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.

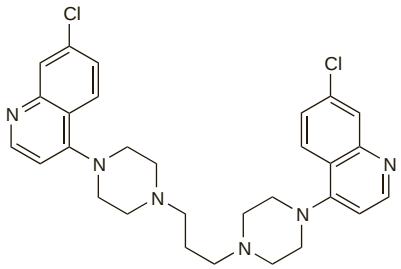
Preparations

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)*

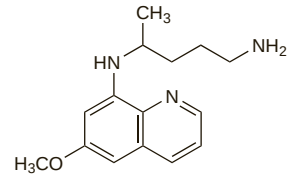
Difosfato de Primaquina; Fosfato de primaquina; Primachin difosfát; Primachina Fosfato; Primachini Phosphas; Primakiinidifosfaatti; Primakindifosfat; Primakin-difoszfát; Primakvino difosfatas; Primaquine Diphosphate; Primaquine, diphosphate de; Primaquine, Phosphate de; Primaquini diphosphas; Primaquini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

of about 51 kg. There have been several other reports of primaquine-resistant *P. vivax*,[4-7] and the suggestion has been made that higher doses of primaquine (15 mg twice daily for 14 days, to give a total dose of 6 mg/kg assuming a body-weight of 70 kg) should be considered wherever the vivax malaria was acquired.[7,8] A systematic review[9] concluded that when used with chloroquine, a 14-day course of primaquine 15 mg daily was more effective than a 5-day course in preventing relapses of vivax malaria. The 5-day course of primaquine plus chloroquine appeared to be no better than chloroquine alone.

Variable responses to primaquine in the Amazonian region were attributed to considerable variation in the content of primaquine both between and within batches of tablets; primaquine content ranged from 19 to 168% of the labelled content.[10]

In the USA, the CDC[11] have suggested the use of primaquine at the end of prophylaxis to prevent relapses due to *P. vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic. In those who have taken chloroquine, doxycycline, or mefloquine as prophylaxis, primaquine is usually given during the last 2 weeks of prophylaxis, but may also be taken immediately after prophylaxis is completed. When atovaquone plus proguanil is taken as prophylaxis, primaquine may be given either during the last 7 days and then for an additional 7 days, or for 14 days after atovaquone plus proguanil prophylaxis is completed. The recommended daily dose of primaquine for terminal prophylaxis is 30 mg for adults and 600 micrograms/kg for children.

Primaquine has also been tried for prophylaxis of falciparum and vivax malaria; use for a year produced effective cover and was well tolerated by Javanese men without G6PD deficiency.[12] It was also effective for prophylaxis in Colombian military personnel; it was noted that primaquine prophylaxis could be stopped 1 week after departing the endemic area.[13]

1. Molyneux M, Fox R. Diagnosis and treatment of malaria in Britain. *BMJ* 1993; **306:** 1175–80.
2. Luzzi GA, *et al.* Treatment of primaquine-resistant Plasmodium vivax malaria. *Lancet* 1992; **340:** 310.
3. Bunnag D, *et al.* High dose of primaquine in primaquine resistant vivax malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 218–19.
4. Collins WE, Jeffrey GM. Primaquine resistance in Plasmodium vivax. *Am J Trop Med Hyg* 1996; **55:** 243–9.
5. Signorini L, *et al.* Short report: primaquine-tolerant Plasmodium vivax in an Italian traveler from Guatemala. *Am J Trop Med Hyg* 1996; **55:** 472–3.
6. Smoak BL, *et al.* Plasmodium vivax infections in US Army troops: failure of primaquine to prevent relapse in studies from Somalia. *Am J Trop Med Hyg* 1997; **56:** 231–4.
7. Doherty JF, *et al.* Treatment of Plasmodium vivax malaria—time for a change? *Trans R Soc Trop Med Hyg* 1997; **91:** 76.
8. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004; **39:** 1336–45.
9. Galappaththy GNL, *et al.* Primaquine for preventing relapses in people with Plasmodium vivax malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/03/08).
10. Petralanda I. Quality of antimalarial drugs and resistance to Plasmodium vivax in Amazonian region. *Lancet* 1995; **345:** 1433.
11. CDC. Malaria. In: *The Yellow Book*: *CDC Health Information for International Travel; 2008.* Available at: http://wwwn.cdc.gov/travel/yellowBookCh4-Malaria.aspx (accessed 10/03/08)
12. Fryauff DJ, *et al.* Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet* 1995; **346:** 1190–3.
13. Soto J, *et al.* Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Ann Intern Med* 1998; **129:** 241–4.

Pneumocystis pneumonia. Primaquine with clindamycin is used in the treatment of pneumocystis pneumonia as an alternative to co-trimoxazole[1] (see p.521). Treatment has usually lasted 3 weeks, with primaquine being given by mouth in daily doses equivalent to 30 mg of the base, and clindamycin usually being given intravenously in doses of 600 mg four times daily or 300 to 450 mg four times daily by mouth.[2] The *BNF* suggests clindamycin 600 mg by mouth every 8 hours with primaquine 30 mg daily by mouth for mild to moderate disease.

A randomised multicentre study[3] compared this latter regimen (primaquine 30 mg daily and clindamycin 600 mg three times daily) with co-trimoxazole and with a combination of dapsone and trimethoprim in 181 AIDS patients who had confirmed mild to moderate pneumocystis pneumonia. Primaquine-clindamycin was as effective as the other two regimens, although the authors suggested that the combination might be best avoided in patients with severe myelosuppression.

Primaquine with clindamycin is not normally recommended for prophylaxis although there are reports of it being tried.[4] A retrospective examination[5] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Benfield T, *et al.* Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr* 2008; **48:** 63–7.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter 2007.
3. Safrin S, *et al.* Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS: a double-blind, randomized trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. *Ann Intern Med* 1996; **124:** 792–802.
4. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
5. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Preparations

USP 31: Primaquine Phosphate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Primacin; ***Braz.:*** Primakinder; ***India:*** Malirid; PMQ-INGA; Primacip.

Proguanil Hydrochloride *(BANM, rINNM)*

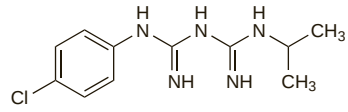
Bigumalum; Chloriguane Hydrochloride; Chloroguanide Hydrochloride; Hidrocloruro de proguanil; Proguanide Hydrochloride; Proguaniilihydrokloridi; Proguanil, chlorhydrate de; Proguanil hydrochlorid; Proguanil-hidroklorid; Proguanilhydroklorid; Proguanili hydrochloridum; Proguanilo hidrochloridas; RP-3359; SN-12,837. 1-(4-Chlorophenyl)-5-isopropylbiguanide hydrochloride.

Прогуанила Гидрохлорид

$C_{11}H_{16}ClN_5,HCl$ = 290.2.

CAS — 500-92-5 (proguanil); 637-32-1 (proguanil hydrochloride).

ATC — P01BB01.



(proguanil)

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

Ph. Eur. 6.2 (Proguanil Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane. Protect from light.

Stability. Although the Ph. Eur. 6.2 directs that proguanil hydrochloride should be protected from light, stability studies[1,2] suggest that it is a very stable compound with only small amounts of its major decomposition product 4-chloroaniline being formed during thermal and photochemical stress.

1. Owoyale JA, Elmarakby ZS. Effect of sunlight, ultraviolet irradiation and heat on proguanil. *Int J Pharmaceutics* 1989; **50:** 219–21.
2. Taylor RB, *et al.* A chemical stability study of proguanil hydrochloride. *Int J Pharmaceutics* 1990; **60:** 185–90.

Adverse Effects and Precautions

Apart from mild gastric intolerance, diarrhoea, and some reports of aphthous ulceration there appear to be few adverse effects associated with usual doses of proguanil hydrochloride. There have been rare reports of hypersensitivity reactions including urticaria and angioedema. Rare cases of seizures and psychotic events have also been reported. Haematological changes have been reported in patients with severe renal impairment. Overdosage may produce epigastric discomfort, vomiting, and renal irritation leading to haematuria.

Proguanil should be used with caution in patients with renal impairment; dosage should be reduced accordingly (see under Uses and Administration, below).

Proguanil may be taken during pregnancy, but UK guidelines recommend that folate supplements (folic acid 5 mg daily) should also be given; however, the combination of proguanil with atovaquone should be avoided as data regarding the safety of atovaquone are lacking.

◊ Until 1985 proguanil was generally taken in a dose of 100 mg daily for malaria prophylaxis with few adverse effects. Although there was no increase in serious adverse effects when the dose was increased to 200 mg daily, and it began to be used with chloroquine, there were an increasing number of reports of reversible aphthous ulceration.[1] Chloroquine may exacerbate this effect.[2] There has also been a report of reversible alopecia in women and scaling of the skin in both men and women using proguanil.[3]

Megaloblastic anaemia and pancytopenia were associated with proguanil accumulation in 2 patients with renal failure.[4]

Stevens-Johnson syndrome has been reported[5] in a patient taking proguanil with atovaquone.

1. Peto TEA. Toxicity of antimalarial drugs. *J R Soc Med* 1989; **82** (suppl 17): 30–4.
2. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; **335:** 164.
3. Hanson SN, *et al.* Hairloss and scaling with proguanil. *Lancet* 1989; **i:** 225.
4. Boots M, *et al.* Megaloblastic anemia and pancytopenia due to proguanil in patients with chronic renal failure. *Clin Nephrol* 1982; **18:** 106–8.
5. Emberger M, *et al.* Stevens-Johnson syndrome associated with Malarone antimalarial prophylaxis. Abstract: *Clin Infect Dis* 2003; **37:** 158. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/06/08)

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

Interactions

Fluvoxamine. Fluvoxamine can virtually abolish[1] the metabolism of proguanil to its active metabolite cycloguanil via an inhibitory effect on the cytochrome P450 isoenzyme CYP2C19.

1. Jeppesen U, *et al.* The CYP2C19 catalyzed bioactivation of proguanil is abolished during fluvoxamine intake. *Eur J Clin Pharmacol* 1997; **52** (suppl): A134.

Warfarin. For a report of haematuria and high prothrombin ratio in a patient stabilised on warfarin who took proguanil for malaria prophylaxis, see p.1429.

Pharmacokinetics

Proguanil is readily absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations occurring within about 4 hours. Proguanil is metabolised in the liver to the active metabolite cycloguanil. Peak plasma concentrations of cycloguanil occur approximately 1 hour after those of the parent drug. The elimination half-lives of both proguanil and cycloguanil are about 20 hours. About 40 to 60% of proguanil is eliminated in the urine, of which 60% is unchanged and 30% cycloguanil. There is also some elimination via the faeces. Proguanil is distributed into breast milk in small amounts (which are not adequate to provide chemoprophylaxis for the infant).

◊ Early studies found proguanil to be well absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 4 hours.[1] In more recent studies, peak plasma concentrations of proguanil have been achieved within 2 to 4 hours.[2-4] Plasma protein binding for proguanil is 75%.[5] Proguanil is metabolised in the liver[3] to the active metabolite cycloguanil and to *p*-chlorophenylbiguanide which is inactive. Peak plasma concentrations of cycloguanil occur about 5.3 hours after doses of proguanil.[4] Unlike proguanil and *p*-chlorophenylbiguanide, cycloguanil is not concentrated in erythrocytes and thus concentrations of cycloguanil in plasma and whole blood are similar.[4] The elimination half-lives for proguanil and cycloguanil are about 20 hours.[3,4] A review of early studies states that 40 to 60% of a dose of proguanil is excreted in the urine, 60% of this as the unchanged drug, 30% as cycloguanil, and 8% as *p*-chlorophenylbiguanide.[1] About 10% of a dose is excreted in the faeces.[1] However, these values can vary greatly and wide interindividual variations in the ability to metabolise proguanil to cycloguanil have been reported.[3,6,7] Malaria prophylaxis with proguanil might be less effective in poor metabolisers although this has not been proved conclusively[8] and, anyway, other factors such as lack of protection against mosquitoes and sensitivity of the malaria parasite might be more important.[9]

Plasma concentrations of cycloguanil may be reduced in the third trimester of pregnancy.[10]

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Kelly JA, *et al.* The kinetics of proguanil during prophylaxis. *Trans R Soc Trop Med Hyg* 1986; **80:** 338.
3. Watkins WM, *et al.* Variability in the metabolism of proguanil to the active metabolite cycloguanil in healthy Kenyan adults. *Trans R Soc Trop Med Hyg* 1990; **84:** 492–5.
4. Wattanagoon Y, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in healthy subjects. *Br J Clin Pharmacol* 1987; **24:** 775–80.
5. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
6. Ward SA, *et al.* Inter-subject variability in the metabolism of proguanil to the active metabolite cycloguanil in man. *Br J Clin Pharmacol* 1989; **27:** 781–7.
7. Helsby NA, *et al.* The multiple dose pharmacokinetics of proguanil. *Br J Clin Pharmacol* 1993; **35:** 653–6.
8. Mberu EK, *et al.* Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough. *Trans R Soc Trop Med Hyg* 1995; **89:** 658–9.
9. Skjelbo E, *et al.* Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clin Pharmacol Ther* 1996; **59:** 304–11.
10. Wangboonskul J, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. *Eur J Clin Pharmacol* 1993; **44:** 247–51.

Uses and Administration

Proguanil is a biguanide compound that has little antimalarial activity until metabolised in the body to the active antimalarial drug cycloguanil. Cycloguanil, like pyrimethamine, inhibits plasmodial dihydrofolate re-