1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product

ZMC

(Artemether 20 mg & Lumefantrine 120 mg tablets)

1.2 Strength

20 mg & 120 mg

1.3 Pharmaceutical Form

Oral dosage form

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Artemether	20 mg
Lumefantrine	120 mg
Excipients	q.s.

3. PHARMACEUTICAL FORM

Oral Dosage Form

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Artemether and Lumefantrine is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults.

Consideration should be given to official guidance regarding the appropriate use of ant malarial agents.

4.2. Posology and method of administration

Artemether and Lumefantrine is not recommende d for use in children below 5 kg body weight due to lack of data on safety and efficacy

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms.
Dosage for treatment and stand-by emergency treatment

25 to < 35 kg body weight

Three film coated tablets as a single dose at the time of initial diagnosis or as soon as symptoms appear, three film coated tablets again after 8 hours and then three film coated tablets twice dail y (in the morning and evening) on each of the follo wing two days (total course comprises 18 Film coated tablets).

Dosage in patients with impaired renal or hepatic function

No specific studies have been p erformed in these pa tient populations. No specif ic dose adjustment recommendations can be made for these patients

Most patients with acute m alaria present with so me degree of hep atic impairment. In clinical trials the a dverse event profile did not dif fer in patients with and those without hepa tic impairment.

Moreover, baseline abn ormalities in liver f unction tests improved in nearly all patients af ter treatment with Artemether and Lumefantrine.

New and recrudescent infections

Data for a lim ited number of patients show that ne w and rec rudescent infections can be trea ted with a second course of Artemether and Lumefantrine.

4.3. Contra-indications

Artemether and Lumefantrine are 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,

- Aeuroleptics, antidepressive agents,

- Aertain 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 special 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 (see section 4.6).

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 (see section 4.5) 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 halofantrine dose.

Artemether and Lumefantrine is not indicated and has not been evaluated for prophylaxis.

Artemether and Lumefantrine 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.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether and Lumefantrine has the potential to cause QT prolongation (see section 5.1).

Caution is recommended when combining Artemether and Lumefantrine 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 and Lumefantrine (see sections 4.5 and 5.2).

Caution is recommended when combining Artemether and Lumefantrine with hormonal contraceptives. Artemether and Lumefantrine 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 4.5).

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

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 5.2).

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 and Lumefantrine in patients with renal impairment is recommended. Caution is

advised when administering Artemether and Lumefantrine 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. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution is advised when administering Artemether and Lumefantrine to patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.

Elderly

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 and Lumefantrine. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether and Lumefantrine cannot be recommended.

4.5. Interactions with other Drug products and other forms of interaction

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Artemether and Lumefantrine 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 (see section 4.3)

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 with drugs that are metabolised by this iso-enzyme is contra indicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated (see sections 4.3 and 5.2).

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with MALFANTRIN-DS (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 alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phonation, St. John's Wort is contraindicated with Artemether and Lumefantrine .

Inducers should not be administered at least one month after Artemether and Lumefantrine 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 should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section 4.4).

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

Mefloquine

A drug interaction study with Artemether and Lumefantrine 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 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 (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 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 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.

Concomitant use requiring caution

Interactions affecting the use of Artemether and Lumefantrine

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

Artemether and Lumefantrine 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 treatment.

Interaction with weak to moderate inducers of CYP3A4

When Artemether and Lumefantrine 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 4.4).

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 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, 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.

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.

Interactions resulting in effects of Artemether and Lumefantrine on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Artemether and Lumefantrine 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 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 4.4 and 4.6).

Drug-food/drink interactions

Artemether and Lumefantrine 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 4.2).

Grapefruit juice should be used cautiously during Artemether and Lumefantrine treatment

4.6. Pregnancy and lactation

Pregnancy

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.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether and Lumefantrine (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 and Lumefantrine treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

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 4.4).

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking MALFORTE PLUS 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 r esume until at least on e week after the last dose of MALFORTE PLUS unless potential benefits to the mother and child outweigh the risks of Artemether and Lumefantrine

4.7. Effects on ability to drive and use machines

Patients receiving Artemether and Lumefantrineshould be warn ed that dizz iness or f atigue/asthenia may occur in which case they should not drive or use machines.

4.8. ADVERSE REACTIONS

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 inf ants 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 ch ildren of 12 years of age and below (incidence estimates)**
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 %)
ElectrocardiogramQT 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.

4.9 Overdose

No case of overdose has been reported..

If overdosage is suspected, symptomatic and supportive therapy should be initiated based on the clinical picture. The ECG and electrolytes (e.g. potassium) should be monitored

Early signs of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group : Antimalarials, blood schizontocide

ATC Code : P01 BF01

5.2 Pharmacokinetic Properties

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 Lumether 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%).

Metabolism

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*. 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 Lumether.

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.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the Artemether and Lumefantrine dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Artemether and Lumefantrine as Film coated tablets and crushed tablets in healthy adults. Systemic exposure to lumefantrine was similar following administration of Artemether and Lumefantrine Film coated tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the Film coated than for the intact tablet. These findings are not considered to be clinically relevant for the use of the Film coated tablets in the paediatric population since adequate efficacy of Artemether and Lumefantrine tablets was demonstrated in this population.

Special populations

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of MALFORTE PLUS) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant 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. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin,

no dose adjustment for the use of Artemether and Lumefantrine in patients with renal impairment is advised.

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.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed with artemether at 25 mg/kg for 7 or 14 days and dogs dosed at 20 mg/kg for 8 days or longer, but lesions were not observed after shorter courses of drug or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7-fold greater than the estimated artemether 24 h AUC in humans on day 1 of the standard 3-day oral treatment regimen; oral exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent to about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

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 m g/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.

Fertility

After artemether-lumefantrine administration for 10 w eeks in ma les and 2 week s in fe males, reduced fertility occurred at 1000 mg/kg/day where altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity and other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. General toxicity was observed in males and females at doses ≥ 300 mg/kg/day. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to th is finding in humans is unknown.

Juvenile toxicity studies

A specific study to investigate the ne urotoxicity of artemether in j uvenile rats involved oral administration of a rtemether during four different dosing intervals, at doses of 30 o r 80 mg/kg/day on po st partum days 7 to 13, and at doses of 30 or 1 20 mg/kg/day on p ost partum days 14 to 2 1, 22 to 2 8, or 29 to 3 6. Mortality, clinical signs and reductions in body weight parameters occurred most notably during the first two dosing intervals. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect of orally administered artemether on the brain of juvenile rats.

Juvenile studies in the rat indicate that very young animals (aged 7-21 days) are more sensitive to artemether than adult animals. There is no difference in sensitivity in slightly older (3-5 weeks of age) animals following 13 weeks of artemether/lumefantrine administration. Consistent with the later data, clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses ≥600 mg/kg/day only, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at hi gher doses than intended for use in man. In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefrantrine and the ma in metabolite desbutyl-lumefantrine showed some inhibitory potential in on e of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC_{50} values, the o rder 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).

Additional studies were performed to evaluate the in vitro effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at Cmax or greater than 1000

if they are estimated using the calculated free Cmax. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Croscarmellose Sodium BP	BP 2018
Lactose (Monohydrate) BP	BP 2018
Hydroxy Propyl Methyl Cellulose (Hypromellose) BP	BP 2018
Polysorbate 80 (Tween-80) BP	BP 2018
Purified water BP	BP 2018
Croscarmellose Sodium BP	BP 2018
Purified Talc BP	BP 2018
Magnesium Stearate BP	BP 2018

6.2. Incompatibilities

None

6.3. Shelf life

24 Months.

6.4 Special precautions for storage

Store below above 30 ^{o}C.

Store in the original package, in order to protect from moisture.

6.5. Nature and contents of container

6 tablets packed in one Blister. Such 1 blister packed in unit printed duplex board carton along with its package insert.

6.6. Instruction for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SYNCOM FORMULATIONS (India) LIMITED

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