

Coartem®

Antimalarial, artemisinin and derivatives

COMPOSITION AND PHARMACEUTICAL FORM

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 tablet contains 20 mg artemether and 120 mg lumefantrine.

For a full list of excipients, see section EXCIPIENTS.

Yellow, round and flat tablet with bevelled edges and score on one side. Imprint: one side "N/C", other side "CG".

INDICATIONS

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

Treatment, including stand-by emergency treatment of adults, children and infants 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 business 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 to be carried by the traveller for self-administration ("stand-by emergency treatment").

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

DOSAGE AND ADMINISTRATION

Tablets for oral administration.

The dose should be taken with food or drinks rich in fat such as milk. 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.

Treatment and stand-by emergency treatment

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

Dosage in adults and children weighing 35 kg and above or more than 12 years of age

A standard 3 days treatment schedule with a total of 6 doses is recommended as follows. Four tablets as a single dose at the time of initial diagnosis, again 4 tablets after 8 hours and then 4 tablets twice daily (morning and evening) on each of the following two days (total course comprises 24 tablets).

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 tablets per dose, depending on bodyweight.

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

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

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

The tablet/s may be crushed for administration to infants and children. A dispersible tablet (Coartem Dispersible) is available in some endemic countries for administration to the paediatric patients.

Dosage in elderly patients

Although no studies have been carried out in the elderly, no special precautions or dosage adjustments are considered necessary in such patients.

Dosage in patients with mild to moderate renal or hepatic impairment

No specific studies have been carried out in these groups of patients. However, there is no significant renal excretion of lumefantrine, artemether and DHA in human studies; therefore, no dose adjustment for the use of Coartem in patients with renal impairment is advised. No specific dose adjustment recommendations can also be made for patients with hepatic impairment (for patients with severe renal and/or hepatic insufficiency, see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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.

New and recrudescence infections

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

CONTRAINDICATIONS

Coartem is contraindicated in:

- Hypersensitivity to artemether, lumefantrine or to any of the excipients of Coartem.
- Patients with severe malaria according to WHO definition.
- First trimester of pregnancy in situations where other suitable and effective anti-malarials are available (see section PREGNANCY AND LACTATION).
- 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. hypokalaemia or hypomagnesaemia.
- Patients taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Like other antimalarials (e.g. halofantrine, quinine, quinidine), Coartem has the potential to cause QTc prolongation although no clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) has been reported (see section PHARMACODYNAMICS).

Coartem has not been studied for efficacy and safety in patients with severe hepatic or renal insufficiency and therefore no recommendations can be made for these groups of patients (see section PHARMACOKINETICS).

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.

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

Coartem should not be used with drugs metabolized by CYP2D6 (see section CONTRAINDICATIONS) and caution is recommended when combining Coartem with substrates, inhibitors or inducers of CYP3A4 as the therapeutic effects of some drugs could be altered (see sections INTERACTIONS and PHARMACOKINETICS).

INTERACTIONS

Although the likelihood of Coartem interactions with other drugs is minimal in view of its short duration of administration and wide therapeutic index, three specific pharmacokinetic and pharmacodynamic drug-drug interaction studies with ketoconazole (a potent CYP3A4 inhibitor), mefloquine, and quinine have been conducted in healthy volunteers.

Interaction with other antimalarials (see also section SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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.

Interaction with a CYP450 3A4 inhibitor (ketoconazole)

Both artemether and lumefantrine are metabolised predominantly 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.

Interaction with anti-retroviral drugs

No formal drug-drug interaction studies between Coartem and anti-retroviral drugs have been performed.

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with Coartem requires caution (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Interaction with CYP450 enzymes

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 CYP3A4 activity. Although the magnitude of the changes was generally low and are 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.

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 (e.g. neuroleptics and tricyclic antidepressants) is contraindicated (see section CONTRAINDICATIONS).

Also see sections SPECIAL WARNINGS AND PRECAUTIONS FOR USE and PHARMACOKINETICS.

PREGNANCY AND LACTATION

Pregnancy

Based on animal data, Coartem is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections CONTRAINDICATIONS and PRECLINICAL SAFETY DATA).

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 (see section PRECLINICAL SAFETY DATA)

Coartem treatment is contraindicated during the first trimester of pregnancy in situations where other effective anti-malarials are available. However, it should not be withheld in life-threatening situations where no other effective anti-malarials are available (see section CONTRAINDICATIONS). During the second and the third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Women of child-bearing potential

As Coartem is contraindicated during the first trimester of pregnancy, women should not conceive while on Coartem treatment for malaria. This includes women prescribed Coartem for stand-by emergency treatment of malaria during their travel, in case they may require treatment for malaria.

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.

Lactation

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 (4 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients receiving Coartem should be warned that dizziness or fatigue/asthenia might occur in which case they should not drive or use machines.

UNDESIRABLE EFFECTS

The frequency of adverse events reported during clinical trials with Coartem was similar to or lower than that of other antimalarial drugs used as comparators.

Coartem appeared to be well tolerated by infants, children and adults. 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.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Table 1 represents a pooled safety analysis of adverse reactions from clinical trials in adults and adolescents >12 years of age or ≥ 35 kg body weight using the recommended 6-dose regimen.

Table 1

Metabolism and nutrition disorders	
Very common:	Anorexia
Psychiatric disorders	
Very common:	Sleep disorders
Nervous system disorders	
Very common:	Headache, dizziness
Uncommon:	Somnolence, hypoaesthesia, ataxia
Cardiac disorders	
Very common:	Palpitation
Respiratory, thoracic and mediastinal disorders	
Common:	Cough
Gastrointestinal disorders	
Very common:	Vomiting, abdominal pain, nausea
Common:	Diarrhoea
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia
General disorders and administration site conditions	
Very common:	Asthenia, fatigue
Uncommon:	Gait abnormal
Investigations	
Common:	Liver function tests increased
Uncommon:	Electrocardiogram QT corrected interval prolonged

Table 2 is compiled from a pooled safety analysis of 4 studies in infants and children ≤ 12 years of age and ≥ 5 kg to < 35 kg body weight receiving a 6-dose regimen of Coartem or Coartem Dispersible.

Table 2

Immune system disorders	
Rare:	Hypersensitivity
Metabolism and nutrition disorders	
Very common:	Anorexia
Psychiatric disorders	
Uncommon:	Sleep disorders
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Somnolence
Cardiac disorders	
Uncommon:	Palpitation
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough
Gastrointestinal disorders	
Very common:	Vomiting
Common:	Abdominal pain, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Common:	Rash
Uncommon:	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 corrected interval prolonged

In this pooled safety analysis, mood swings have been reported in less than 1.2% of the paediatric patients treated with Coartem, but they were not considered drug-related by the Investigators.

Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (1.2% of adolescents and adults, no cases in children); involuntary muscle contractions (1.3% of children).

Listing of adverse drug reactions from post-marketing spontaneous reports

The following additional adverse drug reactions have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Hypersensitivity reactions including urticaria and angioedema have been rarely reported.

OVERDOSE

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

PHARMACODYNAMICS

Pharmacodynamic effects

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

The antimalarial activity of the combination of lumefantrine and artemether in Coartem is greater than that of either substance alone. In a double-blind comparative study in adults in China (n = 157), the 28-day cure rate of Coartem when given as 4 doses was 94%, compared with 90% for lumefantrine and 46% for artemether based in intent-to-treat (ITT) population, when given as monotherapy. For the evaluable population, the 28-day cure rates were 100% for Coartem compared with 92% for lumefantrine and 55% for artemether when given as monotherapy.

In areas where multi-drug-resistant strains of *P. falciparum* malaria are common and in the resident population, 28-day cure rates with the 6-dose regimen (given over 60 or 96 h) were 81% and 90% for Coartem versus 94% and 96% for mefloquine/artesunate, based on the ITT population. For the evaluable population, 28-day cure rates were 97% and 95% for Coartem and 100% for mefloquine/artesunate.

In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with Coartem was 96 h. Coartem was associated with more rapid gametocyte clearance than any comparator other than mefloquine/artesunate. Coartem is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In non-immune adult patients living in regions free of malaria but with malaria acquired when travelling in endemic regions, a similar efficacy and safety profile was shown. In an open study (n=165) in adults the 28-day cure rate for Coartem given as the 6-dose regimen was 96% (119/124) for the evaluable and 74.1% (120/162) for the ITT population. The difference between evaluable and ITT population cure rates was due to 38 patients who were excluded from the evaluable population for the following reasons: 33 patients were lost to follow up, 19 of whom had no evaluation, 14 of whom had parasitic clearance at Day 7 but their efficacy

status at Day 28 was unknown and 5 patients took concomitant medications that were not permitted by the protocol. All these patients were considered as treatment failures in the ITT analysis.

Efficacy data in infants and children

In an open, multicenter clinical study conducted in Africa in 310 children weighing ≥ 5 kg to ≤ 25 kg and receiving a 6-dose Coartem according to body weight ranges, the mean 28-day parasitological cure rate (PCR corrected) was 93.9% for the ITT population and 96.7% for the evaluable population.

In a randomised, investigator-blinded trial comparing the efficacy of 6-dose Coartem Dispersible tablets vs Coartem (crushed) according to body weight ranges administered in children between 5 kg and 35 kg body weight with an age of 12 years or less, the 28-day parasitological cure rate (PCR corrected) for the primary analysis population was 97.8% and 98.5%, respectively and for the ITT population was 95% and 96.2%, respectively.

Children from non-endemic countries were not included in clinical trials.

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 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, QTcB prolongation of >500 msec was reported in one patient (0.1%). No patients had QTcF >500 msec. In clinical trials conducted in adults, QTcB prolongation of >500 ms was reported in 0.9% of patients while QTcF prolongation of >500 msec was reported in 0.3% of patients.

No clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) has been reported.

PHARMACOKINETICS

Pharmacokinetic characterisation of Coartem is limited by the lack of an intravenous formulation, and the very high inter- and intraindividual 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 is also bound to human serum proteins (47% to 76%). Protein binding to human plasma protein is linear.

Biotransformation

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and INTERACTIONS).

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. Lumefantrine is eliminated very slowly with a terminal half-life of 2 to 3 days in healthy volunteers and 4 to 6 days in patients with falciparum malaria. 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.

Pharmacokinetics in special patient populations

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency, or in elderly patients. 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 in patients with renal impairment is advised.

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

PRECLINICAL SAFETY DATA

General toxicity

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

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

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.

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

Artemisinin derivatives 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/foetotoxicity 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.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Cardiovascular Pharmacology

In toxicity studies in dogs, only at higher doses than intended for use in man (≥ 600 mg/kg/day), there was some evidence of prolongation of the QTc interval. 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 estimated IC₅₀ values, the order of potency of HERG current block was halofantrine (IC₅₀ = 0.04 micromolar) > chloroquine (2.5 micromolar) > mefloquine (2.6 micromolar) > desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar). A study in healthy adult volunteers indicates prolongation of QTcF can occur with standard dosing of Coartem (see sections CONTRAINDICATIONS, SPECIAL WARNINGS AND PRECAUTIONS FOR USE and PHARMACODYNAMICS).

EXCIPIENTS

Polysorbate 80, hydroxypropylmethyl cellulose, microcrystalline cellulose, silica colloidal anhydrous, croscarmellose sodium and magnesium stearate.

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

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

INSTRUCTIONS FOR USE AND HANDLING, AND DISPOSAL

For the treatment of children and infants, the 24 tablet pack might be prescribed. The prescriber and pharmacist should instruct the parent or caregiver on the posology for their child and that a variable number of 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 tablets should be discarded or returned to the pharmacist (see section DOSAGE AND ADMINISTRATION).

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

Manufacturer:

See folding box.

International Package Leaflet

Information issued: May 2009

® = registered trademark

Novartis Pharma AG, Basel, Switzerland