Chloroquine and hydroxychloroquine have also been reported to be of use in **palindromic rheumatism**.[9-11]

1. Suarez-Almazor ME, *et al.* Antimalarials for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 17/05/05).
2. HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995; **98:** 156–68.
3. Clegg DO, *et al.* Safety and efficacy of hydroxychloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with methotrexate and hydroxychloroquine. *J Rheumatol* 1997; **24:** 1896–1902.
4. O'Dell JR. Triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine in patients with rheumatoid arthritis. *Rheum Dis Clin North Am* 1998; **24:** 465–77.
5. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1164–70.
6. Pavelka K, *et al.* Hydroxychloroquine sulphate in the treatment of rheumatoid arthritis: a double blind comparison of two dose regimens. *Ann Rheum Dis* 1989; **48:** 542–6.
7. Brewer EJ, *et al.* Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. *N Engl J Med* 1986; **314:** 1269–76.
8. Grondin C, *et al.* Slow-acting antirheumatic drugs in chronic arthritis of childhood. *Semin Arthritis Rheum* 1988; **18:** 38–47.
9. Richardson MR, Zalin AM. Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; **294:** 741.
10. Hanonen P, *et al.* Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; **294:** 1289.
11. Youssef W, *et al.* Palindromic rheumatism: a response to chloroquine. *J Rheumatol* 1991; **18:** 35–7.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p.1512) as alternatives or adjuncts to corticosteroid therapy. For references to the use of hydroxychloroquine, see under Chloroquine, p.603.

Skin disorders. For reference to the use of hydroxychloroquine in a variety of skin disorders, see under Chloroquine, p.603.

Systemic lupus erythematosus. Antimalarials have been widely used in the treatment of lupus erythematosus (p.1513), particularly its cutaneous manifestations, although much of the evidence is based on case series and reports.[1] Hydroxychloroquine is most widely used, as it is thought to have fewer adverse effects than chloroquine, although any benefit with chloroquine generally starts to become evident within several weeks of starting treatment, whereas it may take up to 2 months for any effect of hydroxychloroquine to be seen. For extracutaneous disease, antimalarials are often combined with other drugs; treatment may be continued for many years. For reference to precautions to reduce the risk of retinopathy see Effects on the Eyes, under Adverse Effects of Chloroquine, p.600.

1. Wozniacka A, McCauliffe DP. Optimal use of antimalarials in treating cutaneous lupus erythematosus. *Am J Clin Dermatol* 2005; **6:** 1–11.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p.1189) is usually with an anticoagulant. Hydroxychloroquine has been described by some as an antiplatelet agent[1] and although its mechanism of action is uncertain the incidence of fatal pulmonary embolism has been reduced in patients given hydroxychloroquine prophylactically after total hip replacement;[2] the usual daily divided oral dose was about 800 mg from the day before surgery until discharge; larger doses had been used.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; **308:** 235–46.
2. Loudon JR. Hydroxychloroquine and postoperative thromboembolism after total hip replacement. *Am J Med* 1988; **85:** (suppl 4A): 57–61.

Preparations

BP 2008: Hydroxychloroquine Tablets;
USP 31: Hydroxychloroquine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Axokine; Evoquin; Metirel; Narbon; Plaquenil; Polirreumin; ***Austral.:*** Plaquenil; ***Austria:*** Plaquenil; ***Belg.:*** Plaquenil; ***Braz.:*** Plaquinol; Reuquinol; ***Canad.:*** Apo-Hydroxyquine; Plaquenil; ***Chile:*** Plaquinol; ***Cz.:*** Plaquenil; ***Denm.:*** Ercoquin; Plaquenil; ***Fin.:*** Oxiklorin; Plaquenil†; ***Fr.:*** Plaquenil; ***Ger.:*** Quensyl; ***Gr.:*** Plaquenil; ***Hong Kong:*** Plaquenil; ***India:*** HCQS; ***Irl.:*** Plaquenil; ***Israel:*** Plaquenil; ***Ital.:*** Plaquenil; ***Malaysia:*** Plaquenil; ***Mex.:*** Plaquenil; ***Neth.:*** Plaquenil; ***Norw.:*** Plaquenil; ***NZ:*** Plaquenil; ***Philipp.:*** Plaquenil; ***Port.:*** Plaquinol; ***Rus.:*** Plaquenil (Плаквенил); ***Singapore:*** Plaquenil; ***Spain:*** Dolquine; ***Swed.:*** Plaquenil; ***Switz.:*** Plaquenil; ***Thai.:*** Hydroquin; Plaquenil; ***UK:*** Plaquenil; ***USA:*** Plaquenil; ***Venez.:*** Plaquinol.

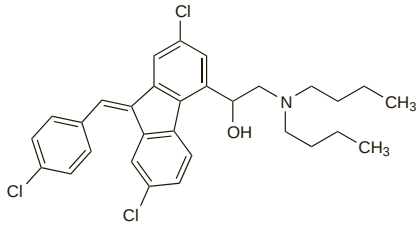
Lumefantrine *(BAN, rINN)*

Benflumelol; Benflumetol; Lumefantrina; Luméfantrine; Lumefantrinum. 2,7-Dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9*H*-fluorene-4-methanol.

Лумефантрин

$C_{30}H_{32}Cl_3NO$ = 528.9.

CAS — 82186-77-4.



Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

Adverse effects associated with lumefantrine in combination with artemether commonly include headache, dizziness, sleep disturbance, palpitations, gastrointestinal disturbances, anorexia, pruritus, rash, cough, arthralgia, myalgia, and fatigue. Lumefantrine-artemether should be given with caution in severe hepatic or renal impairment and ECG and blood potassium monitored.

Effects on the blood. Severe haemolytic anaemia necessitating corticosteroid treatment, blood transfusion, and haemodialysis occurred in a patient after taking 8 lumefantrine-artemether tablets after a malarial attack.[1] It was considered that, given its molecular similarity to other antimalarials known to cause haemolysis, the causative drug was probably lumefantrine.

1. Mérat S, *et al.* Case report: combination artemether-lumefantrine and haemolytic anaemia following a malarial attack. *Trans R Soc Trop Med Hyg* 2003; **97:** 433–4.

Pharmacokinetics

The bioavailability of lumefantrine after oral doses is variable; absorption begins after a lag-time of up to 2 hours and bioavailability is substantially increased when given with food, particularly meals high in fat. Peak plasma concentrations occur after about 6 to 8 hours. Lumefantrine is almost completely protein bound. It is considered to be metabolised mainly in the liver and is excreted in the faeces. The elimination half-life is reported to be between 4 to 6 days in patients with malaria.

◊ References.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37:** 105–25.
2. Ezzet F, *et al.* Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* 2000; **44:** 697–704.

Uses and Administration

Lumefantrine is a dichlorobenzylidine derivative given by mouth in combination with artemether (p.598) for the treatment of uncomplicated falciparum malaria. It is a blood schizontocide with a relatively slow onset of action but it has a longer duration of action than artemether.

The following doses are recommended by WHO; 6 doses in total are given, starting at diagnosis and repeated after 8, 24, 36, 48, and 60 hours. Each dose is:

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

◊ References.

1. Omari AAA, *et al.* Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 19/07/06).
2. Omari AAA, *et al.* Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/07/06).
3. Kokwaro G, *et al.* Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. *Expert Opin Pharmacother* 2007; **8:** 75–94.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Riamet; ***Austria:*** Riamet; ***Belg.:*** Co-Artesiane; ***Cz.:*** Riamet; ***Fr.:*** Riamet; ***Ger.:*** Riamet; ***Gr.:*** Riamet; ***Hong Kong:*** Riamet†; ***Neth.:*** Riamet; ***Norw.:*** Riamet†; ***Port.:*** Riamet; ***S.Afr.:*** Coartem; ***Swed.:*** Riamet; ***Switz.:*** Riamet; ***Thai.:*** Coartem; ***UK:*** Riamet.

Mefloquine Hydrochloride

(BANM, USAN, rINNM)

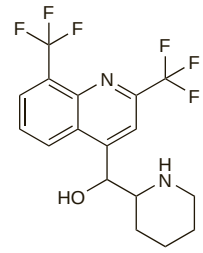
Hidrocloruro de mefloquina; Meflochin-hydrochlorid; Meflokiini-hydrokloridi; Meflokin-hidroklorid; Meflokinhydroklorid; Meflokvino hidrochloridas; Méfloquine, chlorhydrate de; Mefloquini hydrochloridum; Ro-21-5998 (mefloquine); Ro-21-5998/001 (mefloquine hydrochloride); WR-142490 (mefloquine). (*RS*)-[2,8-Bis(trifluoromethyl)-4-quinolyl]-(*SR*)-(2-piperidyl)methanol hydrochloride.

Мефлохина Гидрохлорид

$C_{17}H_{16}F_6N_2O,HCl$ = 414.8.

CAS — 53230-10-7 (mefloquine); 51773-92-3 (mefloquine hydrochloride).

ATC — P01BC02.



(mefloquine)

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

Ph. Eur. 6.2 (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 31 (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

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

Stability. A report of the photolytic degradation of mefloquine hydrochloride in water.[1]

1. Tønnesen HH, Grislingaas A-L. Photochemical stability of biologically active compounds II: photochemical decomposition of mefloquine in water. *Int J Pharmaceutics* 1990; **60:** 157–62.

Adverse Effects

Since mefloquine has a long elimination half-life, adverse effects may occur or persist up to several weeks after the last dose.

The most frequent adverse effects of mefloquine are nausea, diarrhoea, vomiting, abdominal pain, anorexia, headache, dizziness, loss of balance, somnolence, and sleep disorders, notably insomnia and abnormal dreams.

Neurological or psychiatric disturbances have also been reported with mefloquine and include sensory and motor neuropathies, tremor, ataxia, visual disturbances, tinnitus and hearing impairment, convulsions, anxiety, depression, confusion, hallucinations, panic attacks, emotional instability, aggression and agitation, and acute psychosis. There have been rare reports of suicidal ideation.

Other adverse effects include skin rashes, pruritus and urticaria, hair loss, muscle weakness, myalgia, liver function disturbances, and very rarely thrombocytopenia and leucopenia. There have been rare occurrences of erythema multiforme and Stevens-Johnson syndrome. Anaphylaxis has occurred rarely. Cardiovascular effects have included hypotension, hypertension,

tachycardia or palpitations, bradycardia, QT prolongation, and other minor ECG changes. There have been isolated cases of atrioventricular block.

Incidence of adverse effects. The frequencies of adverse effects reported[1] in 134 soldiers given mefloquine hydrochloride 250 mg weekly for malaria chemoprophylaxis were: diarrhoea (48%), nausea (13%), vomiting (2%), headache (13%), and dizziness (7%). All of 7 healthy subjects who received a dose of mefloquine hydrochloride 15 mg/kg had symptoms that included vertigo, nausea, dizziness, and lightheadedness.[2] The manufacturers reported that dizziness occurred in 24% of patients with malaria treated with 750 mg of mefloquine, in 38% treated with 1000 mg, and in 96% treated with 1500 mg; splitting a dose into two doses given 8 hours apart can reduce the incidence of dizziness.[3] A prospective study involving 3673 patients found that anorexia, nausea, vomiting, dizziness, and sleep disorders were 1.1 to 1.4 times more frequent in patients receiving mefloquine 25 mg/kg for treatment of malaria than in those receiving 15 mg/kg, and that vomiting could be reduced by 40% if the higher dose was split and given as 15 mg/kg followed by a further 10 mg/kg after 16 to 24 hours.[4] The frequency of adverse effects is reported to be higher in subjects who become dehydrated.[5]

There has been concern that the adverse effects of mefloquine, especially neuropsychiatric reactions, might limit its use for the prophylaxis of malaria but, as discussed under Effects on the Nervous System, below, the incidence of adverse effects does not appear to be greater than with other prophylactic schedules.

1. Arthur JD, *et al.* Mefloquine prophylaxis. *Lancet* 1990; **335:** 972.
2. Patchen LC, *et al.* Neurologic reactions after a therapeutic dose of mefloquine. *N Engl J Med* 1989; **321:** 1415.
3. Stürchler D, *et al.* Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; **322:** 1752–3.
4. ter Kuile FO, *et al.* Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bull WHO* 1995; **73:** 631–42.
5. Perry IC. Malaria prophylaxis. *BMJ* 1995; **310:** 1673.

Effects on the blood. Agranulocytosis was reported[1] in a patient with malaria 48 hours after treatment with a 1250-mg course of mefloquine. The patient had previously taken 250 mg of mefloquine weekly for 7 weeks without side-effects. Thrombotic thrombocytopenic purpura has been reported[2] in a patient after taking two standard weekly doses of mefloquine for malaria prophylaxis. Symptoms improved after plasmapheresis.

1. Hennequin C, *et al.* Agranulocytosis during treatment with mefloquine. *Lancet* 1991; **337:** 984.
2. Fiaccadori E, *et al.* Thrombotic-thrombocytopenic purpura following malaria prophylaxis with mefloquine. *J Antimicrob Chemother* 2006; **57:** 160–1.

Effects on the liver. Acute fatty liver was reported[1] in a patient who had recently received mefloquine 250 mg weekly for 5 weeks for malaria prophylaxis. Symptoms resolved with fluid, electrolyte, and albumin replacement, after stopping mefloquine. In another report,[2] acute elevation of liver transaminases, associated with severe acute hepatitis, occurred in a patient with pre-existing mild hepatic impairment following a 6-week course of mefloquine 250 mg weekly.

1. Grieco A, *et al.* Acute fatty liver after malaria prophylaxis with mefloquine. *Lancet* 1999; **353:** 295–6.
2. Gotsman I, *et al.* Mefloquine-induced acute hepatitis. *Pharmacotherapy* 2000; **20:** 1517–19.

Effects on the nervous system. Neuropsychiatric reactions have been associated with the use of mefloquine although various figures have been reported for their frequency. The UK CSM has quoted[1] figures of 1 in 10 000 to 1 in 20 000 for severe reactions to *prophylactic* doses and similarly the manufacturers report that 1 in 10 000 patients given mefloquine prophylaxis will have serious problems. Others consider that the incidence of serious reactions is extremely low,[2] with a frequency of about 1 in 80 000. The manufacturers have also reported that most reactions in patients taking mefloquine for prophylaxis appear to occur after the first dose and have suggested that monitoring after the first dose could identify 40% of those at risk of neuropsychiatric effects.[3] Some authorities consider that over 75% of such reactions to mefloquine are apparent by the third dose.[4] This may allow for tolerability problems with mefloquine prophylaxis to be identified before travel. There has been much discussion on the comparative tolerability of antimalarials used for chemoprophylaxis. The incidence of adverse events, including neuropsychiatric events, was comparable for mefloquine and chloroquine in 2 uncontrolled questionnaire studies, one in tourists[5] and one in US Peace Corps volunteers.[6] However, in a more recent questionnaire in travellers,[7] although the incidence of reported adverse events was similar for mefloquine and chloroquine plus proguanil, neuropsychiatric adverse events were significantly more common in mefloquine recipients. In two randomised controlled studies,[8,9] both in military personnel, there was no difference between CNS symptoms in those given weekly mefloquine and those receiving chloroquine (with or without proguanil). In one of these studies,[9] a subgroup receiving a loading dose of mefloquine daily for 3 days initially had a higher incidence of CNS events. A review[10] of 10 controlled studies found no significant difference in the rates of withdrawal and overall incidence of adverse effects for mefloquine and alternative prophylactic regimens, but mefloquine was more likely than other drugs to cause insomnia and fatigue. Women may be at greater risk of adverse effects than men, and WHO has commented that the occurrence of such adverse effects may mean that only highly motivated occupational subgroups or individuals at high risk of infection with chloroquine-resistant malaria will be willing to continue with mefloquine prophylaxis.[11]

Neuropsychiatric reactions are more frequent after the higher doses of mefloquine used for *treatment* than those used for prophylaxis. Some workers have estimated that overall 1 in 8000 mefloquine users have such reactions, with the incidence 60 times higher after treatment than after prophylaxis.[12] Other workers who have used mefloquine in nearly 14 000 treatments calculated that the overall frequency of serious neuropsychiatric reactions was 1 per 1754 treatments; it therefore appeared that serious neuropsychiatric reactions were 10 times more probable after treatment than with prophylactic use of mefloquine.[13]

A severe neurological syndrome associated with mefloquine treatment, with agitation, delirium, stupor, hyperpyrexia, mydriasis, and generalised rigors responded rapidly to treatment with physostigmine, suggesting a central anticholinergic aetiology.[14]

A discrete post-malaria neurological syndrome (including an acute confusional state or acute psychosis, convulsions, and tremor) has been seen on recovery from falciparum malaria and there appeared to be a strong association with mefloquine although it was not the only risk factor.[15] Nevertheless the risk was considered unacceptable and the recommendation made[15] that, where there was an effective alternative drug, mefloquine should not be used after initial treatment of severe malaria.

Emergence delirium during recovery from general anaesthesia after mefloquine prophylaxis has been reported in 3 cases.[16]

1. Committee on Safety of Medicines. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems* 1996; **22:** 6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023214 (accessed 18/06/08)
2. Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996; **347:** 326.
3. Stürchler D, *et al.* Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; **322:** 1752–3.
4. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. *Commun Dis Public Health* 2003; **6:** 180–99. Also available at: http://www.hpa.org.uk/cdph/issues/CDPHvol6/No3/6(3)p180-99.pdf (accessed 06/07/06)
5. Steffen R, *et al.* Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; **341:** 1299–1303.
6. Lobel HO, *et al.* Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341:** 848–51.
7. Barrett PJ, *et al.* Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996; **313:** 525–8. Correspondence. *ibid.*; 1552–4.
8. Croft AMJ, *et al.* Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. *Trans R Soc Trop Med Hyg* 1997; **91:** 199–203.
9. Boudreau E, *et al.* Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol* 1993; **44:** 257–65.
10. Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *BMJ* 1997; **315:** 1412–16. Correspondence. *ibid.* 1998; **316:** 1980–1.
11. Anonymous. Mefloquine effectiveness impaired by high withdrawal rates. *WHO Drug Inf* 1998; **12:** 7–8.
12. Weinke T, *et al.* Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991; **45:** 86–91.
13. Luxemburger C, *et al.* Mefloquine for multidrug-resistant malaria. *Lancet* 1991; **338:** 1268.
14. Speich R, Haller A. Central anticholinergic syndrome with the antimalarial drug mefloquine. *N Engl J Med* 1994; **331:** 57–8.
15. Mai NTH, *et al.* Post-malaria neurological syndrome. *Lancet* 1996; **348:** 917–21.
16. Gullahorn GM, *et al.* Anaesthesia emergence delirium after mefloquine prophylaxis. *Lancet* 1993; **341:** 632.

Effects on the oesophagus. Oesophageal ulceration in one patient and discomfort in another 4 was attributed to swallowing mefloquine tablets with insufficient fluid.[1]

1. Phillips M. Antimalarial mefloquine. *Med J Aust* 1994; **161:** 227–8.

Effects on the skin. Isolated cases of Stevens-Johnson syndrome,[1] severe facial lesions,[2] exfoliative dermatitis,[3] toxic epidermal necrolysis,[4] and cutaneous vasculitis[5] have been associated with use of mefloquine for malaria prophylaxis.

For a comparison of the incidence of pruritus induced by various antimalarials, see under Chloroquine, p.600.

1. Van den Enden E, *et al.* Mefloquine-induced Stevens-Johnson syndrome. *Lancet* 1991; **337:** 683.
2. Shlim DR. Severe facial rash associated with mefloquine. *JAMA* 1991; **266:** 2560.
3. Martin GJ, *et al.* Exfoliative dermatitis during malarial prophylaxis with mefloquine. *Clin Infect Dis* 1993; **16:** 341–2.
4. McBride SR, *et al.* Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis. *Lancet* 1997; **349:** 101.
5. White AC, *et al.* Cutaneous vasculitis associated with mefloquine. *Ann Intern Med* 1995; **123:** 894.

Overdosage. Cardiac, hepatic, and neurological symptoms have been reported in a patient who inadvertently received 5.25 g of mefloquine over 6 days.[1] All symptoms disappeared rapidly when mefloquine was stopped.

1. Bourgeade A, *et al.* Intoxication accidentelle à la méfloquine. *Presse Med* 1990; **19:** 1903.

Precautions

Tasks requiring fine coordination such as driving should not be undertaken during treatment with mefloquine or for at least 3 weeks afterwards; in the case of prophylactic use, care should be exercised while taking mefloquine and for at least 3 weeks after stopping it. The use of mefloquine for malaria prophylaxis is contra-indicated in patients with a history of psychiatric (including depression) or convulsive disorders. Increased plasma concentrations may occur in patients with hepatic impairment. Mefloquine should be stopped should symptoms suggestive of psychiatric disturbance occur during prophylaxis, and an alternative antimalarial substituted. Mefloquine is teratogenic in *animals* and its use during pregnancy is best avoided; however, in areas of chloroquine-resistant *Plasmodium falciparum*, WHO states that mefloquine may normally be taken for malaria prophylaxis during the second and third trimesters of pregnancy. It is recommended that women should also avoid becoming pregnant during, and for 3 months after, mefloquine use and that mothers should not breast feed while taking mefloquine. Mefloquine should be used with caution in patients with renal impairment and in those with cardiac conduction disorders.

Porphyria. For a discussion of the problems of the use of antimalarials in patients with porphyria and a comment that mefloquine may be safe for use in such patients, see under Precautions for Chloroquine, p.601.

Pregnancy. Licensed product information for mefloquine reports that it is teratogenic in *rodents*. There is limited information on its effects in humans. One study in Thailand cited by WHO[1] found no difference between mefloquine and quinine in pregnancy outcome, but the numbers of treated patients who were in their first trimester were very small and its use should be kept to a minimum in that stage of pregnancy. Further spontaneous reports of exposure to mefloquine during the first trimester of pregnancy collected by the manufacturer revealed 24 fetal abnormalities and 17 spontaneous or missed abortions in 358 pregnancies, although a causal relationship was not established,[2] and a later study by the manufacturer involving 1627 reports of exposure during pregnancy appeared to show a similar incidence of congenital malformation to that in offspring of unexposed women.[3] In 53 army service women who inadvertently used mefloquine in pregnancy, and for whom pregnancy outcome was known, there were 17 elective abortions, 12 spontaneous abortions, one molar pregnancy, and 23 healthy live births, with no major congenital malformations.[4] The rate of spontaneous abortions was considered high.[4] A prospective cohort study involving 236 pregnant women who received an antimalarial in the first trimester did not find an increased risk of spontaneous abortion or anomaly in women who took mefloquine compared with other antimalarials, and the rate of spontaneous abortion was comparable with background rates.[5]

Confidence in the safety of mefloquine has increased, and WHO now considers mefloquine suitable for malaria prophylaxis in the second and third trimesters;[6] WHO has stated its use is not recommended in the first trimester because of limited information on its safety. Authorities in the UK consider that use may sometimes be justified in the first trimester in areas of high risk of acquiring falciparum malaria; inadvertent use is not an indication to terminate pregnancy.[7]

Pregnancy should be avoided during and for 3 months after prophylactic use.

1. WHO. Practical chemotherapy of malaria: report of a WHO scientific group. *WHO Tech Rep Ser 805* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_805.pdf (accessed 18/06/05)
2. Palmer KJ, *et al.* Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.
3. Vanhauwere B, *et al.* Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. *Am J Trop Med Hyg* 1998; **58:** 17–21.
4. Smoak BL, *et al.* The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army service women. *J Infect Dis* 1997; **176:** 831–3.
5. Phillips-Howard PA, *et al.* Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *J Travel Med* 1998; **5:** 121–6.
6. WHO. *International travel and health.* 2008 ed. Available at: http://www.who.int/ith/ (accessed 18/06/08)
7. 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)

Interactions

Halofantrine should not be given with or after mefloquine because of the increased potential to induce haz-

ardous cardiac arrhythmias, as discussed under Effects on the Heart on p.603. There is an increased risk of convulsions when mefloquine is used with chloroquine, quinidine, or quinine.

Alcohol. There has been a case report[1] of a patient who had neuropsychiatric disturbances after consuming a large quantity of alcohol with mefloquine; subsequent abstinence from alcohol led to complete reversal of the reactions.

1. Wittes RC, Saginur R. Adverse reaction to mefloquine associated with ethanol ingestion. *Can Med Assoc J* 1995; **152:** 515–17.

Antibacterials. Studies in healthy subjects have indicated that *ampicillin*[1] or *tetracycline*[2] could increase blood concentrations of mefloquine. Convulsions have been precipitated in 3 non-epileptic patients who were given mefloquine and the quinolone antibacterials *ciprofloxacin, ofloxacin,* or *sparfloxacin*.[3]

1. Karbwang J, *et al.* Effect of ampicillin on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1991; **40:** 631–3.
2. Karbwang J, *et al.* Effect of tetracycline on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1992; **43:** 567–9.
3. Mangalvedhekar SS, *et al.* Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration. *Natl Med J India* 2000; **13:** 47.

Antidepressants. Licensed product information for mefloquine states that in patients taking tricyclic antidepressants use of mefloquine may theoretically contribute to prolongation of the QT interval.

Antiepileptics. Licensed product information states that mefloquine may reduce seizure control by lowering the plasma concentration of antiepileptics, including carbamazepine, phenobarbital, and phenytoin. For the effect of mefloquine on *valproate*, see p.511. For its effect on *carbamazepine*, see p.475.

Antihistamines. Giving mefloquine with antihistamines may theoretically contribute to the prolongation of QT intervals; however, this is not considered to be an absolute contra-indication.

Antimalarials. It is well established that the use of *halofantrine* with or after mefloquine is contra-indicated because of the risk of hazardous cardiac arrhythmias. Mefloquine and other related compounds such as *quinine*, *quinidine*, and *chloroquine* may be given together only under close medical supervision because of possible additive cardiac toxicity; there is also an increased risk of convulsions.

A study in healthy subjects indicated that use of *primaquine* could increase blood concentrations of mefloquine and might increase the incidence of adverse effects due to mefloquine,[1] but others reported no such interaction.[2]

1. MacLeod CM, *et al.* Interaction of primaquine with mefloquine in healthy males. *J Clin Pharmacol* 1990; **30:** 841.
2. Karbwang J, *et al.* Pharmacokinetics of mefloquine in the presence of primaquine. *Eur J Clin Pharmacol* 1992; **42:** 559–60.

Antipsychotics. The use of mefloquine with *phenothiazines* or *pimozide* may theoretically contribute to prolonged QT intervals, although this is not considered to be an absolute contra-indication.

Cardiovascular drugs. It has been recommended that mefloquine should be used with extreme caution in patients also taking *antiarrhythmics*, *beta blockers*, *calcium-channel blockers*, or *digitalis*, until more was known about the risks of cardiotoxicity, since theoretically these drugs might contribute to prolongation of the QT interval. An increased risk of ventricular arrhythmias has been reported when mefloquine is given with *amiodarone*.

Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient who was taking *propranolol*.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Metoclopramide. Use with metoclopramide may increase plasma concentrations of mefloquine.[1]

1. Na Bangchang K, *et al.* The effect of metoclopramide on mefloquine pharmacokinetics. *Br J Clin Pharmacol* 1991; **32:** 640–1.

Vaccines. Unfortunately, conflicting advice has been issued concerning the use of mefloquine after typhoid vaccination, for details see p.2241.

Pharmacokinetics

The pharmacokinetics of mefloquine may be altered by malaria infection in a manner similar to those of quinine, the main effects being reductions in both its volume of distribution and its overall clearance.

Mefloquine is well absorbed from the gastrointestinal tract but there is marked interindividual variation in the time required to achieve peak plasma concentrations. Mefloquine is about 98% bound to plasma proteins and high concentrations have been reported in red blood cells. It is widely distributed throughout the body. Mefloquine has a long elimination half-life; mean values of about 21 days have been reported for some patients, although like other pharmacokinetic data on mefloquine there is considerable variation in reported figures. Subtherapeutic concentrations of mefloquine may persist in the blood for several months. Mefloquine is metabolised in the liver. Little of a dose is excreted in the urine and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.

Mefloquine is distributed into breast milk in small amounts.

◊ Reviews of pharmacokinetic studies of mefloquine reveal considerable interindividual variation for several pharmacokinetic parameters and some evidence that there might be pharmacokinetic differences between ethnic groups.[1,2] Mefloquine is well absorbed by healthy subjects and by patients with uncomplicated malaria after oral doses.[3,4] In patients with complicated malaria adequate blood concentrations have been obtained by the nasogastric route but this route cannot be relied upon for seriously ill patients[5] as absorption may be incomplete.[1] Mefloquine has a large apparent volume of distribution but this is reduced in the presence of malaria.[6,7] In children given mefloquine with sulfadoxine and pyrimethamine as tablets crushed and mixed with a glucose syrup, maximum blood-mefloquine concentrations were higher and reached in a shorter time compared with equivalent doses in adults.[8] In pregnant women with uncomplicated malaria blood concentrations were lower than in non-pregnant women and the apparent volume of distribution was larger.[9] Once-weekly prophylactic doses of mefloquine resulted in steady-state conditions at about 10 doses with no evidence of subsequent accumulation.[10]

Mefloquine is metabolised in the liver[11] largely into 2,8-bis(trifluoromethyl)-4-quinoline carboxylic acid [Ro-21-5104][12] but this metabolite appears to be inactive against *Plasmodium falciparum*.[13] Only a small percentage of a dose is excreted in the urine[14] and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.[1] Mefloquine has an extremely long plasma elimination half-life; again there is considerable interindividual variation and mean values ranging from 13.9 to 27.5 days have been quoted, the smaller figure of the range referring to a formulation that did not provide as good absorption as the preparation now in use.[1]

Mefloquine is distributed into breast milk, but a single dose study in 2 women[15] indicated that the concentration of mefloquine in milk was only a small proportion of that seen in plasma.

1. Karbwang J, White NJ. Clinical pharmacokinetics of mefloquine. *Clin Pharmacokinet* 1990; **19:** 264–79.
2. Palmer KJ, *et al.* Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.
3. Karbwang J, *et al.* The pharmacokinetics of mefloquine when given alone or in combination with sulphadoxine and pyrimethamine in Thai male and female subjects. *Eur J Clin Pharmacol* 1987; **32:** 173–7.
4. Looareesuwan S, *et al.* Studies of mefloquine bioavailability and kinetics using a stable isotope technique: a comparison of Thai patients with falciparum malaria and healthy caucasian volunteers. *Br J Clin Pharmacol* 1987; **24:** 37–42.
5. Chanthavanich P, *et al.* Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34:** 1028–36.
6. Juma FD, Ogeto JO. Mefloquine disposition in normals and in patients with severe Plasmodium falciparum malaria. *Eur J Drug Metab Pharmacokinet* 1989; **14:** 15–17.
7. Karbwang J, *et al.* A comparison of the pharmacokinetics of mefloquine in healthy Thai volunteers and in Thai patients with falciparum malaria. *Eur J Clin Pharmacol* 1988; **35:** 677–80.
8. Singhasivanon V, *et al.* Pharmacokinetic study of mefloquine in Thai children aged 5-12 years suffering from uncomplicated falciparum malaria treated with MSP or MSP plus primaquine. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 27–32.
9. Na Bangchang K, *et al.* Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 321–3.
10. Pennie RA, *et al.* Steady state pharmacokinetics of mefloquine in long-term travellers. *Trans R Soc Trop Med Hyg* 1993; **87:** 459–62.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.
13. Håkanson A, *et al.* Comparison of the activity in vitro of mefloquine and two metabolites against Plasmodium falciparum. *Trans R Soc Trop Med Hyg* 1990; **84:** 503–4.
14. Schwartz DE, *et al.* Urinary excretion of mefloquine and some of its metabolites in African volunteers at steady state. *Chemotherapy* 1987; **33:** 305–8.
15. Edstein MD, *et al.* Excretion of mefloquine in human breast milk. *Chemotherapy* 1988; **34:** 165–9.

Uses and Administration

Mefloquine is a 4-methanolquinoline antimalarial related to quinine. It is a blood schizontocide effective against all forms of malaria including chloroquine- or multidrug-resistant strains of *Plasmodium falciparum*, although some strains are naturally resistant to mefloquine. It is used for the treatment of uncomplicated falciparum malaria and chloroquine-resistant vivax malaria, and also for malaria prophylaxis. Mefloquine is also used after treatment with an artemisinin derivative for acute uncomplicated malaria, to reduce the risk of recrudescence.

Mefloquine is given orally as the hydrochloride but variation in the way doses are expressed could lead to confusion. In the UK and elsewhere, doses are expressed in terms of the base and a dose of 250 mg base is equivalent to about 274 mg of mefloquine hydrochloride. In the USA, doses are expressed in terms of the hydrochloride and a dose of 250 mg is therefore equivalent to only about 228 mg of mefloquine base. Doses in the USA could therefore be about 10% less than elsewhere.

Doses recommended in the UK are as follows.

- For the *treatment of malaria*, mefloquine base 20 to 25 mg/kg (up to a maximum of 1.5 g) as a single dose or preferably in 2 or 3 divided doses 6 to 8 hours apart
- For the *prophylaxis of malaria*, a dose of mefloquine base 250 mg once weekly in adults and children over 45 kg. Children weighing 5 to 19 kg may be given one-quarter the adult dose; those weighing 20 to 30 kg, half the adult dose; and those weighing 31 to 45 kg three-quarters the adult dose

  Prophylaxis should be started 1 to 3 weeks before exposure and continued for 4 weeks after leaving the malarious area

For other dosage recommendations, see under Malaria, below.

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

TREATMENT. Clinical studies have shown mefloquine to be effective in the treatment of chloroquine- or multidrug-resistant falciparum malaria. It is also effective in benign malarias, but is not normally required since they usually respond to chloroquine.

Mefloquine has been widely used as an alternative to regimens using quinine for the treatment of chloroquine-resistant or multidrug-resistant strains of *Plasmodium falciparum.* It is now also used with an artemisinin derivative in multidrug resistance (see p.599).

As there is no parenteral formulation of mefloquine currently available it can only be used in patients who can take oral medication and is therefore unsuitable for sole treatment in severe infections. Mefloquine has produced adequate blood concentrations by the nasogastric route, but this route cannot be relied upon in seriously ill patients.[1] If mefloquine is given to patients after parenteral doses of quinine, it is recommended that a period of 12 hours should be allowed after the last dose of quinine to avoid toxicity.

In the UK, the recommended dose for the treatment of malaria is the equivalent of 20 to 25 mg of mefloquine base per kg bodyweight, as a single dose or preferably in two or three divided doses 6 to 8 hours apart, to a maximum of 1.5 g. The manufacturers recommend a lower dose of 15 mg/kg for the partially immune. In the USA, the manufacturers recommend 1250 mg of mefloquine hydrochloride given as a single dose. WHO[2] recommends a dose of mefloquine base of 25 mg/kg given over 2 or 3 days (15 mg/kg followed by 10 mg/kg a day later, or 8.3 mg/kg daily for 3 days).

WHO[3] considers that drugs used for the treatment of uncomplicated falciparum malaria may in principle be carried as a *standby* for use in similar doses for the emergency self-treatment of malaria, although mefloquine is not recommended by WHO as a first-line regimen.

PROPHYLAXIS. It had been hoped that mefloquine could be reserved for the treatment of malaria, but increasing drug resistance to chemoprophylactic regimens has led to it being widely used for malaria prophylaxis. WHO recommends[3] that mefloquine should be used where there is a high risk of falciparum malaria and drug resistance or a moderate to low risk but with high drug resistance. For **adults** the equivalent of 250 mg of mefloquine base is given every week, starting 1 to 3 weeks before departure, and continuing throughout the period of exposure and for 4 weeks after leaving the malarious area. Starting mefloquine prophylaxis 2 to 3 weeks before exposure allows for detection of possible adverse effects before travelling (see Effects on the Nervous System, above, for concerns about neurotoxicity). It is now considered that mefloquine prophylaxis can be given for periods of up to one year instead of the previous limit of 3 months.

Mefloquine is considered to be suitable[3] for prophylaxis in the second and third trimesters of pregnancy. Pregnancy should be avoided during and for 3 months after stopping the drug.

Recommended dosages of mefloquine for prophylaxis in **children** are generally based on 5 mg/kg as a single weekly dose in children weighing over 5 kg.[3] The doses now usually used in the

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.

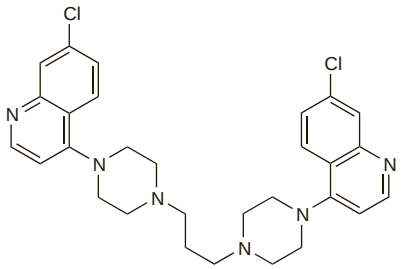
Preparations

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)*

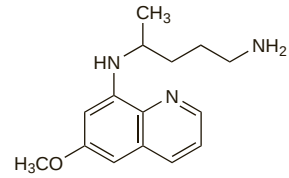
Difosfato de Primaquina; Fosfato de primaquina; Primachin difosfát; Primachina Fosfato; Primachini Phosphas; Primakiinidifosfaatti; Primakindifosfat; Primakin-difoszfát; Primakvino difosfatas; Primaquine Diphosphate; Primaquine, diphosphate de; Primaquine, Phosphate de; Primaquini diphosphas; Primaquini 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