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)*

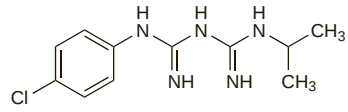
Bigumalum; Chloriguane Hydrochloride; Chloroguanide Hydrochloride; Hidrocloruro de proguanil; Proguanide Hydrochloride; Proguaniilihydrokloridi; Proguanil, chlorhydrate de; Proguanil hydrochlorid; Proguanil-hidroklorid; Proguanilhydroklorid; Proguanili hydrochloridum; Proguanilo hidrochloridas; RP-3359; 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-

ductase and thus disrupts synthesis of nucleic acids in the parasite. Cycloguanil is active against pre-erythrocytic forms and is a slow-acting blood schizontocide. It also has some sporontocidal activity, rendering the gametocytes non-infective to the mosquito vector.

The value of proguanil is limited by the rapid development of resistance.

Proguanil is used orally as the hydrochloride for the chemoprophylaxis of malaria, with chloroquine or atovaquone. The schizontocidal activity of cycloguanil on erythrocytic forms is too slow for cycloguanil or proguanil to be used alone for the treatment of malaria, but proguanil hydrochloride is given combined with atovaquone for the treatment of uncomplicated falciparum malaria.

For *prophylaxis* of malaria in combination with chloroquine, the usual adult daily dose of proguanil hydrochloride is 200 mg taken after food. For prophylaxis in combination with atovaquone 250 mg, the daily dose of proguanil hydrochloride is 100 mg. It is generally recommended that chemoprophylaxis for travellers should start 1 week before exposure to malaria, but if this is not possible it can be started 1 to 2 days prior to travel. Use should continue throughout exposure and for at least 4 weeks (1 week when proguanil is given with atovaquone) after leaving a malarious area.

In the *treatment* of uncomplicated falciparum malaria, adult doses are proguanil hydrochloride 400 mg together with atovaquone 1 g, each orally as a single dose for 3 consecutive days.

For children's doses in the prophylaxis and treatment of malaria, see below.

Cycloguanil was also formerly given by intramuscular injection as an oily suspension of the embonate.

◊ Reviews.

1. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
2. Marra F, *et al*. Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.
3. Nakato H, *et al*. A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* 2007; **60:** 929–36.

Administration in children. Dosage recommendations for proguanil with **chloroquine** for **malaria prophylaxis** in children have varied. UK malaria experts[1] have suggested the following prophylactic oral doses for children based on fractions of the adult dose of 200 mg daily:

- under 6.0 kg (0 to 12 weeks of age): one-eighth the adult dose
- 6 to 9.9 kg (3 to 11 months): one-quarter the adult dose
- 10 to 15.9 kg (1 year to 3 years 11 months): three-eighths 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

They noted that body-weight was a better guide to dosage than age for children over 6 months.

Children may be given proguanil with **atovaquone** for the **prophylaxis** of malaria in the following doses, based on the adult dose of 100 mg of proguanil hydrochloride daily:

- children weighing 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- over 40 kg: the adult dose

Doses of proguanil with atovaquone for the **treatment** of malaria, based on the adult dose of 400 mg of proguanil hydrochloride daily, are:

- children weighing 5 to 8 kg: one-eighth the adult dose
- 9 to 10 kg: three-sixteenths the adult dose
- 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- 40 kg and over: the adult dose

1. 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)

Administration in renal impairment. Proguanil is excreted by the kidneys and should be given in reduced dosage or avoided in patients with renal impairment. The following oral doses have been recommended based on creatinine clearance (CC):

- CC 20 to 59 mL/minute: 100 mg daily
- CC 10 to 19 mL/minute: 50 mg every other day
- CC less than 10 mL/minute: 50 mg once weekly

Preparations

BP 2008: Proguanil Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Paludrine; ***Austria:*** Paludrine; ***Belg.:*** Paludrine; ***Denm.:*** Paludrine; ***Fin.:*** Paludrine†; ***Fr.:*** Paludrine; ***Ger.:*** Paludrine; ***India:*** Laveran; ***Irl.:*** Paludrine; ***Israel:*** Paludrine; ***Ital.:*** Paludrine; ***Malaysia:*** Paludrine†; ***Neth.:*** Paludrine; ***Norw.:*** Paludrine; ***Port.:*** Paludrine; ***S.Afr.:*** Paludrine†; ***Swed.:*** Paludrine; ***Switz.:*** Paludrine; ***UK:*** Paludrine.

Multi-ingredient: ***Austral.:*** Malarone; ***Austria:*** Malarone; Promal; ***Belg.:*** Malarone; ***Canad.:*** Malarone; ***Cz.:*** Malarone; ***Denm.:*** Malarone; ***Fr.:*** Malarone; Savarine; ***Ger.:*** Malarone; ***Gr.:*** Malarone; ***Hong Kong:*** Malarone; ***Hung.:*** Malarone; ***Irl.:*** Malarone; ***Israel:*** Malarone; ***Ital.:*** Malarone; ***Malaysia:*** Malarone; ***Neth.:*** Malarone; ***Norw.:*** Malarone; ***NZ:*** Malarone; ***Pol.:*** Malarone; ***S.Afr.:*** Daramal-Paludrine†; Malanil; ***Singapore:*** Malarone; ***Spain:*** Malarone; ***Swed.:*** Malarone; ***Switz.:*** Malarone; ***UK:*** Malarone; ***USA:*** Malarone.

Pyrimethamine *(BAN, rINN)*

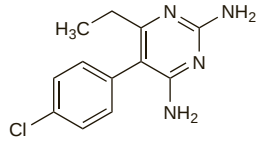
BW-50-63; Pirimetamin; Pirimetamina; Pirimetaminas; Pirymetamina; Pyrimetamiini; Pyrimetamin; Pyrimethamin; Pyriméthamine; Pyrimethaminum; RP-4753. 5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diyldiamine.

Пириметамин

$C_{12}H_{13}ClN_4$ = 248.7.

CAS — 58-14-0.

ATC — P01BD01.



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

Ph. Eur. 6.2 (Pyrimethamine). An almost white crystalline powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Pyrimethamine). A white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 125 of chloroform; slightly soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Use of pyrimethamine for prolonged periods, as used to be the case when it was **given alone** for the prophylaxis of malaria, can cause depression of haematopoiesis due to interference with folic acid metabolism. Skin rashes and hypersensitivity reactions also occurred.

Larger doses, such as those used in the treatment of toxoplasmosis, may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain, and vomiting; haematological effects such as megaloblastic anaemia, leucopenia, thrombocytopenia, and pancytopenia are also more likely to occur. CNS effects including headache, dizziness, and insomnia have also been reported.

Pulmonary eosinophilia has been reported in patients taking pyrimethamine **with other antimalarials**. Severe and sometimes fatal reactions have occurred when pyrimethamine has been used with sulfadoxine (*Fansidar*), including erythema multiforme and the Stevens-Johnson syndrome, and toxic epidermal necrolysis; there have also been isolated reports of hepatotoxicity. Agranulocytosis occurs more frequently when pyrimethamine is used with dapsone (*Maloprim*) and fatalities have been reported.

Acute overdosage with pyrimethamine can cause gastrointestinal effects and CNS stimulation with vomiting, excitability, and convulsions. Tachycardia, respiratory depression, circulatory collapse, and death may follow. Treatment of overdosage is symptomatic.

Adverse effects with dapsone. Between 1972 and 1988, the UK CSM received 76 reports of reactions that were attributed to the use of pyrimethamine with dapsone (*Maloprim*), of which 40 (53%) were considered to be serious, including 6 deaths.[1] The incidence was estimated to be 1 in 9100 for serious reactions and 1 in 60 200 for fatalities. Serious blood disorders including agranulocytosis, granulocytopenia, or leucopenia occurred in 15 patients (estimated incidence of 1 in 20 000), five of whom died. The other death was in a patient with myocarditis. Three patients had cyanosis due to methaemoglobinaemia. Respiratory disorders such as pulmonary eosinophilia, flu-like syndrome, and dyspnoea occurred in 6 patients. In 4 patients skin disorders were the principal effect and included epidermal necrolysis, angioedema, and bullous eruptions. Hepatic disorders were also reported in 4 patients. Three women using pyrimethamine-dapsone during pregnancy delivered malformed babies, one of them being stillborn. Other effects in 4 patients included convulsions, exacerbated epilepsy, pancreatitis, or a generalised allergic reaction.

A review[2] of 21 cases of agranulocytosis associated with pyrimethamine-dapsone concluded that, although agranulocytosis can occur very rarely in patients taking pyrimethamine or dapsone alone, agranulocytosis due to the combination appears to be caused by an idiosyncratic reaction to dapsone exacerbated by pyrimethamine. Of the 18 individuals for whom dosage was certain, 12 had been taking one tablet of pyrimethamine-dapsone twice weekly, twice the recommended dose of one tablet once weekly. Of the 9 patients who died, 6 had been taking one tablet twice weekly and one patient had taken one tablet once weekly; the dosage was uncertain in the remaining patients. The time of onset of symptoms had been 7 to 9 weeks after starting therapy in 16 of 19 of the patients.

Some consider that pyrimethamine with dapsone may produce some degree of immunosuppression and render users more susceptible to common infections. A higher incidence of non-specific upper respiratory-tract infections occurred in military recruits taking the combination than in those not given antimalarial prophylaxis.[3]

Pulmonary eosinophilia has also occurred in patients taking pyrimethamine with dapsone but, as there have also been similar reports of pulmonary toxicity in patients taking pyrimethamine with sulfadoxine (see below) or pyrimethamine with chloroquine, it has been suggested that pyrimethamine is probably the causative agent.[4]

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–5.
2. Hutchinson DBA, *et al*. Agranulocytosis associated with Maloprim: review of cases. *Hum Toxicol* 1986; **5:** 221–7.
3. Lee PS, Lau EYL. Risk of acute non-specific upper respiratory tract infections in healthy men taking dapsone–pyrimethamine for prophylaxis against malaria. *BMJ* 1988; **296:** 893–5.
4. Davidson AC, *et al*. Pulmonary toxicity of malaria prophylaxis. *BMJ* 1988; **297:** 1240–1.

Adverse effects with sulfonamides. Severe and potentially fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been associated with the combined use of pyrimethamine with sulfadoxine (*Fansidar*) for malaria prophylaxis. The reported incidence of these reactions has varied with surveys in the UK,[1] USA,[2] and Sweden[3] yielding similar results and a survey from Switzerland[4] finding a much lower incidence. The overall rate of serious reactions to pyrimethamine-sulfadoxine in the UK has been estimated to be 1 in 2100. The estimates for severe cutaneous reactions were 1 in 4900 in the UK, 1 in 5000 to 1 in 8000 in the USA, 1 in 10 000 in Sweden, and 1 in 150 000 in Switzerland, and the death rates were 1 in 11 100 in the UK, 1 in 11 000 to 1 in 25 000 in the USA, and 1 in 35 000 in Sweden; no fatalities were reported in Switzerland. Workers on the Swiss survey had suggested that the high incidence of cutaneous reactions reported in the USA might have been due to concurrent therapy with chloroquine but this has been disputed.[5] The authors of the UK survey[1] suggested that the lower incidence reported in Switzerland may have been due to the different methods used to estimate the amount of drug usage. Whether this toxicity is due to the combined use of pyrimethamine and sulfadoxine is unclear as the estimated frequency of fatal reactions associated with the use of sulfadoxine alone in Mozambique[6] was 1 in 50 000.

There have been isolated reports of other severe or life-threatening reactions associated with the use of pyrimethamine-sulfadoxine when used alone or with chloroquine, including hepatotoxicity[7-9] (estimated incidence of 1 in 11 100 in the UK[1]), fatal multisystem toxicity,[10] drug fever and photodermatitis,[11] agranulocytosis,[11] and erythroderma resembling Sézary syndrome.[12] Severe pulmonary reactions have also occurred[3,13] but, as similar reactions have also been reported when pyrimethamine has been used with other antimalarials, including dapsone, it has been suggested that pyrimethamine is the causative agent (see Adverse Effects with Dapsone, above). Hyperammonaemia and carnitine deficiency with deterioration in mental status has been reported in a patient given pyrimethamine and sulfadiazine for the treatment of toxoplasmosis.[14]

Severe megaloblastic anaemia in a patient taking pyrimethamine and sulfadiazine for toxoplasmosis of the CNS[15] was treated by withdrawing pyrimethamine and giving folinic acid orally, together with a single platelet infusion.

For a comparison of the incidence of pruritus induced by various antimalarials including pyrimethamine with sulfadoxine, see Effects on the Skin under Chloroquine, p.600.

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–5.
2. Miller KD, *et al*. Severe cutaneous reactions among American travelers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35:** 451–8.