implantation losses, and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at 105 mg/kg/day, about two times the clinical dose based on body surface area comparisons.

Other artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives (e.g, artesunate) demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. Similar findings were not seen in animal reproductive studies using artemether.

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 [see *Adverse Reactions (6.2)*].

14 CLINICAL STUDIES

14.1 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* in HIV negative patients in 8 clinical studies. 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 China, Thailand, sub-Saharan Africa, Europe, and South America. Patients who had clinical features of severe malaria, severe cardiac, renal, or hepatic impairment were excluded.

The studies include two 4-dose studies assessing the efficacy of the components of the regimen, a study comparing a 4-dose versus a 6-dose regimen, and 5 additional 6-dose regimen studies.

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

- 28 day cure rate, defined as 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.

Studies 1 and 2: The two studies which assessed the efficacy of Coartem Tablets (4 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine) compared to each component alone were randomized, double-blind, comparative, single center, conducted in China. The efficacy results (Table 5) support that the combination of artemether and lumefantrine in Coartem Tablets had a significantly higher 28-day cure rate compared to artemether and had a significantly faster parasite clearance time (PCT) and fever clearance time (FCT) compared to lumefantrine.

Table 5: Clinical Efficacy of Coartem Tablets versus Components (mITT Population[1]

Study No. **Region/patient ages**	**28-day cure rate[2]** n/N (%) patients	**Median FCT[3]** [25th,75th percentile]	**Median PCT** [25th,75th percentile]
Study 1 China, ages 13 - 57 years			
Coartem Tablets	50/51 (98.0)	24 hours [9, 48]	30 hours [24, 36]
Artemether[4]	24/52 (46.2)	21 hours [12, 30]	30 hours [24, 33]
Lumefantrine[5]	47/52 (90.4)	60 hours [36, 78]	54 hours [45, 66]
Study 2 China, ages 12 - 65 years			
Coartem Tablets	50/52 (96.2)	21 hours [6, 33]	30 hours [24, 36]
Lumefantrine[6]	45/51 (88.2)	36 hours [12, 60]	48 hours [42, 60]

[1]In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[2]Efficacy cure rate based on blood smear microscopy.
[3]For patients who had a body temperature > 37.5°C at baseline only
[4]95% CI (Coartem Tablets – artemether) on 28-day cure rate: 37.8%, 66.0%
[5]P-value comparing Coartem Tablets to lumefantrine on parasite clearance time (PCT) and fever clearance time (FCT): < 0.001
[6]P-value comparing Coartem Tablets to lumefantrine on parasite clearance time (PCT): < 0.001 and on fever clearance time (FCT): < 0.05

Results of 4-dose studies conducted in areas with high resistance such as Thailand during 1995-96 showed lower efficacy results than the above studies. Therefore, Study 3 was conducted.

Study 3: Study 3 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 in mITT subjects was 81% (96/118) for the Coartem Tablets 6-dose arm as compared to 71% (85/120) in the 4-dose arm.

Studies 4, 5, 6, 7, and 8: In these studies, Coartem Tablets were administered as the 6-dose regimen.

In study 4, a total of 150 adults and children aged ≥2 years received Coartem Tablets. In study 5, a total 164 adults and children ≥12 years received Coartem Tablets. Both studies were conducted in Thailand.

Study 6 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 7 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 8 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.

Results of 28-day cure rate, median parasite clearance time (PCT), and fever clearance time (FCT) for Studies 3 to 8 are reported in Table 6.

Table 6: Clinical Efficacy of 6-dose Regimen of Coartem Tablets

Study No. Region/ages	28-day cure rate[1] n/N (%) patients		Median FCT[2]	Median PCT
	mITT[3]	Evaluable	[25th, 75th percentile]	[25th, 75th percentile]
Study 3 Thailand, ages 3 – 62 years	96/118 (81.4)	93/96 (96.9)	35 hours	44 hours
Early failure[4]	0	0	[20, 46]	[22, 47]
Late failure[5]	4 (3.4)	3 (3.1)		
Lost to follow up	18 (15.3)			
Other[6]	0			
Study 4 Thailand, ages 2 – 63 years	130/149 (87.2)	130/134 (97.0)	22 hours	NA
Early failure[4]	0	0	[19, 44]	
Late failure[5]	4 (2.7)	4 (3.0)		
Lost to follow up	13 (8.7)			
Other[6]	2 (1.3)			
Study 5 Thailand, ages 12 – 71 years	148/164 (90.2)	148/155 (95.5)	29 hours	29 hours
Early failure[4]	0	0	[8, 51]	[18, 40]
Late failure[5]	7 (4.3)	7 (4.5)		
Lost to follow up	9 (5.5)			
Other[6]	0			
Study 6				

Europe/Columbia, ages 16 – 66 years	120/162 (74.1)	119/124 (96.0)	37 hours [18, 44]	42 hours [34, 63]
Early failure[4]	6 (3.7)	1 (0.8)		
Late failure[5]	3 (1.9)	3 (2.4)		
Lost to follow up	17 (10.5)			
Other[6]	16 (9.9)	1 (0.8)		
Study 7 Africa, ages 2 months – 9 years	268/310 (86.5)	267/300 (89.0)	8 hours [8, 24]	24 hours [24, 36]
Early failure[4]	2 (0.6)	0		
Late failure[5]	34 (11.0)	33 (11.0)		
Lost to follow up	2 (0.6)			
Other[6]	4 (1.3)			
Study 8 Africa, ages 3 months – 12 years	374/452 (82.7)	370/419 (88.3)	8 hours [8, 23]	35 hours [24, 36]
Early failure[4]	13 (2.9)	0		
Late failure[5]	49 (10.8)	49 (11.7)		
Lost to follow up	6 (1.3)			
Other[6]	10 (2.2)			

[1] Efficacy cure rate based on blood smear microscopy
[2] For patients who had a body temperature > 37.5°C at baseline only
[3] In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[4] Early failures were usually defined as patients withdrawn for unsatisfactory therapeutic effect within the first 7 days or because they received another antimalarial medication within the first 7 days
[5] Late failures were defined as patients achieving parasite clearance within 7 days but having parasite reappearance including recrudescence or new infection during the 28 day follow-up period
[6] Other includes withdrawn due to protocol violation or non-compliance, received additional medication after day 7, withdrew consent, missing day 7 or 28 assessment

In all studies, patients' signs and symptoms of malaria resolved when parasites were cleared.

In studies conducted in areas with high transmission rates, such as Africa, reappearance of *P. falciparum* parasites may be due to recrudescence or a new infection.

The efficacy by body weight category for studies 7 and 8 is summarized in Table 7.

Table 7: Clinical Efficacy by Weight for Pediatric Studies

Study No. Age category	Coartem Tablets 6-dose Regimen		
	mITT population[1]		Evaluable population
	Median PCT [25th,75th percentile]	28-day cure rate[2] n/N (%) patients	28-day cure rate[2] n/N (%) patients
Study 7			
5 - <10 kg	24 [24, 36]	133/154 (86.4)	133/149 (89.3)
10 - <15 kg	35 [24, 36]	94/110 (85.5)	94/107 (87.9)
15 -25 kg	24 [24, 36]	41/46 (89.1)	40/44 (90.9)
Study 8[3]			
5 - <10 kg	36 [24, 36]	61/83 (73.5)	61/69 (88.4)
10 - <15 kg	35 [24, 36]	160/190 (84.2)	157/179 (87.7)
15 - <25 kg	35 [24, 36]	123/145 (84.8)	123/140 (87.9)

25 - <35 kg	26 [24, 36]	30/34 (88.2)	29/31 (93.5)

[1] In mITT analysis, patients whose status was uncertain were classified as treatment failures.
[2] Efficacy cure rate based on blood smear microscopy
[3] Coartem Tablets administered as crushed tablets

The efficacy of Coartem Tablets for the treatment *P. falciparum* infections mixed with *P. vivax* was assessed in a small number of patients. Coartem Tablets are only active against the erythrocytic phase of *P. vivax* malaria. Of the 43 patients with mixed infections at baseline, all cleared their parasitemia within 48 hours. However, parasite relapse occurred commonly (14 /43; 33%). Relapsing malaria caused by *P. vivax* requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoite forms that may remain dormant in the liver.

16 HOW SUPPLIED/STORAGE AND HANDLING

Coartem (artemether/lumefantrine) Tablets

20mg/120mg Tablets - yellow, round flat tablets with beveled edges and scored on one side. Tablets are imprinted with N/C on one side and CG on the other.

Bottle of 24	NDC 0078-0568-45
Unit dose carton of 24 tablets (4 x 6-tablet blister cards)	NDC 0078-0568-43

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see *USP Controlled Room Temperature*].

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2).

17.1 Information for Safe Use

- Instruct patients to take Coartem Tablets with food. Patients who do not have an adequate intake of food are at risk for recrudescence of malaria.
- Patients hypersensitive to artemether, lumefantrine, or to any of the excipients should not receive Coartem Tablets.
- Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia.
- Instruct patients to inform their physician if they are taking any other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistamines (terfenadine, astemizole), or cisapride.
- Instruct patients to notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

- Instruct patients to avoid medications that are metabolized by the cytochrome enzyme CYP2D6 while receiving Coartem Tablets since these drugs also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).
- Inform patients that based on animal data, Coartem Tablets administered during pregnancy may result in fetal loss. Fetal defects have been reported when artemisinins are administered to animals.
- Halofantrine and Coartem Tablets should not be administered within one month of each other due to potential additive effects on the QT interval.
- Antimalarials should not be given concomitantly with Coartem Tablets, unless there is no other treatment option, due to limited safety data.
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Coartem Tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval.
- Closely monitor food intake in patients who received mefloquine immediately prior to treatment with Coartem Tablets.
- Use Coartem Tablets cautiously in patients receiving other drugs that are substrates, inhibitors or inducers of CYP3A4, including grapefruit juice, especially those that prolong the QT interval or are anti-retroviral drugs.
- Coartem Tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- Inform patients that Coartem Tablets can cause hypersensitivity reactions. Instruct patients to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

17.2 FDA-Approved Patient Labeling

Patient Information
Coartem®
(co-AR-tem)
(artemether and lumefantrine)
Tablets

Read this patient information before you start taking Coartem. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is Coartem?

Coartem is a prescription medicine used to treat uncomplicated malaria in adults and children who weigh at least 11 pounds (5 kg).

Who should not take Coartem?

Do not take Coartem if you are allergic to any of the ingredients. See the end of this leaflet for a complete list of ingredients in Coartem.

What should I tell my healthcare provider before taking Coartem?

Before you take Coartem, tell your healthcare provider about all your medical conditions including if you have:

- heart disease or a family history of heart problems or heart disease
- liver or kidney problems
- recently taken other medicines used to treat malaria
- if you are pregnant or are planning to become pregnant. Coartem may increase your risk for loss of pregnancy. Fetal defects have been reported when artemisinins are administered to animals. Talk to your healthcare provider before taking Coartem.
- if you are breast-feeding. It is not known if Coartem passes into your breast milk. You and your doctor will decide the best way to feed your baby if you take Coartem.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Coartem and other medicines may affect each other causing side effects. Coartem may affect the way other medicines work and other medicines may affect how Coartem works.

Especially tell your doctor if you take:

- any other medicines to treat or prevent malaria
- medicines for your heart

- antipsychotic medicines
- antidepressants
- antibiotics
- antihistamines
- Cisapride (Propulsid®)
- medicines to treat HIV-infection
- hormonal methods of birth control (for example, birth control pills or patch)

Ask your healthcare provider if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take Coartem?

- Take Coartem exactly as prescribed.
- If you weigh 77 pounds (35 kg) or more, one dose of Coartem is 4 tablets.
- If you weigh less than 77 pounds (35 kg), your healthcare provider will tell you how many tablets to take for each dose.
- A full course of treatment is 6 doses of Coartem taken over 3 days:

  Day 1: take 1 dose; 8 hours later take 1 dose

  Day 2: take 1 dose in the morning, 1 dose in the evening

  Day 3: take 1 dose in the morning, 1 dose in the evening

  Take Coartem for 3 days even if you are feeling better.
- Every dose of Coartem should be taken with food, such as milk, infant formula pudding, porridge, or broth. It is important for you to eat as soon as you can so that your malaria will go away and not get worse.
- Do not drink grapefruit juice while you take Coartem. Drinking grapefruit juice during treatment with Coartem can cause you to have too much medicine in your blood.
- Coartem may be crushed and mixed with one to two teaspoons of water in a clean container.
- If you vomit within 1 hour of taking Coartem you should take another dose of Coartem. If you vomit the second dose, tell your healthcare provider. A different medicine may need to be prescribed for you.

Tell your healthcare provider right away if:

- your malaria does not get better
- you vomited any of your doses of Coartem
- you are not able to eat

- you get flu-like symptoms (chills, fever, muscle pains, or headaches) again after you have finished your treatment with Coartem.
- you have any change in the way your heart beats or a loss of consciousness (fainting).

What are the possible side effects of Coartem?

Coartem can cause serious side effects including:

- **A heart problem called QT prolongation** that can cause an abnormal heartbeat can happen in people who take Coartem. The chance of this happening is higher in people with a family history of prolonged QT interval, low potassium (hypokalemia), and in people who take medicines to control heartbeats.
- **Allergic reactions.** Symptoms of an allergic reaction include: rash, hives, fast heartbeat, trouble swallowing or breathing, swelling of lips, tongue, face, tightness of the throat, or trouble speaking. If you have a serious allergic reaction, stop taking Coartem and get emergency medical help right away.

The most common side effects in adults are:

- headache
- feeling dizzy
- feeling weak
- loss of appetite
- muscle and joint pain or stiffness
- feeling tired
- chills
- fever

The most common side effects in children are:

- fever
- cough
- vomiting
- headache
- loss of appetite

These are not all the possible side effects of Coartem. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Coartem?

Store Coartem between 59°F to 86°F (15°C to 30°C).

Keep Coartem and all medicines out of the reach of children.

General information about the safe and effective use of Coartem.

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use Coartem for a condition for which it was not prescribed. Do not give Coartem to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about Coartem. If you would like more information about Coartem talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Coartem that is written for health professionals. For more information call 1-888-294-6287.

What are the ingredients in Coartem?

Active ingredients include: artemether, lumefantrine

Inactive ingredients include: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate 80

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