Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

COATAL SOFT GELATIN CAPSULES (Artemether 20 mg + Lumefantrine 120 mg)

2. Qualitative and quantitative composition

Each soft gelatin capsule contains:

Artemether Ph. Int…… 20 mg

Lumefantrine Ph. Int……...120 mg

Excipients…….Q.S.

Approved colour used in capsule shell

3. Pharmaceutical form

Soft gelatin capsule

Oval shape, Orange colour soft gelatin capsule containing yellow coloured oily suspension.

4. Clinical particulars

4.1 Therapeutic indications

Coatal Soft Gelatin Capsules is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above.

4.2 Posology and method of administration

Posology: For oral use.

Table 1: Number of Coatal Soft Gelatin Capsules for treatment according to weight bands

Weight in Kgs.	Total Capsules	Dosage Regimen					
		Day-1		Day-2		Day-3	
		0 Hours (Initial dose)	8 Hours (after 1st dose)	24 Hours	36 Hours	48 Hours	60 Hours
≥35 kg (or ≥ 12 years of age)	24	4 Capsules	4 Capsules	4 Capsules	4 Capsules	4 Capsules	4 Capsules
25kg to < 35 kg	18	3 Capsules	3 Capsules	3 Capsules	3 Capsules	3 Capsules	3 Capsules
15 kg to < 25 kg	12	2 Capsules	2 Capsules	2 Capsules	2 Capsules	2 Capsules	2 Capsules
≥ 5 kg to < 15 kg	6	1 Capsule	1 Capsule	1 Capsule	1 Capsule	1 Capsule	1 Capsule

Do not exceed the dosage prescribed.

Infants weighing less than 5 kg:

The safety and efficacy of Artemether 20 mg + Lumefantrine 120 mg capsules have not been established in infants weighing less than 5 kg and no dosing recommendations can be made.

Older people

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

Renal or hepatic impairment

No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Coatal Soft Gelatin Capsules to patients with severe renal or hepatic problems.

Method of administration

Soft gelatin capsule for oral administration.

To increase absorption, Coatal Soft Gelatin Capsules should be taken with food or a milky drink (see section Pharmacokinetic properties). If patients are unable to tolerate food, Coatal Soft Gelatin Capsules 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.

4.3 Contraindications

Coatal Soft Gelatin Capsules is contraindicated in:

- patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- patients with severe malaria according to WHO definition.
- patients with a personal or family history of congenital prolongation of the QTc interval or sudden death, or with any other clinical condition known to prolong the QTc interval, such as patients with a history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe cardiac diseases.
- patients taking drugs that are known to prolong QTc interval 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 antihistamines (terfenadine, astemizole)
  -cisapride
- patients with known disturbances of electrolyte balance e.g. hypokalaemia or

hypomagnesaemia

- patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine
- patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John's wort

4.4 Special warnings and precautions for use

Coatal Soft Gelatin Capsules is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section Fertility, pregnancy and lactation).

Coatal Soft Gelatin Capsules 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, Coatal Soft Gelatin Capsules should not be given concurrently with any other antimalarial agent (see section Interaction with other medicinal products and other forms of interaction) unless there is no other treatment option.

If a patient deteriorates whilst taking Coatal Soft Gelatin Capsules, 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 Coatal Soft Gelatin Capsules.

If quinine is given after Coatal Soft Gelatin Capsules, close monitoring of the ECG is advised (see section Interaction with other medicinal products and other forms of interaction).

If Coatal Soft Gelatin Capsules is given after mefloquine, close monitoring of food intake is advised (see section Interaction with other medicinal products and other forms of interaction).

In patients previously treated with halofantrine, Coatal Soft Gelatin Capsules should not be administered earlier than one month after the last halofantrine dose.

Coatal Soft Gelatin Capsules is not indicated and has not been evaluated for prophylaxis of malaria.

Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules, (see section Interaction with other medicinal products and other forms of interaction).

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Coatal Soft Gelatin Capsules has the potential to cause QT prolongation (see section Pharmacodynamic

properties).

Caution is recommended when combining Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules (see sections Interaction with other medicinal products and other forms of interaction and Pharmacokinetic properties).

Caution is recommended when combining Coatal Soft Gelatin Capsules with hormonal contraceptives. Coatal Soft Gelatin Capsules 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 (see sections Interaction with other medicinal products and other forms of interaction).

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 Coatal Soft Gelatin Capsules in patients with renal impairment is recommended. Caution is advised when administering Coatal Soft Gelatin Capsules 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 (see section Pharmacokinetic properties). In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

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 Coatal Soft Gelatin Capsules. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of

Coatal Soft Gelatin Capsules 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

Coatal Soft Gelatin Capsules 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 antihistamines (terfenadine, astemizole), cisapride, flecainide (see section Contraindications)

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 Coatal Soft Gelatin Capsules 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 (see sections Contraindications and Pharmacokinetic properties).

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Coatal Soft Gelatin Capsules (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 Coatal Soft Gelatin Capsules alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Coatal Soft Gelatin Capsules (see section Contraindications).

Inducers should not be administered at least one month after Coatal Soft Gelatin Capsules administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs (see section Special warnings and precautions for use)

Data on safety and efficacy are limited, and Coatal Soft Gelatin Capsules should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section Special warnings and precautions for use).

If Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules. In patients previously treated with halofantrine, Coatal Soft Gelatin Capsules should not be administered earlier than one month after the last halofantrine dose (see section Special warnings and precautions for use).

Mefloquine

A drug interaction study with Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules (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 Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules.

Concomitant use requiring caution

Interactions affecting the use of Coatal Soft Gelatin Capsules

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 Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Coatal Soft Gelatin Capsules should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc (see Section Contraindications), due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Coatal Soft Gelatin Capsules is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy (see section Special warnings and precautions for use).

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. Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules, and increased lumefantrine concentrations may cause QT prolongation (see Section Special warnings and precautions for use).

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 Coatal Soft Gelatin Capsules.

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 Coatal Soft Gelatin Capsules.

Interactions resulting in effects of Coatal Soft Gelatin Capsules on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Coatal Soft Gelatin Capsules 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 (see sections Special warnings and precautions for use and Pharmacokinetic properties).

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, Coatal Soft Gelatin Capsules 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 (see sections Special warnings and precautions for use and Fertility, pregnancy and lactation).

Drug-food/drink interactions

Coatal Soft Gelatin Capsules should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see Section Posology and method of administration).

Grapefruit juice should be used cautiously during Coatal Soft Gelatin Capsules 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 (see section Special warnings and precautions for use).

Pregnancy

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from pregnancy studies including over 1200 pregnant women who were exposed to artemether-lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity (see section Preclinical safety data).

Coatal Soft Gelatin Capsules treatment is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section Special warnings and precautions for use). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, Coatal Soft Gelatin Capsules treatment should 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 Coatal Soft Gelatin Capsules 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 Coatal Soft Gelatin Capsules unless potential benefits to the mother and child outweigh the risks of Coatal Soft Gelatin Capsules treatment.

Fertility

There is no information on the effects of Coatal Soft Gelatin Capsules on human fertility (see section Preclinical safety data).

4.7 Effects on ability to drive and use machines

Patients receiving Coatal Soft Gelatin Capsules 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 20 mg + Lumefantrine 120 mg Soft Gelatin Capsules 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 20 mg + Lumefantrine 120 mg Soft Gelatin Capsules 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)**
Blood and lymphatic system disorders		
Delayed haemolytic anaemia[#]	Not known	Not known
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
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 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

*: 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.

#: Has been reported up to a few weeks after treatment has been stopped.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

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, Artemisinin and derivatives, combinations

ATC code: P01BF01

Mechanism of Action

Coatal Soft Gelatin Capsules, a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively, is an antimalarial agent. Aremether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). The anti-malarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine, exerts its anti-malarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of ß-hematin by forming a complex with hemin. Both

artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis.

Activity In Vitro and In Vivo

Aremether and lumefantrine are active against the erythrocytic stages of Plasmodium falciparum.

Drug Resistance

Strains of P. falciparum with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected in vitro or in vivo, but not maintained in the case of artemether. The clinical relevance of such an effect is not known.

5.2 Pharmacokinetic properties

Artemether is absorbed 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 concentrations about 6 to 8 hours after administration.

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7% respectively). Artemether are cleared from plasma with elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with a terminal half-life of 3-6 days.

No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

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 in animals.

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 (see section Fertility, pregnancy and breast-feeding for data in humans).

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, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. 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 (see sections Special warnings and precautions for use and Pharmacodynamic properties).

6. Pharmaceutical particulars

6.1 List of excipients

Refined Soya Oil, Light Liquid Paraffin, Soya Lecithin, Butylated Hydroxy Anisole, Butylated Hydroxy Toluene, Polyoxyl 40 hydrogenated castor oil (Kolliphor).

Capsule shell: Gelatin, Glycerin, Methyl Paraben, Propyl Paraben, Purified Water, Sunset

Yellow, Titanium Dioxide.

6.2 Incompatibilities

None known.

6.3 Shelflife

Three years from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C in a cool & dry place.

6.5 Nature and contents of container

Coatal Soft Gelatin Capsules is Oval shape, Orange colour soft gelatin capsule containing yellow coloured oily suspension, packed in printed aluminium foil and Clear PVC foil blister containing 6 capsules.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

M/s. GENEITH PHARM LTD.

12 Adewale Crescent, Off Ewenla Street,

Off, Oshodi, Apapa, Lagos,

Nigeria.

8. Marketing authorization number(s)

KD/476 05/02/2022

9. Date of first authorisation/renewal of the authorisation

15/02/2023

10. Date of revision of the text

14/02/2028