1 NAME OF THE MEDICINAL PRODUCT

Binart 80/480 Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Yellow-coloured biconvex-shaped uncoated tablets.

Each uncoated tablet contains:

Artemether (PhI) 80 mg

Lumefantrine (PhI) 480 mg

Excipients q.s.

3 PHARMACEUTICAL FORMS

Oral Tablets

4 Clinical particulars

4.1 Therapeutic indications

Artemether & Lumefantrine Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum (P. falciparum)* in patients 2 months of age and older with a bodyweight of 5 kg and above.

4.2 Posology and method of administration

Posology

Artemether & Lumefantrine Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

For patients who are unable to swallow the tablets such as infants and children, Artemether & Lumefantrine Tablets may be crushed and mixed with a small amount of water (1 to 2 teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours after administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

Dosage in Adult Patients (greater than 16 years of age)

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Four tablets as a single initial dose, 4 tablets again after 8 hours, and then 4 tablets twice-daily (morning and evening) for the following 2 days (total course of 24 tablets). For patients weighing less than 35 kg,

Dosage in Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended as below:

5 kg to less than 15 kg bodyweight: One tablet as an initial dose, 1 tablet again after 8 hours, and then 1 tablet twice daily (morning and evening) for the following 2 days (total course of 6 tablets).

15 kg to less than 25 kg bodyweight: Two tablets as an initial dose, 2 tablets again after 8 hours, and then 2 tablets twice daily (morning and evening) for the following 2 days (total course of 12 tablets).

25 kg to less than 35 kg bodyweight: Three tablets as an initial dose, 3 tablets again after 8 hours, and then 3 tablets twice daily (morning and evening) for the following 2 days (total course of 18 tablets).

35 kg bodyweight and above: Four tablets as a single initial dose, 4 tablets again after 8 hours, and then 4 tablets twice daily (morning and evening) for the following 2 days (total course of 24 tablets).

Method of administration

Tablets for oral administration.

4.3 Contraindications

Artemether & Lumefantrine Caplet is contraindicated in:

patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

patients with severe malaria according to WHO definition*.

patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. 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 (proarrythmic). These drugs include:

- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride.
- flecainide

patients with a history of symptomatic cardiac arrythmias 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.

patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*). (*Presence of one or more of the following clinical or laboratory features:

Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

Prolongation of the QT Interval Some antimalarials (e.g., halofantrine, quinine, quinidine) including Artemether & Lumefantrine Tablets have been associated with prolongation of the QT interval on the electrocardiogram (ECG).

Artemether & Lumefantrine Tablets should be avoided in patients:

• With congenital prolongation of the QT interval (e.g., long QT syndrome) or any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.

• With a family history of congenital prolongation of the QT interval or sudden death.

• With known disturbances of electrolyte balance, e.g., hypokalemia or hypomagnesemia.

• Receiving other medications that prolong the QT interval, such as Class IA (quinidine, procainamide, disopyramide), or Class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents)

• Receiving medications that are metabolized by the cytochrome enzyme CYP2D6, which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine)

Use of QT Prolonging Drugs and Other Antimalarials

Halofantrine and Artemether & Lumefantrine Tablets should not be administered within 1 month of each other due to the long elimination half-life of lumefantrine (3 to 6 days) and potential additive effects on the QT interval.

Antimalarials should not be given concomitantly with Artemether & Lumefantrine Tablets, unless there is no other treatment option, due to limited safety data.

Drugs that prolong the QT interval, including antimalarials such as quinine and quinidine, should be used cautiously following Artemether & Lumefantrine Tablets, due to the long elimination half-life of lumefantrine (3 to 6 days) and the potential for additive effects on the QT interval; ECG monitoring is advised if use of drugs that prolong the QT interval is medically required

If mefloquine is administered immediately prior to Artemether & Lumefantrine Tablets, there may be a decreased exposure to lumefantrine, possibly due to a mefloquine-induced decrease in bile production. Therefore, patients should be monitored for decreased efficacy and food consumption should be encouraged while taking Artemether & Lumefantrine Tablets

Drug Interactions With CYP3A4

When Artemether & Lumefantrine Tablets are coadministered with substrates of CYP3A4, it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Artemether & Lumefantrine Tablets are coadministered with an inhibitor of CYP3A4, including grapefruit juice, it may result in increased concentrations of artemether and/or lumefantrine and potentiate QT prolongation. When Artemether & Lumefantrine Tablets are coadministered with inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Drugs that have a mixed effect on CYP3A4, especially antiretroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and those that have an effect on the QT interval should be used with caution in patients taking Artemether & Lumefantrine Tablets .
Artemether & Lumefantrine Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Artemether & Lumefantrine.

Drug Interactions With CYP2D6
Administration of Artemether & Lumefantrine Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Artemether & Lumefantrine Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine

Recrudescence
Food enhances absorption of artemether and lumefantrine following administration of Artemether & Lumefantrine Tablets. Patients who remain averse to food during treatment should be closely

monitored as the risk of recrudescence may be greater In the event of recrudescent P. falciparum infection after treatment with Artemether & Lumefantrine Tablets, patients should be treated with a different antimalarial drug.

Hepatic and Renal Impairment
Artemether & Lumefantrine Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment

Plasmodium vivax Infection
Artemether & Lumefantrine Tablets have been shown in limited data (43 patients) to be effective in treating the erythrocytic stage of P. vivax infection. However, relapsing malaria caused by P. vivax requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoites forms that may remain dormant in the liver.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampin

Oral administration of rifampin, a strong CYP3A4 inducer, with Artemether & Lumefantrine Tablets resulted in significant decreases in exposure to artemether, DHA (metabolite of artemether), and lumefantrine by 89%, 85%, and 68%, respectively, when compared to exposure values after Artemether & Lumefantrine Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort is contraindicated with Artemether & Lumefantrine Tablets

Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Artemether & Lumefantrine Tablets resulted in a moderate increase in exposure to artemether, DHA, and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Artemether & Lumefantrine Tablets is necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Artemether & Lumefantrine Tablets should be used cautiously with drugs that inhibit CYP3A4

Antiretroviral Drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Antiretroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Therefore, the effects of antiretroviral drugs on the exposure to artemether, DHA, and lumefantrine are also variable Artemether & Lumefantrine Tablets should be used cautiously in patients on antiretroviral drugs because decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether & Lumefantrine Tablets, and increased lumefantrine concentrations may cause QT prolongation

Prior Use of Mefloquine

Administration of 3 doses of mefloquine followed 12 hours later by a 6-dose regimen of Artemether & Lumefantrine Tablets in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio. However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of Artemether & Lumefantrine Tablets

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 CYP3A4. Therefore, Artemether & Lumefantrine Tablets may potentially reduce the effectiveness of hormonal contraceptives. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Artemether & Lumefantrine

CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 *in vitro*. Administration of Artemether & Lumefantrine Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Artemether & Lumefantrine Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine).

Sequential Use of Quinine

A single dose of intravenous quinine (10 mg/kg bodyweight) concurrent with the final dose of a 6-dose regimen of Artemether & Lumefantrine Tablets demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with Artemether & Lumefantrine Tablets due to the long elimination half-life of lumefantrine and the potential for additive QT effects; ECG monitoring is advised if use of drugs that prolong the QT interval is medically required

Interaction With Drugs That are Known to Prolong the QT Interval

Artemether & Lumefantrine Tablets are to be used with caution when coadministered with drugs that may cause prolonged QT 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.

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4.6 Fertility, pregnancy and lactation

Risk Summary

Published data from clinical studies and pharmacovigilance data have not established an association with artemether/lumefantrine use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Malaria during and after pregnancy increases the risk for adverse pregnancy and neonatal outcomes, including maternal anemia, severe malaria, spontaneous abortion, stillbirths, preterm delivery, low birth weight, intrauterine growth restriction, congenital malaria, and maternal and neonatal mortality.

Data

Human Data

While available studies cannot definitively establish the absence of risk, a meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy, data

from observational, and open label studies including more than 1200 pregnant women in their second- or third trimester exposed to artemether-lumefantrine compared to other antimalarials, and pharmacovigilance data have not demonstrated an increase in major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Published epidemiologic studies have important methodological limitations which hinder interpretation of data, including inability to control for confounders, such as underlying maternal disease, and maternal use of concomitant medications and missing information on the dose and duration of use.

Animal Data

Pregnant rats dosed orally during the period of organogenesis [gestational days (GD) 7 through 17] at 50 mg/kg/day artemether-lumefantrine combination (corresponding to 7 mg/kg/day artemether or higher, a dose of less than half the maximum recommended human dose (MRHD) of 1120 mg artemether-lumefantrine per day (based on body surface area (BSA) comparisons), showed increases in fetal loss, early resorptions, and postimplantation loss. No adverse effects were observed in animals dosed at 25 mg/kg/day artemether-lumefantrine (corresponding to 3.6 mg/kg/day of artemether), about one-third the MRHD (based on BSA comparison). Similarly, oral dosing in pregnant rabbits during organogenesis (GD 7 through GD 19) at 175 mg/kg/day, (corresponding to 25 mg/kg/day artemether) about 3 times the MRHD (based on BSA comparisons) resulted in abortions, preimplantation loss, post implantation loss and decreases in the number of live fetuses.

No adverse reproductive effects were detected in rabbits at 105 mg/kg/day artemether-lumefantrine (corresponding to 15 mg/kg/day artemether), about 2 times the MRHD. Artemether and other artemisinins are associated with maternal toxicity and embryotoxicity and malformations in animals at clinically relevant exposures; however, lumefantrine doses as high as 1000 mg/kg/day, showed no evidence to suggest maternal, embryo- or fetotoxicity or teratogenicity in rats and rabbits. The relevance of the findings from the animal reproductive studies to human risk is unclear.

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Use of Artemether & Lumefantrine may reduce the efficacy of hormonal contraceptives. Advise patients using hormonal contraceptives to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Artemether & Lumefantrine *[see Drug Interactions (7.5)]*.

Infertility

In animal fertility studies, administration of repeated doses of artemether-lumefantrine combination to female rats (for 2 to 4 weeks) resulted in pregnancy rates that were reduced by one half. In male rats dosed for approximately 3 months with artemether-lumefantrine combination, abnormal sperm cells, decreased sperm motility, and increased testes weight were observed.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether & Lumefantrine Caplet should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

The following serious and otherwise important adverse reactions are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions
- Prolongation of the QT Interval
- Use of QT Prolonging Drugs and Other Antimalarials
- Drug Interactions with CYP3A4
- Drug Interactions with CYP2D6

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The data described below reflect exposure to a 6-dose regimen of Artemether & Lumefantrine Tablets in 1979 patients including 647 adults (older than 16 years) and 1332 children (16 years and younger). For the 6-dose regimen, Artemether & Lumefantrine Tablets was studied in active-controlled (366 patients) and noncontrolled, open-label trials (1613 patients). The 6-dose Artemether & Lumefantrine Tablets population was patients with malaria between ages 2 months and 71 years: 67% (1332) were 16 years and younger and 33% (647) were older than 16 years. Males represented 73% and 53% of the adult and pediatric populations, respectively. The majority of adult patients were enrolled in studies in Thailand, while the majority of pediatric patients were enrolled in Africa.

Tables 1 and 2 show the most frequently reported adverse reactions (greater than or equal to 3%) in adults and children respectively who received the 6-dose regimen of Artemether & Lumefantrine Tablets. Adverse reactions collected in clinical trials included signs and symptoms at baseline, but only treatment emergent adverse events, defined as events that appeared or worsened after the start of treatment, are presented below. In adults, the most frequently reported adverse reactions were headache, anorexia, dizziness, and asthenia. In children, the adverse reactions were pyrexia, cough, vomiting, anorexia, and headache. Most adverse reactions were mild, did not lead to discontinuation of study medication, and resolved.

In limited comparative studies, the adverse reaction profile of Artemether & Lumefantrine Tablets appeared similar to that of another antimalarial regimen.

Discontinuation of Artemether & Lumefantrine Tablets due to adverse drug reactions occurred in 1.1% of patients treated with the 6-dose regimen overall: 0.2% (1/647) in adults and 1.6% (21/1332) in children.

Table 1: Adverse Reactions Occurring in 3% or More of Adult Patients Treated in Clinical Trials With the 6-dose Regimen of Artemether & Lumefantrine Tablets

System Organ Class	Preferred Term	Adults* N = 647 (%)
Nervous system disorders	Headache	360 (56)
	Dizziness	253 (39)
Metabolism and nutrition disorders	Anorexia	260 (40)
General disorders and administration site conditions	Asthenia	243 (38)
	Pyrexia	159 (25)
	Chills	147 (23)
	Fatigue	111 (17)
	Malaise	20 (3)
Musculoskeletal and connective tissue disorders	Arthralgia	219 (34)
	Myalgia	206 (32)

Gastrointestinal disorders	Nausea	169 (26)
	Vomiting	113 (17)
	Abdominal pain	112 (17)
	Diarrhea	46 (7)
Psychiatric disorders	Sleep disorder	144 (22)
	Insomnia	32 (5)
Cardiac disorders	Palpitations	115 (18)
Hepatobiliary disorders	Hepatomegaly	59 (9)
Blood and lymphatic system disorders	Splenomegaly	57 (9)
	Anemia	23 (4)
Respiratory, thoracic and mediastinal disorders	Cough	37 (6)
Skin and subcutaneous tissue disorders	Pruritus	24 (4)
	Rash	21 (3)
Ear and labyrinth disorders	Vertigo	21 (3)
Infections and infestations	Malaria	18 (3)
	Nasopharyngitis	17 (3)

*Adult patients defined as greater than 16 years of age.

Table 2: Adverse Reactions Occurring in 3% or More of Pediatric Patients Treated in Clinical Trials With the 6-dose Regimen of Artemether & Lumefantrine Tablets

System Organ Class	Preferred Term	Children* N = 1332 (%)
General disorders and administration site conditions	Pyrexia	381 (29)
	Chills	72 (5)
	Asthenia	63 (5)
	Fatigue	46 (3)
Respiratory, thoracic and mediastinal disorders	Cough	302 (23)
Gastrointestinal disorders	Vomiting	242 (18)
	Abdominal pain	112 (8)
	Diarrhea	100 (8)
	Nausea	61 (5)
Infections and infestations	*Plasmodium falciparum* infection	224 (17)
	Rhinitis	51 (4)
Metabolism and nutrition disorders	Anorexia	175 (13)
Nervous system disorders	Headache	168 (13)
	Dizziness	56 (4)
Blood and lymphatic system disorders	Splenomegaly	124 (9)
	Anemia	115 (9)
Hepatobiliary disorders	Hepatomegaly	75 (6)
Investigations	Aspartate aminotransferase increased	51 (4)
Musculoskeletal and connective tissue disorders	Arthralgia	39 (3)
	Myalgia	39 (3)
Skin and subcutaneous tissue disorders	Rash	38 (3)

*Children defined as patients less than or equal to 16 years of age.

Clinically significant adverse reactions reported in adults and/or children treated with the 6-dose regimen of Artemether & Lumefantrine Tablets, which occurred in clinical studies at less than 3% regardless of causality are listed below:

Blood and Lymphatic System Disorders: eosinophilia

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: conjunctivitis

Gastrointestinal Disorders: constipation, dyspepsia, dysphagia, peptic ulcer

General Disorders: gait disturbance

Infections and Infestations: abscess, acrodermatitis, bronchitis, ear infection, gastroenteritis, helminthic infection, hook-worm infection, impetigo, influenza, lower respiratory tract infection, malaria, nasopharyngitis, oral herpes, pneumonia, respiratory tract infection, subcutaneous abscess, upper respiratory tract infection, urinary tract infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, hematocrit decreased, lymphocyte morphology abnormal, platelet count decreased, platelet count increased, white blood cell count

decreased, white blood cell count increased

Metabolism and Nutrition Disorders: hypokalemia

Musculoskeletal and Connective Tissue Disorders: back pain

Nervous System Disorders: ataxia, clonus, fine motor delay, hyperreflexia, hypoesthesia, nystagmus, tremor

Psychiatric Disorders: agitation, mood swings

Renal and Urinary Disorders: hematuria, proteinuria

Respiratory, Thoracic and Mediastinal Disorders: asthma, pharyngo-laryngeal pain

Skin and Subcutaneous Tissue Disorders: urticaria

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Artemether & Lumefantrine Tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Hypersensitivity Reactions:* anaphylaxis, urticaria, angioedema, and serious skin reactions (bullous eruption) have been reported.
- *Blood and Lymphatic System Disorders:* Cases of delayed hemolytic anemia have been reported following treatment with artemether-lumefantrine, mostly when used for treatment of severe malaria in patients initially treated with IV/parenteral artesunate. Artemether & Lumefantrine Tablets should not be used to treat severe malaria as it is not an approved indication.

4.9 Overdose

There is no information on overdoses of Artemether & Lumefantrine Tablets higher than the doses recommended for treatment.
In cases of suspected overdosage, symptomatic and supportive therapy, which would include ECG and blood electrolyte monitoring, should be given as appropriate.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code:

P01 BF01.

Pharmacodynamic effects

Mechanism of Action

Artemether & Lumefantrine Tablets, a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively, is an antimalarial agent. Artemether is rapidly metabolized into an active metabolite DHA. The antimalarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine exerts its antimalarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of -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*

Artemether and lumefantrine are active against the erythrocytic stages of *P. falciparum*.

Drug Resistance

There is a potential for development of resistance to artemether and lumefantrine. 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. Alterations in some genetic regions of *P. falciparum [multidrug resistant 1 (pfmdr1)*, *chloroquine resistance transporter (pfcrt)*, and *kelch 13 (K13)]* based on *in vitro* testing

and/or identification of isolates in endemic areas where artemether/lumefantrine treatment was administered, have been reported. The clinical relevance of these findings are not known.

Effects on the Electrocardiogram

In a healthy adult volunteer parallel-group study including a placebo and moxifloxacin control-group (n = 42 per group), the administration of the 6-dose regimen of Artemether & Lumefantrine Tablets was associated with prolongation of QTcF (Fridericia). Following administration of a 6-dose regimen of Artemether & Lumefantrine Tablets consisting of 4 tablets per dose (total of 4 tablets of 80 mg artemether/480 mg lumefantrine) taken with food, the maximum mean change from baseline and placebo adjusted QTcF was 7.5 msec (1-sided 95% upper confidence interval: 11 msec).
There was a concentration-dependent increase in QTcF for lumefantrine.

In clinical trials conducted in children, no patient had QTcF greater than 500 msec. Over 5% of patients had an increase in QTcF of over 60 msec.
In clinical trials conducted in adults, QTcF prolongation of greater than 500 msec was reported in 3 (0.3%) patients. Over 6% of adults had a QTcF increase of over 60 msec from baseline

CLINICAL STUDIES

Treatment of Acute, Uncomplicated *P. falciparum* Malaria

The efficacy of Artemether & Lumefantrine Tablets was evaluated for the treatment of acute, uncomplicated malaria caused by *P. falciparum* in HIV negative patients in 8 clinical studies. Uncomplicated malaria was defined as symptomatic *P. falciparum* malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction.
Baseline parasite density ranged from 500/mcL to 200,000/mcL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in partially immune and non-immune adults and children (greater than or equal to 5 kg body weight) with uncomplicated malaria in China, Thailand, sub-Saharan Africa, Europe, and South America. Patients who had clinical features of severe malaria, severe cardiac, renal, or hepatic impairment were excluded.

The studies include two 4-dose studies assessing the efficacy of the components of the regimen, a study comparing a 4-dose versus a 6-dose regimen, and 5 additional 6-dose regimen studies.

Artemether & Lumefantrine Tablets were administered at 0, 8, 24, and 48 hours in the 4-dose regimen, and at 0, 8, 24, 36, 48, and 60 hours in the 6-dose regimen. Efficacy endpoints consisted of:

- 28-day cure rate, defined as clearance of asexual parasites (the erythrocytic stage) within 7 days without recrudescence by Day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature greater than 37.5°C at baseline)

The modified intent-to-treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least 1 dose of study drug. Evaluable patients generally are all patients who had a Day 7 and a Day 28 parasitological assessment or experienced treatment failure by Day 28.

Studies 1 and 2: The 2 studies, which assessed the efficacy of Artemether & Lumefantrine Tablets (4 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine) compared to each component alone, were randomized, double-blind, comparative, single center, conducted in China. The efficacy results (Table 3)

support that the

combination of artemether and lumefantrine in Artemether & Lumefantrine Tablets had a significantly higher 28-day cure rate compared to artemether and had a significantly faster PCT and FCT compared to lumefantrine.

Table 3: Clinical Efficacy of Artemether & Lumefantrine Tablets Versus Components (mITT Population)[1]

Study No. Region/patient ages	28-day cure rate[2] n/N (%) patients	Median FCT[3] [25th, 75th percentile]	Median PCT [25th, 75th percentile]
Study 1			
China, ages 13 to 57 years			
Artemether & Lumefantrine Tablets	50/51 (98.0)	24 hours [9, 48]	30 hours [24, 36]
Artemether[4]	24/52 (46.2)	21 hours [12, 30]	30 hours [24, 33]
Lumefantrine[5]	47/52 (90.4)	60 hours [36, 78]	54 hours [45, 66]
Study 2			
China, ages 12 to 65 years			
Artemether & Lumefantrine Tablets	50/52 (96.2)	21 hours [6, 33]	30 hours [24, 36]
Lumefantrine[6]	45/51 (88.2)	36 hours [12, 60]	48 hours [42, 60]

Abbreviations: FCT, fever clearance time; mITT, modified intent-to-treat; PCT, parasite clearance time.

[1]In mITT analysis, patients whose status was uncertain were classified as treatment failures.

[2]Efficacy cure rate based on blood smear microscopy.

[3]For patients who had a body temperature greater than 37.5°C at baseline only.

[4]95% Confidence Interval (Artemether & Lumefantrine Tablets–artemether) on 28-day cure rate: 37.8%, 66.0%.

[5]P-value comparing Artemether & Lumefantrine Tablets to lumefantrine on PCT and FCT: < 0.001.

[6]P-value comparing Artemether & Lumefantrine Tablets to lumefantrine on PCT: < 0.001 and on FCT: < 0.05.

Results of 4-dose studies conducted in areas with high resistance such as Thailand during 1995-96 showed lower efficacy results than the above studies. Therefore, Study 3 was conducted.

Study 3: Study 3 was a randomized, double-blind, 2-center study conducted in Thailand in adults and children (aged greater than or equal to 2 years), which compared the 4-dose regimen (administered over 48 hours) of Artemether & Lumefantrine Tablets to a 6-dose regimen (administered over 60 hours). Twenty-eight day cure rate in mITT subjects was 81% (96/118) for the Artemether & Lumefantrine Tablets 6-dose arm as compared to 71% (85/120) in the 4-dose arm.

Studies 4, 5, 6, 7, and 8: In these studies, Artemether & Lumefantrine Tablets were administered as the 6-dose regimen.

In study 4, a total of 150 adults and children aged greater than or equal to 2 years received Artemether & Lumefantrine Tablets. In study 5, a total 164 adults and children greater than or equal to 12 years received Artemether & Lumefantrine Tablets. Both studies were conducted in Thailand.

Study 6 was a study of 165 non-immune adults residing in regions non-endemic for malaria (Europe and Colombia) who contracted acute uncomplicated *P. falciparum* malaria when traveling in endemic regions.

Study 7 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature greater than or equal to 37.5□C.

Study 8 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to less than 35 kg, with fever (greater than or equal to 37.5°C axillary or greater than or equal to 38°C rectally) or history of fever in the preceding 24 hours.

Results of 28-day cure rate, median PCT, and FCT for Studies 3 to 8 are reported in Table 6.

Table 4: Clinical Efficacy of 6-dose Regimen of Artemether & Lumefantrine Tablets

Study Region/ages	No. Patients	28-day cure rate[1] n/N (%) mITT[3]	Evaluable	Median [25th, 75th percentile]	Median P [25th, 75th percentile]
Study 3 Thailand, ages 3–62 years		96/118 (81.4)	93/96 (96.9)	35 hours	44 hours
	Early failure[4]	0	0	[20, 46]	[22, 47]
3 (3.1)	Late failure[5]	4 (3.4)			
	Lost to follow-up	18 (15.3)			
	Other[6]	0			
Study 4 Thailand, ages 2–63 years		130/149 (87.2)	130/134 (97.0)	22 hours	NA
	Early failure[4]	0	0	[19, 44]	
	Late failure[5]	4 (2.7)	4 (3.0)		
	Lost to follow-up	13 (8.7)			
	Other[6]	2 (1.3)			
Study 5 Thailand, ages 12–71 years		148/164 (90.2)	148/155 (95.5)	29 hours	29 hours
	Early failure[4]	0	0	[8, 51]	[18, 40]
7 (4.5)	Late failure[5]	7 (4.3)			
	Lost to follow-up	9 (5.5)			
	Other[6]	0			
Study 6 Europe/Columbia, ages 16–66 years		120/162 (74.1)	119/124 (96.0)	37 hours	42 hours
	Early failure[4]	6 (3.7)	1 (0.8)	[18, 44]	[34, 63]
3 (2.4)	Late failure[5]	3 (1.9)			
	Lost to follow-up	17 (10.5)			
	Other[6]	16 (9.9)	1 (0.8)		
Study 7 Africa, ages 2 months–9 years		268/310 (86.5)	267/300 (89.0)	8 hours	24 hours
	Early failure[4]	2 (0.6)	0	[8, 24]	[24, 36]
33 (11.0)	Late failure[5]	34 (11.0)			
	Lost to follow-up	2 (0.6)			
	Other[6]	4 (1.3)			
Study 8 Africa, ages 3 months–12 years		374/452 (82.7)	370/419 (88.3)	8 hours [8, 23]	35 hours [24, 36]
	Early failure[4]	13 (2.9)	0		
	Late failure[5]	49 (10.8)	49 (11.7)		
	Lost to follow-up	6 (1.3)			
	Other[6]	10 (2.2)			

FCT[2]

Abbreviations: FCT, fever clearance time; mITT, modified intent-to-treat; PCT, parasite clearance time; NA, not applicable.

[1]Efficacy cure rate based on blood smear microscopy.

[2]For patients who had a body temperature greater than 37.5°C at baseline only.

[3]In mITT analysis, patients whose status was uncertain were classified as treatment failures.

[4]Early failures were usually defined as patients withdrawn for unsatisfactory therapeutic effect within the first 7 days or because they received another antimalarial medication within the first 7 days.

[5]Late failures were defined as patients achieving parasite clearance within 7 days but having parasite reappearance including recrudescence or new infection during the 28-day follow-up period.

[6]Other includes withdrawn due to protocol violation or non-compliance, received additional medication after day 7, withdrew consent, missing day 7 or 28 assessment.

In all studies, patients' signs and symptoms of malaria resolved when parasites were cleared.

In studies conducted in areas with high transmission rates, such as Africa, reappearance of *P. falciparum* parasites may be due to recrudescence or a new infection.

The efficacy by body weight category for studies 7 and 8 is summarized in Table 5.

Table 5: Clinical Efficacy by Weight for Pediatric Studies

Study No. **Age category**	**Artemether & Lumefantrine Tablets 6-dose Regimen**		
	mITT Population[1]		**Evaluable Population**
	Median PCT [25th, 75th percentile]	**28-day cure rate[2] n/N (%) patients**	**28-day cure rate[2] n/N (%) patients**
Study 7			
5 to < 10 kg	24 [24, 36]	133/154 (86.4)	133/149 (89.3)
10 to < 15 kg	35 [24, 36]	94/110 (85.5)	94/107 (87.9)
15 to 25 kg	24 [24, 36]	41/46 (89.1)	40/44 (90.9)
Study 8[3]			
5 to < 10 kg	36 [24, 36]	61/83 (73.5)	61/69 (88.4)
10 to < 15 kg	35 [24, 36]	160/190 (84.2)	157/179 (87.7)
15 to < 25 kg	35 [24, 36]	123/145 (84.8)	123/140 (87.9)
25 to < 35 kg	26 [24, 36]	30/34 (88.2)	29/31 (93.5)

Abbreviations: mITT, modified intent-to-treat; PCT, parasite clearance time.

[1]In mITT analysis, patients whose status was uncertain were classified as treatment failures.

[2]Efficacy cure rate based on blood smear microscopy.

[3]Artemether & Lumefantrine Tablets administered as crushed tablets.

The efficacy of Artemether & Lumefantrine Tablets for the treatment *P. falciparum* infections mixed with *P. vivax* was assessed in a small number of patients. Artemether & Lumefantrine Tablets are only active against the erythrocytic phase of *P. vivax* malaria. Of the 43 patients with mixed infections at baseline, all cleared their parasitemia within 48 hours. However, parasite relapse occurred commonly (14/43; 33%). Relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoite forms that may remain dormant in the liver.

5.2 Pharmacokinetic properties

Absorption

Following administration of Artemether & Lumefantrine Tablets to healthy volunteers and patients with malaria, 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. The single dose (4 tablets) pharmacokinetic parameters for artemether, DHA, an active antimalarial metabolite of artemether, and lumefantrine in adult Caucasian healthy volunteers are given in Table 6. Multiple dose data after the 6-dose regimen of Artemether & Lumefantrine Tablets in adult malaria patients are given in Table 7.

Table 6: Single Dose Pharmacokinetic Parameters[a] for Artemether, Dihydroartemisinin, and Lumefantrine Under-Fed Conditions

	Study 2102 (n = 50)	**Study 2104 (n = 48)**
Artemether		
C_{max} (ng/mL)	60.0 ± 32.5	83.8 ± 59.7
T_{max} (h)	1.50	2.00
AUC_{last} (ng·h/mL)	146 ± 72.2	259 ± 150
$t_{½}$ (h)	1.6 ± 0.7	2.2 ± 1.9
DHA		
C_{max} (ng/mL)	104 ± 35.3	90.4 ± 48.9
T_{max} (h)	1.76	2.00
AUC_{last} (ng·h/mL)	284 ± 83.8	285 ± 98.0
$t_{½}$ (h)	1.6 ± 0.6	2.2 ± 1.5
Lumefantrine		
C_{max} (µg/mL)	7.38 ± 3.19	9.80 ± 4.20
T_{max} (h)	6.01	8.00
AUC_{last} (µg·h/mL)	158 ± 70.1	243 ± 117
$t_{½}$ (h)	101 ± 35.6	119 ± 51.0

Abbreviations: DHA, dihydroartemisinin; SD, standard deviation; AUC, area under the curve.

[a]Mean ± SD C_{max}, AUC_{last}, $t_{½}$ and Median T_{max}.

Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers, the relative bioavailability of artemether was increased between 2- to 3-fold, and that of lumefantrine 16-fold when Artemether & Lumefantrine Tablets were taken after a high-fat meal compared under fasted conditions. Patients should be

encouraged to take Artemether & Lumefantrine Tablets with a meal as soon as food can be tolerate.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin (DHA) is also bound to human serum proteins (47% to 76%). Protein binding to human plasma proteins is linear.

Biotransformation

In human liver microsomes and recombinant CYP450 enzymes, the metabolism of artemether was catalyzed predominantly by CYP3A4/5. Dihydroartemisinin (DHA) is an active metabolite of artemether. The metabolism of artemether was also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19. *In vitro* studies with artemether at therapeutic concentrations revealed no significant inhibition of the metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11. *In vitro* studies with artemether, DHA, and lumefantrine at therapeutic concentrations revealed no significant induction of the metabolic activities of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, or CYP3A5.

During repeated administration of Artemether & Lumefantrine Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHA area under the curve (AUC) ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. This suggests that there was induction of enzymes responsible for the metabolism of artemether.

In human liver microsomes and in recombinant CYP450 enzymes, lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine. The systemic exposure to the metabolite desbutyl-lumefantrine was less than 1% of the exposure to the parent compound. *In vitro*, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Caution is recommended when combining Artemether & Lumefantrine Tablets with substrates, inhibitors, or inducers of CYP3A4, especially antiretroviral drugs and those that prolong the QT interval (e.g., macrolide antibiotics, pimozide)

Coadministration of Artemether & Lumefantrine Tablets with CYP2D6 substrates may result in increased plasma concentrations of the CYP2D6 substrate and increase the risk of adverse reactions. In addition, many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Artemether & Lumefantrine Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine)

Elimination

Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with an elimination half-life of 3 to 6 days in healthy volunteers and in patients with *falciparum* malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

In 16 healthy volunteers, neither lumefantrine nor artemether was found in the urine after administration of Artemether & Lumefantrine Tablets, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.

Specific Populations

Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. There is no significant renal excretion of lumefantrine, artemether, and DHA in healthy volunteers and while clinical experience in this population is limited, no dose adjustment in renal impairment is recommended

Pediatric Patients

The PK of artemether, DHA, and lumefantrine were obtained in 2 pediatric studies by sparse sampling using a population-based approach. PK estimates derived from a composite plasma concentration profile for artemether, DHA, and lumefantrine are provided in Table 4.

Systemic exposure to artemether, DHA, and lumefantrine, when dosed on an mg/kg body weight basis in pediatric patients (greater than or equal to 5 to less than 35 kg body weight), is comparable to that of the recommended dosing regimen in adult patients.

Table 7: Summary of Pharmacokinetic Parameters for Lumefantrine, Artemether, and DHA in Pediatric and Adult Patients With Malaria Following Administration of a 6-dose Regimen of Artemether & Lumefantrine Tablets

Drug	Adults[1]	Pediatric Patients (body weight, kg)[2]		
		5 to < 15	15 to < 25	25 to < 35
Lumefantrine				
Mean C_{max}, range (mcg/mL)	5.60–9.0	4.71–12.6		Not Available
Mean AUC_{last}, range (mcg·h/mL)	410–561	372–699		Not Available
Artemether				
Mean C_{max} ± SD (ng/mL)	186 ± 125	223 ± 309	198 ± 179	174 ± 145
Dihydroartemisinin				
Mean C_{max} ± SD (ng/mL)	101 ± 58	54.7 ± 58.9	79.8 ± 80.5	65.3 ± 23.6

Abbreviations: AUC, area under the curve; DHA, dihydroartemisinin; SD, standard deviation.

[1]There are a total of 181 adults for lumefantrine pharmacokinetic parameters and a total of 25 adults for artemether and dihydroartemisinin pharmacokinetic parameters.

[2]There are 477 children for the lumefantrine pharmacokinetic parameters; for artemether and dihydroartemisinin pharmacokinetic parameters there are 55, 29, and 8 children for the 5 to less than 15, 15 to less than 25 and the 25 to less than 35 kg groups, respectively.

Geriatric Patients

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

5.3 Preclinical safety data

Carcinogenesis

Carcinogenicity studies were not conducted.

Mutagenesis

No evidence of mutagenicity was detected. The artemether-lumefantrine combination was evaluated using the *Salmonella* and *Escherichia*/mammalian-microsome mutagenicity test, the gene mutation test with Chinese hamster cells V79, the cytogenetic test on Chinese hamster cells *in vitro*, and the rat micronucleus test, *in vivo*.

Impairment of Fertility

Pregnancy rates were reduced by about one-half in female rats dosed for 2 to 4 weeks with the artemether- lumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on BSA comparisons). Male rats dosed for 89 to 93 days showed increases in abnormal sperm (87% abnormal) at 30 mg/kg doses (about one- third the clinical dose). Higher doses (about 9 times the MRHD) resulted in increased testes weights, decreased sperm motility, and 100% abnormal sperm cells.

Animal Toxicology and/or Pharmacology

Neonatal rats (7 to 21 days old) were more sensitive to the toxic effects of artemether (a component of Artemether & Lumefantrine Tablets) than older juvenile rats or adults. Mortality and severe clinical signs were observed in neonatal rats at doses which were well tolerated in pups above 22 days old.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

- Microcrystalline cellulose
- Croscarmellose Sodium
- Colloidal Anhydrous Silica
- Hypromellose

 Polysorbate 80

 Saccharin sodium

 Crospovidone

 Flavour Cherry

 Permaseal 11035-31

 Magnesium stearate

 Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30° C in a dry place

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

1. PVC/PCTFE/PVC-Alu blister of 12 tablets in a printed show box along with a leaflet. 30 show boxes packed in a printed outer carton box.

2. PVC/PCTFE/PVC-Alu blister of 6 tablets in a printed show box along with a leaflet. 30 show boxes packed in a printed outer carton box.

3 PVC/PCTFE/PVC-Alu blister of 12 tablets, 30 blister in a printed show box along with a leaflet.

4 PVC/PCTFE/PVC-Alu blister of 6 tablets, 30 blister in a printed show box along with a leaflet

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials

None.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

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9. NAFDAC REGISTRATION NUMBER(S)

Not available