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

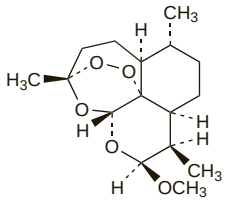
Artemisinina, derivados.

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.



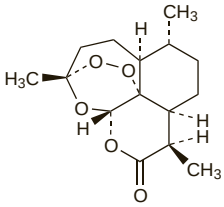
Pharmacopoeias. In *Chin.* and *Int.*

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.



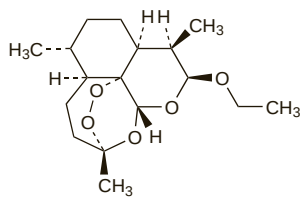
Pharmacopoeias. In *Chin., Int.,* and *Viet.*

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.



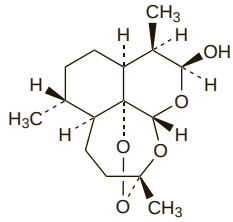
Pharmacopoeias. In *Int.*

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.



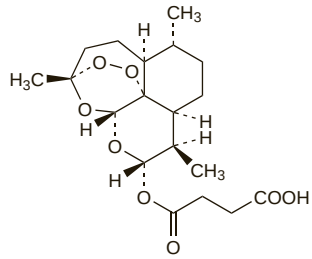
Pharmacopoeias. In *Chin.* and *Int.*

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.

The following doses are recommended by WHO for the treatment of uncomplicated falciparum malaria.

Artesunate, when used with other antimalarials (amodiaquine, mefloquine, or pyrimethamine-sulfadoxine), is given orally to adults and children in a dose of 4 mg/kg daily, as a single dose, for 3 days.

Artemether is given orally with lumefantrine; 6 doses in total are given, the first at diagnosis and repeated after 8, 24, 36, 48, and 60 hours. Each dose is:

- adults and children weighing over 34 kg, artemether 80 mg with lumefantrine 480 mg
- children 5 to 14 kg, artemether 20 mg with lumefantrine 120 mg
- children 15 to 24 kg, artemether 40 mg with lumefantrine 240 mg
- children 25 to 34 kg, artemether 60 mg with lumefantrine 360 mg

For parenteral use in severe malaria, WHO recommends:

- for adults or children, **artesunate** 2.4 mg/kg intravenously or intramuscularly, repeated after 12 and 24 hours and then once daily thereafter
- as an alternative in children, **artemether** 3.2 mg/kg intramuscularly, followed by 1.6 mg/kg daily thereafter. For both drugs the patient should be transferred to oral therapy as soon as possible

A fixed-dose combination product containing artesunate and amodiaquine (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.

Other derivatives of artemisinin, such as artemotil and alpha-beta arteether, are under investigation or commercial development (see Administration of Artemisinin Derivatives, below).

◊ Reviews.

1. McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 17/05/05).
2. McIntosh HM, Olliaro P. Artemisinin derivatives for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 17/05/05).
3. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: a review. *J Postgrad Med* 2004; **50:** 40–4.
4. Ashley EA, White NJ. Artemisinin-based combinations. *Curr Opin Infect Dis* 2005; **18:** 531–6.
5. Davis TME, *et al.* Artemisinin-based combination therapies for uncomplicated malaria. *Med J Aust* 2005; **182:** 181–5.
6. 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).
7. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. *Clin Pharmacokinet* 2008; **47:** 91–102.

Administration of artemisinin derivatives. To overcome the poor solubility of *artemisinin* in water a number of dosage forms and routes have been tried. Also, several more potent derivatives with more suitable pharmaceutical properties have been developed, notably the methyl ether derivative, *artemether*, and the ethyl ether derivative, *artemotil*, which are more lipid soluble; the sodium salt of the hemisuccinate ester, *sodium artesunate*, which is soluble in water but appears to have poor stability in aqueous solutions; and *sodium artelinate*, which is both soluble and stable in water. Other derivatives that have been studied include *arteflene*.

Several preparations of artemisinin derivatives are available either commercially or for studies organised by bodies such as WHO. These include oral formulations of artemether, artesunate, artemisinin itself, and *artenimol*; intramuscular formulations of artemotil, artemether, and artesunate; intravenous formulations of *artelinic acid* and artesunate; and suppositories of artemisinin, artesunate, and artinimol.

Malaria. The overall management of malaria and the place of artemisinin derivatives in current recommendations are discussed on p.594. In an attempt to delay the development of resistance to these compounds, WHO at one time recommended that their use be restricted to the treatment of malaria in areas of documented multidrug resistance and that they should not be used at all for prophylaxis. However, the development of resistance to conventional treatment has now led WHO to recommend the use in such circumstances of combination therapies containing artemisinin derivatives (artemisinin-based combination therapies, also known as ACTs). The following combination therapies are recommended:

- artemether-lumefantrine
- artesunate plus amodiaquine
- artesunate plus pyrimethamine-sulfadoxine (*Fansidar*)
- artesunate plus mefloquine

Artemether-lumefantrine is now also recommended in the UK as an alternative to quinine-based therapy for uncomplicated falciparum malaria.

In acute uncomplicated malaria artemisinin derivatives are usually given by mouth. Those used have been artemisinin, artemether, or artesunate. Parenteral therapy is generally necessary in severe malaria and WHO recommends[1] artesunate intravenously or intramuscularly in adults and children, or artemether intramuscularly in children, as alternatives to quinine for severe malaria. A systematic review[2] has suggested that intravenous artesunate should be the drug of choice in adults with severe malaria, particularly if acquired in Asia. Rectal artesunate has been successful and is recommended by WHO[1] if parenteral therapy is not possible.

1. 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)
2. Jones KL, *et al.* Artesunate versus quinine for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 05/06/08).

Schistosomiasis. Findings of a reduced intensity of *Schistosoma mansoni* infection in patients treated with sodium artesunate for malaria[1] prompted further investigation into the use of artemisinin derivatives for the control of schistosomiasis (p.138). A double-blind placebo-controlled study[2] in children negative for *S. mansoni* found a significantly lower incidence of infection in those given artemether orally. There was also a significant reduction in the prevalence of *Plasmodium falciparum* infection. A number of studies in China have confirmed the benefits of artemether or artesunate, often with praziquantel, against *S. japonicum*.[3]

1. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; **94:** 90–1.
2. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; **355:** 1320–5.
3. Xiao S-H. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Trop* 2005; **96:** 153–67.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Arinate; Artesiane; ***Braz.:*** Paluther; Plasmotrim; ***China:*** Cotecxin; ***India:*** Betamotil; E Mal; Falcigo; Falcinil; Larinate; Larither; Mosether; Rapither-AB; ***Neth.:*** Artecef; ***Thai.:*** Plasmotrim†.

Multi-ingredient: ***Austral.:*** Riamet; ***Austria:*** Riamet; ***Belg.:*** Amonate; Co-Arinate; Co-Artesiane; ***China:*** Artemodi; Duo-Cotecxin; ***Cz.:*** Riamet; ***Fr.:*** Riamet; ***Ger.:*** Riamet; ***Gr.:*** Riamet; ***Hong Kong:*** Riamet†; ***India:*** Artemal†; Larimal†; ***Neth.:*** Riamet; ***Norw.:*** Riamet†; ***Port.:*** Riamet; ***S.Afr.:*** Coartem; ***Swed.:*** Riamet; ***Switz.:*** Riamet; ***Thai.:*** Coartem; ***UK:*** Riamet.

Chloroquine *(BAN, rINN)*

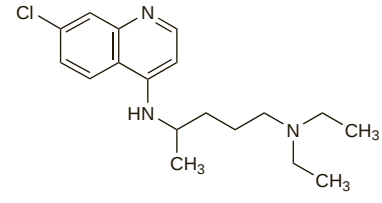
Chloroquinum; Cloroquina; Klorokiini; Klorokin. 4-(7-Chloro-4-quinolylamino)pentyldiethylamine; 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

Хлорохин

$C_{18}H_{26}ClN_3$ = 319.9.

CAS — 54-05-7.

ATC — P01BA01.



Pharmacopoeias. In *US*.

USP 31 (Chloroquine). A white or slightly yellow, odourless, crystalline powder. M.p. 87° to 92°. Very slightly soluble in water; soluble in chloroform, in ether, and in dilute acids. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Chloroquine Hydrochloride *(BANM, rINNM)*

Chloroquine, Chlorhydrate de; Chloroquini Hydrochloridum; Hidrocloruro de cloroquina.

Хлорохина Гидрохлорид

$C_{18}H_{26}ClN_3,2HCl$ = 392.8.

CAS — 3545-67-3.

ATC — P01BA01.

Pharmacopoeias. *US* includes an injection.

Chloroquine Phosphate *(BANM, rINNM)*

Chingaminum; Chlorochin-difosfát; Chlorochinium Phosphoricum; Chlorochinum Diphosphoricum; Chlorochiny fosforan; Chlorokvino fosfatas; Chloroquine, phosphate de; Chloroquini Diphosphas; Chloroquini phosphas; Fosfato de cloroquina; Klorokiinifosfaatti; Klorokinfosfat; Klorokin-foszfát; Quingamine; SN-7618.

Хлорохина Фосфат

$C_{18}H_{26}ClN_3,2H_3PO_4$ = 515.9.

CAS — 50-63-5.

ATC — P01BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Chloroquine Phosphate). A white or almost white, hygroscopic, crystalline powder. It exists in two forms, one melting at about 195° and the other at about 218°. Freely soluble in water; very slightly soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 3.8 to 4.3. Store in airtight containers. Protect from light.

USP 31 (Chloroquine Phosphate). A white, odourless, crystalline powder, which slowly discolours on exposure to light. It exists in two polymorphic forms, one melting between 193° and 195° and the other between 210° and 215°; mixture of the two forms melts between 193° and 215°. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions have a pH of about 4.5.

Chloroquine Sulfate *(rINNM)*

Chlorochin-sulfát monohydrát; Chlorochiny siarczan; Chlorokvino sulfatas; Chloroquine, sulfate de; Chloroquine Sulphate *(BANM)*; Chloroquini sulfas; Chloroquini Sulfas Monohydricus; Chloroquini Sulphas; Klorokiinisulfaatti; Klorokinsulfat; Klorokin-szulfát; RP-3377; Sulfato de cloroquina.

Хлорохина Сульфат

$C_{18}H_{26}ClN_3,H_2SO_4,H_2O$ = 436.0.

CAS — 132-73-0 (anhydrous chloroquine sulfate).

ATC — P01BA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*

Ph. Eur. 6.2 (Chloroquine Sulphate). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in alcohol. An 8% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

Sorption. Studies using low concentrations of chloroquine phosphate or chloroquine sulfate indicate that chloroquine exhibits pH-dependent binding to several materials used in medical equipment and membrane filters, including soda glass and various plastics such as cellulose acetate, cellulose propionate, methacrylate butadiene styrene, polypropylene, PVC, ethylvinyl acetate, and polyethylene.[1-3] Although this effect may not be of relevance at doses used clinically,[4] laboratory workers undertaking assays and sensitivity testing must recognise that significant reductions in concentrations can occur when chloroquine is prepared or stored in equipment made from these materials.[2,3] As the effect of borosilicate glass or polystyrene appears to be minimal, it has been suggested that they may be suitable for use in such procedures.[2,3]

Similar sorption has also been reported during membrane filtration of solutions of amodiaquine hydrochloride, mefloquine hydrochloride, or quinine sulfate.[1]

1. Baird JK, Lambros C. Effect of membrane filtration of antimalarial drug solutions on in vitro activity against Plasmodium falciparum. *Bull WHO* 1984; **62:** 439–44.
2. Yahya AM, *et al.* Binding of chloroquine to glass. *Int J Pharmaceutics* 1985; **25:** 217–23.
3. Yahya AM, *et al.* Investigation of chloroquine binding to plastic materials. *Int J Pharmaceutics* 1986; **34:** 137–43.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Adverse Effects

Adverse effects experienced with dosage regimens of chloroquine used in the treatment and prophylaxis of malaria are generally less common and less severe than those associated with the higher doses used for prolonged periods in rheumatoid arthritis.

Frequent adverse effects of chloroquine include headache, various skin eruptions, pruritus, and gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. More rarely, mental changes including psychotic episodes, agitation, and personality changes may occur. Convulsions have been reported.

Visual disturbances such as blurred vision and difficulties in focusing have occurred but these are more common with higher doses, when they may be associated with keratopathy or retinopathy, as discussed under Effects on the Eyes, below. Keratopathy usually occurs in the form of corneal opacities and is normally reversible when chloroquine is withdrawn. Retinopathy is the most serious adverse effect of chloroquine on the eyes