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

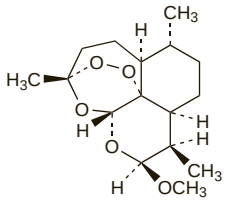
Artemisinina, derivados.

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.



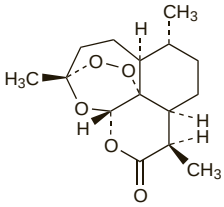
Pharmacopoeias. In *Chin.* and *Int.*

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.



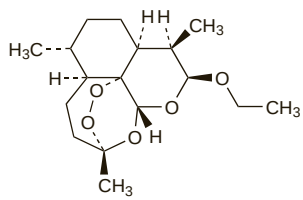
Pharmacopoeias. In *Chin., Int.,* and *Viet.*

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.



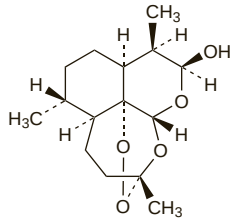
Pharmacopoeias. In *Int.*

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.



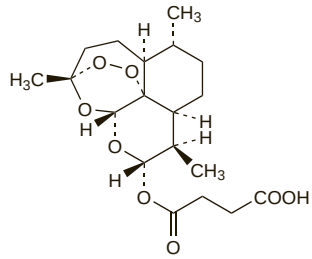
Pharmacopoeias. In *Chin.* and *Int.*

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.