

Interactions affecting the use of Artemether 20 mg and Lumefantrine 120 mg Tablets

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 20 mg and Lumefantrine 120 mg Tablets -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 20 mg and Lumefantrine 120 mg Tablets is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Artemether 20 mg and Lumefantrine 120 mg Tablets should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Artemether 20 mg and Lumefantrine 120 mg Tablets is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy

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

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Artemether 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets, 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 20 mg and Lumefantrine 120 mg Tablets.

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 20 mg and Lumefantrine 120 mg Tablets.

Interactions resulting in effects of Artemether 20 mg and Lumefantrine 120 mg Tablets on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets 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 20 mg and Lumefantrine 120 mg Tablets treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month

Pregnancy

Based on animal data, Artemether 20 mg and Lumefantrine 120 mg Tablets 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.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether 20 mg and Lumefantrine 120 mg Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Artemether 20 mg and Lumefantrine 120 mg Tablets 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.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether 20 mg and Lumefantrine 120 mg Tablets should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Artemether 20 mg and Lumefantrine 120 mg Tablets unless potential benefits to the mother and child outweigh the risks of Artemether 20 mg and Lumefantrine 120 mg Tablets treatment.

Fertility

There is no information on the effects of Artemether 20 mg and Lumefantrine 120 mg Tablets on human fertility

4.7 Effects on ability to drive and use machines
Patients receiving Artemether 20 mg and Lumefantrine 120 mg Tablets should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

Hypersensitivity, Decreased appetite, Sleep disorders, Insomnia, Headache, Dizziness, Paraesthesia, Ataxia, hypoaesthesia, Somnolence, Clonus, Palpitations, Electrocardiogram QT prolonged, Cough, Vomiting, Abdominal pain, Nausea, Diarrhoea.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01.

Pharmacodynamic effects

Artemether 20 mg and Lumefantrine 120 mg Tablets 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 malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

5.2 Pharmacokinetic properties

Pharmacokinetic characterization of Artemether 20 mg and Lumefantrine 120 mg Tablets 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).

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of Artemether 20 mg and Lumefantrine 120 mg Tablets. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of Lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of Lumefantrine ranged between 108 and 243 µg·h/mL. 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 20 mg and Lumefantrine 120 mg Tablets 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 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).

Biotransformation

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*.

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of Artemether 80 mg and Lumefantrine 480 mg Tablets, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the in vitro data described in section.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration of Artemether 20 mg and Lumefantrine 120 mg Tablets over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). Systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations..

Elimination

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

hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether 20 mg and Lumefantrine 120 mg Tablets.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither Lumefantrine nor artemether was found in urine after administration of Artemether 20 mg and Lumefantrine 120 mg Tablets, and only traces of dihydroartemisinin were detected

(urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

In animals (rats and dogs), no unchanged Artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of Lumefantrine were eliminated in bile/faeces.

6. Pharmaceutical particulars

List of Excipients

Croscarmellose Sodium (Vivasol)
Methyl Paraben
Propyl Paraben
HPMC E-15 cps
Purified water
MCC (Avicel 102)
Magnesium Stearate
Aerosil
Purified Talc
PEG
Titanium dioxide
Isopropyl Alcohol
Methylene Dichloride

6.2 Incompatibilities

Not applicable.

7. Marketing authorisation holder

Celogen Pharma Pvt. Ltd.
Navi Mumbai