ARTEFAN DISPERSIBLE 20/120 (Artemether 20 mg and Lumefantrine 120 mg Dispersible Tablets)

Summary of Product Characteristics

1. Name of the Medical Product

1.1 Product Name:

ARTEFAN DISPERSIBLE 20/120 (Artemether 20 mg and Lumefantrine 120 mg Dispersible Tablets)

1.2 Strength:

Each dispersible tablet contains:

Artemether Ph. Int (20 mg) Lumefantrine (120 mg)

1.3 Pharmaceutical Dosage Form:

Oral

2. Quality and Quantitative Composition

Active Ingredients

Artemether	Ph. Int	20.00	Active
Lumefantrine	IH	120.00	Active

3. Pharmaceutical Form:

Tablet

4. Clinical Particulars

4.1 Therapeutic Indications:

ARTEFAN DT 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. ARTEFAN DT Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported.

Limitations of Use:

- ARTEFAN DT Tablets are not approved for patients with severe or

complicated P. falciparum malaria.

- ARTEFAN DT Tablets are not approved for the prevention of malaria.

4.2 Posology and Method of Administration:

Administration Instructions

ARTEFAN DT 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, ARTEFAN DT 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).

Dosage in Patients with Hepatic or Renal Impairment

No specific published pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In published clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

In published clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in published clinical studies. There is no significant renal excretion of lumefantrine, artemether, and dihydroartemisinin (DHA) in healthy volunteers and while clinical experience in this population is limited, no dose adjustment is recommended.

Caution should be exercised when administering Artemether and Lumefantrine Tablets in patients with severe hepatic or renal impairment.

Pediatric Use

The safety and effectiveness of Artemether and Lumefantrine Tablets have been established in pediatric patients aged 2 months and older with a bodyweight of 5 kg and above for the treatment of acute, uncomplicated malaria. The safety and effectiveness of Artemether and Lumefantrine Tablets have not been established in pediatric patients younger than 2 months old or weigh less than 5 kg. Pediatric patients from non-endemic countries were not included in published clinical trials.

Geriatric Use

Clinical studies published of Artemether and Lumefantrine Tablets did not

include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Artemether and Lumefantrine Tablets.

Hepatic and Renal Impairment

No specific published pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Artemether and Lumefantrine Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether, and DHA, no dose adjustment for the use of Artemether and Lumefantrine Tablets in patients with renal impairment is advised. No dosage adjustment is necessary in patients with mild-to-moderate hepatic impairment

4.3 Contraindications:

Hypersensitivity

Known hypersensitivity to artemether, lumefantrine, or to any of the excipients of Artemether and Lumefantrine Tablets.

Strong CYP3A4 Inducers

Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort with Artemether and Lumefantrine Tablets can result in decreased

concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

4.4 Special warning and precautions for use:

Prolongation of the QT Interval

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

Artemether and 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 and 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 and 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 and 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 and 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 and Lumefantrine Tablets

Drug Interactions with CYP3A4

When Artemether and 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 and 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 and 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 and Lumefantrine Tablets.

Artemether and 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 and Lumefantrine

Drug Interactions with CYP2D6

Administration of Artemether and 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 and 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 and 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 and Lumefantrine Tablets, patients should be treated with a different antimalarial drug.

Hepatic and Renal Impairment

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

Plasmodium vivax Infection

Artemether and 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 Interactions with other medicinal products and other forms of Interaction:
Rifampin

Oral administration of rifampin, a strong CYP3A4 inducer, with Artemether and 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 and Lumefantrine Tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort is contraindicated with Artemether and Lumefantrine Tablets

Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Artemether and Lumefantrine Tablets resulted in a

moderate increase in exposure to artemether, DHA, and lumefantrine in a published study of 15 healthy subjects. No dose adjustment of Artemether and 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 and 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 and 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 and 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 and 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 and 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 and 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 and Lumefantrine.

CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 in vitro. Administration of Artemether and 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 and 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 and 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 and 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 and 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

4.6 Pregnancy and Lactation:

Pregnancy

Risk Summary

Published data from published 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.

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.

Human Data

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

Lactation

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 and Lumefantrine and any potential adverse effects on the breastfed infant from Artemether and Lumefantrine or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

Use of Artemether and 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 and Lumefantrine.

Infertility

In published 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 machine:

This drug may make you feel dizzy or tired or weak. Do not drive, use machinery, or do anything that needs alertness until you can do it safely. Limit alcoholic beverages.

4.8 Undesirable Effects:

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

- 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 published 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 and 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 and Lumefantrine Tablets was studied in published active-controlled (366 patients) and noncontrolled, open-label trials (1613 patients). The 6-dose Artemether and 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 published 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 and Lumefantrine Tablets. Adverse reactions collected in published 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 published comparative studies, the adverse reaction profile of Artemether and Lumefantrine Tablets appeared similar to that of another antimalarial regimen.

Discontinuation of Artemether and 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 and 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)

Table 2: Adverse Reactions Occurring in 3% or More of Pediatric Patients Treated in Clinical Trials With the 6-dose Regimen of Artemether and 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 and Lumefantrine Tablets, which occurred in published 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 post approval use of Artemether and 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 and Lumefantrine Tablets should not be used to treat severe malaria as it is not an approved indication.

Reporting of suspected adverse reactions:

Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdosage:

There is no information on overdoses of Artemether and 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: P01BF01

Mechanism of action

Artemether and Lumefantrine Tablets, a fixed dose combination of artemether and lumefantrine in the ratio of 1:6, is an antimalarial agent.

Microbiology

Mechanism of Action

Artemether and 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 β-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 published 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 and Lumefantrine Tablets was associated with prolongation of QTcF (Fridericia). Following administration of a 6-dose regimen of Artemether and 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 published 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 published 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.

5.2 Pharmacokinetics Properties :

Absorption

Following administration of Artemether and 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. 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 and Lumefantrine Tablets were

taken after a high-fat meal compared under fasted conditions. Patients should be encouraged to take Artemether and Lumefantrine Tablets with a meal 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 (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 published 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 published 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 and 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 and 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 and 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 and 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 and Lumefantrine Tablets, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.

5.3 Preclinical Safety Data :

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 and 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, Mannitol,

Low Substituted Hydroxypropyl Cellulose, Crospovidone, Aspartame,

Colloidal Anhydrous Silica,

Capsaroma Flavour Orange DC 116 PH,

Capsaroma Flavour Peppermint DC 117 PH, Magnesium Stearate

6.2 Incompatibilities: Not applicable

6.3 Shelf Life: 36 Months

6.4 Special Precautions for storage: Do not store above 30°C.

6.5 Nature and contents of container:

6 Tablets in a blister, 1 blister in a carton along with pack insert.

12 Tablets in a blister, 1 blister in a carton along with pack insert.

6 Tablets in a blister, 30 blisters in a carton along with 30 pack inserts.

12 Tablets in a blister, 30 blisters in a carton along with 30 pack inserts.

7. Marketing Authorization Holder:

Ajanta Pharma Ltd. Ajanta House, Charkop Kandivli (West) Mumbai - 400 067 India.

Tel: +91-22-6606 1000

Fax: +91-22-6606 1200

Email: rnd.info@ajantapharma.com

Manufacturing Site Address - I:

Ajanta Pharma Ltd. B-4-5-6, MIDC,

Paithan, Chhatrapati Sambhajinagar, 431148 Maharashtra, India

Tel : +91-2431-664000

Fax : +91-2431-664100

Email: exports@ajantapharma.com

Manufacturing Site Address - II:

Ajanta Pharma Limited Z/103/A, Dahej Sez II, Bharuch – 392 130 Gujarat State, India.

Tel: +91 – 2641 – 275500

Fax: +91 – 2641 – 253053

Email: dhj@ajantapharma.com

8. Marketing Authorization Numbers: H2013/CTD1332/370

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

10. Date of revision of text:

Feb, 2026