Uses and Administration

Atovaquone is a hydroxynaphthoquinone antiprotozoal that is also active against the fungus *Pneumocystis jirovecii*. It is used in the treatment and prophylaxis of pneumocystis pneumonia in patients unable to tolerate co-trimoxazole, and with proguanil in the treatment and prophylaxis of malaria.

In the treatment of mild to moderate **pneumocystis pneumonia**, atovaquone is given orally in a dose of 750 mg with food twice daily as a suspension, for 21 days. For prophylaxis 1500 mg of the suspension is given once daily with food.

Prophylaxis of falciparum **malaria** should start 1 to 2 days before travel to the malarious area, continue daily throughout exposure, and for 7 days after leaving the area. The following doses may be given once daily:

- adults and children over 40 kg: atovaquone 250 mg with proguanil hydrochloride 100 mg
- children 11 to 20 kg: one-quarter the adult dose
- children 21 to 30 kg: one-half the adult dose
- children 31 to 40 kg: three-quarters the adult dose

In the **treatment** of uncomplicated falciparum **malaria**, the following doses are given as a single daily dose for 3 days:

- adults and children over 40 kg: atovaquone 1000 mg with proguanil hydrochloride 400 mg
- children 5 to 8 kg: one-eighth the adult dose
- children 9 to 10 kg: three-sixteenths the adult dose
- children 11 to 20 kg: one-quarter the adult dose
- children 21 to 30 kg: one-half the adult dose
- children 31 to 40 kg: three-quarters the adult dose

Atovaquone with proguanil is one of the antimalarial drugs recommended by some experts to be carried as a **standby** for the emergency treatment of **malaria**. The dose recommended for self-treatment is the same as that for treatment of uncomplicated falciparum malaria.

◊ Reviews.

1. Haile LG, Flaherty JF. Atovaquone: a review. *Ann Pharmacother* 1993; **27:** 1488–94.
2. Artymowicz RJ, James VE. Atovaquone: a new antipneumocystis agent. *Clin Pharm* 1993; **12:** 563–70.
3. Spencer CM, Goa KL. Atovaquone: a review of its pharmacological properties and therapeutic efficacy in opportunistic infections. *Drugs* 1995; **50:** 176–96.
4. Baggish AL, Hill DR. Antiparasitic agent atovaquone. *Antimicrob Agents Chemother* 2002; **46:** 1163–73.
5. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
6. Marra F, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.

Babesiosis. In a prospective, randomised study[1] involving 58 patients with babesiosis (p.823), atovaquone with azithromycin was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Atovaquone 750 mg twice daily with azithromycin 600 mg once daily, or 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, both orally for 7 to 10 days, has been recommended by some experts[2,3] in the USA for the treatment of *Babesia microti* infections. Children may be given atovaquone 20 mg/kg twice daily with azithromycin 12 mg/kg once daily, or 10 mg/kg on day 1 followed by 5 mg/kg once daily thereafter, both by mouth for 7 to 10 days.

1. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; **343:** 1454–8.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/07/08)
3. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Malaria. Atovaquone with proguanil (*Malarone*) is used in the treatment and prophylaxis of uncomplicated malaria caused by *Plasmodium falciparum* (see p.594).

Atovaquone, a blood schizontocide, is associated with an unacceptably high rate of recrudescence when used alone[1,2] for *treatment* but is more successful in malaria when used with proguanil,[2,3] including that produced by multidrug-resistant strains.[4] Use of the combination to treat *P. ovale* and *P. malariae* malarias has also been studied.[5] Atovaquone with proguanil followed by primaquine may also be effective for the treatment of *P. vivax* malaria.[6]

Atovaquone with proguanil has also been found to be useful for *prophylaxis* of falciparum malaria in both children[7] and adults[8] in endemic areas. It may also be used for prophylaxis in non-immune travellers[9,10] and appears to be well tolerated.[10,11]

1. Chiodini PL, *et al.* Evaluation of atovaquone in the treatment of patients with uncomplicated Plasmodium falciparum malaria. *J Antimicrob Chemother* 1995; **36;** 1073–5.
2. Looareesuwan S, *et al.* Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996; **54:** 62–6.
3. Radloff PD, *et al.* Atovaquone and proguanil for Plasmodium falciparum malaria. *Lancet* 1996; **347:** 1511–14.
4. Sabchareon A, *et al.* Efficacy and pharmacokinetics of atovaquone and proguanil in children with multidrug-resistant Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 201–6.
5. Radloff PD, *et al.* Atovaquone plus proguanil is an effective treatment for Plasmodium ovale and P. malariae malaria. *Trans R Soc Trop Med Hyg* 1996; **90:** 682.
6. Looareesuwan S, *et al.* Atovaquone and proguanil hydrochloride followed by primaquine for treatment of plasmodium vivax malaria in Thailand. *Trans R Soc Trop Med Hyg* 1999; **93:** 637–40.
7. Lell B, *et al.* Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet* 1998; **351:** 709–13.
8. Shanks GD, *et al.* Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for Plasmodium falciparum malaria. *Clin Infect Dis* 1998; **27:** 494–9.
9. Overbosch D, *et al.* Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. *Clin Infect Dis* 2001; **33:** 1015–21.
10. 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.
11. Høgh B, *et al.* Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. *Lancet* 2000; **356:** 1888–94.

Microsporidiosis. There is no established effective treatment for microsporidiosis (p.826). Beneficial responses were reported with atovaquone in a preliminary study.[1]

1. Anwar-Bruni DM, *et al.* Atovaquone is effective treatment for the symptoms of gastrointestinal microsporidiosis in HIV-1-infected patients. *AIDS* 1996; **10:** 619–23.

Pneumocystis pneumonia. Atovaquone is one alternative to co-trimoxazole for the treatment of pneumocystis pneumonia (p.521). In open studies, a clinical response to atovaquone was reported in 78% of patients with mild to moderate disease and in 56% of patients with severe disease who were intolerant of, or who failed to respond to, both co-trimoxazole and pentamidine.[1] Comparative studies have shown atovaquone to be less effective than co-trimoxazole[2] and probably less effective than pentamidine,[3,4] but to produce fewer treatment-limiting adverse effects than either.

Atovaquone is also an alternative to co-trimoxazole for both primary or secondary *prophylaxis*, and was as effective as dapsone[5] or inhaled pentamidine[6] in studies in patients intolerant of co-trimoxazole.

1. White A, *et al.* Clinical experience with atovaquone on a treatment investigational new drug protocol for Pneumocystis carinii pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **9:** 280–5.
2. Hughes W, *et al.* Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med* 1993; **328:** 1521–7.
3. Dohn MN, *et al.* Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. *Ann Intern Med* 1994; **121:** 174–80.
4. Lederman MM, van der Horst C. Atovaquone for Pneumocystis carinii pneumonia. *Ann Intern Med* 1995; **122:** 314.
5. El-Sadr WM, *et al.* Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998; **339:** 1889–95.
6. Chan C, *et al.* Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis* 1999; **180:** 369–76.

Toxoplasmosis. Atovaquone, either alone or with pyrimethamine or sulfadiazine, has produced encouraging results for treatment[1-3] or long-term suppression[2-4] of toxoplasmosis (p.826) in patients with AIDS.

1. Kovacs JA, *et al.* Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. *Lancet* 1992; **340:** 637–8.
2. Torres RA, *et al.* Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1997; **24:** 422–9.
3. Chirgwin K, *et al.* Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002; **34:** 1243–50.
4. Katlama C, *et al.* Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. *AIDS* 1996; **10:** 1107–12.

Preparations

USP 31: Atovaquone Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Wellvone; ***Austria:*** Wellvone; ***Belg.:*** Wellvone; ***Canad.:*** Mepron; ***Fr.:*** Wellvone; ***Ger.:*** Wellvone; ***Gr.:*** Wellvone; ***Ital.:*** Wellvone; ***Neth.:*** Wellvone; ***Port.:*** Wellvone; ***S.Afr.:*** Wellvone; ***Spain:*** Wellvone; ***Swed.:*** Wellvone; ***Switz.:*** Wellvone; ***UK:*** Wellvone; ***USA:*** Mepron.

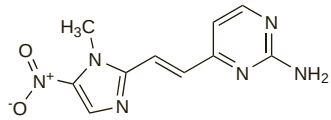
Multi-ingredient: ***Austral.:*** Malarone; ***Austria:*** Malarone; Promal; ***Belg.:*** Malarone; ***Canad.:*** Malarone; ***Cz.:*** Malarone; ***Denm.:*** Malarone; ***Fr.:*** Malarone; ***Ger.:*** Malarone; ***Gr.:*** Malarone; ***Hong Kong:*** Malarone; ***Hung.:*** Malarone; ***Irl.:*** Malarone;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

Azanidazole *(BAN, USAN, rINN)*

Azanidazol; Azanidazolum; F-4. 4-[(*E*)-2-(1-Methyl-5-nitroimidazol-2-yl)vinyl]pyrimidin-2-ylamine.

Азанидазол

$C_{10}H_{10}N_6O_2$ = 246.2.
CAS — 62973-76-6.
ATC — G01AF13; P01AB04.
ATC Vet — QG01AF13; QP51AA04.



Profile

Azanidazole is a 5-nitroimidazole derivative similar to metronidazole (p.837) and is used in the treatment of trichomoniasis in usual oral doses of 200 mg twice daily or 250 mg once daily intravaginally.

Preparations

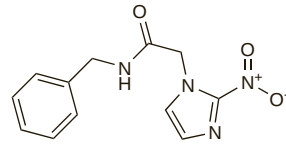
Proprietary Preparations (details are given in Part 3)
Ital.: Triclose.

Benznidazole *(rINN)*

Benznidazol; Benznidazolum; Ro-7-1051. *N*-Benzyl-2-(2-nitroimidazol-1-yl)acetamide.

Бензнидазол

$C_{12}H_{12}N_4O_3$ = 260.2.
CAS — 22994-85-0.
ATC — P01CA02.



Pharmacopoeias. In *Int.*

Adverse Effects

Nausea, vomiting, abdominal pain, peripheral neuropathy, blood dyscrasias, and severe skin reactions have been reported with benznidazole.

◊ A study[1] involving 20 patients with chronic American trypanosomiasis given benznidazole 5 mg/kg daily had to be stopped because of the high incidence of skin rashes and neurological symptoms.

1. Apt W, *et al.* Clinical trial of benznidazole and an immunopotentiator against Chagas disease in Chile. *Trans R Soc Trop Med Hyg* 1986; **80:** 1010.

Pharmacokinetics

Benznidazole is absorbed from the gastrointestinal tract after oral doses.

◊ References.

1. Raaflaub J, Ziegler WH. Single-dose pharmacokinetics of the trypanosomicide benznidazole in man. *Arzneimittelforschung* 1979; **29:** 1611–14.

Uses and Administration

Benznidazole is a 2-nitroimidazole derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease) due to infection with *Trypanosoma cruzi*, especially during the early acute stage of the disease.

Benznidazole has been given orally in a dose of 5 to 7 mg/kg daily in two divided doses usually for 60 days (but see below). Children have been given 10 mg/kg daily in two divided doses.

American trypanosomiasis. Available treatment for American trypanosomiasis (p.827) is generally unsatisfactory, but benznidazole is of value especially in the acute phase. WHO[1] recommends that benznidazole should be given for 60 days but some in the USA[2] suggest courses of 30 to 90 days. Although treatment is usually confined to the acute phase of the disease, therapy during the early chronic phase was reported to be beneficial,[3] and long-term follow-up in patients who had received benznidazole has shown a reduction in cardiac complications and parasitaemia.[4]

1. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 17/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. de Andrade ALSS, *et al*. Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. *Lancet* 1996; **348:** 1407–13.
4. Viotti R, *et al*. Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up. *Am Heart J* 1994; **127:** 151–62.

Preparations

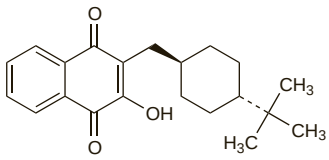
Proprietary Preparations (details are given in Part 3)
Arg.: Radanil; ***Braz.:*** Rochagan; ***Ecuad.:*** Ragonil.

Buparvaquone *(BAN, rINN)*

Buparvacuona; Buparvaquonum; BW-720C. *trans*-2-(4-*tert*-Butylcyclohexylmethyl)-3-hydroxy-1,4-naphthoquinone.

Бупарвахон

$C_{21}H_{26}O_3$ = 326.4.
CAS — 88426-33-9.
ATC Vet — QP51AX22.



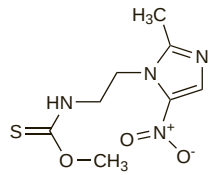
Profile
Buparvaquone is an antiprotozoal used in veterinary practice for the treatment of theileriosis in cattle.

Carnidazole *(BAN, USAN, pINN)*

Carnidazol; Carnidazolum; R-25831; R-28096 (carnidazole hydrochloride). *O*-Methyl [2-(2-methyl-5-nitroimidazol-1-yl)ethyl]-thiocarbamate.

Карнидазол

$C_8H_{12}N_4O_3S$ = 244.3.
CAS — 42116-76-7.
ATC Vet — QP51AA09.



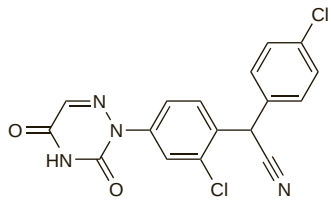
Profile
Carnidazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the control of trichomoniasis in pigeons.

Clazuril *(BAN, USAN, rINN)*

Clazurilo; Clazurilum; Klatsuriili; Klazuril; R-62690. (±)-[2-Chloro-4-(4,5-dihydro-3,5-dioxo-*as*-triazin-2(3*H*)-yl)phenyl]-(*p*-chlorophenyl)acetonitrile.

Клазурил

$C_{17}H_{10}Cl_2N_4O_2$ = 373.2.
CAS — 101831-36-1.
ATC Vet — QP51AJ02.



Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.
Ph. Eur. 6.2 (Clazuril for Veterinary Use; Clazuril BP(Vet) 2008). A white or light yellow powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; freely soluble in dimethylformamide. Protect from light.

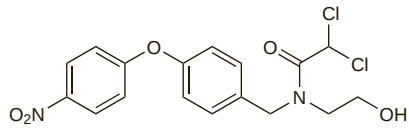
Profile
Clazuril is an antiprotozoal used in veterinary practice for the control of coccidiosis in pigeons.

Clefamide *(BAN, rINN)*

Chlorphenoxamide; Clefamida; Cléfamide; Clefamidum. 2,2-Dichloro-*N*-(2-hydroxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl]-acetamide.

Клефамид

$C_{17}H_{16}Cl_2N_2O_5$ = 399.2.
CAS — 3576-64-5.
ATC — P01AC02.



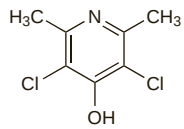
Profile
Clefamide is an antiprotozoal that has been used as a luminal amoebicide in the treatment of *Entamoeba histolytica* infections.

Clopidol *(BAN, USAN, rINN)*

Clopidolum; Clopindol; Meticlorpindol. 3,5-Dichloro-2,6-dimethylpyridin-4-ol.

Клопидол

$C_7H_7Cl_2NO$ = 192.0.
CAS — 2971-90-6.



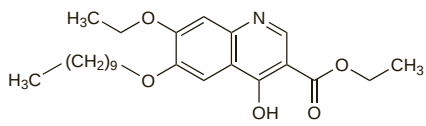
Profile
Clopidol is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry and rabbits either alone or with methyl benzoquate (p.837).

Decoquinate *(BAN, USAN, rINN)*

Décoquinate; Decoquinato; Decoquinatum; HC-1528; M&B-15497. Ethyl 6-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate.

Декохинат

$C_{24}H_{35}NO_5$ = 417.5.
CAS — 18507-89-6.
ATC Vet — QP51AX14.



Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.
BP(Vet) 2008 (Decoquinate). A cream to buff-coloured, odourless or almost odourless, microcrystalline powder. Insoluble in water; practically insoluble in alcohol; very slightly soluble in chloroform and in ether.
USP 31 (Decoquinate). Store in airtight containers.

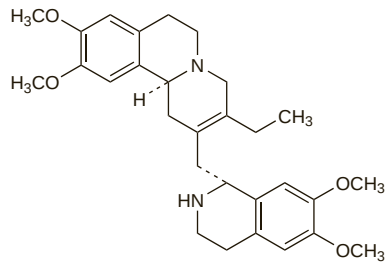
Profile
Decoquinate is an antiprotozoal used in veterinary practice for the control of coccidiosis in calves, sheep, and chickens. It is also used for toxoplasmosis in sheep.

Dehydroemetine Hydrochloride *(BANM, rINNM)*

BT-436; Déhydroémétine, Chlorhydrate de; 2,3-Dehydroemetine Hydrochloride; Dehydroemetini Hydrochloridum; DHE; Hidrocloruro de dehidroemetina; Ro-1-9334. 2,3-Didehydro-6′,7′,10,11-tetramethoxyemetan dihydrochloride; 3-Ethyl-1,6,7,11b-tetrahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl)-4*H*-benzo[*a*]quinolizine dihydrochloride.

Дегидроэметина Гидрохлорид

$C_{29}H_{38}N_2O_4$,2HCl = 551.5.
CAS — 4914-30-1 (dehydroemetine); 2228-39-9 (dehydroemetine hydrochloride).



(dehydroemetine)

NOTE. The name DHE has been used to denote a preparation of dihydroergotamine mesilate.

Pharmacopoeias. In *Int.*

Profile
Dehydroemetine, a synthetic derivative of emetine (p.833), is a tissue amoebicide with similar actions and uses, although probably of a lower toxicity.

Dehydroemetine should be avoided in patients with cardiac, renal, or neuromuscular disease and patients should be monitored for cardiac toxicity during treatment.

When used in the treatment of amoebiasis (p.822), dehydroemetine hydrochloride is given by intramuscular injection in a dose of 1 mg/kg daily (maximum daily dose of 60 mg), generally for up to 4 to 6 days, but for no more than 5 days in children. A dose of 0.5 mg/kg has been suggested for elderly or severely ill patients. At least 6 weeks should elapse before treatment is repeated. Following treatment with dehydroemetine, all patients should receive a luminal amoebicide to eliminate organisms from the colon. Patients with hepatic amoebiasis may be given supplementary treatment with chloroquine.

Liver fluke infections. Dehydroemetine has been given[1] in the treatment of the liver fluke infection fascioliasis (see p.137).

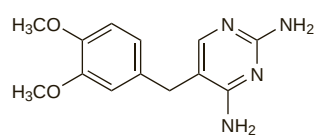
1. Farid Z, *et al*. Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; **82:** 299.

Diaveridine *(BAN, USAN, rINN)*

BW-49-210; Diaveridina; Diavéridine; Diaveridinum; NSC-408735. 5-Veratrylpyrimidine-2,4-diyldiamine.

Диаверидин

$C_{13}H_{16}N_4O_2$ = 260.3.
CAS — 5355-16-8.
ATC Vet — QP51AX18.



Pharmacopoeias. In *Fr.* for veterinary use.

Profile
Diaveridine is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.