



Coartem[®]
artemether/luméfántrine

MONOGRAPH



 NOVARTIS

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Introduction

Malaria - the background, and the challenge

Malaria is a common and serious tropical disease caused by a protozoan parasitic infection transmitted by *Anopheles* mosquitoes. In humans, the disease is caused by one of four species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale* or *P. malariae*.

P. falciparum accounts for the majority of infections, and virtually all deaths from malaria are due to this species.^a This document focuses on malaria caused by *P. falciparum* (*falciparum* malaria).

Malaria is one of the most serious challenges to modern healthcare. Each year, there are hundreds of millions of cases of this disabling disease reported worldwide. Estimates for the annual mortality from malaria range from 0.5 to 2.5 million^b, although we really do not know the true extent of the disease. The figures for reported cases vary widely and suggest that only a small fraction of those in need of treatment ever get access to it.

The vast majority of malaria patients live in endemic, mainly tropical countries. Although malaria has been eradicated from North America and Europe, there has been a resurgence in many parts of the tropics, despite massive control efforts. Moreover, the malaria parasites are developing resistance to current therapies, and the mosquitoes to insecticides.

Despite the significance of the problem, few new therapies have been produced over the last century. Recently however, some new treatments have been under development, particularly combination therapies that include artemisinin derivatives. Coartem[®] is one such therapy.

“Fortunately, the 1990’s have been much more productive, and the new products coming along are very encouraging. By far and away the most exciting are the artemisinin derivatives, notably artesunate and artemether.”

R. Price, 2001^c

a Stürchler D. Global epidemiology of malaria. Schlagenhauf P (ed.) Travelers'malaria. 2001, B C Decker, London, 14-55

b White N, Nosten F, Looareesuwan S, et al. Averting a malaria disaster. The Lancet 1999; 353:1965-1967

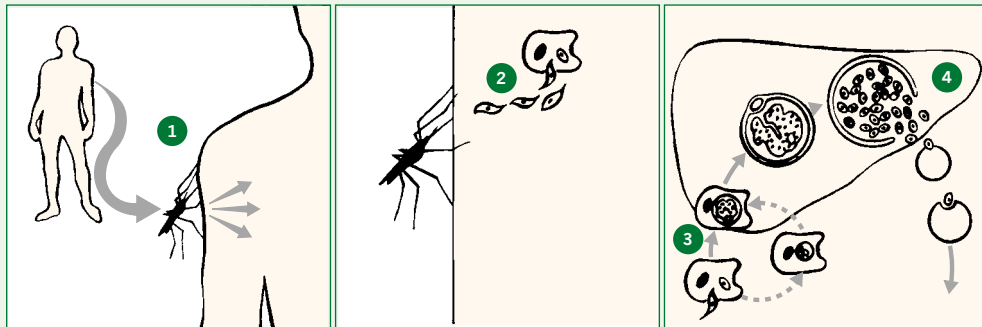
c Price R. Therapeutic options in malaria treatment. Highlights of the Meeting: Travellers' Malaria - New Trends and Treatment Strategies. 7th Conference of The International Society of Travel Medicine, Innsbruck, Austria, May 2001

Malaria - the disease and those most at risk

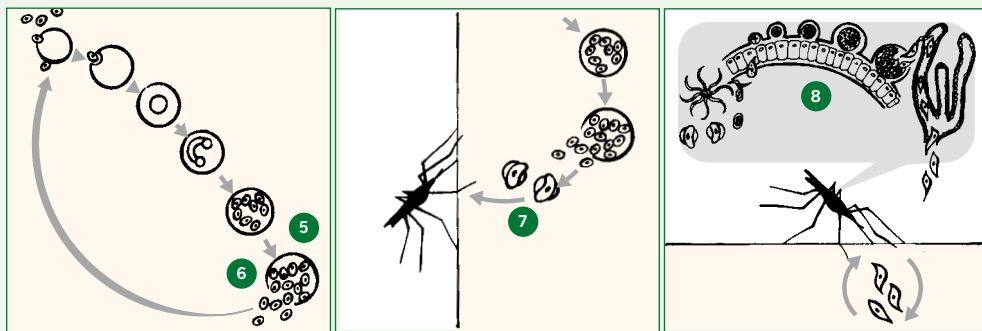
The life cycle of the malaria parasite

Human malarial plasmodia have a highly complex life cycle linking a human host with a mosquito vector. The parasite's sexual reproduction phase takes place in the mosquito, whilst asexual reproduction phases occur in the human.

In very simple terms, the life cycle is as follows:



1. A female mosquito that has already sucked up infected blood from one human passes on a malarial infection by biting another victim.
2. The mosquito's saliva contains **sporozoites** (thread-like forms of the parasite), which pass into the victim's blood.
3. In the human host, the sporozoites rapidly penetrate parenchymal cells of the liver. Here they transform into large **tissue schizonts** that reproduce asexually to generate large numbers of **merozoites**.
4. After 5-20 days, the merozoites rupture the liver cells and start an erythrocytic cycle.



- 5 & 6. During the erythrocytic cycle, the merozoites invade red blood cells in the peripheral blood stream, where they feed and multiply further. This results in a huge, periodic amplification of parasite populations. In 2-day cycles, they rupture the erythrocytes, releasing the merozoites, which promptly invade and destroy more erythrocytes. The release of merozoites produces the characteristic bouts of fever in the patient.
7. After this asexual propagation, some merozoites develop into **gametocytes**, (sexual forms), which are ingested by the next mosquito sucking blood.
8. In the mosquito gut, male and female gametes emerge from the gametocytes and fuse into zygotes, which migrate into the gut wall. There, they produce oocysts, each of which generates around one thousand sporozoites.

After about two weeks, sporozoites migrate into the mosquito's salivary gland. They develop over 9 days or so, becoming highly infective. They are then injected into a human when the mosquito next feeds - thus closing the cycle.



Symptoms, signs and diagnosis

Symptoms of uncomplicated malaria

The very specialised life cycle of the parasite gives rise to a variety of symptoms depending on the stage of infection and the infecting species.

- Fever is virtually always present.
- Common complaints include mild to moderate malaise, fatigue, muscle aches, back pain, headache, dizziness, loss of appetite, nausea, vomiting, abdominal pain, and diarrhoea. Some patients report a dry cough and shortness of breath.
- Gastrointestinal complaints can be considerable, suggesting a diagnosis of gastroenteritis.
- Young children and semi-immune individuals may complain of fever and headache as their only symptoms.

Signs of uncomplicated malaria

- Physical examination usually demonstrates an increased temperature, tachycardia, and warm flushed skin.
- The spleen is often palpable in initial infection, but this is more likely in subsequent attacks. It is usually soft, and may be tender.
- The liver is often enlarged and may be tender; jaundice is not unusual.
- Orthostatic hypotension often occurs during initial infections.
- Mental confusion and cyanosis are sometimes encountered.

Malaria is usually diagnosed by the characteristic signs and symptoms. Care should be taken to rule out influenza, the commonest misdiagnosis. The same applies to other disorders suggested by symptoms often associated with malaria fever, such as diarrhoea and vomiting. Malaria is then treated empirically, without waiting to diagnose the actual species of plasmodium causing the infection.

A definitive diagnosis can usually be made by microscopy of stained blood films. However, other laboratory techniques are now available, including molecular diagnosis, antibody detection and immunological/biochemical detection of various parasite products.

Immediate diagnosis of malaria is essential since complications arise within hours or days of the first symptom, and because falciparum malaria can rapidly progress to severe, life-threatening disease.

Definition of severe malaria and complications (WHO 1990)

One or more of the following criteria in the presence of asexual parasitaemia define severe *falciparum* malaria:

Defining criteria of severe disease

- cerebral malaria (unrousable coma)*
- severe anaemia (Hb <5g/dl)
- renal failure (serum creatinine >3.0 mg/dl)
- pulmonary oedema
- hypoglycaemia (<40 mg/dl)
- circulatory collapse/shock (systolic BP <70 mm Hg in adults; or <50 mm Hg in children < 5 years)
- spontaneous bleeding/disseminated intravascular coagulopathy
- repeated generalised convulsion(s)
- acidaemia/acidosis
- macroscopic haemoglobinuria

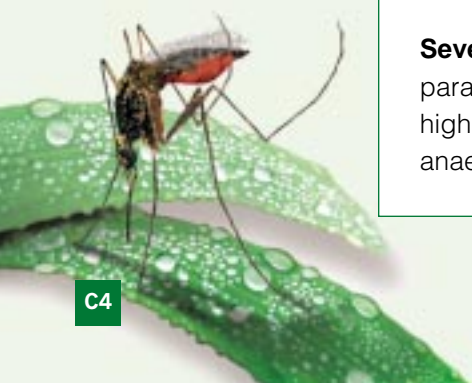
Other manifestations

- impaired consciousness but rousable
- prostration, extreme weakness (inability to stand or sit)
- hyperparasitaemia (>5% RBC infected)
- jaundice (total serum bilirubin >3 mg/dl)
- hyperpyrexia (axillary temp. >98.5°C)

*After generalised convulsion, coma should persist for at least 30 minutes to make the distinction from post-ictal coma

Cerebral malaria is the most serious manifestation of severe *falciparum* malaria and is caused by the adherence of parasitised red blood cells to the walls of small blood vessels. In non-immune patients, cerebral malaria can develop rapidly from uncomplicated disease, and is associated with high parasitaemia. Cerebral malaria is characterised by bleeding, acute neurological symptoms, disturbance of consciousness, coma, and rapid death.

Severe anaemia seems to involve haemolysis caused directly by the parasite, and disruption of the formation of red blood cells. In children in highly endemic areas, repeated, chronic infections lead to a build up of anaemia, which is a major cause of death.



Immunity against malaria and gametocyte carriers

Frequent or chronic exposure to infection with plasmodia parasites over prolonged periods produces some degree of immunity. However, human defence mechanisms are not fully effective against these parasites, and sterile immunity is not possible, even for a short period of time, or even in people living in hyperendemic areas.

Apart from break-through attacks, immune people generally do not develop symptoms, despite being infected with malarial plasmodia. However, such people still develop gametocytes. Therefore, in areas of high endemicity, immune adults represent a large reservoir of infection, which threatens non-immune individuals such as infants and travellers.

The risk of malaria

Anyone living in or travelling to an area with endemic malaria is at risk of infection. But as well as geographic location, risk also varies according time, the immune status of the person, and the degree of their exposure to the parasite.

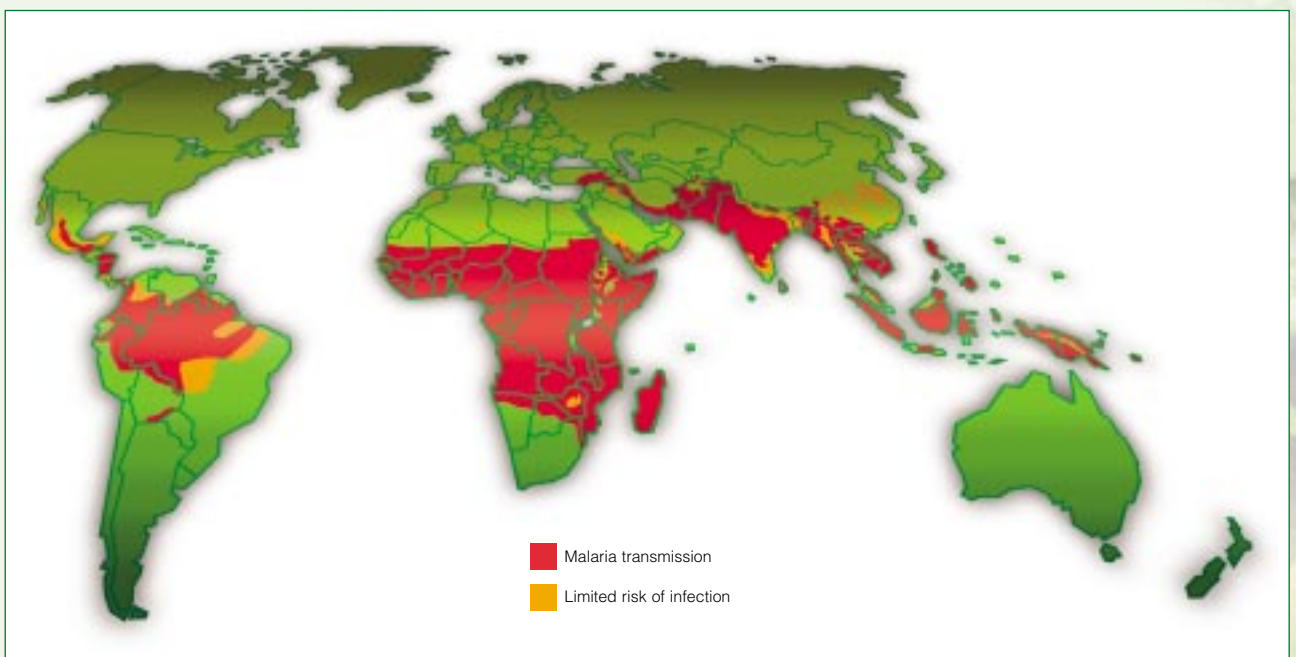
Geographic location -

High-risk areas include sub-Saharan Africa, Madagascar, Sumatra, Borneo, Irian Jaya, Papua New Guinea, Vanuatu and the Solomon Islands, and some districts of Thailand (Trat and Tak) and Brazil (Rondônia, Acre).

Moderate risk areas include South America, the Indian subcontinent including Sri Lanka, and parts of South-East Asia.

Low-risk areas include Northern Africa, Mauritius, Central America, Haiti, and the Near East. Large cities inside risk areas are often free of malaria.

Map of geographic locations of malaria - 2000



Time -

Risk varies both seasonally and diurnally. In areas with seasonal climatic variation, it is highest during the rainy season when mosquito populations increase. In regions with a stable, warm, humid climate, the risk is throughout the year. Activity peaks of anopheline mosquitoes occur from dusk to dawn, although this is variable because these insects have highly adaptable behaviour patterns.

Exposure and immunity -

Immune persons - immunity reduces the risk of developing clinically significant disease compared with non-immune individuals. Acquired immunity however, is partial and wanes when exposure to the parasite has ceased. When previously immune people move outside a malarial area for some years, they are at risk of severe malaria when they return. Moreover, immune people are usually chronically infected and are therefore at risk of breakthrough attacks^d.

Non-immune travellers are at a substantial risk of acquiring falciparum malaria. Each year more than 10,000 travellers from industrialised countries fall ill with the disease on return home after visiting an endemic country.^e For these individuals, this is a seriously disabling disease, which can have important long-term consequences. Moreover, about 1% of travellers infected with *P. falciparum* die, in spite of the availability of intensive care in their own countries.^f

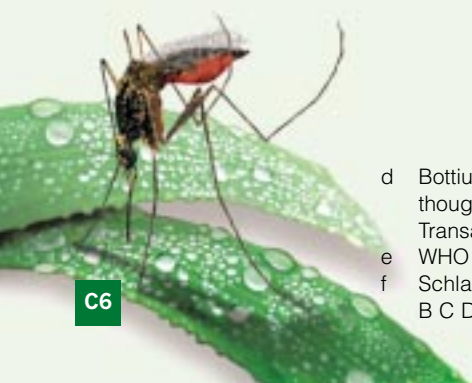
Non-immune natives of countries with endemic malaria are heavily exposed to malarial parasites. Although only a tiny fraction of the infections in countries with endemic malaria is ever reported, the vast majority of cases, and most of the total worldwide fatalities, occur in Africa. Among Africans, children below age five are the main sufferers from malaria.

Pregnant women (especially primigravidas) also form a high-risk group. They are more susceptible to malaria than other women and develop higher parasitaemia and more severe malaria. The placenta harbours high numbers of malaria parasites, exposing the foetus to placental insufficiency, leading to low birth weight and increased infant mortality. Even in uncomplicated disease, fever may lead to abortion or premature delivery.

d Bottius E, Guanzirolli A, Trape J, et al.: Malaria: even more chronic in nature than previously thought; evidence for subpatent parasitaemia detectable by the polymerase chain reaction. *Transact Roy Soc Trop Med Hyg* 1996; 90: 15-19

e WHO 00 International Travel and Health. WHO, Geneva, 2000

f Schlagenhauf P, Muentener P. Imported Malaria. Schlagenhauf P (ed.) *Travelers'malaria*. 2001, B C Decker, London, 495-508



Control options for malaria - prevention and treatment

Broadly speaking, the control options for malaria are prevention and treatment. Drugs are the mainstay for both options.

Preventing malaria

There are two types of preventive measures:

- Avoiding mosquito bites - so reducing the risk of infection. Such prophylactic measures include avoidance of exposure to insects, the use of insecticide-impregnated bed nets and repellents, and control of the mosquito vector by spraying and drainage of habitats.
- Chemoprophylaxis - using drugs to prevent symptomatic infection after transmission has occurred. The aim is to build up plasma levels of antimalarial compounds to kill erythrocytic stages of the parasite and thus prevent clinical disease.

However, effective chemoprophylaxis is often difficult to achieve, largely because of poor compliance. Current chemoprophylactic therapies present a number of drawbacks, mainly related to the complexity of the drug regime, and to adverse events. Residents and long-stay travellers in a risk area rarely use long-term chemoprophylaxis - mainly because of adverse events related to antimalarial drugs.^g Poor compliance and growing resistance of the parasite to various drugs means that prophylaxis often fails and acute treatment becomes necessary.

Treating malaria and the role of drugs

The aim of treatment is to fight an established parasite infection and includes:

- elimination of the parasites
- supportive measures to overcome morbidity associated with infection
- monitoring - to ensure early diagnosis and treatment of complications that can lead to death within hours.

Acute treatment is the 'traditional' role for antimalarial drugs. Current antimalarials are effective and indispensable for eliminating the malarial parasite. However, the range of drugs is limited and reduced efficacy due to increasing resistance, relatively poor tolerability and a cumbersome dosage regimen have led to the drive to develop new compounds.

g Schlagenhauf P, Steffen R. Stand-by treatment of malaria in travelers: a review. *J Trop Med Hyg* 1994; 97: 151-160

The choice of an antimalarial depends on a variety of factors including:

- parasite type
- level of drug resistance
- patient's general health and medical history
- availability of medications in the country of prescription
- intended use (prophylactic or therapeutic).

Coartem® is a new, safe and effective combination therapy that provides an important addition to the armoury against malaria. An overview of its features is given below, and a review of the clinical experiences with this product is given on the following pages.

Coartem® - overview of product characteristics

Coartem®:

- is effective against malaria caused by *P. falciparum* in areas of multi-drug resistance
- eliminates parasites and symptoms significantly faster than most current antimalarials
- is rapidly gametocidal, helping to reduce transmission
- achieves high cure rates:
 - at the 6-dose (24-tablet) regimen in areas with multi-drug resistance and in non-immune travellers
 - at the 4-dose (16-tablet) regimen in areas devoid of multi-drug resistance
- shows no evidence of cardiotoxicity
- is very well tolerated particularly when compared to the most current established antimalarials:
 - does not show any evidence of organ- or system-specific toxicity, cardiotoxicity, or neurotoxicity
- is an easy fixed-dose combination treatment:
 - simplifying compliance
 - tested by GCP standards.



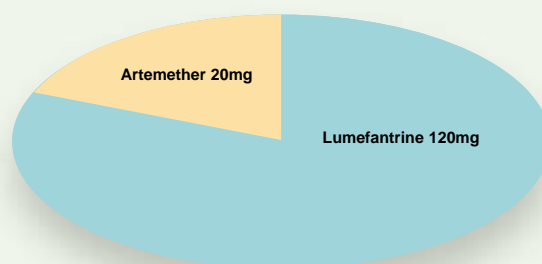
Using Coartem®

Coartem® is indicated for the treatment of *P. falciparum* infections or mixed infections that include *P. falciparum*. Coartem® is available in malaria-endemic countries for treating malaria infections that may be resistant to other antimalarials.



Coartem® is not indicated for prophylaxis, or for treating severe malaria, including cerebral malaria, pulmonary oedema, or renal failure, because treatment of severe malaria requires i.v. or i.m. medication.

Coartem® is an oral formulation. Each pale yellow uncoated tablet contains a fixed combination of artemether and lumefantrine in a 1:6 ratio.



General rules for using Coartem®

When using Coartem® the following general rules should be applied:

- Coartem® should be used in multi-drug resistant areas
- when using Coartem® it is important to take into account
 - the weight of the patient
 - the presumed immunological status of the patient
 - the degree of resistance of locally prevalent *P. falciparum*.

Coartem®:

- is effective against all malaria parasites in peripheral blood, including those resistant to current therapies
- demonstrates significant benefits over current antimalarial therapies:
 - very fast control of malaria symptoms, avoiding progression to cerebral malaria
 - high cure rates (>95%) even in multi-drug resistance areas
 - low recrudescence rates
 - very good tolerability (better than that of most competitors)
 - easy fixed-dose combination regimen, simplifying compliance
 - no requirement for a pre-treatment ECG as there is no evidence of QTc prolongation and cardiotoxicity.

“Lumefantrine [Coartem®] is very different from halofantrine, and very good data from many places have clearly shown that there is no risk of cardiotoxicity.”

C Hatz, 2001 speaking at the 7th International Society of Travel Medicine Conference, Innsbruck

Prescribing Coartem®

Coartem® is for the treatment of malaria patients (adults and children) in countries with endemic falciparum malaria. Coartem® is not for use as a prophylactic.

There are two treatment regimens for Coartem® - the 4-dose and the 6-dose regimens.

Adult dosage schedule

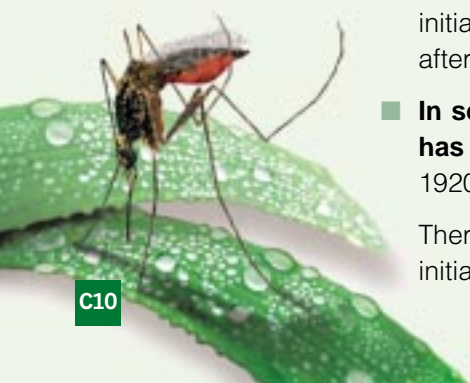
For adults (35 kg and above):

- **In multi-drug resistant areas** use a 6-dose regimen (24 tablets, 480 mg artemether and 2880 mg lumefantrine, given over 3 days) as oral *first-line treatment*.

Therapy is delivered over 3 days: one dose (4 tablets) is given at the time of initial diagnosis, after 8 hours, and subsequently twice daily (morning and afternoon) for two more days.

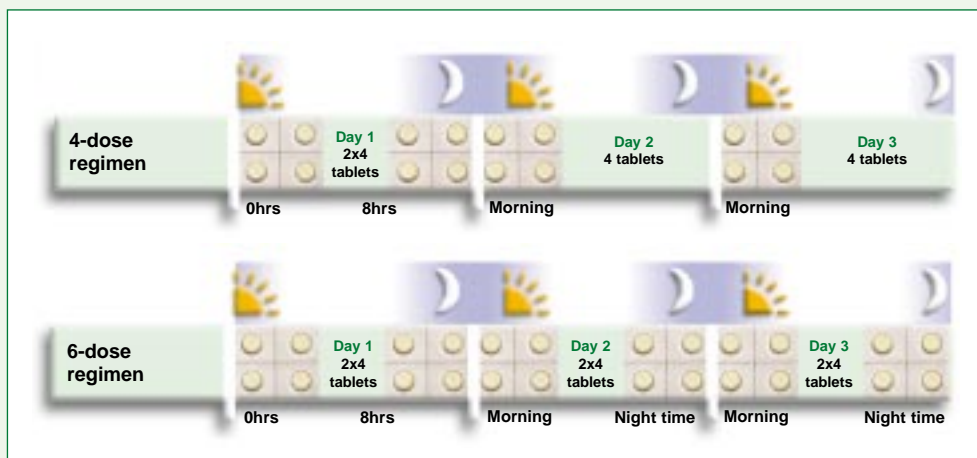
- **In semi-immune patients in areas where resistance to other antimalarials has developed**, use a 4-dose regimen (16 tablets, 320 mg artemether and 1920 mg lumefantrine, given over 2 days) as oral *first-line treatment*.

Therapy is delivered over 2 days: one dose (4 tablets) is given at the time of initial diagnosis and then again 8, 24 and 48 hours thereafter.



Coartem® treatment regimens (adults)

Top: 4-dose (16-tablet) regimen.
Bottom: 6-dose (24-tablet) regimen used for multi-drug resistant areas.



Dosage schedule for small children and low-weight malaria patients

In these patients, the timing of administration of Coartem® remains the same, but both the 4-dose and the 6-dose regimen require adjustment for body weight:

- 5 to <15 kg 1 tablet per dose¹
- 15 to <25 kg 2 tablets per dose
- 25 to <35 kg 3 tablets per dose
- 35 kg and above, adult dose (4 tablets per dose)

¹The minimum body weight limit is:

- 5 kg for the 4-dose regimen
- 10 kg for the 6-dose regimen

There are no data below these weight levels.

Note: The safe use of Coartem® during pregnancy has not been established. Treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus. There are no data on the excretion of the components of Coartem® in breast milk.

Administration and food

Although patients with acute malaria are frequently intolerant of food, Coartem® **should be taken with fluids (particularly drinks containing fats, such as milk) and if possible, with a normal diet as soon as the patient can tolerate food.** Ingestion with fat-containing food and drinks massively improves absorption. Although any risk of recrudescence is very small, patients who remain averse to food during treatment should be closely monitored.

Glossary

- Anopheles:** the genus of mosquitoes that is the vector for the malaria parasite, spreading infection as it bites.
- Artemether:** one of the active ingredients of Coartem®, a fast-acting naturally occurring antimalarial substance.
- Benflumetol:** original name for lumefantrine.
- Cure rate:** usually defined as the 28-day cure rate - i.e., the proportion of patients with clearance of parasites within 7 days, and without subsequent return of the original infection during the 28-day period following the first dose.
- Gametocyte:** sexual form of the malaria parasite that develops in human blood, ready to infect a biting mosquito as it feeds.
- Gametocyte clearance time:** the time from the start of treatment in patients who are gametocyte positive in blood smears at the beginning of a trial, until the first time blood films are negative, and remain so for at least 48 hours.
- Fever clearance time:** the time from the first dose of an antimalarial until the time when the body temperature falls to normal and remains so for at least 48 hours.
- Immunity:** ability of the body to resist infection after having been previously exposed to the infectious organism. In the case of malaria, the immunity developed is not strong, and protection depends upon repeated reinfection to maintain immunity.
- Lumefantrine:** synthesised antimalarial drug, a component of Coartem®. Has a slow onset of action.
- Merozoite:** form of the malaria parasite that develops in huge numbers within the schizonts in the blood or the liver.
- Multi-drug resistance (MDR):** Generally refers to parasites resistant to at least 2 common drugs, eg., chloroquine and sulfadoxine/pyrimethamine)
- Parasite clearance time:** the time needed to clear parasites from the blood (i.e., where parasite numbers fall below the limit of detection in a thick blood smear) and remain undetectable for at least 48 hours.
- Parasite reduction at 24 hours:** the percentage reduction of parasites per μL at 24 hours, compared with parasite density before the first treatment dose of an antimalarial.
- Plasmodium falciparum:** malaria parasite responsible for causing the most dangerous form of malaria.
- Recrudescence:** this occurs when parasites survive in red blood cells after failed or incomplete treatment, and after a brief check, emerge to continue the disease.
- Reinfection:** this is caused by a totally new infection, and is not related to survival of the parasite within the body.
- Resistance:** drug resistance is the ability of the malaria parasite to withstand or avoid the effects of drugs used to prevent or treat infection. It is a widespread and growing problem in almost all malarial regions.
- Schizont:** tiny cyst in which merozoites develop. Schizonts may develop in the blood and in the liver.
- Sporozoite:** the form of malaria parasite, which is injected into the blood by a biting mosquito.
- Transmission:** spread of malaria by biting mosquitoes. The rate of transmission means the number of bites a person can expect to receive, and is a measure of the threat of malaria.
- Vector:** (carrier). An invertebrate animal (e.g. tick, mite, mosquito) capable of transmitting an infectious agent among vertebrates.



From artemether to coartemether

Extracts from sweet wormwood, *Artemisia annua*, have been used for treating fevers in traditional Chinese medicine for some 2000 years, under the name of Qinghaosu. In 1970, Chinese scientists isolated the active component, artemisinin, and developed it for the treatment of malaria.

Artemisinin derivatives

Artemisinin is a sesquiterpene lactone containing a bridged endoperoxide. It has:

- two main lipophilic derivatives, artemether and arteether
- a lesser, hydrophilic derivative, artesunate
- a major metabolite, dihydroartemisinin.

The artemisinin derivatives (artesunate, artemether or arteether) are very fast acting and potent antimalarials that offer an important alternative to current treatments.

Combining antimalarials - the advantages

Artemisinin derivatives have a short elimination half-life (2-3 hours), which means that they carry a smaller risk of developing resistance (see *Summary of Pharmacology*, Page 22). The main drawback of the short half-life is that can produce substantial recrudescence* if artemisinin derivatives are used alone for less than 5 days. For this reason, artemisinins are often used in free combination with other antimalarials.

*Recrudescence occurs when parasites survive in red blood cells after a brief check (e.g., after failed or incomplete drug treatment) and cause the reappearance of the disease

A fixed combination of two antimalarials offers additional important advantages over the free combination of such drugs. Firstly, it facilitates compliance, and secondly, by preventing the patients from taking either drug alone, it helps to prevent the development of resistant *Plasmodia* strains. coartemether is such a fixed combination antimalarial.

Coartemether - a highly effective fixed combination

Each coartemether tablet contains **artemether** (20 mg), a synthetic derivative of artemisinin, and **lumefantrine** (120 mg), a highly lipophilic aryl amino alcohol, structurally resembling halofantrine. Lumefantrine has a much longer elimination half-life (several days) than artemether, and is associated with a low recrudescence rate, but has a slower onset of action. However, when used together, the complementary properties of artemether with its fast onset of action and lumefantrine with its long duration of action and high cure rate result in a highly effective combination.

Developing coartemether for use worldwide

Coartemether was developed during the early 1980s by researchers at the Institute of Microbiology and Epidemiology at the Academy of Military Medical Sciences in the People's Republic of China. It was registered for use in China as an antimalarial in 1992. Subsequently, Novartis Pharma AG further developed the formulation for worldwide registration. It was first approved for use in Europe in Switzerland in 1999.

Unlike free combinations of artemisinins, coartemether has undergone extensive preclinical and clinical studies conducted according to the standards of Good Clinical Practice. (The following sections provide an overview of these studies.) Coartemether is produced under Good Manufacturing Practice conditions.

Efficacy of coartemether

The hallmark of efficacy of an antimalarial is its ability to eliminate the malarial parasite from a patient's blood, so bringing about the disappearance of symptoms.

A variety of studies have evaluated the efficacy of coartemether in terms of speed and degree of parasite elimination, and have shown:

- very fast parasite elimination
- prompt reduction in fever
- effective gametocyte clearance
- cure rates as good as with current options
- effectiveness in multi-drug resistant areas.

Note that in the coartemether efficacy studies detailed in this monograph:

- A placebo group was not included for ethical reasons since untreated *P. falciparum* malaria may be a rapidly fatal disease.
- Statistical significance is expressed by the term significant, which is usually further specified by either a p-value or a 90% or 95% Confidence Interval (CI). Lack of a p-value indicates that there was no significant difference ($p > 0.05$).

Coartemether produces very fast parasite elimination

Fast elimination of parasites reduces the substantial risk of *falciparum* malaria progressing to complicated stages of the disease, and even death. Coartemether eliminates parasites faster than competitors and produces near-total parasite reduction within 24 hours.

Coartemether eliminates parasites faster than many competitors

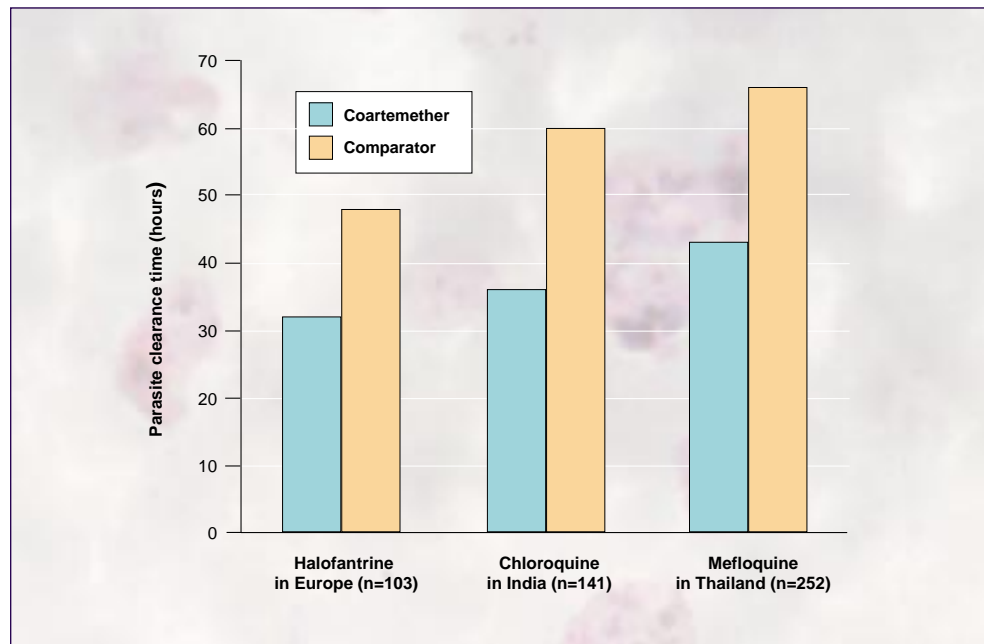
Studies comparing coartemether versus a competitor drug have evaluated parasite clearance time - the most important parameter for assessing the speed of a product's anti-malarial effect.

Parasite clearance time is the time needed to clear parasites from the blood (i.e., where parasite numbers fall below the limit of detection in a thick blood smear) and remain undetectable for at least 48 hours.

Studies measuring parasite clearance time (Fig. 1) revealed significantly shorter median values for the 4-dose (16-tablet) regimen of coartemether than for comparator drugs. These include halofantrine in Europe¹, chloroquine in India², and mefloquine in Thailand³.

Figure 1. Median parasite clearance time in comparative trials

The 4-dose coartemether regimen reduced parasites significantly faster than the comparators ($p < 0.001$).



The 6-dose regimen of coartemether produced similar parasite clearance time values as a combination of mefloquine + artesunate (29 hrs [n = 164] vs. 31 hrs [n = 55]) in a trial in Thailand⁴.

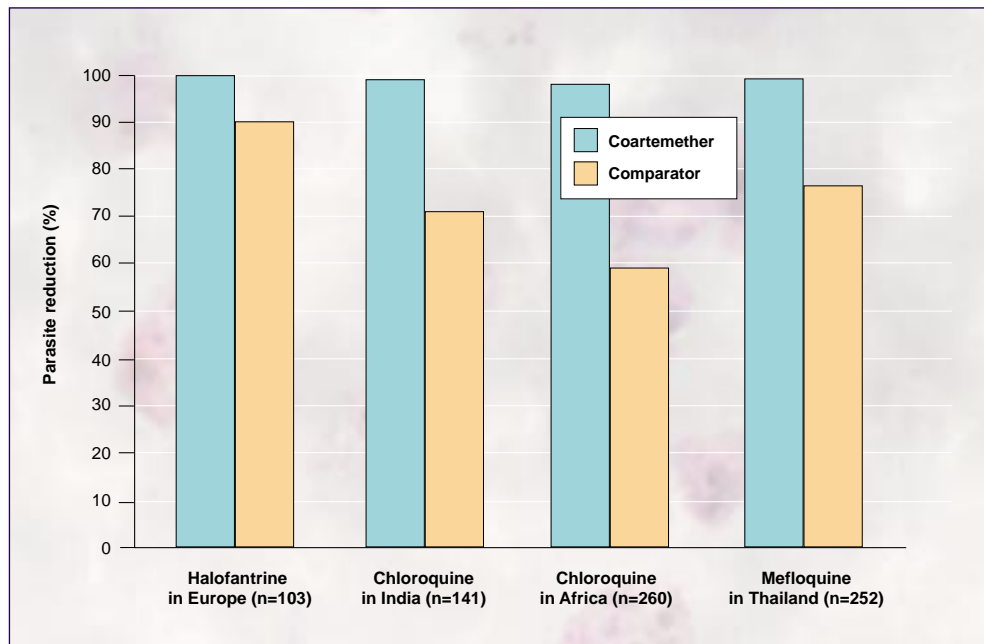
Near-total parasite reduction within 24 hours

A variety of trials show that at 24 hours, median percentage parasite reduction was better with coartemether than with comparator drugs (Fig. 2) - halofantrine in Europe¹, chloroquine in India², chloroquine in Africa (children <5 years)⁵, and mefloquine in Thailand³.

Parasite reduction at 24 hours: the percentage reduction of parasites per μL at 24 hours, compared with parasite density before the first treatment dose.

Figure 2. Faster parasite reduction than comparators

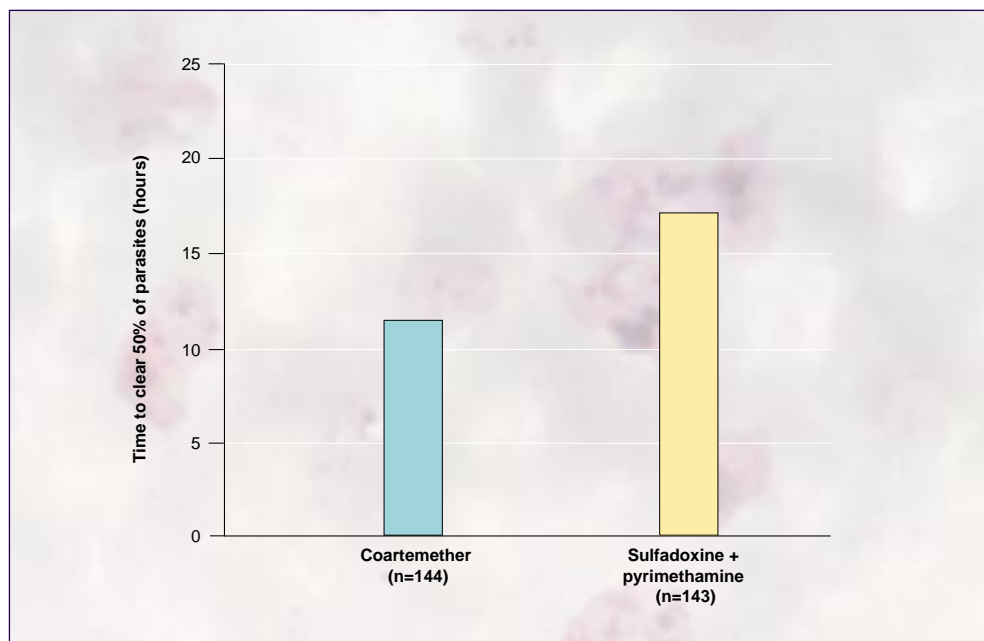
Median percentage parasite reduction at 24 hours was significantly better ($p < 0.001$) for coartemether than for comparators



In a study of African children, coartemether produced a faster time to clear 50% of *P. falciparum* parasites than sulfadoxine + pyrimethamine (Fig. 3).⁶

Figure 3. Time to clear 50% of parasites with coartemether and comparator

Time to clear 50% of the parasites is significantly faster ($p < 0.001$) with coartemether than sulfadoxine + pyrimethamine



The only comparator to produce a parasite reduction at 24 hours as fast as coartemether was the combination of mefloquine + artesunate. In a study conducted in Thailand, both coartemether and mefloquine + artesunate produced in evaluable patients, a median percentage parasite reduction of 100% after 24 hours⁴.

Coartemether produces prompt reduction in fever

Periodic fever is one of the characteristic symptoms of a malaria infection, and contributes to the malaise typical of the acute phase of the disease. It is due to the rupture of human erythrocytes, and the subsequent release of pyrogens into the blood stream associated with the parasite's asexual reproductive phase. Fever clearance time provides a means of measuring the degree of symptom control achieved by antimalarial treatments.

Fever clearance time is the time from the first dose to the time when body temperature falls to normal and remains so for at least 48 hours.

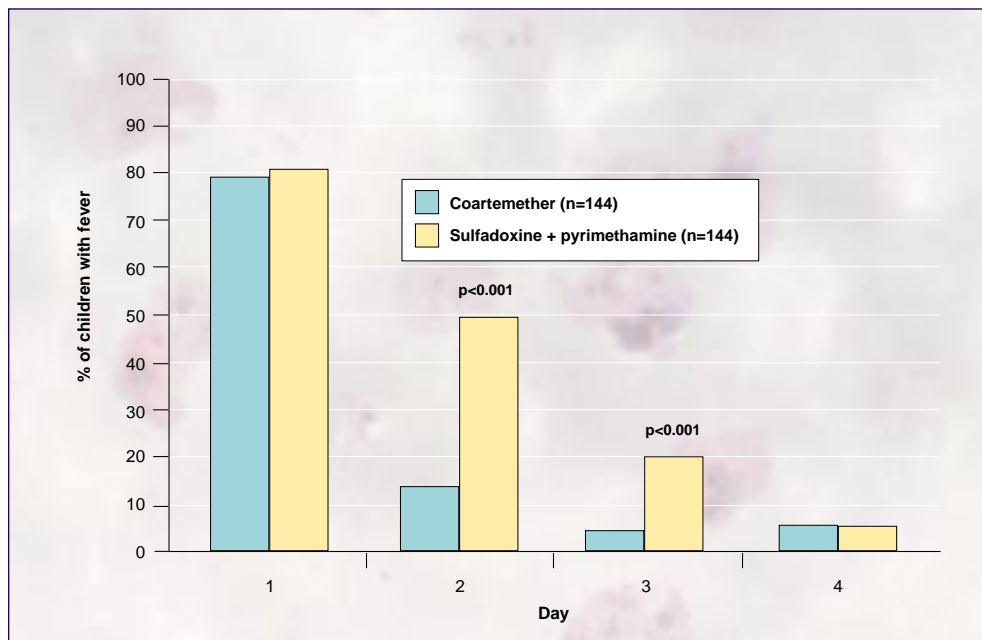
(Note that fever clearance time of coartemether varies markedly for each individual trial cited below - probably as a result of varying usage of antipyretics.)

Coartemether reduced fever significantly faster than certain comparator drugs. For example, when compared with chloroquine in India, the median fever clearance time was 18 hrs versus 27 h ($p=0.046$) India.² When coartemether was compared with mefloquine in Thailand, the median FCT was 32 h versus 54 h ($p=0.003$).³

In African children, fever clearance occurred significantly faster with coartemether than with sulfadoxine + pyrimethamine (Fig. 4).⁶

Figure 4. African children with fever $>37.5^{\circ}\text{C}$

Fever clearance (and hence, symptomatic improvement) occurred faster with coartemether than with sulfadoxine + pyrimethamine



Rapid fever clearance with coartemether is due to the activity of its artemether component on the parasite. This was demonstrated in a study in Chinese patients, where artemether alone and coartemether produced a median fever clearance time of 21 and 24 hours respectively, but for lumefantrine alone, median fever clearance time was much longer, at 60 hours.⁷

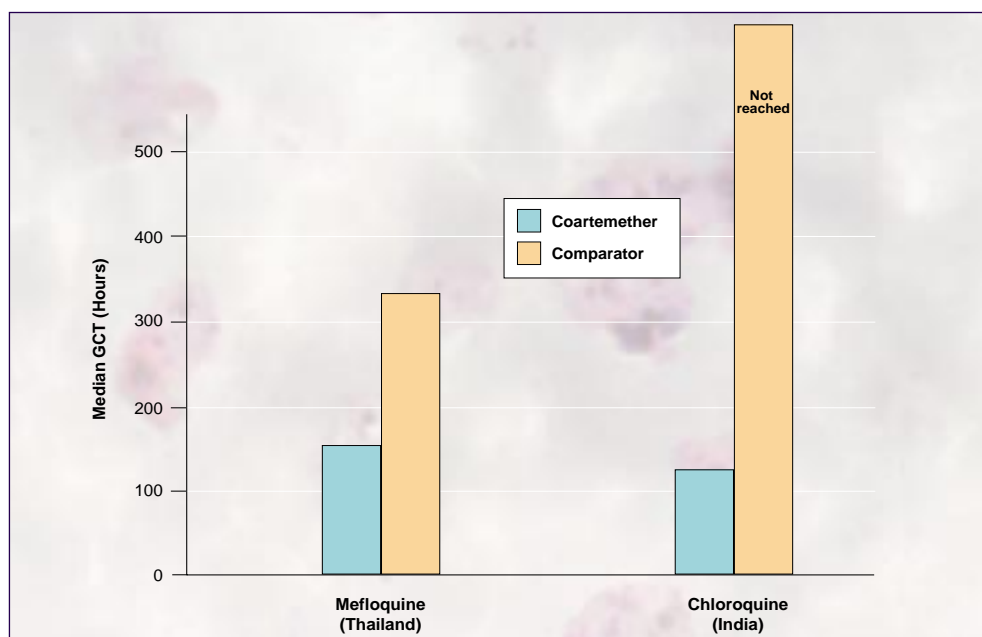
Coartemether produces fast and effective gametocyte clearance

Gametocytes are the stages in the malaria parasite's life cycle that give rise to the sexual reproduction phase in the intestine of anopheline mosquitoes. Since they link the vector and host infectious cycles, they are of key epidemiological importance. The greater the gametocyte carriage rate from mosquito to human, the more likely that malaria will be transmitted in a particular geographical area. Therefore, eradication of gametocytes will theoretically lead to extinction of malaria. Drugs that are effective against gametocytes are thus important in the fight against the disease.

Gametocyte clearance time is defined as the time from the start of treatment in patients who are gametocyte positive in blood smears at the beginning of a trial, until the first time blood films are negative, and remain so for at least 48 hours.

Unlike various other antimalarials, coartemether has good gametocidal properties (Fig. 5). Studies in a hospital setting revealed that gametocyte clearance was significantly faster ($p < 0.001$) with coartemether than with mefloquine in 136 evaluable patients in Thailand (median gametocyte clearance time was 152 hours versus 331 hours).³ Gametocyte clearance time was also faster with coartemether than with chloroquine in a comparative trial in 108 evaluable patients in India (median gametocyte clearance time 120 hours versus not reached).² (Note that in compliance with public health policy in India, primaquine treatment was given on day 8, when approximately 75% of patients on chloroquine had not cleared and had to be censored.)

Figure 5. Faster time to gametocyte clearance with coartemether than comparators
Time to gametocyte clearance was significantly faster with coartemether than mefloquine or chloroquine ($p < 0.001$)



Coartemether was also superior to sulphadoxine + pyrimethamine in The Gambia totally clearing gametocytes by Day 15, whereas 28.9% of children on sulphadoxine + pyrimethamine still had gametocytes at this time ($p < 0.001$).⁶

Coartemether produces excellent cure rates

The cure rate - the proportion of patients cured - measures the capability of a drug to destroy all malarial parasites acquired during a given infection.

Cure rate is usually defined as the **28-day cure rate** - i.e., the proportion of patients with clearance of parasites within 7 days, and without subsequent return of the original infection during the 28-day period following the first dose.

Note that in areas of high malarial transmission, new infections often occur during the 28-day period and may be confused with recrudescence (where parasites survive in red blood cells after a brief check - e.g., after failed or incomplete drug treatment - and cause the reappearance of the disease). In these areas, cure rates may be assessed at 7 and 14 days.

The results from a variety of studies demonstrate that coartemether can produce high 28-day cure rates provided an appropriate dose regimen is used. In particular, the 6-dose (24 tablet) regimen given over 60 hours should be used in known areas of multi-drug resistance such as Thailand and in non-immune travellers.

Since multi-drug resistance and the rate of reinfection are linked with geographic location, cure-rate results are presented according to area.

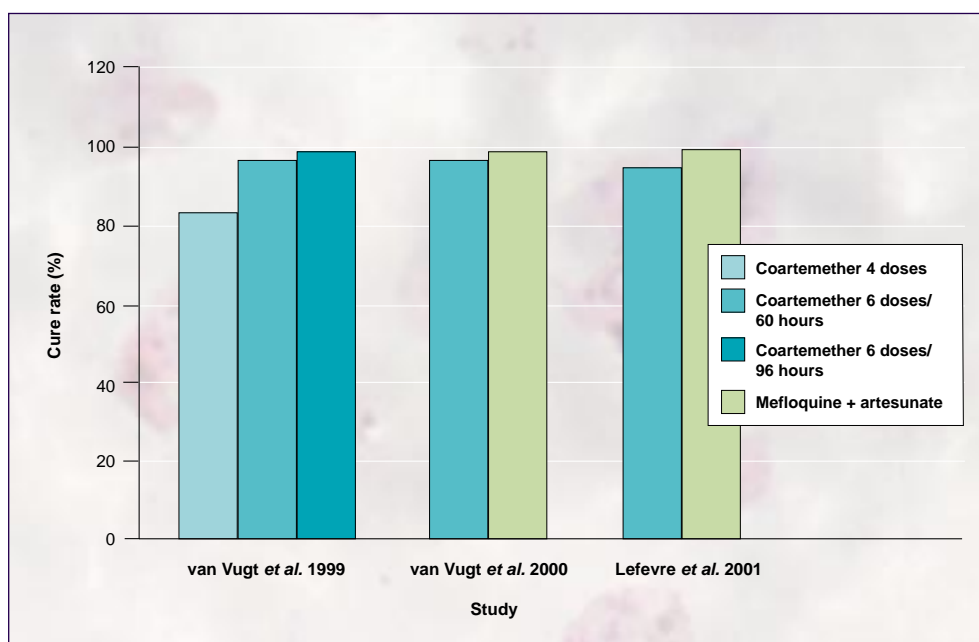
High 28-day cure rates

With coartemether there are very high 28-day cure rates.

Three studies in Thailand, a known multi-drug resistant area, show that the 6-dose regimen of coartemether achieved a 28-day cure rate of 96.9% (95% CI 91.9, 99.4)³, 97.7% (95% CI 93.5, 99.5)⁹ and 95.5% (90% CI 91.7, 97.9)⁴, see Fig.6.

Figure 6. 28-day cure rates in a multi-drug resistant area with 6-dose coartemether

For evaluable patients, the 6-dose coartemether and mefloquine + artesunate achieved near total 28-day cure rates



One of these (van Vugt *et al.* 1999) was a dose-optimisation study for coartemether in multi-drug resistant areas. The 4-dose regimen was compared with two 6-dose regimens (given over either 60 or 96 hours).

For evaluable patients, 28-day cure rates (with 95% CIs in brackets) were as follows (Table 1):

Table 1. 28-day cure rates in a multi-drug resistant area (Thailand)

In this multi-drug resistant area, the 6-dose (24-tablet) regimen of coartemether is necessary to achieve a good cure rate

Coartemether dosage regime:	4 doses/48 hrs	6 doses/60 hrs	6 doses/96 hrs
28-day cure rate:	83.3%	96.9%	99.1%
	(74.7, 90.0)	(91.1, 99.4)	(94.9, 99.1)
	n=102	n=96	n=106

The two other studies (van Vugt *et al.* 2000 and Lefèvre *et al.* 2001) shown in Figure 6 revealed that the 6-dose coartemether produced high 28-day cure rates similar in value to those of the standard, open combination of mefloquine + artesunate.

The results from these 3 studies also demonstrate that the 6-dose regimens of coartemether achieved near-total 28-day cure rates, which were as good as the 28-day cure rates seen with the 4-dose regimen in non-multi-drug resistant and non-hyperendemic areas (see below).

The trial conducted by van Vugt *et al.* 1999, (Figure 6 and Table 1) shows that the 4-dose regimen was however suboptimal in multi-drug resistant regions, with a 28-day cure rate of only 83.3%. Other trials in Thailand revealed similar suboptimal results with the 4-dose regimen.^{3, 10}

Based on the evidence available, the 6-dose (24-tablet) regimen of Riamet®/Coartem® given over three days is recommended for the treatment of:

- infections caught in an area of multi-drug resistance (e.g. South-East Asia)
- infections in non-immune patients (e.g. travellers) who may have a high parasite load.

“The excellent results obtained worldwide with the 3-day artemether-lumefantrine combination [coartemether] suggests that this is an effective treatment in endemic areas.”

N. White *et al.*, 1999²⁰

In non-multi-drug resistant and non-hyperendemic areas, the 4-dose regimen of coartemether produces a good 28-day cure rate. The 28-day cure rate in evaluable patients was 96.1% in China and 95.4% in India (Table 2). As might be expected, cure rates were clearly lower in Europe-based travellers and in Thailand.

Table 2. 28-day cure rate in various regions

The 4-dose regimen of coartemether is sufficient in China and India. Conversely, the 6-dose (24-tablet) regimen of Riamet®/Coartem® is required to achieve a good cure rate in Europe-based travellers, who typically have a high parasite load, and in regions with multi-drug resistance.

	China ¹¹ n=102	India ² n=65	Europe ¹ n=51	Thailand ¹⁰ n=248	Thailand ³ n=114
28-day cure rate	96.1%	95.4%	82.2%	85.2%	69.3%
	(90% CI; 91.8, 98.7)	(95% CI; 87.1, 99.0)	(95% CI; 67.9, 92.0)		(95% CI; 60.0, 77.6)

“In this study, CGP 56697 [coartemether] given as four doses of four tablets over a 48-hour period was well tolerated and highly efficacious in patients with acute, uncomplicated malaria.”

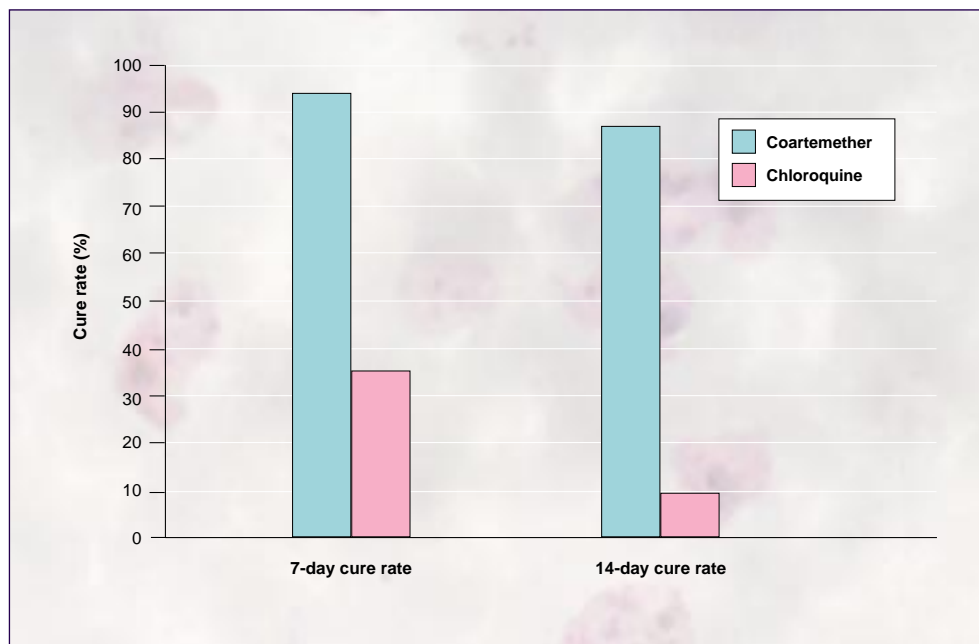
N. Kshirsagar et al., 2000²

Good cure rates in areas of high transmission

Cure rates are usually assessed at 28 days in areas of low disease transmission. In Africa and other regions, *falciparum* malaria is hyperendemic, and reinfection occurs rapidly as few protective measures are available to prevent transmission, and infected mosquitoes are ubiquitous. As 28-day cure rates tend to underestimate the true efficacy of antimalarial drugs, cure-rate assessment may be made at 7 and 14 days in these areas.

In Tanzania, in a trial involving 260 children aged 1-5 years, the 7-day cure rate with coartemether was 94% (25% CI 88.0, 97.5) and the 14-day cure rate was 86.4% (25% CI 78.5, 92.2).⁵ By contrast, the chloroquine 7-day cure rates was considerably lower - at 35.4% (25% CI 25.9, 45.8), whilst the 14-day cure rate was only 10.3% (25% CI 5.1, 18.1) due to both reinfection and resistance (Fig. 7).

Figure 7. 7-day and 14-day cure rates in Tanzania
coartemether gives a significantly higher cure rate ($p < 0.001$) than chloroquine



As part of this study, polymerase chain reaction techniques were used to differentiate new from recrudescent infections.¹² This analysis confirmed that there were substantial reinfections beyond day 7 in this region of high transmission.

Coartemether is effective in multi-drug resistance areas

Drug-resistant plasmodia strains in the tropics are a problem that mainly affects the endemic populations, but at the same time has an impact on travellers. Malaria is known to be resistant to chloroquine treatment in large parts of South America, Africa, the Near East and South-East Asia. In some of these regions - particularly in parts of Thailand, Burma, Malaysia, Oceania, and north-eastern South America - this resistance was not just to one, but to several antimalarials, including sulfadoxine + pyrimethamine, mefloquine, quinine, and halofantrine.

Patients living in such areas of multi-drug-resistance are particularly difficult to treat, as they will not respond to standard doses of current antimalarials, and may not even respond to high-dose regimens.

Coartemether in Thailand

As described previously in *High 28-day cure rates* (page XX), many patients treated with coartemether in comparative clinical trials were recruited in Thailand, a typical multi-drug resistant area.^{10, 3, 9, 4} In this country, with highly resistant parasite strains, the 4-dose regimen of coartemether was inadequate. However, the 6-dose (24-tablet) regimen of coartemether achieved a 28-day cure rate exceeding 95%. The 6-dose regimen is therefore recommended for multi-drug resistant areas such as Thailand.

Such high 28-day cure rates were comparable with those of mefloquine + artesunate, the standard treatment used in Thailand. For example, one study in 200 patients showed that coartemether and mefloquine + artesunate produced 28-day cure rates of 97.7% (95% CI: 93.5, 99.5) and 100% (95% CI: 92.5, 100) respectively.⁹ However, coartemether was better tolerated - 10% of patients in this trial treated with mefloquine + artesunate were unable to tolerate therapy due to vomiting, compared with 2.7% treated with coartemether.

Summary of coartemether efficacy

Coartemether speed of action:

- Parasite reduction and gametocyte reduction occur significantly faster with coartemether than with competitor drugs (except the free combination of mefloquine + artesunate, which also contains a fast-acting artemisinin derivative).
- Therefore, coartemether may be better suited than competitors to reduce the risk of progression of *falciparum* malaria to complicated stages and death. Moreover, its gametocidal efficacy may suggest a role for coartemether in malaria eradication programs.
- Fever clearance occurs fast with coartemether, so helping to reduce morbidity of the patients.

Coartemether cure rate:

- The 4-dose regimen of coartemether (16-tablets, 320 mg artemether and 1920 mg lumefantrine given over 48 hours) achieved very good cure rates in areas without multi-drug resistance, such as India and China.
- In multi-drug resistant areas such as Thailand, very good cure rates (28-day cure rate: 97-98%) were seen with the 6-dose regimen (24 tablets, 480 mg artemether and 2880 mg lumefantrine given over 60 hours), whereas the 4-dose regimen was suboptimal.
- The 6-dose regimen is required for Europe-based travellers. The 28-day cure rates achieved with the 4-dose regimen were sub-optimal due to both a reduced drug load per body weight (because of larger average stature than in regions with endemic malaria) and a high parasite burden (because of the lack of partial immunity).

Based on the clinical evidence available, coartemether seems to be at least as effective as current single or combined malaria treatments, and significantly more effective than chloroquine in India and Tanzania.

Coartemether safety and tolerability

Several current antimalarials have a relatively poor tolerability profile. Some may cause serious and even potentially fatal adverse events. For example, quinine may induce nausea, vomiting, headache, tinnitus, and cardiovascular adverse events. Sulfadoxine + pyrimethamine is associated with a risk of severe cutaneous adverse events.¹³ Mefloquine is contraindicated in patients with a history of epilepsy or psychiatric disorders, and causes neurotoxicity.¹⁴

It is essential that any new antimalarial treatment not only demonstrates high efficacy, but also has a safety profile shown to be at least equivalent if not superior to established drugs. Coartemether has the potential to meet these requirements.

Of particular importance is the distinction between coartemether and halofantrine in terms of the cardiac safety profile. Halofantrine has cardiac arrhythmogenic potential and should only be given under close supervision to patients known to have abnormal QT intervals.¹⁵ There is now strong evidence to show that coartemether has no such adverse effects on the heart (see below).

No evidence of QTc prolongation and cardiotoxicity with coartemether

Coartemether vs. halofantrine

Lumefantrine, one of the active components in coartemether, has chemical structural similarities to halofantrine. Halofantrine can cause defects in cardiac conduction, in particular, a marked QTc prolongation that can produce arrhythmias.

Recent studies comparing halofantrine with coartemether show a clear distinction between the two substances regarding QTc prolongation. A randomised, double-blind, crossover ECG study in 13 healthy male subjects revealed that halofantrine caused a significant, exposure-dependent increase in the QT interval.¹⁶ No such effect was seen with coartemether. Similarly, an *in vitro* study using the HERG K⁺ channel monitoring technique showed that lumefantrine prolonged repolarisation far less and produced a much higher cardiac safety index than halofantrine (48 vs. 0.07).

Mefloquine is reported to enhance the QTc-prolonging effect of halofantrine. In contrast, when coartemether is given following prophylaxis or treatment with mefloquine (a situation that may easily arise in a clinical setting) the QT interval appears not to be adversely affected. A double-blind, parallel group study of 42 healthy male subjects revealed no clinically relevant drug-related effects or significant differences in QTc between treatment with either coartemether or mefloquine when given alone, compared with treatment with mefloquine combined (sequentially) with coartemether.¹⁷

Clinical trial programme

Clear evidence for lack of cardiotoxicity with coartemether comes from the clinical trial programme. Comprehensive ECG monitoring revealed no marked QTc prolongation and no reports of adverse clinical cardiac events with coartemether.¹⁸ The Clinical Safety Review (for details, see next section) evaluated electrocardiographic results from 713 patients. QTc changes (classed as an absolute increase from baseline of 60 ms, or an increase greater than 30 ms with the value greater than 450 ms in males or 470 ms in females) are shown during coartemether versus comparative drug therapy in Table 3

Table 3. QTc changes during coartemether vs.comparative drug therapy

Study	Treatment	n	QTc increase >60 ms	QTc increase > 30 ms and QTc > 450/470
			n (%)	n (%)
Thailand (data on file)	Coartemether	27	–	1 (3.7%)
	quinine	27	2 (7.4%)	5 (18.5%)
India ²	Coartemether	87	5 (5.7%)	4 (4.6%)
	chloroquine	89	6 (6.7%)	9 (10.1%)
Europe ¹	Coartemether	48	4 (8.3%)	4 (8.3%)
	halofantrine	50	13 (26.0%)	13 (26.0%)
Thailand ³	Coartemether	126	1 (0.8%)	4 (3.2%)
	mefloquine	123	4 (3.3%)	8 (6.5%)
Thailand ⁸	Coartemether	149	7 (4.7%)	18 (12.1%)
	mefloquine + artesunate	49	3 (6.1%)	6 (12.2%)

The frequency of QTc prolongations with coartemether were similar or lower than with chloroquine, mefloquine, or mefloquine + artesunate, and much lower than quinine and halofantrine. QTc prolongations were not correlated with plasma concentrations of coartemether, and there were no reports of adverse clinical cardiac events.

“Coartemether] proved to be as effective as the current standard therapy of MAS [mefloquine + artesunate], with no relevant effects on electrocardiographic parameters.”

G. Lefèvre et al., 2001⁴

The frequency of QTc prolongations was broadly similar for children and adults, and for the 4- and 6-dose regimens (Table 4).

Table 4. QTc changes during coartemether therapy (by age and dose)

	n	QTc increase >60 ms n (%)	QTc increase > 30 ms and QTc > 450/470 n (%)
Children (< 12 years) treated with coartemether	112	7 (6.3%)	10 (8.9%)
Adults >12 years treated with coartemether	601	26 (4.3%)	43 (7.2%)
Patients treated with coartemether (4 doses)	498	21 (4.2%)	29 (5.8%)
Patients treated with coartemether (6 doses)	215	12 (5.6%)	24 (11.2%)
Total	713	33 (4.6%)	53 (7.4%)

Tolerability with coartemether in clinical trials

A variety of clinical trials conducted to date revealed that coartemether was very well tolerated. Its favourable safety profile means it can be used for the treatment of acute, uncomplicated *falciparum* malaria for patients living in endemic countries. In addition, it provides a safe treatment option for travellers who visit these areas. An integrated overview of the tolerability and safety (clinical, laboratory and electrocardiographic) of coartemether has been carried out.¹⁸ Details of this Clinical Safety Review are given below.

Clinical Safety Review for coartemether - in summary

A detailed analysis of an extensive clinical trial database in the treatment of acute uncomplicated *falciparum* malaria, comprising 1869 patients (including 611 patients of age 12 years or less - see Table 5 for more details), formed the basis of this review.

The results of the analysis are as follows:

- The most commonly reported adverse effects following coartemether therapy were gastrointestinal (abdominal pain, anorexia, nausea, vomiting, diarrhoea) and of the central nervous system (headache, dizziness). Pruritus and rash were reported by less than 2% of patients.
- Over 90% of the reported adverse events, which could also have been attributed to malaria, were rated mild to moderate in intensity.
- Compared to coartemether, there were significantly higher incidences of vomiting and pruritus with chloroquine, dizziness, nausea and vomiting with mefloquine + artesunate, vomiting and dizziness with quinine and somnolence with pyrimethamine + sulfadoxine.
- There were no serious or persistent neurological side effects related to coartemether administration.

- Coartemether did not lead to any clinically relevant alterations of the laboratory parameters.
- Serial electrocardiographic data were available for 713 patients. The frequency of QT interval prolongation was similar to or lower than that observed with chloroquine, mefloquine, or artesunate + mefloquine; these changes occurred considerably less frequently than with quinine or halofantrine. All patients with QT prolongation remained asymptomatic and no adverse clinical cardiac events were reported.

Table 3. Demographic characteristics of patients treated with coartemether in the Clinical Safety Review

Country	Age range (years)	n	Dose regimen	Median age (years)	Median weight (kg)	Median artemether dose (mg/kg)	Median lumefantrine dose (mg/kg)
The Gambia, Tanzania	<5	368	4-dose	3	12	6.7	40
Thailand	5-12	187	4-dose	9	21	5.9	35.6
China, Thailand, India, Netherlands, France	>12	925	4-dose	25	50	6.3	37.6
Thailand	<12	56	6-dose	9	22	11.4	68.6
Thailand	>12	333	6-dose	23	50	9.6	57.6

“ ... [coartemether’s] excellent tolerability, especially with regard to vomiting, safety profile, and rapid action in clearing parasites from the blood indicate a very promising new combination treatment for malaria.”

S. Looreesuwan et al., 1999³

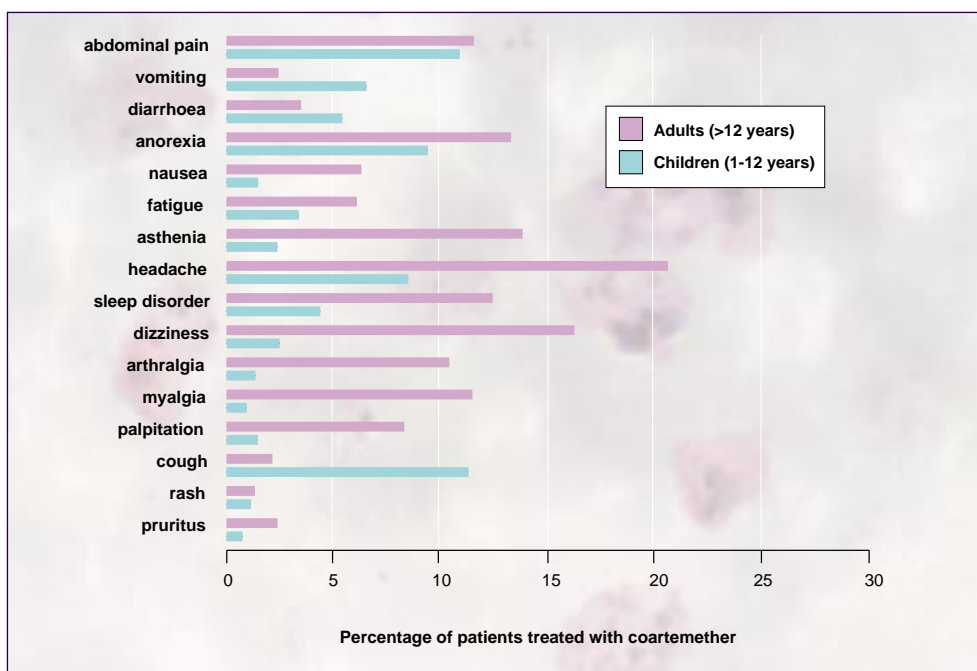
Adverse events

Adverse events documented in the Clinical Safety Review are shown in Fig. 8 below.

Note that evaluating possible drug-related side effects against a background of malaria can be difficult. There is considerable overlap between the treatment emergent symptoms and signs, and those of malaria and concomitant illnesses - such as viral infections and parasitic infestations. Where possible, medical assessment during clinical trials attempted to identify and exclude these specific adverse events.

A standardised method of collecting adverse event information was adopted across the various trials of the Clinical Safety Review. Adverse events that appeared as new or worsened from baseline were classes as treatment emergent symptoms and signs, provided they occurred before the recurrence of parasitaemia/acute malaria.

Figure 8.
Treatment emergent symptoms and signs (incidence 1% or greater) after administration of coartemether



Serious adverse events

The Clinical Safety Review documented 20 reported serious adverse events out of a total of 1869 patients. Nineteen of these adverse events could be explained on the basis of the malarial episode, or represented concurrent illnesses (including severe anaemia in children, unsatisfactory response, pneumonia hepatitis etc.)

Coartemether may have contributed to only one of the reported serious adverse events - the development of haemolytic anaemia in a 35-year-old patient after the drug had been discontinued for 13 days.

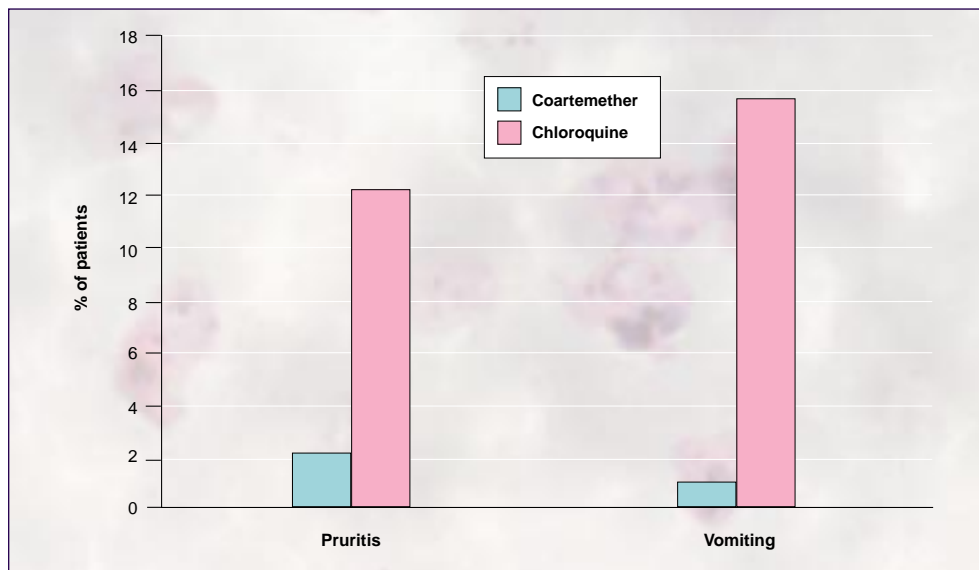
Tolerability data from comparative clinical trials

Nine double-blind/open label comparative trials documented in the Clinical Safety Review, showed that coartemether was equally or better tolerated than chloroquine, mefloquine/mefloquine + artesunate, quinine, sulfadoxine + pyrimethamine and halofantrine.¹⁶ Results from the Clinical Safety Review are as follows:

Compared with chloroquine, coartemether caused less pruritis and less vomiting (Fig. 9).

Figure 9. Pruritis and vomiting with coartemether or chloroquine

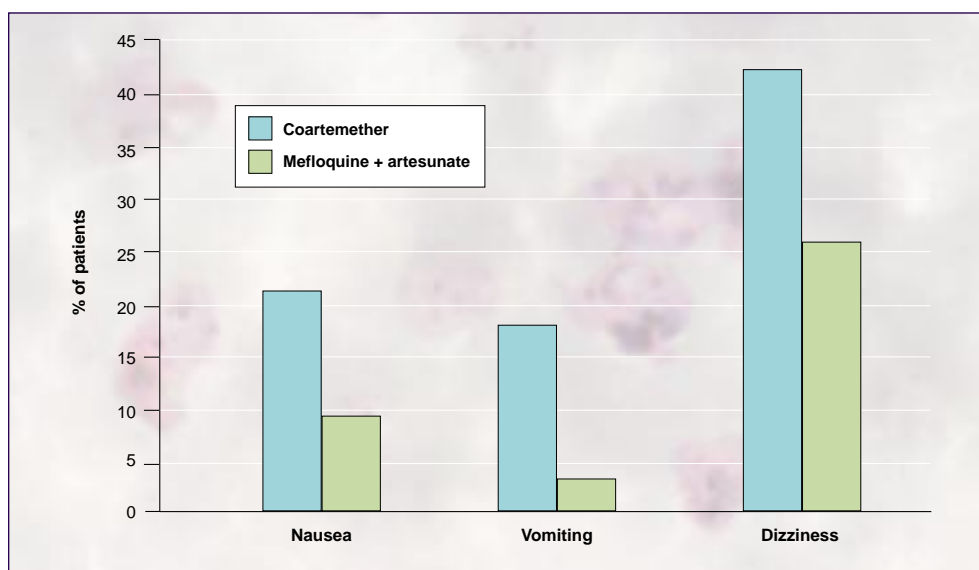
The relative risk of developing pruritis with chloroquine versus coartemether was 5.4 (95% CI 1.2, 23.8; $p=0.018$) and that of vomiting 13.8 (1.9, 103.1; $p<0.001$)



Compared with mefloquine + artesunate, coartemether caused less nausea, vomiting and dizziness (Fig. 10).

Figure 10. Nausea, vomiting and dizziness with coartemether or mefloquine + artesunate

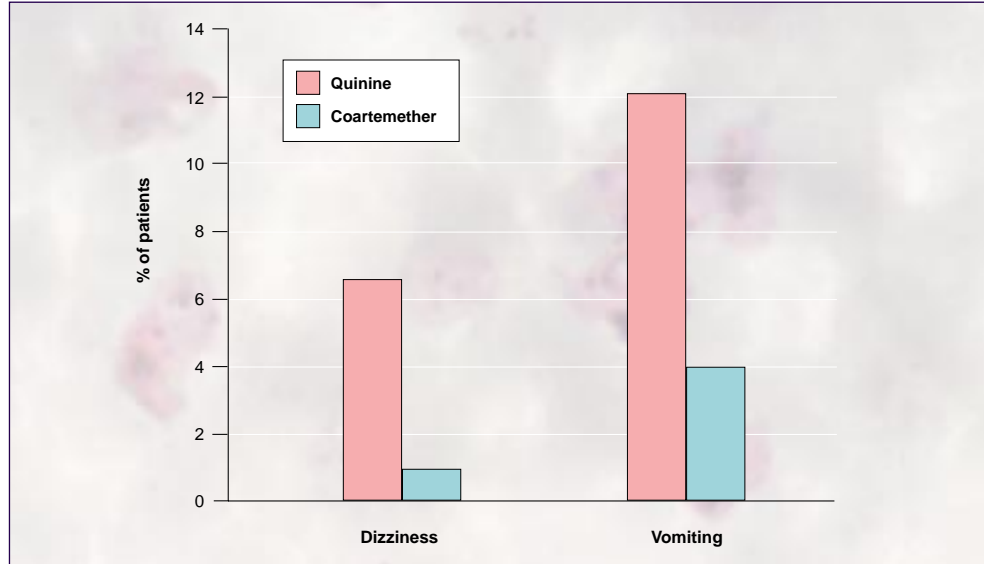
The relative risk of developing nausea with mefloquine + artesunate versus coartemether was 2.3 (95% CI 1.6, 3.2; $p<0.001$), that of vomiting was 5.5 (95% CI 3.2, 9.4; $p<0.001$) and that of dizziness was 1.6 (25% CI 1.3, 2.0; $p<0.001$)



Compared with quinine, coartemether caused less dizziness vomiting (Fig. 11).

Figure 11. Dizziness and vomiting with coartemether or quinine

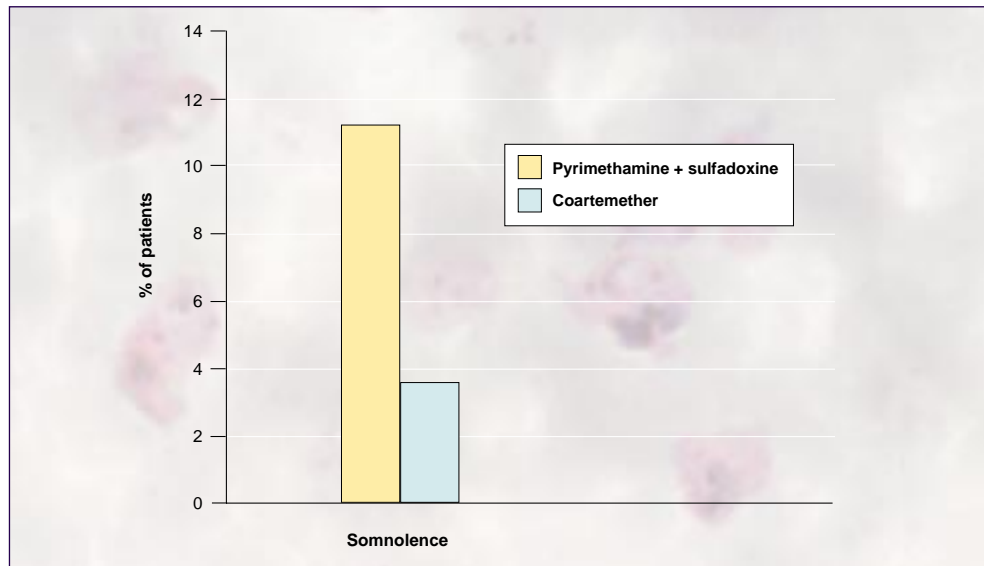
The relative risk of developing dizziness with quinine versus coartemether was 7.2 (95% CI 0.9, 57.5; $p=0.034$), and that of vomiting was 3.3 (95% CI 1.1, 9.9; $p=0.023$)



Compared with pyrimethamine + sulfadoxine, coartemether causes less somnolence in small children (Fig. 12).

Figure 12. Somnolence in small children with coartemether or pyrimethamine + sulfadoxine

The relative risk of developing dizziness with pyrimethamine + sulfadoxine versus coartemether was 3.2 (95% CI 1.2, 8.6; $p=0.013$)



Compared with halofantrine, coartemether caused:

- less diarrhoea (5.9% versus 11.5%)
- less vomiting (2% versus 13.5%)
- more headache (13.7% versus 7.7%).

However, none of these differences reached statistical significance.

No evidence of serious neurotoxicity

The Clinical Safety Review reveals no evidence of serious or persistent neurotoxicity with coartemether. The commonest neurological events associated with coartemether were headache, dizziness, and sleep disturbance. However, a few patients presented with symptoms such as abnormal gait (4 patients), nystagmus (1 adult), ataxia (3 adults), decreased hearing (4 adults), and paraesthesia (15 adults).

Dose-response relationship

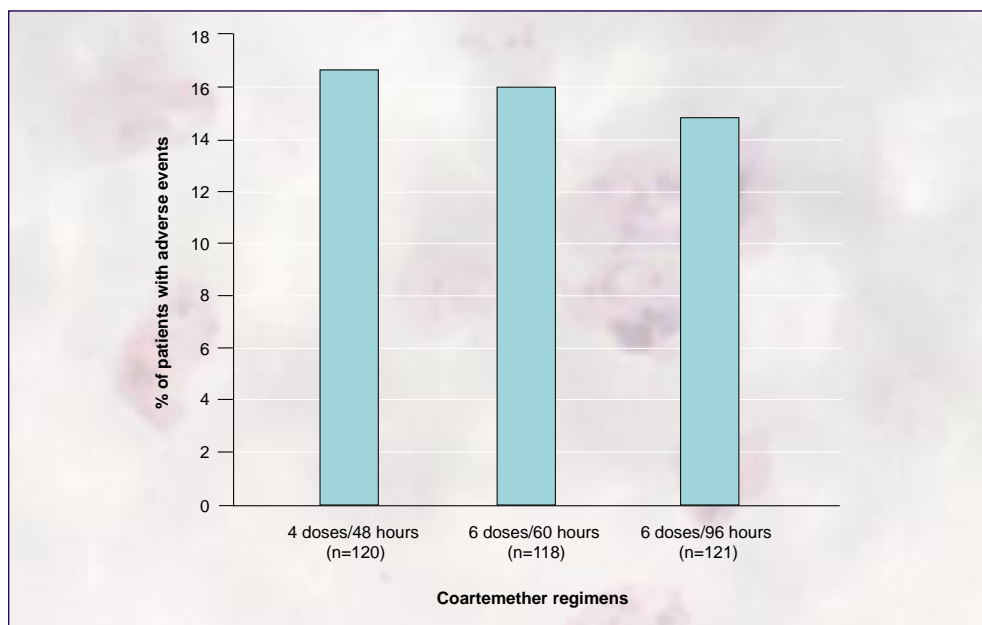
The data available do not allow a firm conclusion to be drawn about the effect of increasing the dose of coartemether on the appearance of adverse events. According to the Clinical Safety Review however, the treatment-emergent symptoms and signs profile was similar for both the 4-dose and 6-dose regimens, although headache and dizziness were observed more frequently with the 6-dose regimen.

A dose-finding study in Thailand showed that percentages of patients presenting with adverse experiences were similar in each treatment group (Fig. 13).⁸

“ ... even with this high-dose regimen, artemether-lumefantrine [coartemether] was very well tolerated and compliance was very good.”

G. Lefèvre et al., 2001⁴

Figure 13. Percentage of patients presenting with adverse events in the 4-dose and 6-dose regimens of coartemether



Laboratory parameters

The Clinical Safety Review revealed the following:

- Anaemia and thrombocytopenia were commonly present at baseline. These parameters became normal or improved considerably with disease resolution following administration of coartemether. Anaemia had a tendency to deteriorate in some patients at Day 4, followed by improvement.
- Reticulocytes when measured showed a tendency to increase during the first week post- coartemether treatment.
- Abnormal baseline liver function tests - hypokalaemia, hyponatraemia, and hypoglycaemia- all known features of acute malaria, resolved after control of the malaria episode.
- Renal function was generally normal at presentation and was not significantly changed with coartemether therapy.

A clinical study was specifically designed to identify any interactions of coartemether with mefloquine when taken concomitantly.¹⁹ There is a possibility of interaction between these two antimalarials because coartemether is a combination of artemether and lumefantrine (both of which are predominantly metabolized through CYP3A4), whilst mefloquine is a substrate (and possible inhibitor) of CYP3A4 (see also *No evidence of QTc prolongation and cardiotoxicity*).

Results from this trial in 42 healthy subjects showed however, that co-administration of coartemether with mefloquine produced no clinically relevant risks of medical hazard due to pharmacokinetic drug-drug interaction. Moreover, the trial suggested that such risks were also unlikely to occur when coartemether was co-administered with other CYP3A4 substrates with similar affinity to that of mefloquine.

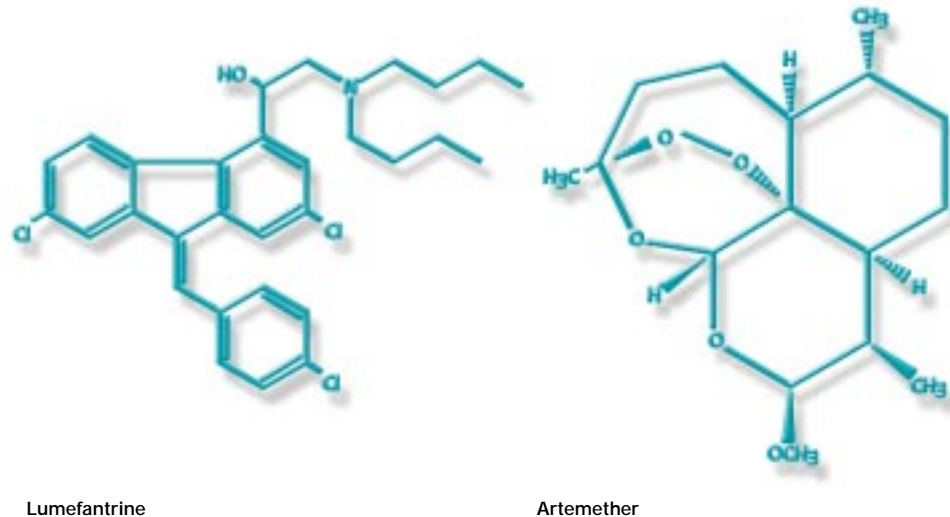
Further specific interaction studies have not been performed with coartemether. Although most patients received antipyretic medications, antibiotics, and fluid and electrolyte replacement, no safety issue attributable to interactions were reported during the clinical study programme. Indeed, the risk for relevant interactions is probably relatively low due to the wide therapeutic index and very short-time administration of coartemether.

Summary of pharmacology of coartemether

Coartemether is a 1:6 fixed-combination drug consisting of two components (Fig. 14), with tablets containing artemether (20 mg) and lumefantrine (120 mg), both of which act as blood schizontocides.¹⁹

Figure 14. Structures of lumefantrine and artemether

Artemether is fast acting with a short half-life. Lumefantrine acts more slowly with a longer half-life.



Mode of action and pharmacodynamics related to the therapeutic effect

The precise antimalarial action of lumefantrine and artemether is unknown, although both appear to act on the parasite's organelles, where they are thought to interfere with the conversion of haem to nontoxic compounds.²⁰

- Artemether contains an endoperoxide bridge, which interacts with haem iron to generate reactive metabolites.
- Lumefantrine is thought to interfere with haem polymerisation, a critical detoxifying pathway for the malaria parasite.

Artemether rapidly reduces parasite biomass and quickly resolves clinical symptoms, whilst the long-acting activity of lumefantrine prevents recrudescence.²¹ This dual effect also appears to reduce the selective pressure on the parasite to develop resistance.

Pharmacokinetics of coartemether

Absorption and bioavailability

Absorption

Under fasted conditions, artemether was rapidly absorbed, reaching peak plasma concentrations about 2 hours after dosing, whilst lumefantrine - a highly lipophilic molecule - was absorbed after a lag time of up to 2 hours, with peak plasma concentrations at 6 to 8 hours post-dose.^{21, 22, 23}

Under fasted conditions, the oral bioavailability of both artemether and lumefantrine was variable and low. However, a high-fat meal increased the bioavailability of lumefantrine 16-fold and that of artemether more than 2-fold.²⁴

In a clinical setting, food also increased the absorption of lumefantrine in patients.²³ During acute malaria, there is marked intra- and inter-patient variability with regard to lumefantrine absorption, probably because of differences in food intake. Acutely ill patients are reluctant to eat and tend to avoid high fat foods. Therefore, to improve bioavailability, patients should be encouraged to take coartemether with a normal diet as soon as food can be tolerated.

Distribution

Both artemether and lumefantrine are highly bound to human serum proteins *in vitro* (95.4% and 99.9%, respectively) - the higher fraction of artemether (33%) being distributed onto α_1 -acid glycoprotein and the main part of lumefantrine (77.1%) being distributed onto high-density lipoproteins.²⁵

Metabolism

Artemether is rapidly and extensively metabolised by human liver microsomes (mostly through the enzyme CYP3A4/5) *in vitro* and *in vivo*, with a substantial first pass metabolism.²⁶ The main metabolite is dihydroartemisinin, which is active.

Lumefantrine is also metabolised predominantly by the enzyme CYP3A4 in human liver microsomes. At therapeutic plasma concentrations, lumefantrine significantly inhibits the enzyme CYP2D6 *in vitro*.²⁶ Therefore, co-administration of compounds with low therapeutic indexes and significant metabolism by CYP2D6 (e.g. neuroleptics and tricyclic antidepressants) might cause clinically relevant drug-drug interactions.

Elimination and excretion

Artemether was rapidly cleared from plasma with a $t_{1/2}$ of approximately 2-3 hours. Conversely, lumefantrine is cleared more slowly, showing a $t_{1/2}$ of 2-3 days in healthy volunteers, and 5-10 days in patients with *falciparum* malaria.¹⁹

No urinary excretion data are available for humans. Animal studies showed no evidence of artemether in faeces or urine of rats and dogs. Various unidentified metabolites were detectable in both faeces and urine. Lumefantrine was eliminated through the liver and bile and primarily excreted in the faeces in rats and dogs, with relatively low qualitative and quantitative recovery of metabolites.²⁰

Toxicology of coartemether

In accordance with international guidelines and GLP standards, Novartis have evaluated the safety of coartemether and its two components in a range of toxicity studies using more than one route of administration, test system and laboratory animal species.

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Novartis Pharma AG
CH-4002 Basel, Switzerland

www.malariaandhealth.com

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