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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Amodiaquine *(BAN, rINN)*

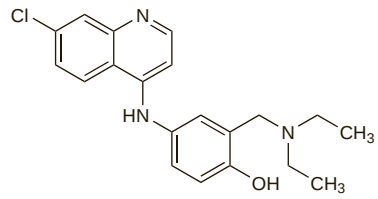
Amodiaquina; Amodiaquinum. 4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl)phenol.

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]

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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).

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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.

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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.

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