SUMMARY OF PRODUCT CHARACTERISTICS

Summary of Product Characteristics

COARTEM® Dispersible

(artemether/lumefantrine)

20 mg/120 mg Dispersible Tablets

Coartem® Dispersible

Antimalarial, artemisinins and derivatives

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Yellow, round, flat tablet with bevelled edges; debossed with: "CD" on one side and "NVR" on other side.

Active substances

Artemether and lumefantrine.

Artemether is a semisynthetic chiral acetal derivative from artemisinin, a bicyclic sesquiterpene lactone endoperoxide isolated from the plant *Artemisia annua*.

Lumefantrine is a racemic mixture of a synthetic fluorene derivative.

One dispersible tablet contains 20 mg artemether and 120 mg lumefantrine.

Excipients

Cellulose microcrystalline, cherry flavour, crospovidone, croscarmellose sodium, hypromellose, magnesium stearate, polysorbate 80, silica colloidal anhydrous and saccharin sodium (8 mg / dispersible tablet).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Coartem Dispersible is a fixed-dose combination of artemether and lumefantrine, which acts as a blood schizontocide. It is indicated for:

Treatment, including stand-by emergency treatment of children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Because Coartem is effective against both drug-sensitive and drug-resistant *P. falciparum* it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

Stand-by emergency treatment:

Most tourists and travellers, considered to be non-immune, will be able to obtain prompt medical attention if malaria is suspected. However, a minority at risk of infection may be unable to obtain such care within 24 hours of the onset of symptoms, particularly if they are in an isolated location far from medical services. In such cases, prescribers are advised to issue Coartem Dispersible to be carried by the parent or caregiver for administration to the travelling child ("standby emergency treatment").

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

DOSAGE REGIMEN AND ADMINISTRATION

The dispersible tablets are indicated only for infants and children. A separate tablet formulation is available for adolescents and adults.

Dosage in infants and children weighing 5 kg to less than 35 kg and 12 years of age or less

A six-dose regimen is recommended with 1 to 3 dispersible tablets per dose, depending on bodyweight.

5 to <15 kg bodyweight: One dispersible tablet at the time of initial diagnosis, 1 dispersible tablet again after 8 hours and then 1 dispersible tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 dispersible tablets).

15 to <25 kg bodyweight: Two dispersible tablets as a single dose at the time of initial diagnosis, 2 dispersible tablets again after 8 hours and then 2 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).

25 to <35 kg bodyweight: Three dispersible tablets as a single dose at the time of initial diagnosis, 3 dispersible tablets again after 8 hours and then 3 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 18 dispersible tablets).

Treatment and standby emergency treatment

The treatment should be administered at the time of initial diagnosis or at onset of symptoms.

New and recrudescent infections

Data for a limited number of patients with Coartem show that new and recrudescent infections can be treated with a second course of the medication.

Special populations

Infants weighing less than 5 kg

The safety and efficacy of Coartem have not been established in infants weighing less than 5 kg and no dosing recommendations can be made (see sections CLINICAL PHARMACOLOGY - Pharmacokinetics and CLINICAL STUDIES).

Renal impairment

No specific studies have been carried out in this group of patients. There was no significant renal excretion of lumefantrine, artemether and dihydroartemisinin (DHA) in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of Coartem in patients with renal impairment is recommended.

Hepatic impairment

No specific studies have been carried out in this group of patients. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution should be exercised in dosing patients with severe hepatic impairment (see section WARNINGS AND PRECAUTIONS). Most patients with acute malaria present with some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with Coartem.

Method of administration

Dispersible Tablets for oral administration

The dispersible tablet(s) composing 1 dose should be completely dispersed in a small amount of water (approximately 10 mL per tablet). The dispersion should be stirred gently and administered to the patient immediately. The glass should be rinsed with an additional small amount of water (approximately 10 mL) and given to the patient immediately.

The dose should be followed by food or drinks rich in fat such as milk. A standard African diet with fat content ranging between 30 and 60 g/day or breast milk were shown to be adequate in Africa. 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.

In the event of vomiting within 1 hour of administration a repeat dose should be taken.

The dispersible tablet is indicated only for infants and children. A separate tablet formulation is available for adolescents and adults.

CONTRAINDICATIONS

Coartem Dispersible is contraindicated in:

- Known hypersensitivity to artemether, lumefantrine or to any of the excipients of Coartem Dispersible.
- Patients with severe malaria according to WHO definition*.
- Patients with a family history of congenital prolongation of the QTc interval or sudden death or with 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.
- Patients taking drugs that are known to prolong the QTc 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,
  - certain non-sedating antihistaminics (terfenadine, astemizole),
  - cisapride.
- Patients with known disturbances of electrolyte balance e.g. hypokalemia or hypomagnesaemia.
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum)*.

* Presence of one or more of the following clinical or laboratory features:

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

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

WARNINGS AND PRECAUTIONS

Coartem has not been evaluated for prophylaxis and is therefore not indicated for prophylaxis.

Coartem has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure.

Coartem is not indicated for, and has not been evaluated in, the treatment of malaria due *to P. vivax, P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. Coartem is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Coartem should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)

Like other antimalarials (e.g. halofantrine, quinine, quinidine), Coartem has the potential to cause QTc prolongation (see section CLINICAL PHARMACOLOGY – QT/QTc prolongation).

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

If a patient deteriorates whilst taking Coartem, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Coartem.

Interactions

Caution in case of concomitant administration of medicines

With other antimalarials: Data on safety and efficacy are limited, and Coartem should therefore not be given concurrently with other antimalarials unless there is no other treatment option. The

long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Coartem.

Patients previously treated with other antimalarials: If Coartem is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. In patients previously treated with halofantrine, Coartem should not be administered earlier than one month after the last halofantrine dose.

With other drugs: Caution is recommended when combining Coartem with substrates, inhibitors or weak to moderate inducers of CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Coartem (see sections INTERACTIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

With hormonal contraceptives: Coartem 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 sections INTERACTIONS and PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Special populations

Coartem has not been studied for efficacy and safety in patients with severe hepatic or renal impairment and therefore no recommendations can be made for these groups of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment (see section CLINICAL PHARMACOLOGY - Pharmacokinetics).

ADVERSE DRUG REACTIONS

Summary of the safety profile

Most of the reported events were of mild to moderate severity and duration, and likely related to the underlying malaria and/or to an unsatisfactory response to the treatment rather than to Coartem although a causal relationship with the use of Coartem could not be excluded for some reports. For other reports alternative factors were identified as the more likely cause of the events (e.g. concomitant drugs, concomitant infections) or the information provided was too scarce to draw any conclusion.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Adverse drug reactions compiled from a pooled safety analysis of 4 studies in infants and children ≤12 years of age receiving a 6-dose regimen of Coartem or Coartem/Riamet Dispersible

Immune system disorders		
	Rare:	Hypersensitivity
Metabolism and nutrition disorders		
	Very common:	Decreased appetite
Psychiatric disorders		
	Uncommon:	Sleep disorder
Nervous system disorders		
	Common:	Headache, dizziness
	Uncommon:	Clonus, somnolence
Cardiac disorders		
	Uncommon:	Palpitations
Respiratory, thoracic and mediastinal disorders		
	Very common:	Cough
Gastrointestinal disorders		
	Very common:	Vomiting
	Common:	Abdominal pain, diarrhea, nausea
Skin and subcutaneous tissue disorders		
	Common:	Rash
	Uncommon:	Urticaria, pruritus
Musculoskeletal and connective tissue disorders		
	Common:	Arthralgia, myalgia
General disorders and administration site conditions		
	Common:	Asthenia, fatigue
Investigations		
	Common:	Liver function tests increased
	Rare:	Electrocardiogram QT prolonged

Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (3.3% of adolescents and adults, no cases in children).

The following adverse reactions were reported in adults with a frequency of uncommon but were not reported in infants or children: hypoesthesia, ataxia, and gait disturbance.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Coartem via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Hypersensitivity reactions including urticaria and angioedema.

INTERACTIONS

Interactions resulting in a contraindication

Interaction with drugs that are known to prolong the QTc interval

Coartem is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride (see section CONTRAINDICATIONS).

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 *in vitro*. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Coartem with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) (see section CONTRAINDICATIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

Interaction with strong inducers of CYP3A4 such as rifampicin

Oral administration of rifampicin (600 mg daily), a strong CYP3A4 inducer, with Coartem Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis co-infected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Coartem alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with Coartem (see section CONTRAINDICATIONS).

Interactions resulting in concomitant use not being recommended

Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Coartem should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section WARNINGS AND PRECAUTIONS).

If Coartem is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Coartem. In patients previously treated with halofantrine, Coartem should not be administered earlier than one month after the last halofantrine dose (see section WARNINGS AND PRECAUTIONS).

As patients to be treated with Coartem may have recently been treated with other antimalarials, interactions with mefloquine and quinine were studied in healthy volunteers. The sequential oral administration of mefloquine prior to Coartem had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant (around 30 to 40%) reduction in plasma levels (C_{max} and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for this decrease in bioavailability.

The concurrent *i.v.* administration of quinine (10 mg/kg BW) with Coartem had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Coartem to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Coartem in 14 additional subjects. It would thus appear that the inherent risk of QTc-prolongation associated with *i.v.* quinine was enhanced by prior administration of Coartem.

In a clinical trial in Thailand some adult patients received Coartem following treatment failures with mefloquine or quinine. One hundred and twenty-one patients received Coartem without any previous antimalarial treatment whereas 34 and 9 patients had measurable quinine or mefloquine, respectively, at enrolment. These patients showed similar safety and pharmacokinetic profiles of Coartem to patients who had no detectable levels of other antimalarials.

Interactions to be considered

Interactions affecting the use of Coartem

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolized by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with Coartem led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Coartem is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Coartem should be used cautiously with drugs that inhibit CYP3A4. Administration of artemether with double concentrated grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug. Grapefruit juice should be avoided during Coartem treatment (see section WARNINGS AND PRECAUTIONS).

Interaction with anti-retroviral drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3-fold, and efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to lopinavir/ritonavir and efavirenz were not significantly affected by concomitant use of Coartem.

Published clinical interaction studies with nevirapine based anti-retroviral treatments suggest that concomitant treatment could result in up to 70% reduced artemether exposure and up to 37% reduced DHA exposure with or without impact on lumefantrine exposure.

Coartem should be used cautiously in patients on anti-retroviral drugs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Coartem, and increased lumefantrine concentrations may cause QT prolongation (see section WARNINGS AND PRECAUTIONS).

Interaction with weak to moderate inducers of CYP3A4

When Coartem is co-administered with weak to moderate inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy (see section WARNINGS AND PRECAUTIONS).

Interactions resulting in effects of Coartem on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Coartem is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Whereas *in-vitro* studies with artemether at therapeutic concentrations revealed no significant inhibition of CYP450 enzymes, artemether and DHA were reported to have a mild inducing effect on CYPs (2C19, 2B6 and 3A) activity. Although the magnitude of the changes was generally low and is not expected to present a problem in the general patient population, it is possible that CYP3A4 induction could alter the therapeutic effects of drugs that are predominantly metabolised by this enzyme (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Coartem may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control (see sections WARNINGS AND PRECAUTIONS and PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Drug-food/drink interactions

Coartem should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see section DOSAGE REGIMEN AND ADMINISTRATION –Method of administration).

Grapefruit juice should be avoided during Coartem treatment.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

Based on animal data, Coartem is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections WARNINGS AND PRECAUTIONS and NON-CLINICAL SAFETY DATA).

Coartem should not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should not be withheld in life-threatening situations where no other suitable and effective antimalarials are available (see section WARNINGS AND PRECAUTIONS). During the second and the third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats. Other artemisinin derivatives have in addition demonstrated teratogenic potential with an increased risk during early gestation.

Human Data

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from an observational pregnancy study including over 300 pregnant women who were exposed to Coartem during the second or third trimester, and published data of another approximately 500 pregnant women who were exposed to artemether-lumefantrine, as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

In addition, there was no apparent increase in adverse pregnancy outcomes based on data from one open label randomized study of over 800 patients treated with Coartem in the second or third trimester.

Animal Data

Reproductive oral toxicity studies in rats with the artemether-lumefantrine combination showed both maternal toxicity and increased post-implantation loss at doses ≥50 mg/kg (corresponding to approximately 7 mg/kg artemether). The artemether-lumefantrine combination was not embryotoxic in rats at a dose of 25 mg/kg (corresponding to 3.6 mg/kg artemether). In rabbits given orally the artemether-lumefantrine combination, maternal toxicity and increased post-implantation loss were seen at 175 mg/kg (corresponding to 25 mg/kg artemether), while the next lower dose level of 105 mg/kg (corresponding to 15 mg/kg artemether) was entirely free of treatment-induced effects. The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemesinin exposures similar to those achieved in humans.

Artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at a dose of 6 mg/kg artesunate and 19.4 mg/kg artemether. In rats, 3 mg/kg artemether was established as the non-toxic dose. In rabbits, artemether produced maternal toxicity and increased post-implantation loss at 30 mg/kg but no materno/embryo/fetotoxicity at doses up to 25 mg/kg. The artemisinin derivative artesunate produced a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose used.

Lumefantrine doses as high as 1,000 mg/kg showed no evidence to suggest materno-, embryo- or fetotoxicity or teratogenicity in rats and rabbits.

Lactation

Risk Summary

Animal data suggest excretion into breast milk but no data are available in humans. Breast-feeding women should not take Coartem. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume before day 28 unless potential benefits to mother and child outweigh the risks of Coartem treatment.

Females and males of reproductive potential

As Coartem should not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available, women should not conceive while on Coartem treatment for malaria. This includes women prescribed Coartem for standby emergency treatment of malaria during their travel, in case they may require treatment for malaria.

Contraception

Women of child-bearing potential should be advised to practice contraception during travel with stand-by emergency treatment, while on Coartem and until the start of the next menstruation after the treatment.

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control (see section WARNINGS AND PRECAUTIONS).

Infertility

There is no information on the effects of Coartem on human fertility (see section NON-CLINICAL SAFETY DATA – Fertility for more detailed information).

OVERDOSAGE

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

CLINICAL PHARMACOLOGY

Pharmacodynamics (PD)

Mechanism of action (MOA)

Coartem contains a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. Artemether is a semisynthetic chiral acetal derived from the naturally occurring substance artemisinin. Lumefantrine is a racemic mixture of a synthetic fluorene derivative. Like other antimalarials (quinine, mefloquine, halofantrine), lumefantrine belongs to the aryl-amino-alcohol family. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates

reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite. Coartem has been reported to have potent activity in terms of clearing gametocytes.

Data from *in vitro* and *in vivo* studies show that Coartem did not induce resistance.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with Coartem in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed.

QT/QTc Prolongation

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of Coartem was associated with prolongation of QTcF. The mean changes compared to placebo from baseline at 68, 72, 96, and 108 h post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 h after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 h after the single dose with a maximal change at 1 h after dose of 14.1 msec.

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.

Pharmacokinetics (PK)

Pharmacokinetic characterisation of Coartem is limited by the lack of an intravenous formulation, and the very high inter- and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6 to 8 hours after administration. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when Coartem was taken after a high-fat meal. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100 % absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

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

Biotransformation/Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans *in vivo*. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity, which is not expected to present a problem in the general patient population (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).

Glucuronidation of dihydroartemisinin is predominately catalyzed by UGT1A9 and UGT2B7.

During repeated administration of Coartem, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for the metabolism of artemether. The clinical evidence of induction is consistent with the *in vitro* data described in section INTERACTIONS.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation.

In humans, the systemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than 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 (see sections CONTRAINDICATIONS and INTERACTIONS).

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours, while lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Coartem.

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

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of both drug components were eliminated in bile/faeces and urine.

Dose proportionality

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

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Coartem as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of Coartem dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the pediatric population since adequate efficacy of Coartem dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Special populations

Pediatric patients (below 18 years)

Systemic exposure to artemether, DHA, and lumefantrine when dosed on a mg/kg body weight basis in pediatric malaria patients (≥5 to <35 kg body weight) is comparable to that of the recommended dosing regimen in adult malaria patients.

Infants weighing <5 kg

Study B2306 showed that exposure to artemether and DHA in infants with uncomplicated *P. falciparum* malaria weighing <5 kg and older than 28 days of age, was on average 2- to 3-fold higher than that in pediatric patients with a body weight ≥5 kg treated with the same dose of Coartem (i.e. 1 tablet of 20 mg/120 mg per dose) (see section CLINICAL STUDIES). However, exposure to lumefantrine was similar to that observed in pediatric patients with a body weight ≥5 kg.

Race/Ethnicity

Pharmacokinetics of artemether, DHA and lumefantrine in the Japanese population was found to be consistent with other populations.

Renal impairment

No specific pharmacokinetic studies have been performed in patients with renal impairment. However, based on the pharmacokinetic data in healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of Coartem Dispersible in patients with renal impairment is advised.

Hepatic impairment

No specific pharmacokinetic studies have been performed in patients with hepatic impairment. Metabolism is the primary clearance mechanism of both artemether and lumefantrine and may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine and/or their metabolites

cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment (see section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

Treatment of Acute Uncomplicated P. falciparum Malaria

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

There are five 6-dose regimen studies and one study comparing 6-dose regimen versus 4-dose regimen.

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

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

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

Table 2 Summary of clinical efficacy studies

Study No.	Study Design /Objective	No. of patients		Population	Year/ Study location
		Coartem/Riamet	Comparator		
A025	Double-blind, randomized (1:1:1), parallel group comparative efficacy/safety of two 6-dose regimens vs a 4-dose regimen	6 doses over 60 h: 118 6 doses over 96 h: 121 4 doses over 48 h: 120	-	Adults Children (≤12 yrs, n = 43)	1996-97 Thailand
A026	Open-label, randomized (3:1), parallel group confirmatory efficacy/safety of 6-dose regimen, in comparison with mefloquine-artesunate (MAS)	150	Mefloquine-artesunate: 50	Adults Children (2-12 yrs, n = 34)	1997-98 Thailand

Study No.	Study Design /Objective	No. of patients		Population	Year/ Study location
		Coartem/Riamet	Comparator		
A028	Open-label, randomized (3:1), parallel group, confirmatory efficacy/safety of 6-dose regimen, in comparison with MAS	164	Mefloquine-artesunate: 55	Adults	1998-99 Thailand
A2401	Open-label, non-comparative efficacy/safety of 6-dose regimen in non-immune patients	165	-	Adults	2001-05 Europe, Columbia
A2403	Open-label, non-comparative efficacy/safety of 6-dose regimen	310	-	Infants/ children (5-25 kg)	2002-03 3 countries in Africa
B2303	Investigator-blind, randomized (1:1), parallel group efficacy/safety of 6-dose regimen	Coartem/Riamet crushed tablet: 452 Coartem/Riamet Dispersible tablet: 447	-	Infants/ children (5-35 kg)	2006-07 5 countries in Africa

Table 3 Clinical efficacy results

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients	Median FCT[2] [25th, 75th percentile]	Median PCT[2] [25th, 75th percentile]
A025[4]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]

[1] Efficacy cure rate based on blood smear microscopy
[2] mITT population
[3] For patients who had a body temperature >37.5°C at baseline only
[4] Only the 6-dose regimen over 60 hours group data is presented
[CT] – Coartem/Riamet tablets administered as crushed tablets
[DT] – Coartem/Riamet Dispersible tablets

Table 3 Clinical efficacy by weight for pediatric studies

Study No. Weight category	Median PCT[1] [25th, 75th percentile]	PCR-corrected 28-day cure rate[2] n/N (%) in evaluable patients
Study A2403 5 - <10 kg	24 [24, 36]	145/149 (97.3)

Study No. Weight category	Median PCT[1] [25th, 75th percentile]	PCR-corrected 28-day cure rate[2] n/N (%) in evaluable patients
10 - <15 kg	35 [24, 36]	103/107 (96.3)
15 -25 kg	24 [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 [24, 36]	65/69 (94.2)
10 - <15 kg	35 [24, 36]	174/179 (97.2)
15 -<25 kg	35 [24, 36]	134/140 (95.7)
25-35 kg	26 [24, 36]	30/31 (96.8)
Study B2303[DT]		
5 - <10 kg	36 [24, 43]	74/78 (94.9)
10 - <15 kg	35 [24, 36]	156/168 (92.9)
15 -<25 kg	25 [24, 36]	137/142 (96.5)
25-35 kg	26 [24, 36]	27/28 (96.4)

[1] mITT population
[2] Efficacy cure rate based on blood smear microscopy
[CT] Coartem/Riamet tablets administered as crushed tablets
[DT] Coartem/Riamet Dispersible tablets

Study A025 was a randomized, double-blind, two-center study conducted in Thailand in adults and children (aged ≥2 years), which compared the 4-dose regimen (administered over 48 hours) of Coartem tablets to a 6-dose regimen (administered over 60 hours). Twenty-eight day cure rate (PCR-corrected) in evaluable patients was 96.9% (93/96) for Coartem tablets 6-dose arm as compared to 83.3% (85/102) in the 4-dose arm.

Studies A026, A028, A2401, A2403, and B2303: In these studies, Coartem tablets were administered as the 6-dose regimen.

In study A026, a total of 150 adults and children aged ≥2 years received Coartem tablets. In study A028, a total 164 adults and children ≥12 years received Coartem tablets. Both studies were conducted in Thailand.

Study A2401 was a study of 165 non-immune adults residing in regions non-endemic for malaria (Europe and Colombia) who contracted acute uncomplicated falciparum malaria when traveling in endemic regions.

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5°C.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours, with the primary objective of demonstrating the non-inferiority of the dispersible tablet in comparison with the tablet (administered crushed) in terms of the 28-day PCR-corrected parasitological cure rate.

Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for all the studies are reported in Table 3.

Study B2306, was a multi-centre, open-label, single-arm study conducted in 20 infants in Africa, Benin and Burkina Faso to evaluate the efficacy, safety and pharmacokinetics of artemether/lumefantrine (AL) dispersible in infants aged >28 days and <5 kg of body weight, who were treated with one AL dispersible tablet (20 mg artemether/120 mg lumefantrine) given twice-

daily for three days and followed up for six weeks (core follow-up) and at the age of 12 months (long-term follow-up).

AL dispersible tablets were well tolerated with reported adverse events of mild to moderate severity. In the per protocol population, PCR-corrected cure rate at days 28 and 42 was 100% (95% CI: 79.4, 100). However, the mean exposure to artemether and DHA was 2- to 3-fold greater than that in infants weighing ≥5 kg and children up to 12 years of age. These exposures exceed exposures associated with neurotoxicity in dogs and the relevance of these exposures in humans is not known (see section NON-CLINICAL SAFETY DATA).

In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with Coartem was 96 hours. Coartem is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites (see section WARNINGS AND PRECAUTIONS).

NON-CLINICAL SAFETY DATA

Based on conventional studies, repeated dose toxicity, and genotoxicity, preclinical data reveal no special hazard for humans administered artemether/lumefantrine in adults and children weighing at least 5 kg for the treatment of malaria when used in accordance with the Product Information.

Adverse drug reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use, were as follows: post-implantation losses and teratogenicity of artemisinin derivatives

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary hematopoiesis.

Neurotoxicity

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

Mutagenicity

No evidence of mutagenicity was detected in *in vitro* or *in vivo* tests with an artemether:lumefantrine combination (consisting of 1 part artemether:6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Due to the short time of treatment carcinogenicity studies with the artemether:lumefantrine combination were not conducted.

Reproductive toxicity studies

See section PREGNANCY, LACTATION AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Fertility

Reduced fertility occurred at 1000 mg/kg/day where altered sperm motility, reduced epididymal sperm count, increased testes weight, and embryotoxicity and other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. General toxicity was observed in males and females at doses ≥ 300 mg/kg/day. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A specific study to investigate the neurotoxicity of artemether in juvenile rats involved oral administration of artemether during four different dosing intervals, at doses of 30 or 80 mg/kg/day on post partum days 7 to 13, and at doses of 30 or 120 mg/kg/day on post partum days 14 to 21, 22 to 28, or 29 to 36. Mortality, clinical signs and reductions in body weight parameters occurred most notably during the first two dosing intervals. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect of orally administered artemether on the brain of juvenile rats.

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

Cardiovascular Safety Pharmacology

In toxicity studies in dogs, only at higher doses than intended for use in man (600mg/kg/day), there was some evidence of prolongation of the QTc interval (safety margin of 1.3- to 2.2-fold for artemether using calculated free C_{max}). In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the currents responsible for cardiac repolarization. This potency was lower than that of the other antimalarial drugs tested. From the IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 0.04 micromolar) > chloroquine (2.5 micromolar) > mefloquine (2.6 micromolar) > desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar).

Additional studies were performed to evaluate the *in vitro* effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at C_{max} or greater than 1000 if they are estimated using the calculated free C_{max}. Based on the available non-clinical data, a potential for

QTc prolongation in the human cannot be discounted. For effects in the human see sections CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY - Pharmacodynamics).

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

Coartem Dispersible should not be used after the date marked "EXP" on the pack.

Coartem Dispersible must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING, AND DISPOSAL

For each dose, the quantity of dispersible tablets based on the child's body weight should be dispersed and administered as indicated in Section DOSAGE REGIMEN AND ADMINISTRATION.

For the treatment of children and infants, the 18 Dispersible tablet pack may be prescribed. The prescriber and pharmacist should instruct the parent or caregiver on the posology for their child and that a variable number of dispersible tablets (depending on the child's body weight) will be requested for the full treatment. Therefore the whole pack may not be used. After successful treatment the remaining dispersible tablets should be discarded or returned to the pharmacist (see section DOSAGE REGIMEN AND ADMINISTRATION).

Manufacturer:

See folding box.

International Package Leaflet

Information issued: July 2018

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