UK[4] for infants and children from 6 kg body-weight and above 3 months of age are as follows:

- 6 to 15.9 kg (3 months to 3 years 11 months), one-quarter the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months), half the adult dose
- 25 to 44.9 kg (8 years to 12 years 11 months), three-quarters the adult dose
- 45 kg and over (13 years or more), the adult dose

In the event of breakthrough malaria during malaria prophylaxis there may be a delay of up to several months before the onset of symptoms in contrast to that seen with other forms of prophylaxis.[5] Mefloquine should not be used for treatment if it has been used for prophylaxis.

1. Chanthavanich P, *et al.* Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34:** 1028–36.
2. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 05/06/06)
3. WHO. *International travel and health*. 2008 ed. Available at: http://www.who.int/ith/ (accessed 18/06/08)
4. 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)
5. Day JH, Behrens RH. Delay in onset of malaria with mefloquine prophylaxis. *Lancet* 1995; **345:** 398.

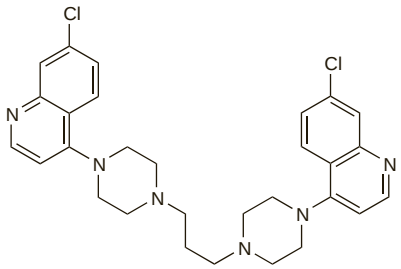
Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tropicur; ***Austral.:*** Lariam; ***Austria:*** Lariam; ***Belg.:*** Lariam; ***Braz.:*** Mephaquin; ***Canad.:*** Lariam; ***Chile:*** Lariam; ***Cz.:*** Lariam; Mephaquin†; ***Denm.:*** Lariam; ***Fin.:*** Lariam; ***Fr.:*** Lariam; ***Ger.:*** Lariam; ***Gr.:*** Lariam; ***Hong Kong:*** Lariam; Mephaquin; ***Hung.:*** Lariam; ***India:*** Larimef; Mefliam; Mefloc; Meflotas; ***Irl.:*** Lariam; ***Israel:*** Lariam; Mephaquin; ***Ital.:*** Lariam; ***Malaysia:*** Lariam; Mephaquin; ***Neth.:*** Lariam; ***Norw.:*** Lariam; ***NZ:*** Lariam; ***Philipp.:*** Lariam; ***Port.:*** Mephaquin; ***S.Afr.:*** Lariam; Mefliam; ***Singapore:*** Lariam; Mephaquin; ***Swed.:*** Lariam; ***Switz.:*** Lariam; Mephaquine; ***Thai.:*** Mephaquin†; Mequin; ***UK:*** Lariam; ***USA:*** Lariam.

Multi-ingredient: ***Switz.:*** Fansimef†.

Piperaquine Phosphate

Piperaquina, fosfato de; Piperaquini Phosphas; 13228-RP. 1,3-Bis[1-(7-chloro-4-quinolyl)-4′-piperazinyl]propane.
$C_{29}H_{32}Cl_2N_6,4H_3PO_4,4H_2O$ = 999.6.
CAS — 85547-56-4.



(piperaquine)

Pharmacopoeias. In *Chin.*

Profile

Piperaquine phosphate is a 4-piperazinoquinoline derivative which has been studied in the treatment and prophylaxis of falciparum malaria. Combined treatment with artenimol is also being investigated. A combination of piperaquine, artinimol, and trimethoprim (*Artecom*) is available in some countries.

◊ References.

1. Davis TME, *et al.* Piperaquine: a resurgent antimalarial drug. *Drugs* 2005; **65:** 75–87.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***China:*** Duo-Cotecxin.

Primaquine Phosphate *(BANM, rINNM)*

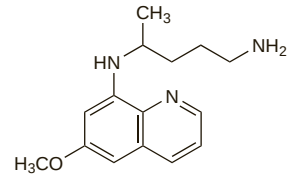
Difosfato de Primaquina; Fosfato de primaquina; Primachin difosfát; Primachina Fosfato; Primachini Phosphas; Primakiinidifosfaatti; Primakindifosfat; Primakin-difoszfát; Primakvino difosfatas; Primaquine Diphosphate; Primaquine, diphosphate de; Primaquine, Phosphate de; Primaquini diphosphas; Primaquini Phosphas; Primaquinum Phosphoricum; SN-13,272. (*RS*)-8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline diphosphate.

Примахина Фосфат

$C_{15}H_{21}N_3O,2H_3PO_4$ = 455.3.

CAS — 90-34-6 (primaquine); 63-45-6 (primaquine phosphate).

ATC — P01BA03.



(primaquine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Primaquine Diphosphate). An orange crystalline powder. Soluble in water; practically insoluble in alcohol. Protect from light.
USP 31 (Primaquine Phosphate). An orange-red, odourless, crystalline powder. Soluble 1 in 15 of water; insoluble in chloroform and in ether. Its solutions are acid to litmus. Protect from light.

Adverse Effects

Adverse effects with therapeutic doses of primaquine are usually minimal but abdominal pain and gastric distress are more common if taken on an empty stomach. Larger doses may cause nausea and vomiting. Methaemoglobinaemia may occur occasionally. Haemolytic anaemia can occur in persons with G6PD deficiency (see below). Other uncommon effects include mild anaemia and leucocytosis. Hypertension and cardiac arrhythmias have been reported on rare occasions. Primaquine may rarely produce leucopenia or agranulocytosis, usually after overdosage. Other effects associated with overdosage include gastrointestinal symptoms, haemolytic anaemia, and methaemoglobinaemia with cyanosis.

◊ Many adverse effects have been reported after use of primaquine[1] but some, including pruritus and disturbances of visual accommodation, are considered to be inadequately documented or doubtfully attributed to the drug.

Acute intravascular haemolysis is the most serious toxic hazard of primaquine, especially in people with G6PD deficiency, other defects of the erythrocytic pentose phosphate pathway of glucose metabolism, or some types of haemoglobinopathy. In individuals with G6PD deficiency the severity of haemolysis is directly related to the degree of deficiency and to the quantity of primaquine given. In patients with the African variant the standard course of primaquine generally produces a moderate and self-limiting anaemia, while in those with the Mediterranean and related Asian variants, haemolysis can result in progressive haemoglobinaemia and haemoglobinuria which can be fatal. Whenever possible, therapy with primaquine should be delayed until the acute stage of malaria has been brought under control by a blood schizontocide because of the risk of inducing haemolysis and compromising the gastrointestinal tolerance of therapy.

1. Clyde DF. Clinical problems associated with the use of primaquine as a tissue schizontocidal and gametocytocidal drug. *Bull WHO* 1981; **59:** 391–5.

Precautions

Primaquine should be used cautiously in acutely ill patients with any serious systemic disease characterised by a tendency to granulocytopenia such as rheumatoid arthritis or lupus erythematosus. It should also be used with care in patients with G6PD deficiency. Primaquine should be withdrawn if signs of haemolysis or methaemoglobinaemia occur and the blood count should be monitored periodically.

Pregnancy. Radical cure of vivax or ovale malarias with primaquine should be delayed in pregnant women until after delivery.[1]

1. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.

Interactions

Primaquine should not be used with drugs liable to induce haemolysis or bone marrow depression. Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Antimalarials. The pharmacokinetics of primaquine were not altered by *mefloquine* in healthy subjects,[1] although the effect of primaquine on mefloquine pharmacokinetics is uncertain (see under Mefloquine, p.607). In a study in patients with malaria, *quinine* reduced the plasma concentrations of primaquine, although the clinical importance of the interaction was unclear.[1]

1. Edwards G, *et al.* Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. *Br J Clin Pharmacol* 1993; **35:** 193–8.

Pharmacokinetics

Primaquine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after a dose is taken and then rapidly diminish with a reported elimination half-life of 3 to 6 hours. It is widely distributed into body tissues.

Primaquine is rapidly metabolised in the liver, its major metabolite being carboxyprimaquine, and little unchanged drug is excreted in the urine. Carboxyprimaquine accumulates in the plasma on repeated dosage.

◊ References.

1. Fletcher KA, *et al.* Studies on the pharmacokinetics of primaquine. *Bull WHO* 1981; **59:** 407–12.
2. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
3. Mihaly GW, *et al.* Pharmacokinetics of primaquine in man, I: studies of the absolute bioavailability and effects of dose size. *Br J Clin Pharmacol* 1985; **19:** 745–50.
4. Ward SA, *et al.* Pharmacokinetics of primaquine in man, II: comparison of acute vs chronic dosage in Thai subjects. *Br J Clin Pharmacol* 1985; **19:** 751–5.
5. Bhatia SC, *et al.* Pharmacokinetics of primaquine in patients with P. vivax malaria. *Eur J Clin Pharmacol* 1986; **31:** 205–10.
6. Rønn A, Bygbjerg I. Unexpected high primaquine concentrations in acutely ill malaria patients. *Lancet* 1993; **341:** 305.

Uses and Administration

Primaquine is an 8-aminoquinoline antimalarial that is effective as a tissue schizontocide against intrahepatic forms of all types of malaria parasite and is used to produce radical cure of vivax and ovale malarias.

Primaquine phosphate is given orally and doses may be expressed in terms of the base; primaquine phosphate 26.4 mg is equivalent to about 15 mg of primaquine base.

When used for *radical cure* of vivax or ovale **malaria**, a course of treatment with a blood schizontocide must be given first to kill any erythrocytic parasites. Primaquine phosphate is then given orally, usually in a dose equivalent to 15 mg of the base daily for 14 days but higher doses or longer courses may be required to overcome resistance in some strains of *P. vivax* (see below); WHO has advised that for uncomplicated malaria in travellers, infections acquired south of the equator should be treated with primaquine 500 micrograms/kg daily for 14 days and those acquired north of the equator with 250 micrograms/kg daily for 14 days. A dose for children is 250 micrograms/kg daily for 14 days.

For patients with G6PD deficiency the use of up to 45 mg (children 750 micrograms/kg) once every 7 days for 8 weeks has been suggested to minimise haemolysis (but see under Adverse Effects, above).

Primaquine is also gametocytocidal and a single dose of 750 micrograms/kg (to a maximum of 45 mg) has been suggested to *prevent transmission* of falciparum malaria particularly in areas where there is potential for re-introduction of malaria.

Primaquine is also used with clindamycin in the treatment of **pneumocystis pneumonia** in AIDS patients (below).

Malaria. The overall treatment and prophylaxis of malaria and the place of primaquine in current recommendations are described on p.594.

Despite the generally successful use of oral primaquine for radical cure of benign malarias,[1] there has been a report[2] of a patient weighing 84 kg who had relapse of vivax malaria after treatment including primaquine 15 mg given daily for 21 days; no further symptoms occurred after a second course of 15 mg given daily for 3 months. It was suggested that a daily dose of 15 mg might be inadequate for patients weighing more than 50 kg and that patients with vivax malaria who have relapsed after the standard course of primaquine, and possibly those with vivax malaria acquired in South-East Asia or Melanesia, should receive a total dose of 6 mg/kg in daily doses of 15 to 22.5 mg. A report from Thailand,[3] where primaquine-resistant strains of *Plasmodium vivax* are increasing, showed that a dose of primaquine 22.5 mg daily for 14 days was safe and more effective in preventing relapses than 15 mg daily in patients with an average body-weight