資料3－3　アーテメター/ルメファントリン（artemether/lumefantrine）

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Coartem Tablets safely and effectively. See full prescribing information for Coartem Tablets.

Coartem (artemether/lumefantrine) Tablets
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

- Coartem (artemether and lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above (1)
- Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported (1)
- Coartem Tablets should not be used to treat severe malaria or to prevent malaria (1)

----------DOSAGE AND ADMINISTRATION----------

- Coartem Tablets should be taken with food. (2.1, 5.2)
- Tablets may be crushed and mixed with one to two teaspoons of water immediately prior to administration to patients, including children (2.1)
- Coartem Tablets should be administered over 3-days for a total of 6 doses: an initial dose, second dose after 8 hours and then twice daily (morning and evening) for the following two days (2.2, 2.3)
- The adult dosage for patients with bodyweight of 35 kg and above is 4 tablets per dose for a total of 6 doses (2.2)
- The number of tablets per dose for children is determined by bodyweight, as shown in the chart below (2.3):

Tablets per dose by bodyweight; total of 6 doses over 3 days

5 to < 15 kg	1 tablet
15 to < 25 kg	2 tablets
25 to < 35 kg	3 tablets
35 kg and over	4 tablets

----------DOSAGE FORMS AND STRENGTHS----------

Tablets are scored and contain 20 mg artemether and 120 mg lumefantrine. (3)

----------CONTRAINDICATIONS----------

- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients (4.1)

----------WARNINGS AND PRECAUTIONS----------

- Avoid use in patients with known QT prolongation, those with hypokalemia or hypomagnesemia, and those taking other drugs that prolong the QT interval (5.1, 12.5)
- Halofantrine and Coartem Tablets should not be administered within one month of each other due to potential additive effects on the QT interval. (5.1, 5.2, 12.3)
- Antimalarials should not be given concomitantly, unless there is no other treatment option, due to limited safety data. (5.2)
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Coartem Tablets; (5.1, 5.2, 7.6, 12.3)
- Substrates, inhibitors, or inducers of CYP3A4, including antiretroviral medications, should be used cautiously with Coartem Tablets, due to a potential loss of efficacy of the concomitant drug or additive QT prolongation (5.3, 7.1, 7.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions in adults (> 30%) are headache, anorexia, dizziness, asthenia, arthralgia and myalgia. The most common adverse reactions in children (> 12%) are pyrexia, cough, vomiting, anorexia and headache. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 Inhibitors: Use cautiously due to potential for QT prolongation (5.3, 7.1)
- Mefloquine: If used immediately before treatment, monitor for decreased efficacy of Coartem Tablets and encourage food consumption (2.1, 7.2)
- Hormonal Contraceptives: Effectiveness may be reduced; use an additional method of birth control (5.3, 7.3)
- Anti-Retrovirals: Use cautiously due to potential for QT prolongation, loss of anti-viral efficacy, or loss of antimalarial efficacy of Coartem Tablets (5.3, 7.3)
- CYP2D6 Substrates: Monitor for adverse reactions and potential QT prolongation (5.1, 5.4, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may increase fetal loss. (8.1)
- Nursing Mothers: Use caution when administering to a nursing woman (8.3)
- Pediatric Use: Studied in children 2 months of age and older with a bodyweight of 5 kg and greater. (8.4)
- Geriatric Use: Not studied in geriatric patients (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION
- 2.1 Administration Instructions
- 2.2 Dosage in Adult Patients (>16 years of age)
- 2.3 Dosage in Pediatric Patients
- 2.4 Dosage in Patients with Hepatic or Renal Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS
- 4.1 Hypersensitivity

5 WARNINGS AND PRECAUTIONS
- 5.1 Prolongation of the QT Interval
- 5.2 Use of QT Prolonging Drugs and Other Antimalarials
- 5.3 Drug Interactions with CYP3A4
- 5.4 Drug Interactions with CYP2D6
- 5.5 Recrudescence
- 5.6 Hepatic and Renal Impairment

6 ADVERSE REACTIONS
- 6.1 Serious Adverse Reactions
- 6.2 Clinical Studies Experience
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Ketoconazole
- 7.2 Prior Use of Mefloquine
- 7.3 CYP3A4 Metabolism: Hormonal Contraceptives and Anti-Retroviral Drugs
- 7.4 CYP2D6 Substrates
- 7.5 Sequential Use of Quinine

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic and Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Effects on the Electrocardiogram

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Treatment of Acute, Uncomplicated *P. falciparum* Malaria

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
- 17.1 Information for Safe Use
- 17.2 FDA-Approved Patient Labeling

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Coartem (artemether/lumefantrine) Tablets are indicated for treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above. Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported [see *Clinical Studies (14.1)*].

Limitations of Use:

- Coartem Tablets are not approved for patients with severe or complicated *P. falciparum* malaria.
- Coartem Tablets are not approved for the prevention of malaria.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Coartem 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, Coartem Tablets may be crushed and mixed with a small amount of water (one to two 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 of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

2.2 Dosage in Adult Patients (>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 two days (total course of 24 tablets).

For patients weighing less than 35 kg, see Dosage in Pediatric Patients (2.3).

2.3 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 two 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 two 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 two 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 two days (total course of 24 tablets).

2.4 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. No specific dose adjustments are needed for patients with mild to moderate renal impairment.

Caution should be exercised when administering Coartem Tablets in patients with severe hepatic or renal impairment [see *Warnings and Precautions (5.6)*].

3 DOSAGE FORMS AND STRENGTHS

Coartem Tablets contain 20 mg of artemether and 120 mg of lumefantrine. Coartem Tablets are supplied as yellow, round, flat tablets with beveled edges and scored on one side. Tablets are imprinted with N/C on one side and CG on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients of Coartem Tablets [see *Adverse Reactions (6.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Prolongation of the QT Interval

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

Coartem 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); certain non-sedating antihistaminics (terfenadine, astemizole), or cisapride [see *Clinical Pharmacology (12.5)*].
- receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.4), Drug Interactions (7.4)* and *Clinical Pharmacology (12.3)*].

5.2 Use of QT Prolonging Drugs and Other Antimalarials

Halofantrine and Coartem Tablets should not be administered within one month of each other due to the long elimination half-life of lumefantrine (3-6 days) and potential additive effects on the QT interval [see *Warnings and Precautions (5.1),* and *Clinical Pharmacology (12.3)*].

Antimalarials should not be given concomitantly with Coartem 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 Coartem Tablets, due to the long elimination half-life of lumefantrine (3-6 days) and the potential for additive effects on the QT interval. [see *Warnings and Precautions (5.1), Drug Interactions (7.5),* and *Clinical Pharmacology (12.3)*].

If mefloquine is administered immediately prior to Coartem 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 Coartem Tablets [see *Dosage and Administration (2.1), Drug Interactions (7.2),* and *Clinical Pharmacology (12.3)*].

5.3 Drug Interactions with CYP3A4

When Coartem Tablets are co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Coartem 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 Coartem Tablets are co-administered with inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy [see *Drug Interactions (7.1)*].

Drugs that have a mixed effect on CYP3A4, especially Anti-Retroviral drugs, and those that have an effect on the QT interval should be used with caution in patients taking Coartem Tablets [see *Drug Interactions (7.3)*].

Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control [see *Drug Interactions (7.3)*].

5.4 Drug Interactions with CYP2D6

Administration of Coartem 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 Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1), Drug Interactions (7.4)* and *Clinical Pharmacology (12.3)*].

5.5 Recrudescence

Food enhances absorption of artemether and lumefantrine following administration of Coartem Tablets. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater [see *Dosage and Administration (2.1)*].

In the event of recrudescent *P. falciparum* infection after treatment with Coartem Tablets, patients should be treated with a different antimalarial drug.

5.6 Hepatic and Renal Impairment

Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment [see *Dosage and Administration (2.4)*].

5.7 *Plasmodium vivax* Infection

Coartem 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.

6 ADVERSE REACTIONS

6.1 Serious Adverse Reactions

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

- Hypersensitivity Reactions [see *Contraindications (4.1)* and *Postmarketing Experience (6.3)*].

6.2 Clinical Studies 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 Coartem Tablets in 1,979 patients including 647 adults (older than 16 years) and 1,332 children (16 years and younger). For the 6-dose regimen, Coartem Tablets was studied in active-controlled (366 patients) and non-controlled, open-label trials (1,613 patients). The 6-dose Coartem Tablets population was patients with malaria between ages 2 months and 71 years: 67% (1,332) 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 (≥3%) in adults and children respectively who received the 6-dose regimen of Coartem 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 Coartem Tablets appeared similar to that of another antimalarial regimen.

Discontinuation of Coartem 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% (21/1,332) in children.

Table 1: Adverse Reactions Occurring in 3% or More of Adult Patients Treated in Clinical Trials with the 6-dose Regimen of Coartem 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)

System Organ Class	Preferred term	Adults* N=647 (%)
	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 >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 Coartem Tablets

System organ class	Preferred Term	Children* N=1,332 (%)
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)

System organ class	Preferred Term	Children* N=1,332 (%)
	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 ≤ 16 years of age

Clinically significant adverse reactions reported in adults and/or children treated with the 6-dose regimen of Coartem Tablets which occurred in clinical studies at < 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, hookworm 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, hypoaesthesia, 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

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Coartem 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 including urticaria and angioedema. Serious skin reactions (bullous eruption) have been rarely reported.

7 DRUG INTERACTIONS

7.1 Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Coartem Tablets resulted in a moderate increase in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether), and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Coartem 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, Coartem Tablets should be used cautiously with drugs that inhibit CYP3A4 [see *Warnings and Precautions (5.1, 5.3)*].

7.2 Prior Use of Mefloquine

Administration of three doses of mefloquine followed 12 hours later by a 6-dose regimen of Coartem 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 Coartem Tablets [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

7.3 CYP3A4 Metabolism: Hormonal Contraceptives and Anti-Retroviral Drugs

Artemether induces CYP3A4 and both artemether and lumefantrine are metabolized primarily by CYP3A4.

Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should

be advised to use an additional non-hormonal method of birth control [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

Anti-Retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. No formal drug-drug interaction studies between Coartem Tablets and ARTs have been performed. However, Coartem Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation or a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Coartem Tablets [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

7.4 CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 *in vitro*. Administration of Coartem 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 Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1, 5.4)* and *Clinical Pharmacology (12.3)*].

7.5 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 Coartem 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 Coartem Tablets due to the long elimination half life of lumefantrine and the potential for additive QT effects. [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Coartem Tablets (including a third of patients who were exposed in the first trimester), and published data of over 1000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate.

The efficacy of Coartem Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Coartem Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant rats dosed during the period of organogenesis at or higher than a dose of about half the highest clinical dose of 1120 mg artemether-lumefantrine per day (based on body surface area comparisons), showed increases in fetal loss, early resorptions and post implantation loss. No adverse effects were observed in animals dosed at about one-third the highest clinical dose. Similarly, dosing in pregnant rabbits at about three times the clinical dose (based on body surface area 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 two times the clinical dose. Embryo-fetal loss is a significant reproductive toxicity. Other artemisinins are known to be embryotoxic in animals. However, because metabolic profiles in animals and humans are dissimilar, artemether exposures in animals may not be predictive of human exposures [see *Nonclinical Toxicology (13.2)*]. These data cannot rule out an increased risk for early pregnancy loss or fetal defects in humans.

8.3 Nursing Mothers

It is not known whether artemether or lumefantrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Coartem Tablets are administered to a nursing woman. Animal data suggest both artemether and lumefantrine are excreted into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

8.4 Pediatric Use

The safety and effectiveness of Coartem Tablets have been established for the treatment of acute, uncomplicated malaria in studies involving pediatric patients weighing 5 kg or more [see *Clinical Studies (14.1)*]. The safety and efficacy have not been established in pediatric patients who weigh less than 5 kg. Children from non-endemic countries were not included in clinical trials.

8.5 Geriatric Use

Clinical studies of Coartem Tablets did not include sufficient numbers of subjects aged 65 years and over to determine 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 Coartem Tablets.

8.6 Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic and/or renal impairment [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.6)*].

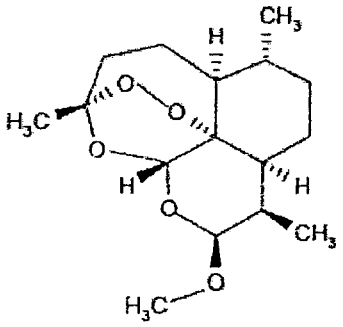
10 OVERDOSAGE

There is no information on overdoses of Coartem Tablets higher than the doses recommended for treatment.

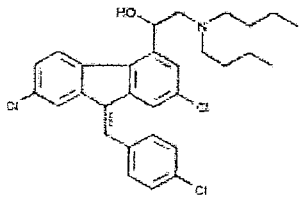
In cases of suspected overdosage, symptomatic and supportive therapy, which would include ECG and blood electrolyte monitoring, should be given as appropriate.

11 DESCRIPTION

Coartem Tablets contain a fixed combination of two antimalarial active ingredients, artemether, an artemisinin derivative, and lumefantrine. Both components are blood schizontocides. The chemical name of artemether is (3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine. Artemether is a white, crystalline powder that is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. It has the empirical formula $C_{16}H_{26}O_5$ with a molecular weight of 298.4, and the following structural formula:



The chemical name of lumefantrine is (±)-2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluorene-4-yl]ethanol. Lumefantrine is a yellow, crystalline powder that is freely soluble in N,N-dimethylformamide, chloroform, and ethyl acetate; soluble in dichloromethane; slightly soluble in ethanol and methanol; and insoluble in water. It has the empirical formula $C_{30}H_{32}Cl_3NO$ with a molecular weight of 528.9, and the following structural formula:



Coartem Tablets are for oral administration. Each Coartem Tablet contains 20 mg of artemether and 120 mg lumefantrine. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Coartem Tablets, a fixed dose combination of artemether and lumefantrine in the ratio of 1:6, is an antimalarial agent [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Absorption

Following administration of Coartem 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, dihydroartemisinin (DHA), an active antimalarial metabolite of artemether, and lumefantrine in adult Caucasian healthy volunteers are given in Table 3. Multiple dose data after the 6-dose regimen of Coartem Tablets in adult malaria patients are given in Table 4.

Table 3: Single Dose Pharmacokinetic Parameters[a] for Artemether, Dihydroartemisinin (DHA), 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

[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 two- to three-fold, and that of lumefantrine sixteen-fold when Coartem Tablets were taken after a high-fat meal compared under fasted conditions. . Patients should be encouraged to take Coartem Tablets with a meal as soon as food can be tolerated [see *Dosage and Administration (2.1)*].

Distribution

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

During repeated administration of Coartem Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHA 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 CYP3A4/5 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 Coartem Tablets with substrates, inhibitors, or inducers of CYP3A4, especially anti-retroviral drugs and those that prolong the QT interval (e.g., macrolide antibiotics, pimozide, terfenadine, astemizole, cisapride) [see *Warnings and Precautions (5.1, 5.3)*].

Co-administration of Coartem 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 Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see *Warnings and Precautions (5.1, 5.4)*].

Elimination

Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with a terminal half-life of 3-6 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.

No urinary excretion data are available for humans. In animal studies, artemether metabolites were largely excreted in the urine. However, urinary excretion of artemether, lumefantrine and lumefantrine metabolites was negligible. While animal data are informative, they do not always predict human results.

Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment [see *Dosage and Administration (2.4)*].

Pediatric Patients

The PK of artemether, DHA, and lumefantrine were obtained in two 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 a mg/kg body weight basis in pediatric patients ($\geq$5 to <35 kg body weight), is comparable to that of the recommended dosing regimen in adult patients.

Table 4: Summary of Pharmacokinetic Parameters for Lumefantrine, Artemether and DHA in Pediatric and Adult Patients with Malaria Following Administration of a 6-dose Regimen of Coartem Tablets

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

[1] 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 < 15, 15 to < 25 and the 25 to < 35 kg groups, respectively.

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

Geriatric Patients

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

Drug Interactions

Ketoconazole (potent CYP3A4 inhibitor)

Concurrent oral administration of ketoconazole (400 mg on Day 1 followed by 200 mg on days 2, 3, 4 and 5) with Coartem Tablets (single dose of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet) with a meal led to an increase in exposure, in terms of area under the curve (AUC), of artemether (2.3-fold), DHA (1.5 fold), and lumefantrine (1.6-fold) in 13 healthy subjects. The pharmacokinetics of ketoconazole were not evaluated. Based on this study, dose adjustment of Coartem Tablets is considered unnecessary when administered with ketoconazole or other CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Coartem Tablets should be used cautiously with other drugs that inhibit CYP3A4 (e.g., anti-retroviral drugs, macrolide antibiotics, antidepressants, imidazole antifungal agents) [see *Warnings and Precautions (5.1, 5.3)*].

Antimalarials

The oral administration of mefloquine in 14 healthy volunteers administered as three doses of 500 mg, 250 mg and 250 mg, followed 12 hours later by Coartem Tablets (6 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet), had no effect on plasma concentrations of artemether or the artemether/DHA ratio. In the same study, there was a 30% reduction in C_{max} and 40% reduction in AUC of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production.

Intravenous administration of a single dose of quinine (10 mg/kg bodyweight) concurrent with the last dose of a 6-dose regimen of Coartem Tablets had no effect on systemic exposure of DHA, lumefantrine or quinine in 14 healthy volunteers. Mean AUC of artemether were 46% lower when administered with quinine compared to Coartem Tablets alone. This decrease in artemether exposure is not thought to be clinically significant. However, quinine should be used cautiously in patients following treatment with Coartem Tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval [see *Warnings and Precautions (5.2)*].

Anti-Retroviral Drugs

No formal drug-drug interaction studies between Coartem Tablets and Anti-Retroviral drugs (ARTs), such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors, have been performed. Due to variable patterns of inhibition, induction or competition for CYP3A4 with anti-retroviral drugs, Coartem Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation, a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Coartem Tablets [see *Warnings and Precautions (5.3)*].

Hormonal Contraceptives

No formal drug-drug interaction studies between Coartem Tablets and hormonal contraceptives have been performed. However, artemether may induce CYP3A4/5, reducing the effectiveness of hormonal contraceptives [see *Warnings and Precautions (5.3)*].

12.4 Microbiology

Mechanism of Action

Coartem 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 dihydroartemisinin (DHA). The anti-malarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine, exerts its anti-malarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of 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 *Plasmodium falciparum*.

Drug Resistance

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

12.5 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 Coartem Tablets was associated with prolongation of QTcF (Fridericia). Following administration of a 6-dose regimen of Coartem 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 CI: 11 msec). There was a concentration-dependent increase in QTcF for lumefantrine.

In clinical trials conducted in children, no patient had QTcF >500 msec. Over 5% of patients had an increase in QTcF of over 60 msec.

In clinical trials conducted in adults, QTcF prolongation of >500 msec was reported in 3 (0.3%) of patients. Over 6% of adults had a QTcF increase of over 60 msec from baseline.

13 NONCLINICAL TOXICOLOGY

13.1 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 body surface area comparisons). Male rats dosed for 70 days showed increases in abnormal sperm (87 % abnormal) and increased testes weights at 30 mg/kg doses (about one third the clinical dose). Higher doses (about 9 times the clinical dose) resulted in decreased sperm motility and 100 % abnormal sperm cells.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicity

Pregnant rats dosed during the period of organogenesis, at or higher than 60 mg/kg/day with the artemether-lumefantrine combination (a dose about half the highest clinical dose based on body surface area comparisons), showed increases in the number of dead fetuses, early resorptions and post implantation losses. No adverse effects were observed in animals dosed at 40 mg/kg (about one third the clinical dose). Similarly, dosing in pregnant rabbits at 175 mg/kg/day (about three times the highest clinical dose based on body surface area comparisons) resulted in abortions, preimplantation losses, post