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)*

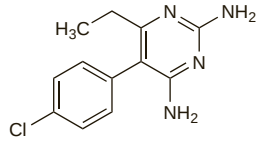
BW-50-63; Pirimetamin; Pirimetamina; Pirimetaminas; Pirymetamina; Pyrimetamiini; Pyrimetamin; Pyrimethamin; Pyriméthamine; Pyrimethaminum; RP-4753. 5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diyldiamine.

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.

3. Hellgren U, *et al.* Adverse reactions to sulphadoxine–pyrimethamine in Swedish travellers: implications for prophylaxis. *BMJ* 1987; **295:** 365–6.
4. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine–pyrimethamine in Switzerland. *Lancet* 1986; **i:** 610.
5. Rombo L, *et al.* Does chloroquine contribute to the risk of serious adverse reactions to Fansidar? *Lancet* 1985; **ii:** 1298–9.
6. Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet* 1985; **ii:** 1072–3.
7. Lazar HP, *et al.* Fansidar and hepatic granulomas. *Ann Intern Med* 1985; **102:** 722.
8. Wejstal R, *et al.* Liver damage associated with Fansidar. *Lancet* 1986; **i:** 854–5.
9. Zitelli BJ, *et al.* Fatal hepatic necrosis due to pyrimethamine–sulfadoxine (Fansidar). *Ann Intern Med* 1987; **106:** 393–5.
10. Selby CD, *et al.* Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine (Fansidar). *BMJ* 1985; **290:** 113–14.
11. Olsen VV, *et al.* Serious reactions during malaria prophylaxis with pyrimethamine–sulfadoxine. *Lancet* 1982; **ii:** 994.
12. Langtry JAA, *et al.* Erythroderma resembling Sézary syndrome after treatment with Fansidar and chloroquine. *BMJ* 1986; **292:** 1107–8.
13. Svanbom M, *et al.* Unusual pulmonary reaction during short term prophylaxis with pyrimethamine–sulfadoxine (Fansidar). *BMJ* 1984; **288:** 1876.
14. Sekas G, Harbhajan PS. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95:** 112–13.
15. Chute JP, *et al.* Severe megaloblastic anemia complicating pyrimethamine therapy. *Ann Intern Med* 1995; **122:** 884–5.

Overdosage. Reports of overdosage with pyrimethamine in infants.

1. Akinyanju O, *et al.* Pyrimethamine poisoning. *BMJ* 1973; **4:** 147–8.
2. Elmalem J, *et al.* Les accidents graves lors de la prescription de pyriméthamine chez les nourrissons traités pour une toxoplasmose. *Therapie* 1985; **40:** 357–9.

Precautions

Pyrimethamine may aggravate subclinical folic acid deficiency and it should not be given to patients with conditions associated with folate deficiency such as megaloblastic anaemia. Blood counts are required with prolonged treatment, and when large doses of pyrimethamine are used, as in the treatment of toxoplasmosis, blood counts should be checked twice weekly. Folinic acid, which does not interfere with the action of pyrimethamine against malaria or toxoplasmosis, has been given to prevent haematological toxicity due to pyrimethamine and its use is especially recommended if pyrimethamine is given during pregnancy. (Folic acid may be used as an alternative to folinic acid in malaria, but it interferes with the action of pyrimethamine against toxoplasmosis). For further information concerning use during pregnancy, see below.

Pyrimethamine should be given with caution to patients with renal or hepatic impairment. When patients with convulsive disorders need to receive large doses, as in the treatment of toxoplasmosis, it is recommended that small starting doses should be used.

When pyrimethamine is used with sulfonamides or dapsone, the general precautions applicable to those drugs should also be taken (see under Sulfamethoxazole, p.340 and under Dapsone, p.262) and treatment should be stopped immediately if any skin reactions, sore throat, or shortness of breath occurs.

Breast feeding. Pyrimethamine is distributed into breast milk[1] but as no adverse effects have been reported in breast-fed infants, the American Academy of Pediatrics considers breast feeding to be compatible with the use of pyrimethamine for malaria prophylaxis.[2] However, exposure of the infant to other folate antagonists should be avoided. The large doses of pyrimethamine used for treating toxoplasmosis may distribute into breast milk in sufficient quantities to interfere with folic acid metabolism in nursing infants.

1. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22:** 733–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

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

Pregnancy. There have been concerns over the use of pyrimethamine during pregnancy as it has been shown to be teratogenic in *animal* studies.[1] In one report, severe congenital defects in a stillborn infant were attributed to the use of pyrimethamine in early pregnancy,[2] but the association was considered to be questionable.[3] Other instances of congenital malformations with pyrimethamine and dapsone are given under Adverse Effects with Dapsone, above.

Others[4] suggest that intermittent preventive therapy for malaria with pyrimethamine-sulfadoxine has a favourable safety profile in pregnancy. WHO considers that pyrimethamine combinations may be used after the first trimester of pregnancy in the treatment of toxoplasmosis,[5] and that pyrimethamine-sulfadoxine may be used in all trimesters for treatment in high-risk malaria-endemic regions.[6]

1. Anonymous. Pyrimethamine combinations in pregnancy. *Lancet* 1983; **ii:** 1005–7. Correction. *ibid.*; 1378.
2. Harpey J-P, *et al.* Teratogenicity of pyrimethamine. *Lancet* 1983; **ii:** 399.
3. Smithells RW, Sheppard S. Teratogenicity of Debendox and pyrimethamine. *Lancet* 1983; **ii:** 623–4.
4. Peters PJ, *et al.* Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety* 2007; **30:** 481–501.
5. WHO. *WHO model formulary.* Geneva: WHO, 2004.
6. WHO. *Guidelines for the treatment of malaria.* Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 16/06/06)

Interactions

Use of pyrimethamine with other folate antagonists such as co-trimoxazole, trimethoprim, methotrexate, or phenytoin may exacerbate bone marrow depression.

Lorazepam. Signs of mild liver toxicity in 2 of 5 subjects who received lorazepam and pyrimethamine appeared to confirm earlier suspicions that giving these drugs together could cause hepatotoxicity. Both patients tolerated each drug when given separately.[1]

1. Briggs M, Briggs M. Pyrimethamine toxicity. *BMJ* 1974; **1:** 40.

Zidovudine. Studies *in vitro* and in *animals* suggest that zidovudine could reduce the effectiveness of pyrimethamine in the treatment of toxoplasmic encephalitis.[1] Furthermore, the dose of zidovudine may need to be altered if these drugs are used together as there has been a report that pyrimethamine with sulfadoxine (*Fansidar*) prolonged the serum half-life of zidovudine.[2]

1. Israelski DM, *et al.* Zidovudine antagonizes the action of pyrimethamine in experimental infection with Toxoplasma gondii. *Antimicrob Agents Chemother* 1989; **33:** 30–4.
2. Klein RS. Prophylaxis of opportunistic infections in individuals infected with HIV. *AIDS* 1989; **3** (suppl 1): S161–S173.

Pharmacokinetics

Pyrimethamine is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations of about 200 nanograms/mL are obtained 2 to 6 hours after a dose of 25 mg orally. It is mainly concentrated in the kidneys, lungs, liver, and spleen and about 80 to 90% is bound to plasma proteins.

It is metabolised in the liver and slowly excreted via the kidney, the average half-life in plasma being about 4 days. Several metabolites have been detected in the urine. Pyrimethamine crosses the placenta. It is distributed into breast milk (see under Breast Feeding in Precautions, above).

◊ References.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Cook IF, *et al.* Race-linked differences in serum concentrations of dapsone, monoacetyldapsone and pyrimethamine during malaria prophylaxis. *Trans R Soc Trop Med Hyg* 1986; **80:** 897–901.
3. Weiss LM, *et al.* Pyrimethamine concentrations in serum and cerebrospinal fluid during treatment of acute toxoplasma encephalitis in patients with AIDS. *J Infect Dis* 1988; **157:** 580–3.
4. Hellgren U, *et al.* Plasma concentrations of sulfadoxine-pyrimethamine, mefloquine and its main metabolite after regular malaria prophylaxis for two years. *Trans R Soc Trop Med Hyg* 1991; **85:** 356–7.
5. Winstanley PA, *et al.* The disposition of oral and intramuscular pyrimethamine/sulphadoxine in Kenyan children with high parasitaemia but clinically non-severe falciparum malaria. *Br J Clin Pharmacol* 1992; **33:** 143–8.
6. Newton CRJC, *et al.* A single dose of intramuscular sulfadoxine-pyrimethamine as an adjunct to quinine in the treatment of severe malaria: pharmacokinetics and efficacy. *Trans R Soc Trop Med Hyg* 1993; **87:** 207–10.
7. Jacobson JM, *et al.* Pyrimethamine pharmacokinetics in human immunodeficiency virus-positive patients seropositive for Toxoplasma gondii. *Antimicrob Agents Chemother* 1996; **40:** 1360–5.
8. Klinker H, *et al.* Plasma pyrimethamine concentrations during long-term treatment for cerebral toxoplasmosis in patients with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 1623–7.
9. Trenque T, *et al.* Human maternofoetal distribution of pyrimethamine-sulphadoxine. *Br J Clin Pharmacol* 1998; **45:** 179–80.
10. Trenque T, *et al.* Population pharmacokinetics of pyrimethamine and sulfadoxine in children with congenital toxoplasmosis. *Br J Clin Pharmacol* 2004; **57:** 735–41.
11. Barnes KI, *et al.* Sulfadoxine-pyrimethamine pharmacokinetics in malaria: pediatric dosing implications. *Clin Pharmacol Ther* 2006; **80:** 582–96.

Uses and Administration

Pyrimethamine is a diaminopyrimidine antimalarial used with a sulfonamide in the treatment of malaria and toxoplasmosis. Pyrimethamine with sulfadoxine has been tried in the treatment of actinomycetoma and for prophylaxis of pneumocystis pneumonia. Pyrimethamine alone or with sulfadoxine has also been tried in the treatment of isosporiasis.

Pyrimethamine exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase, thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is active against pre-erythrocytic forms and is also a slow-acting blood schizontocide. It also has some sporontocidal activity; it does not prevent the formation of gametocytes but renders them non-infective to the mosquito vector. It is mainly effective against *Plasmodium falciparum* but has some activity against *P. vivax*.

The development of plasmodial resistance has rendered obsolete the use of pyrimethamine on its own in malaria. Combinations of pyrimethamine with long-acting sulfonamides, such as sulfadoxine or sulfametopyrazine, are now used, although resistance has also developed to them.

For the *treatment* of uncomplicated falciparum **malaria**, pyrimethamine is given orally with sulfadoxine in a fixed dose ratio of 1 to 20 (*Fansidar*). WHO recommends that a single dose of pyrimethamine-sulfadoxine be used with artesunate given for 3 days; in areas of susceptibility and where artesunate is unavailable, amodiaquine may be used with pyrimethamine-sulfadoxine. The following doses of pyrimethamine-sulfadoxine are recommended:

- adults and children aged over 13 years, pyrimethamine 75 mg with sulfadoxine 1.5 g
- infants 5 to 11 months, pyrimethamine 12.5 mg with sulfadoxine 250 mg
- children 1 to 6 years, pyrimethamine 25 mg with sulfadoxine 500 mg
- children 7 to 13 years, pyrimethamine 50 mg with sulfadoxine 1 g

A combination of pyrimethamine with sulfametopyrazine has been used similarly.

Pyrimethamine and pyrimethamine combinations are no longer recommended for *prophylaxis* of malaria. Combined preparations of pyrimethamine with sulfadoxine (*Fansidar*), and with dapsone in a fixed ratio of 1 to 8 (*Maloprim*), have been used in areas of chloroquine or multidrug resistance, although other antimalarials are now preferred.

Pyrimethamine given with a sulfonamide such as sulfadiazine is used in the treatment of **toxoplasmosis**. Alternatively, pyrimethamine may be given with clindamycin in AIDS patients with toxoplasmosis unable to tolerate a sulfonamide. For details of dosage regimens used, see below.

Isosporiasis. Isosporiasis (p.824) usually responds well to treatment with co-trimoxazole, but there is a high incidence of recurrence in immunocompromised patients, such as those with AIDS, and some form of maintenance therapy is generally required. Oral therapy with co-trimoxazole 960 mg given three times weekly or pyrimethamine 25 mg with sulfadoxine 500 mg given weekly were found to be equally effective maintenance regimens.[1] Pyrimethamine given alone in daily doses of 50 to 75 mg with folate therapy may be of use in the treatment of patients sensitive to sulfonamides.[2]

1. Pape JW, *et al.* Treatment and prophylaxis of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **320:** 1044–7.
2. Weiss LM, *et al.* Isospora belli infection: treatment with pyrimethamine. *Ann Intern Med* 1988; **109:** 474–5.

Malaria. The overall treatment and prophylaxis of malaria and the place of pyrimethamine-sulfadoxine (Fansidar) in current recommendations are discussed on p.594.

Mycetoma. For reference to the use of pyrimethamine as part of the treatment of actinomycetoma, see under Mycetoma, p.180.

Pneumocystis pneumonia. For a mention of pyrimethamine with either dapsone or sulfadoxine for the prophylaxis of pneumocystis pneumonia, and a discussion of conventional prophylaxis and treatment, see p.521.

Toxoplasmosis. Pyrimethamine is given, usually with sulfadiazine or another appropriate sulphonamide, in the treatment of toxoplasmosis (p.826). Folinic acid is also given to counteract the megaloblastic anaemia associated with these drugs.

Oral doses suggested by WHO[1] are:

- in *pregnancy* (second and third trimesters), pyrimethamine 25 mg daily for 3 to 4 weeks with sulfadiazine 3 g daily in 4 divided doses
- in *neonates*, pyrimethamine 1 mg/kg daily, with sulfadiazine 85 mg/kg daily in 2 divided doses; treatment should be given for 6 months if there is overt neonatal disease, or for 4 weeks to those without overt disease but whose mother was infected during pregnancy
- in *immunodeficiency*, pyrimethamine 200 mg in divided doses on the first day, then 75 to 100 mg daily for at least 6 weeks, followed by a suppressive dose of 25 to 50 mg daily; sulfadiazine is also given in a dose of 4 to 6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2 to 4 g daily
- in *chorioretinitis*, pyrimethamine 75 mg daily for 3 days, then 25 mg daily for 4 weeks, followed in unresponsive patients by 50 mg daily for a further 4 weeks; sulfadiazine is also given in a dose of 2 g daily in 4 divided doses

Pyrimethamine with clindamycin is an alternative in patients unable to tolerate a sulfonamide.

Other drugs that have been tried with pyrimethamine include azithromycin,[2] clarithromycin,[3] and doxycycline.[4,5]

Alternative regimens tried for long-term maintenance therapy in patients with AIDS have included pyrimethamine plus sulfadiazine given twice weekly[6,7] or pyrimethamine alone in doses of 25 mg or 50 mg daily or 50 mg three times weekly.[8-10] However, results from a study involving 396 patients suggested that the mortality rate was higher in those receiving pyrimethamine 25 mg three times weekly for primary prophylaxis than in those receiving placebo.[11] Pyrimethamine with dapsone given once a week can provide effective prophylaxis but was not well tolerated.[12] Pyrimethamine with sulfadoxine, also given once weekly, was of benefit in bone-marrow transplant recipients.[13]

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Preparations

BP 2008: Pyrimethamine Tablets;
USP 31: Pyrimethamine Tablets; Sulfadoxine and Pyrimethamine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Daraprim; ***Austral.:*** Daraprim; ***Austria:*** Daraprim; ***Belg.:*** Daraprim; ***Braz.:*** Daraprin; ***Canad.:*** Daraprim; ***Chile:*** Daraprim; ***Fr.:*** Malocide; ***Ger.:*** Daraprim; ***Irl.:*** Daraprim†; ***Israel:*** Daraprim†; ***Malaysia:*** Fansidar; ***Mex.:*** Daraprim; ***Neth.:*** Daraprim; ***Pol.:*** Daraprim; ***S.Afr.:*** Daraprim; ***Spain:*** Daraprim; ***Switz.:*** Daraprim; ***Thai.:*** Daraprim†; ***UK:*** Daraprim; ***USA:*** Daraprim.

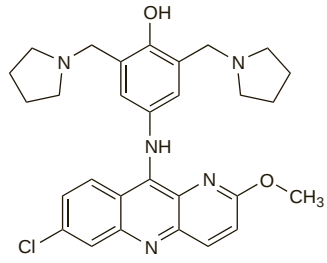
Multi-ingredient: ***Austral.:*** Fansidar; Maloprim; ***Belg.:*** Co-Arinate; Daffafin; Malastop†; ***Braz.:*** Fansidar; ***Canad.:*** Fansidar†; ***Denm.:*** Fansidar†; ***Fr.:*** Fansidar; ***India:*** Artemal†; Laridox; Pyralfin; Pyramet; Rimodar; ***Indon.:*** Fansidar; Suldox; ***Irl.:*** Fansidar; Maloprim†; ***Israel:*** Fansidar; ***Ital.:*** Metakelfin; ***Malaysia:*** Madomine; ***Philipp.:*** Fansidar; ***S.Afr.:*** Fansidar; Maloprim†; ***Singapore:*** Madomine†; Pyrisone; ***Switz.:*** Fansidar; Fansimef†; ***Thai.:*** Vivaxine†; ***UK:*** Fansidar; ***USA:*** Fansidar.

Pyronaridine Phosphate *(rINNM)*

Fosfato de pironaridina; Malaridine Phosphate; Pyronaridine, Phosphate de; Pyronaridini Phosphas. 7-Chloro-2-methoxy-10-[3,5-bis(pyrrolidinomethyl)-4-hydroxyanilino]benzo-[*b*]-1,5-naphthyridine phosphate.

Пиронаридина Фосфат

$C_{29}H_{32}ClN_5O_2,4H_3PO_4$ = 910.0.
CAS — 74847-35-1 (pyronaridine); 76748-86-2 (pyronaridine phosphate).



(pyronaridine)

Pharmacopoeias. In *Chin.*

Profile

Pyronaridine is a naphthyridine derivative used in China in the treatment of vivax malaria and chloroquine-resistant falciparum malaria. Its use has also been investigated in Africa and in Thailand. Combination of pyronaridine with artesunate is also being investigated. Pyronaridine has been given as the phosphate by mouth or by intramuscular or intravenous injection.

◊ References.

1. Shao B-R. A review of antimalarial drug pyronaridine. *Chin Med J* 1990; **103:** 428–34.
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3. Chen C, *et al.* Studies on a new antimalarial compound: pyronaridine. *Trans R Soc Trop Med Hyg* 1992; **86:** 7–10.
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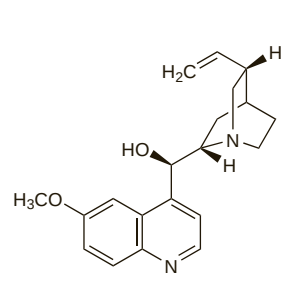
Quinine *(BAN)*

Chinina; Chininum; Kiniini; Kinin; Quinina. (8*S*,9*R*)-6′-Methoxycinchonan-9-ol; (α*R*)-α-(6-Methoxy-4-quinolyl)-α-[(2*S*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2$ = 324.4.
CAS — 130-95-0 (anhydrous quinine).
ATC — P01BC01.



Description. Quinine is the chief alkaloid of various species of *Cinchona* (Rubiaceae). It is an optical isomer of quinidine.

Quinine Bisulfate

Chininum Bisulfuricum; Neutral Quinine Sulphate; Quinina, bisulfato de; Quinine Acid Sulphate; Quinine Bisulphate *(BANM)*; Quinini Bisulfas.

$C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$ = 548.6.
CAS — 549-56-4 (anhydrous quinine bisulfate).
ATC — P01BC01.

Pharmacopoeias. In *Br.*, *Int.*, and *Viet.*

BP 2008 (Quinine Bisulphate). Colourless crystals or a white crystalline powder. It effloresces in dry air. Freely soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 2.8 to 3.4. Protect from light.

Quinine Dihydrochloride *(BANM)*

Chinini Dihydrochloridum; Neutral Quinine Hydrochloride; Quinina, dihidrocloruro de; Quinine Acid Hydrochloride; Quinini Dihydrochloridum.

$C_{20}H_{24}N_2O_2,2HCl$ = 397.3.
CAS — 60-93-5.
ATC — P01BC01.

Pharmacopoeias. In *Br.*, *Chin.*, and *Int.*
Viet. includes the injection.
BP 2008 (Quinine Dihydrochloride). A white or almost white powder. Very soluble in water; soluble in alcohol. A 3% solution in water has a pH of 2.0 to 3.0. Protect from light.

Quinine Etabonate

Euquinina; Euquinine; Quinina, etilcarbonato de; Quinine Ethyl Carbonate.

$C_{23}H_{28}N_2O_4$ = 396.5.
CAS — 83-75-0.
ATC — P01BC01.

Pharmacopoeias. In *Jpn.*

Quinine Hydrobromide *(BANM)*

Basic Quinine Hydrobromide; Chinini Bromidum; Quinina, hidrobromuro de; Quinine Monohydrobromide.

$C_{20}H_{24}N_2O_2,HBr,H_2O$ = 423.3.
CAS — 549-49-5 (anhydrous quinine hydrobromide).
ATC — P01BC01.

Pharmacopoeias. In *Fr.*

Quinine Hydrochloride *(BANM)*

Basic Quinine Hydrochloride; Chinin hydrochlorid dihydrát; Chinini hydrochloridum; Chininii Chloridum; Chininium Chloratum; Chinino hidrochloridas; Chininum Hydrochloricum; Chininy chlorowodorek; Kiniiniihydrokloridi; Kinin-hidroklorid; Kininhydroklorid; Quinina, hidrocloruro de; Quinine, chlorhydrate de; Quinine Monohydrochloride; Quinini Hydrochloridum; Quinini Hydrochloridum Dihydricum.

$C_{20}H_{24}N_2O_2,HCl,2H_2O$ = 396.9.
CAS — 130-89-2 (anhydrous quinine hydrochloride); 6119-47-7 (quinine hydrochloride dihydrate).
ATC — P01BC01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.*
Ph. Eur. 6.2 (Quinine Hydrochloride). White or almost white, or colourless, fine, silky needles, often grouped in clusters. Soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

Quinine Sulfate

Basic Quinine Sulphate; Chinin sulfát dihydrát; Chinini sulfas; Chinino sulfatas; Chininum Sulfuricum; Chininy siarczan; Kiniinisulfaatti; Kininsulfat; Kinin-szulfát; Quinina, sulfato de; Quinine, sulfate de; Quinine Sulphate *(BANM)*; Quinini Sulfas; Quinini Sulfas Dihydricus.

$(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$ = 782.9.
CAS — 804-63-7 (anhydrous quinine sulfate); 6119-70-6 (quinine sulfate dihydrate).
ATC — P01BC01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Quinine Sulphate). A white or almost white, crystalline powder or fine, colourless needles. Slightly soluble in water; sparingly soluble in boiling water and in alcohol. A 1% suspension in water has a pH of 5.7 to 6.6. Protect from light.
USP 31 (Quinine Sulfate). It is the sulfate of an alkaloid obtained from the bark of species of *Cinchona*. White, odourless, fine needle-like crystals, usually lusterless, making a light and readily compressible mass. It darkens on exposure to light. Soluble 1 in 500 of water and 1 in 120 of alcohol; sparingly soluble in water at 100°; slightly soluble in chloroform; freely soluble in alcohol at 80° and in a mixture of 2 parts of chloroform and one part of dehydrated alcohol; very slightly soluble in ether; Its saturated solution in water is neutral or alkaline to litmus. Protect from light.

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

Adverse Effects

Quinine or its salts given in usual therapeutic doses may give rise to a train of symptoms known as cinchonism, characterised in its mild form by tinnitus, impaired hearing, headache, nausea, and disturbed vision, with, in its more severe manifestations, vomiting, abdominal pain, diarrhoea, and vertigo.