SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artefan 80/480
Artemether 80 mg and Lumefantrine 480 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Artefan 80/480 is a fixed dose combination of Artemether and Lumefantrine.
Each Artefan 80/480 tablet contains 80 milligrams of Artemether and 480 milligrams of Lumefantrine
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
Artefan 80/480 is 'Yellow coloured, capsule shaped, biconvex, uncoated tablets with breakline on one side.'

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Artefan 80/480 Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum (P. falciparum)* in patients weighing above 35 kg.
Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported.

Limitations of Use:

- Artefan 80/480 Tablets are not approved for patients with severe or complicated *P. falciparum* malaria.
- Artefan 80/480 Tablets are not approved for the prevention of malaria.

4.2 Posology and method of administration

Administration Instructions
Artefan 80/480 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 80/480 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
One tablet should be taken twice a day for three days (total six doses). The first dose should be followed by a second dose after 8 hours. The following two days the doses of Artefan 80/480 Tablets should be given twice daily, morning and evening.

Dosage in Patients with Hepatic or Renal Impairment
No specific 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 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 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 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 Artefan 80/480 Tablets in patients with severe hepatic or renal impairment.

4.3 Contraindications

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

Strong CYP3A4 Inducers
Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort with Artemether & Lumefantrine Tablets can result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy

4.4 Special warnings and precautions for use
Prolongation of the QT Interval
Some antimalarials (e.g., halofantrine, quinine, quinidine) including Artefan 80/480 Tablets have been associated with prolongation of the QT interval on the electrocardiogram (ECG).

Artefan 80/480 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 co-administered with substrates of CYP3A4, it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Artemether & Lumefantrine Tablets are co-administered 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 co-administered 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 Tablets.

Drug Interactions with CYP2D6
Administration of Artemether & Lumefantrine Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered 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

DRUG INTERACTIONS
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 Tablets.

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

4.6 Pregnancy and lactation

Pregnancy
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.

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

Females and Males of Reproductive Potential
Contraception
Use of Artemether & Lumefantrine Tablets 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 Tablets.

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
Not available

4.8 Undesirable effects

ADVERSE REACTIONS

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 non-controlled, 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

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.

Trials With the 6-dose Regimen of Artemether & Lumefantrine Tablets

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: urticarial

Post-marketing Experience
The following adverse reactions have been identified during post approval 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

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

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.

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 catalysed 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).
Co-administration 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.

Microbiology
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 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 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.

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 & 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 BP,
Crosopovidone BP,
Sodium Lauryl Sulphate BP,
Colloidal Silicon Dioxide USPNF,
Purified Talc BP,
Magnesium Stearate BP

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

Artefan 80/480 tablets
Each blister card contains 6 tablets and 30 tablets, and it is packed in a carton along with pack insert.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER
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8. Market authorization number

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9. Date of authorization

Jan 30, 2019