NOVARTIS

COARTEM®

(Artemether/Lumefantrine)

20 mg/120 mg, tablets

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1. NAME OF THE MEDICINE

COARTEM (20 mg/120 mg tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COARTEM tablet contains 20 mg artemether and 120 mg lumefantrine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow, round and flat tablet with bevelled edges and scored on one side. Debossed: one side “N/C”, other side “CG”.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of uncomplicated *Plasmodium falciparum* malaria, including chloroquine-resistant *Plasmodium falciparum* malaria, and the acute stage of *Plasmodium vivax* malaria in adults, children and infants, up to 65 kg body weight living in malaria-endemic and non-endemic areas. Appropriate treatment to eradicate the liver forms of *Plasmodium vivax* should be added for *Plasmodium vivax* malaria or mixed malaria.

There is no experience on the treatment of complicated malaria with COARTEM.
There is no adequate experience in patients weighing over 65 kg.

4.2 Posology and method of administration

4.2.1 Posology

The dose should be taken with food or drinks rich in fat such as milk. Consumption of 30–60 g of fat per day or breast milk is adequate for this purpose.

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.

An intensive 3-day course is recommended, with one to four tablets (depending on bodyweight) given as a single dose at the time of initial diagnosis, one to four tablets again after 8 hours and then one to four tablets twice daily on each of the following two days (total course comprises 6, 12, 18 or 24 tablets depending on bodyweight).

Dosage:

35 to < 65 kg bodyweight

Four tablets as a single dose at the time of initial diagnosis, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) on each of the following two days (total course comprises 24 tablets).

≥ 65 kg bodyweight

No adequate experience has been acquired in the use of COARTEM in patients weighing more than 65 kg.

4.2.2 Special populations

Geriatric patients (65 years or above):

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

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 4.4). 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.

New and recrudescent infections in adults and children:
Data for a limited number of patients treated with COARTEM show that new and recrudescent infections can be treated with a second course of COARTEM.

4.2.3 Paediatric population

Dosage in infants and children weighing 5 kg to less than 35 kg and 12 years of age or less:
The prescriber and pharmacist should instruct the parent or caregiver on the dosage 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.
The COARTEM tablet/s may be crushed for administration to infants and children.

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).

35 to < 65 kg bodyweight

Four tablets as a single dose at the time of initial diagnosis, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) on each of the following two days (total course comprises 24 tablets).

4.3 Contraindications

- Hypersensitivity to artemether, lumefantrine or to any of the excipients of COARTEM.
- Patients with severe malaria according to WHO definition.
- Pregnancy, especially the first trimester of pregnancy in situations where other suitable anti- malarials are available (see section 4.6).
- Women breastfeeding their babies.
- 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 medicines that are known to prolong the QTc interval such as:
    - anti-dysrhythmics of classes IA and III,
    - neuroleptics, antidepressant agents,
    - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents,
    - certain non-sedating antihistamines (astemizole),
    - cisapride.
- Patients with known disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia.
- Patients taking any medicine which is metabolised 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).

4.4 Special warnings and precautions for use

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

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. Therefore, sequential treatment with an appropriate antimalarial should be used to achieve hypnozoite eradication in case of co-infection with *Plasmodium vivax*.

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

COARTEM should not be used in patients with a prolonged QTc interval (see sections 4.3 and 5.1).

In children and infants with bodyweight between 5 and 25 kg, QTc prolongation of 30 to 60 msecs was seen in up to 35 % of treated subjects. In those suffering from dehydration and/or electrolyte imbalance, a minority of subjects (9 %) showed QTc prolongation of > 60 msecs. It was not possible either to confirm or to rule out whether these changes were associated with the disease and its course, or with the use of COARTEM.

Caution in case of concomitant administration of medicines:
Patients previously treated with other anti-malarials:

When COARTEM is given sequentially to mefloquine or quinine, close monitoring of food intake (for mefloquine) or ECG (for quinine) is necessary. In addition, because data on safety and efficacy are limited, COARTEM should not be given concurrently with antimalarials other than mefloquine or quinine. In patients previously treated with halofantrine, COARTEM should be administered at least one month after the last halofantrine dose.

With other anti-malarials:

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.

With other medicines:

COARTEM should not be used with medicines metabolised by CYP2D6 (see section 4.3) and caution is advised when combining COARTEM with substrates, inhibitors or inducers of CYP3A4 as the therapeutic effects of some medicines could be altered (see sections 4.3, 4.5 and 5.2).

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 section 4.6).

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 5.2).

Post-marketing experience:

Post-marketing data although inconclusive suggest a possible association between lumefantrine/artemether combination and the development of Stevens-Johnson Syndrome and/or Toxic Epidermal Necrolysis (TEN) cannot be excluded.

4.5 Interaction with other medicines and other forms of interaction

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

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 4.3).

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 4.3).

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 4.4).

Interaction with other anti-malarials:

As patients to be treated with COARTEM may have recently been treated with other anti-malarials, 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 (Cmax and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Based on this study, 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 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. In the different clinical trials, asymptomatic prolongation of QTc intervals by > 30 ms, with an actual QTc > 450 ms in males and > 470 ms in females, was observed in approximately 5 % of patients treated with various dose regimens of COARTEM. It is possible that these changes were disease-related. No correlation was found between QTc-prolongation and peak plasma concentration in individual patients.

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. 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.

Interaction with anti-retroviral medicines:
Both artemether and lumefantrine are metabolised 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 4.4).

Interaction with CYP450 enzymes:
Whereas, in vitro studies with artemether at therapeutic concentrations revealed no significant inhibition with 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 is not expected to present a problem in the general patient population, it is possible that CYP3A4

induction could alter the therapeutic effects of medicines that are predominantly metabolised by this enzyme.

Interaction with drugs metabolised 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 medicines that are metabolised by this iso-enzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated (see section 4.3). (Also see sections 4.4 and 5.2).

Interaction of COARTEM 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 4.4 and 4.6).

Food/drink interactions

COARTEM should be taken with food or drinks rich in fat such as milk (breastmilk or formula milk) as the absorption of both artemether and lumefantrine is increased (see section 4.2).

Grapefruit juice should be avoided during COARTEM treatment.

4.6 Fertility, pregnancy and lactation

Based on animal data, COARTEM is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see section 4.3).

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

COARTEM is contraindicated in pregnancy, especially 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 4.3).

4.6.1 Women of childbearing potential/Contraception in males and females

As COARTEM is contraindicated especially in the first trimester of pregnancy, women should not conceive while on COARTEM treatment for malaria.

Women of child-bearing potential should use effective contraception while on treatment with COARTEM and continue with contraception until one month after the completion of 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 4.4).

4.6.2 Pregnancy

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.

Data from observational and open label studies in over 1200 pregnant women exposed to artemether- lumefantrine in their second or third trimester, and pharmacovigilance data have not demonstrated an increase in adverse pregnancy outcomes or teratogenic effects.

4.6.3 Breastfeeding

Animal data suggest excretion into breast milk, but no data are available in humans. Breastfeeding women should not take COARTEM. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breastfeeding should not resume before day 28 after stopping.

4.6.4 Fertility

There is no information on the effects of COARTEM on human fertility.

4.7 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.

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency 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 report. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

Metabolism and nutrition disorders	
Very common	Decreased appetite
Psychiatric disorders	
Very common	Sleep disorder
Nervous system disorders	
Very common:	Headache, dizziness
Common	Clonus
Uncommon:	Somnolence, hypoaesthesia, ataxia
Cardiac disorders	
Very common:	Palpitations, QT prolongation
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
Uncommon:	Urticaria
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia
General disorders and administration site conditions	
Very common:	Asthenia, fatigue
Uncommon:	Gait disturbance
Investigations	
Uncommon	Electrocardiogram QT prolonged, liver function test increased

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

Immune system disorders	
Rare:	Hypersensitivity

Metabolism and nutrition disorders	
Common	Mood swings
Very common	Decreased appetite
Psychiatric disorders	
Uncommon	Sleep disorder
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Clonus, somnolence
Cardiac disorders	
Uncommon:	Palpitations, QT prolongation
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	Urticaria, pruritus
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia

General disorders and administration site conditions	
Common:	Asthenia, fatigue
Investigations	
Common	Liver function test increased
Uncommon	Electrocardiogram QT 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 investigators.

Adverse events reported during use with non-recommended regimens not included in this pooled safety analysis paraesthesia (3,3 % of adolescents and adults, no cases in children); involuntary muscle contractions (1,3 % of 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It

allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity. In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.6 Medicines against protozoa

Pharmacotherapeutic group: Antimalarials, artemisinins and derivatives. ATC code: P01BF01

Mechanism of action

Pharmacodynamic effects

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 1h 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.

5.2 Pharmacokinetics properties

Pharmacokinetic characterisation of artemether and lumefantrine 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, and/or Cmax).

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 6-8 hours after administration.

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 artemether and lumefantrine were taken after a high-fat meal.

Food has been shown to increase the absorption of lumefantrine approximately two-fold in patients with malaria. 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 dihydroartemisinin (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 4.4 and 4.5).

Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT2B7.

During repeated administration of the combination tablet, 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 4.5.

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 4.3 and 4.5).

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 artemether and lumefantrine.
No urinary excretion data are available for humans.

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

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 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 4.4).

Geriatric patients (65 years or above)

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

5.2.1 Paediatric patients (below 18 years, weighing ≥ 5 kg to < 35 kg)

Systemic exposure to artemether, dihydroartemisinin (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.

Following repeated administration of COARTEM (alone or in combination with mefloquine), serum artemether levels decreased significantly, while levels of the metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This indicates that there was induction of the enzyme responsible for the metabolism of artemether.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polysorbate 80 and silica colloidal anhydrous.

Sugar free.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Protect from heat and moisture. Store below 30 °C.
Keep the blisters in the outer carton until required for use, to protect the tablets from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC blisters containing tablets in packs of 24 tablets.

6.6 Special precautions for disposal

No specific requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd
Magwa Crescent West, Waterfall City,
Jukskei View, Johannesburg,
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8. REGISTRATION NUMBER(S)

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Country	*Registration number*	*Scheduling status*
Namibia	04/20.2.6/0540	NS2
Botswana	BOT0400691	S2

ATC code: P01BF01 - Artemisinin and derivatives, combinations

Name and address of manufacturer:

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