en at intervals at least one month apart. For maximum benefit 2 to 3 doses of IPT should be given. For further information on the use of pyrimethamine in pregnancy, see under Precautions for Pyrimethamine, p.611. In areas of low or unstable malaria transmission, where pregnant women have low immunity to malaria, use of insecticide-treated nets and prompt case management of pregnant women with fever and malarial illness is recommended. In addition, all pregnant women should take iron and folate supplements.

Prophylaxis during breast feeding. It is generally accepted for most antimalarials that the amounts distributed into breast milk and consumed by nursing infants are too small to be harmful, although they are also too small to provide protection.[2,15] However, doxycycline is contra-indicated during breast feeding, and advice regarding atovaquone-proguanil varies: in the UK it is contra-indicated, though it may be used if no suitable alternative is available,[16] but in the USA it may be given once the infant weighs over 5 kg.[15] Although there has been concern that infants given prophylaxis with mefloquine who also ingested the drug from breast milk might be receiving excessive quantities,[15] mefloquine is probably safe to use in breast-feeding mothers.[16]

Prophylaxis in children. Chloroquine and proguanil may be given in scaled down doses to children of all ages but the choice of alternative drugs may be restricted, especially in very young children, and consideration should be given to whether their travel to malarious areas is absolutely necessary (see also above). Mefloquine is an option for use in children and infants weighing 5 kg or more if travelling to areas with chloroquine-resistant *P. falciparum* and atovaquone-proguanil (*Malarone*) may be given to children weighing 11 kg or more; the CDC considers that it may be used in infants weighing at least 5 kg. Doxycycline is contra-indicated in children less than 8 years of age, and higher age limits may apply in some countries such as the UK.[2,15,16]

Prophylaxis in epilepsy. In subjects with a history of epilepsy, the UK guidelines[16] advise that both chloroquine and mefloquine are unsuitable for prophylaxis. In areas without chloroquine resistance, proguanil alone is recommended. In areas with a high risk of chloroquine resistance, atovaquone-proguanil (*Malarone*) or doxycycline may be considered, but the metabolism of doxycycline may be influenced by antiepileptics. Dapsone with pyrimethamine (*Maloprim*) was considered to have been of particular value in travellers with epilepsy, especially children, but is no longer available in the UK.

Prophylaxis in HIV-infected travellers. HIV-infected travellers may take chloroquine routinely for antimalarial prophylaxis but its potential immunosuppressive effects should be recognised; proguanil, mefloquine, or doxycycline can also be used. Although patients with AIDS may be at increased risk of adverse effects to sulfonamides, a combination such as pyrimethamine-sulfadoxine (*Fansidar*) can be used for standby treatment if an alternative is not available.

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2. WHO. *International travel and health.* 2008 ed. Available at: http://www.who.int/ith/en (accessed 04/03/08)
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9. Lalloo DG, *et al.*. HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; **54:** 111–21.
10. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (issued 28th June 2004, updated 24th May 2007). Available at: http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf (accessed 28/09/07)
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12. Orton L, Garner P. Drugs for treating uncomplicated malaria in pregnant women. Available in The Cochrane Database of Systemic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 19/05/06).
13. Manenti F, *et al.* Treatment of hyperreactive malarial splenomegaly syndrome. *Lancet* 1994; **343:** 1441–2.
14. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 18/08/05).
15. CDC. Malaria. In: *The Yellow Book*: *CDC Health Information for International Travel; 2008.* Available at: http://wwwn.cdc.gov/travel/yellowBookCh4-Malaria.aspx (accessed 28/09/07)
16. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Amodiaquine *(BAN, rINN)*

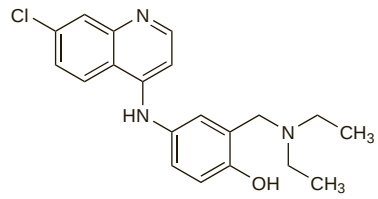
Amodiaquina; Amodiaquinum. 4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl)phenol.

Амодиахин

$C_{20}H_{22}ClN_3O$ = 355.9.

CAS — 86-42-0.

ATC — P01BA06.



Pharmacopoeias. In *Int.* and *US.*

USP 31 (Amodiaquine). Very pale yellow to light tan-yellow, odourless, powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in 1.0N hydrochloric acid. Store in airtight containers.

Amodiaquine Hydrochloride *(BANM, rINNM)*

Amodiaquine, Chlorhydrate d'; Amodiaquini Hydrochloridum; Hidrocloruro de amodiaquina. 4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl)phenol dihydrochloride dihydrate.

Амодиахина Гидрохлорид

$C_{20}H_{22}ClN_3O,2HCl,2H_2O$ = 464.8.

CAS — 69-44-3 (anhydrous amodiaquine hydrochloride); 6398-98-7 (amodiaquine hydrochloride dihydrate).

ATC — P01BA06.

Pharmacopoeias. In *Fr.*, *Int.*, and *US*.

USP 31 (Amodiaquine Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 78 of alcohol; very slightly soluble in chloroform, in ether, and in benzene. Store in airtight containers.

Sorption. For reference to loss of amodiaquine hydrochloride from solutions during membrane filtration, see Chloroquine, p.599.

Adverse Effects and Precautions

As for Chloroquine, p.599, although amodiaquine was associated with hepatitis and a much higher incidence of agranulocytosis when it was used for the prophylaxis of malaria.

Incidence of adverse effects. Early isolated reports of severe neutropenia with amodiaquine usually concerned use in anti-inflammatory doses for rheumatoid arthritis, but there was a cluster of cases in 1986 associated with its use in malaria prophylaxis.[1] In all, 23 cases of agranulocytosis, 7 of which were fatal, were reported in the UK, USA, and Switzerland during a 12-month period ending March 1986. Nearly all of these patients had used the drug at a dosage of 400 mg weekly and the periods of exposure ranged from 3 to 24 weeks.[1] Some of these patients also had evidence of liver damage[1] and there have been other reports of hepatotoxicity associated with the prophylactic use of amodiaquine.[2] Examination of data submitted to the UK CSM[3] suggested that the frequency of adverse reactions to amodiaquine was about 1 in 1700 for serious reactions, 1 in 2200 for blood disorders, 1 in 15 650 for serious hepatic disorders, and 1 in 15 650 for fatal reactions. In contrast the frequency of agranulocytosis in users in France[4] has been estimated to be 1 in 25 000. Worldwide[4] the risk of severe reactions appears to be between 1 in 1000 and 1 in 5000. The manufacturers reportedly had 42 cases of serious adverse effects during amodiaquine prophylaxis, between 1985 and 1991; there were 28 cases of agranulocytosis (9 deaths) and 14 of hepatitis (3 deaths).[5] Whether there was significantly less risk when amodiaquine was given for treatment of malaria rather than prophylaxis was not certain.[6]

It has been suggested that an immunological reaction to amodiaquine quinone imine, which can be produced by autoxidation among other processes, may partially account for amodiaquine's greater tendency to induce agranulocytosis compared with chloroquine.[7,8]

The acute toxicity of amodiaquine appears to differ from that of chloroquine in that there have been no reports of cardiovascular symptoms after overdosage with amodiaquine[9] but intoxication with amodiaquine is also far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions, and involuntary movements.[9]

1. Anonymous. Amodiaquine and agranulocytosis. *WHO Drug Inf* 1987; **1:** 5–6.
2. Larrey D, *et al.* Amodiaquine-induced hepatitis. *Ann Intern Med* 1986; **104:** 801–3.
3. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–5.
4. Anonymous. Development of recommendations for the protection of short-stay travellers to malaria endemic areas: memorandum from two WHO meetings. *Bull WHO* 1988; **66:** 177–96.
5. Olliaro P, *et al.* Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet* 1996; **348:** 1196–1201.
6. White NJ. Can amodiaquine be resurrected? *Lancet* 1996; **348:** 1184–5.
7. Winstanley PA, *et al.* The toxicity of amodiaquine and its principal metabolites towards mononuclear leucocytes and granulocyte/monocyte colony forming units. *Br J Clin Pharmacol* 1990; **29:** 479–85.
8. Park BK, Kitteringham NR. Drug–protein conjugation and its immunological consequences. *Drug Metab Rev* 1990; **22:** 87–144.
9. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.

Pregnancy. A study[1] to assess the safety and efficacy of amodiaquine or amodiaquine plus sulfadoxine-pyrimethamine in 900 pregnant women (in their second or third trimester) reported that PCR-corrected parasitological failure by day 28 was 14%, 11%, 3%, and 0% in those given chloroquine, sulfadoxine-pyrimethamine, amodiaquine alone, and amodiaquine plus sulfadoxine-pyrimethamine, respectively. No serious adverse effects were reported.

WHO considers that amodiaquine may be an alternative to chloroquine for treatment of malaria due to *P. vivax* during pregnancy (see Treatment of Malaria during Pregnancy, under Malaria, p.594).

1. Tagbor H, *et al.* Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet* 2006; **368:** 1349–56.

Pharmacokinetics

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract. Amodiaquine is rapidly converted in the liver to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more. Amodiaquine and desethylamodiaquine have been detected in the urine several months after use.

◊ References.

1. Winstanley P, *et al.* The disposition of amodiaquine in man after oral administration. *Br J Clin Pharmacol* 1987; **23:** 1–7.
2. White NJ, *et al.* Pharmacokinetics of intravenous amodiaquine. *Br J Clin Pharmacol* 1987; **23:** 127–35.
3. Winstanley PA, *et al.* The disposition of amodiaquine in Zambians and Nigerians with malaria. *Br J Clin Pharmacol* 1990; **29:** 695–701.
4. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.

Uses and Administration

Amodiaquine is a 4-aminoquinoline antimalarial with an action similar to that of chloroquine (p.602). It is as effective as chloroquine against chloroquine-sensitive strains of *Plasmodium falciparum* and is also effective against some chloroquine-resistant strains, although resistance to amodiaquine has developed and there may be partial cross-resistance between amodiaquine and chloroquine. To prevent the emergence and spread of drug resistant parasites WHO recommends that amodiaquine be given with an artemisinin derivative, such as artesunate, for the treatment of falciparum malaria. Amodiaquine is not recommended for the prophylaxis of malaria because of resistance and the risk of major toxicity.

Amodiaquine is given orally as the hydrochloride, but doses are expressed in terms of amodiaquine base; amodiaquine hydrochloride 260 mg is equivalent to about 200 mg of amodiaquine base. For the treatment of falciparum malaria and uncomplicated chloroquine-resistant vivax malaria a total dose of 30 mg/kg is given over 3 days (10 mg/kg daily for 3 days). Treatment of vivax malaria must be followed by radical cure with primaquine.

A fixed-dose combination product of amodiaquine and artesunate (ASAQ) has been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance, and is available in some countries.

◊ References.

1. Olliaro P, Mussano P. Amodiaquine for treating malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 17/05/05).
2. McIntosh HM, Jones KL. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/07/06).
3. Bukirwa H, Critchley J. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).

Preparations

USP 31: Amodiaquine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Fr.: Flavoquine; ***India:*** Basoquin; Camoquin; Ipcaquin†.

Multi-ingredient: ***Belg.:*** Amonate; ***China:*** Artemodi; ***India:*** Larimal†.

Artemisinin Derivatives

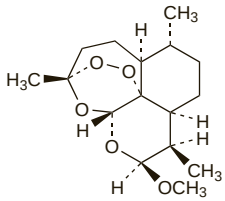
Artemisinina, derivados.

Artemether *(BAN, rINN)*

Artemeetteri; Artemeter; Artemetero; Artéméther; Artemetherum; Dihydroartemisinin Methyl Ether; Dihydroqinghaosu Methyl Ether; *o*-Methyldihydroartemisinin; SM-224. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.

Артеметер

$C_{16}H_{26}O_5$ = 298.4.
CAS — 71963-77-4.
ATC — P01BE02.



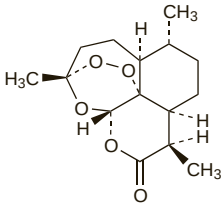
Pharmacopoeias. In *Chin.* and *Int.*

Artemisinin *(rINN)*

Arteannuin; Artemisinina; Artémisinine; Artemisinine; Artemisininum; Huanghuahaosu; Qinghaosu. (3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one.

Артемизинин

$C_{15}H_{22}O_5$ = 282.3.
CAS — 63968-64-9.
ATC — P01BE01.



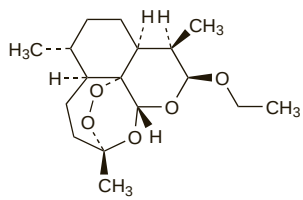
Pharmacopoeias. In *Chin., Int.,* and *Viet.*

Artemotil *(rINN)*

Artémotil; Artemotilo; Artemotilum; Beta-arteether; Dihydroartemisinin Ethyl Ether; Dihydroqinghaosu Ethyl Ether; SM-227. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-ethoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.

Артемотил

$C_{17}H_{28}O_5$ = 312.4.
CAS — 75887-54-6.
ATC — P01BE04.



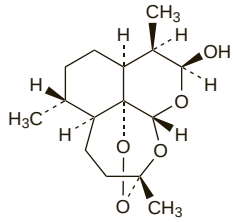
Pharmacopoeias. In *Int.*

Artenimol *(USAN, rINN)*

Arténimol; Artenimolum; Dihydroartemisinin; Dihydroqinghaosu. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol.

Артенимол

$C_{15}H_{24}O_5$ = 284.3.
CAS — 81496-81-3.
ATC — P01BE05.



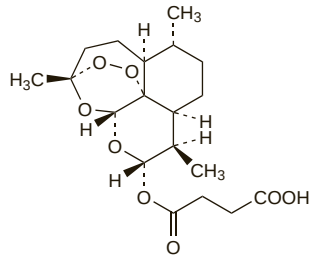
Pharmacopoeias. In *Chin.* and *Int.*

Artesunate *(BAN, USAN, rINN)*

Artésunate; Artesunato; Artesunatum. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate.

Артезунат

$C_{19}H_{28}O_8$ = 384.4.
CAS — 83507-69-1; 88495-63-0; 182824-33-5.
ATC — P01BE03.



Pharmacopoeias. In *Int.* and *Viet.*

Sodium Artesunate *(BANM, rINNM)*

Artésunate de Sodium; Artesunato sódico; Dihydroartemisinin Hemisuccinate Sodium; Dihydroqinghaosu Hemisuccinate Sodium; Natrii Artesunatum; SM-804. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate sodium.

Натрий Артезунат

$C_{19}H_{27}O_8Na$ = 406.4.

Adverse Effects and Precautions

Artemisinin and its derivatives appear to be generally well tolerated, although there have been reports of mild gastrointestinal disturbance (including nausea, vomiting, diarrhoea, and abdominal pain), dizziness, headache, tinnitus, neutropenia, elevated liver enzyme values, and ECG abnormalities including prolongation of the QT interval.

Evidence of severe neurotoxicity has been seen in *animals* given high doses.

◊ General references to adverse effects associated with artemisinin derivatives.

1. Price R, *et al.* Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg* 1999; **60:** 547–55.

Effects on the blood. For a report of severe haemolytic anaemia occurring in patient after taking artemether-lumefantrine, see p.605.

Effects on the heart. Bradycardia was reported in 10 of 34 patients who received artemether orally for 4 days.[1]

1. Karbwang J, *et al.* Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; **340:** 1245–8.

Effects on the nervous system. Neurotoxicity has been reported in *animals* given artemotil or artemether.[1] An *in-vitro* study[2] has shown that artenimol (dihydroartemisinin), the metabolite common to all artemisinin derivatives currently used, is neurotoxic. There has been a report[3] of acute cerebellar dysfunction manifesting as ataxia and slurred speech in a patient who took a 5-day course of artesunate by mouth.

1. Brewer TG, *et al.* Neurotoxicity in animals due to arteether and artemether. *Trans R Soc Trop Med Hyg* 1994; **88** (suppl 1): 33–6.
2. Wesche DL, *et al.* Neurotoxicity of artemisinin analogs in vitro. *Antimicrob Agents Chemother* 1994; **38:** 1813–19.
3. Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. *N Engl J Med* 1997; **336:** 1328.

Pregnancy. Artesunate or artemether was used to treat multidrug-resistant falciparum malaria in 83 pregnant women in Thailand; of 73 pregnancies resulting in live births none showed evidence of any congenital abnormality.[1] Sixteen of the women were given artesunate during the first trimester; of these, 12 had normal deliveries, 1 was lost to study, and 3 had spontaneous abortions.

No undue adverse effects on the neonates occurred in a study[2] involving 45 women treated for multidrug-resistant malaria during their second or third trimester of pregnancy with either artemether or artemether plus mefloquine. Intramuscular artemether was also used to treat chloroquine/quinine-resistant falciparum malaria in 28 pregnant women in eastern Sudan. Artemether was given to 1 woman during the first trimester, to 12 during the second trimester, and to 15 during the third trimester. One baby was delivered at 32 weeks but died 6 hours later; all the other babies were delivered at full term and there were no reports of congenital abnormalities.[3]

WHO[4] recommends that, where available, artesunate is the first option, and artemether is the second, for the parenteral treatment of severe falciparum malaria during the second and third trimesters. In the first trimester, until more evidence becomes available, artesunate may be considered as an option.

1. McGready R, *et al.* Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 1998; **92:** 430–3.
2. Sowunmi A, *et al.* Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine[sic]-pyrimethamine-resistant falciparum malaria during pregnancy. *J Obstet Gynaecol* 1998; **18:** 322–7.
3. Adam I, *et al.* Artemether in the treatment of falciparum malaria during pregnancy in eastern Sudan. *Trans R Soc Trop Med Hyg* 2004; **98:** 509–13.
4. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 21/06/06)

Interactions

Use of artemisinin derivatives with drugs that prolong the QT interval should be avoided if possible; caution is advised when artemisinin derivatives are given with other antimalarials that have this propensity.

Grapefruit juice. The oral bioavailability of artemether may be increased if taken with grapefruit juice.[1]

1. van Agtmael MA, *et al.* The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. *Clin Pharmacol Ther* 1999; **66:** 408–14.

Pharmacokinetics

Peak plasma concentrations have been achieved in about 3 hours after oral doses of artemether, in about 6 hours after intramuscular injection of artemether, and in about 11 hours after rectal artemisinin. Artemisinin derivatives (but not artemisinin) are rapidly hydrolysed to various extents to the active metabolite arterimol (dihydroartemisinin). Reported elimination half-lives have been about 45 minutes after intravenous doses of artesunate, about 4 hours after rectal artemisinin, and about 4 to 11 hours after intramuscular or oral artemether. There are very few published data on the pharmacokinetics of artemotil, but its elimination half-life appears to be longer than that of artemether.

◊ Reviews.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37:** 105–25.
2. Navaratnam V, *et al.* Pharmacokinetics of artemisinin-type compounds. *Clin Pharmacokinet* 2000; **39:** 255–70.

Uses and Administration

Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua*, a herb that has traditionally been used in China for the treatment of malaria. It is a potent and rapidly acting blood schizontocide active against *Plasmodium vivax* and against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*.

Artemisinin has been given orally or rectally in the treatment of malaria; regimens were often empirical with typical rectal doses ranging from 10 to 40 mg/kg daily over a variable number of days. However, it has largely been replaced in practice by its derivatives such as artemether and artesunate.