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.
5. Bern C, *et al.* Evaluation and treatment of Chagas disease in the United States: a systematic review. *JAMA* 2007; **298:** 2171–81.
6. Gallerano RH, *et al.* Therapeutic efficacy of allopurinol in patients with chronic Chagas' disease. *Am J Trop Med Hyg* 1990; **43:** 159–66.
7. Apt W, *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; **59:** 133–8.
8. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; **97:** 23–9.

Acetarsol *(BAN, rINN)*

Acetaminohydroxyphenylarsonsäure; Acétarsol; Acetarsolum; Acetarsone; Acetphenarsinum; Asetarsoli; Osarsolum. 3-Acetamido-4-hydroxyphenylarsonic acid.

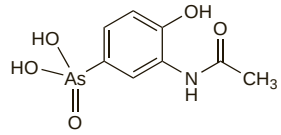
Ацетарсол

$C_8H_{10}AsNO_5$ = 275.1.

CAS — 97-44-9.

ATC — A07AX02; G01AB01; P01CD02.

ATC Vet — QA07AX02; QG01AB01; QP51AD05.



Profile

Acetarsol, a pentavalent organic arsenical derivative, was formerly given orally in the treatment of intestinal amoebiasis and vaginally in the treatment of trichomoniasis, but the use of pentavalent arsenical compounds has been abandoned in favour of more effective and less toxic drugs. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p.2260.

Acetarsol suppositories were once tried in the treatment of proctitis. Acetarsol lithium and acetarsol sodium have been included in some preparations for minor mouth infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Rus.:*** Osarbon (Осарбон).

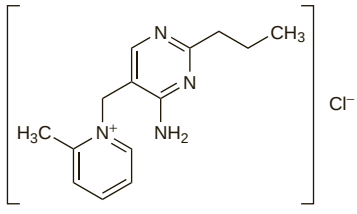
Amprolium Hydrochloride *(BANM, rINNM)*

Amprolii Hydrochloridum; Amprolium, Chlorhydrate d'; Hidrocloruro de amprolio. 1-(4-Amino-2-propylpyrimidin-5-ylmethyl)-2-methylpyridinium chloride hydrochloride.

Амproлия Гидрохлорид

$C_{14}H_{19}ClN_4,HCl$ = 315.2.

CAS — 121-25-5 (amprolium); 137-88-2 (amprolium hydrochloride).



(amprolium)

Pharmacopoeias. In *Fr.* and *US* for veterinary use only. Also in *BP(Vet).*

BP(Vet) 2008 (Amprolium Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform; very slightly soluble in ether.

USP 31 (Amprolium). A white to light yellow powder. Freely soluble in water, in alcohol, in dimethylformamide and in methyl alcohol; sparingly soluble in dehydrated alcohol; practically insoluble in acetone, in butyl alcohol, and in isopropyl alcohol.

Profile

Amprolium hydrochloride is an antiprotozoal used in veterinary practice, alone or with other drugs such as ethopabate, for the control of coccidiosis in pigeons and in poultry.

Pentavalent Antimony Compounds

Antimonio pentavalente, compuestos de.

Meglumine Antimonate

Antimoniato de meglumina; Antimony Meglumine; Meglumine Antimoniate; Protostib; RP-2168. 1-Deoxy-1-methylamino-D-glucitol antimonate.

Меглумина Антимонат

$C_7H_{18}NO_8Sb$ = 366.0.

CAS — 133-51-7.

ATC — P01CB01.

ATC Vet — QP51AB01.

Sodium Stibogluconate *(BAN, rINN)*

Estibogluconato de sodio; Natrii Stibogluconas; Natriumstibogluconaatti; Natriumstiboglukonat; Sod. Stibogluc.; Sodium Antimony Gluconate; Sodyum Stiboglukonat; Stibogluconate de Sodium; Stibogluconat-Natrium.

Натрия Стибоглюконат

CAS — 16037-91-5.

ATC — P01CB02.

ATC Vet — QP51AB02.

Description. A pentavalent antimony compound of indefinite composition. It has been represented by the formula $C_6H_9Na_2O_9Sb$ but usually there are less than 2 atoms of Na for each atom of Sb. Solutions may be sterilised by autoclaving.

Pharmacopoeias. In *Br., Chin., Int.,* and *It.*

BP 2008 (Sodium Stibogluconate). It is mainly the disodium salt of μ-oxy-bis[gluconato(3-)O^2,O^3,O^4-hydroxo-antimony]. It contains not less than 30.0% and not more than 34.0% of antimony(V), calculated with reference to the dried and methanol-free substance. It is a colourless, odourless or almost odourless, mostly amorphous powder. Very soluble in water; practically insoluble in alcohol and in ether. A solution in water containing 10% of pentavalent antimony has a pH of 5.0 to 5.6 after autoclaving.

Adverse Effects, Treatment, and Precautions

As for Trivalent Antimony Compounds, p.141.

Adverse effects are generally less frequent and less severe with the pentavalent antimony compounds sodium stibogluconate and meglumine antimonate than with trivalent compounds such as antimony sodium tartrate. Nevertheless, similar precautions should be observed, especially in patients on high-dose therapy.

Intramuscular injections of sodium stibogluconate can be painful and intravenous use has been associated with thrombophlebitis.

◊ Common adverse effects of pentavalent antimony are anorexia, vomiting, nausea, malaise, arthralgia and myalgia, headache, lethargy, and pancreatitis. ECG changes are dose-dependent and most commonly include T-wave inversion and prolonged QT interval. Renal damage is a rarely reported toxic effect. Pentavalent antimony is usually well tolerated. Serious adverse effects when they occur usually involve the liver or the heart when it is prudent to interrupt the course temporarily.

References.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 17/07/08)
2. Aronson NE, *et al.* Safety and efficacy of intravenous sodium stibogluconate in the treatment of leishmaniasis: recent US military experience. *Clin Infect Dis* 1998; **27:** 1457–64.

Breast feeding. The amount of antimony distributed into the breast milk of a patient given sodium stibogluconate was considered not to constitute a hazard and oral absorption was not detected in an *animal* study.[1] The American Academy of Pediatrics also considers that the use of antimony is usually compatible with breast feeding.[2] Others, however, have felt that more safety evaluation was required before antimony could be considered completely safe during breast feeding.[3]

1. Berman JD, *et al.* Concentration of Pentostam in human breast milk. *Trans R Soc Trop Med Hyg* 1989; **83:** 784–5.
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 02/06/04)
3. Verschoyle RD. Comment. *Trop Dis Bull* 1990; **87:** 919.

Effects on the blood. Although thrombocytopenia is associated with leishmaniasis, there are case reports of it also being associated with sodium stibogluconate.[1,2]

1. Braconier JH, Miörner H. Recurrent episodes of thrombocytopenia during treatment with sodium stibogluconate. *J Antimicrob Chemother* 1993; **31:** 187–8.
2. Hepburn NC. Thrombocytopenia complicating sodium stibogluconate therapy for cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1993; **87:** 691.

Effects on the heart. The ECG was monitored during 65 courses of treatment with sodium stibogluconate in 59 Kenyan patients with leishmaniasis.[1] ECG abnormalities developed during 35 treatment courses. They were qualitatively similar to those previously described during treatment with trivalent antimonial drugs, but occurred less frequently and later during the course of treatment. The most common abnormality was inversion and/or decreased amplitude of T waves. Incidence was related to total daily dose and duration of treatment. One patient died suddenly during the 4th week of treatment with antimony 60 mg/kg daily. Other deaths probably related to cardiac toxicity have been reported in patients receiving 60 mg/kg daily[2] and 30 mg/kg daily.[3] It has been recommended[1] that for treatment with sodium stibogluconate ECGs should be obtained every 3 to 4 days in patients given antimony 20 mg/kg daily for more than 20 days or a higher dose for more than 10 days. If Stokes-Adams attacks or ventricular tachyarrhythmias develop, sodium stibogluconate should be stopped and appropriate treatment given. A retrospective study[4] in patients treated with sodium stibogluconate for mostly cutaneous leishmaniasis found that the mean QT_c interval steadily increased throughout the period of treatment, reaching a potentially toxic threshold by the third week, but cardiotoxicity was seen only in one elderly patient who had hypokalaemia and pre-existing cardiovascular morbidity. Identification before treatment of factors that may increase cardiovascular risk is important.

1. Chulay JD, *et al.* Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). *Am J Trop Med Hyg* 1985; **34:** 702–9.
2. Bryceson ADM, *et al.* Visceral leishmaniasis unresponsive to antimonial drugs II: response to high dosage sodium stibogluconate or prolonged treatment with pentamidine. *Trans R Soc Trop Med Hyg* 1985; **79:** 705–14.
3. Thakur CP. Harmful effect of high stibogluconate treatment of kala-azar in India. *Trans R Soc Trop Med Hyg* 1986; **80:** 672–3.
4. Lawn SD, *et al.* Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. *Trans R Soc Trop Med Hyg* 2006; **100:** 264–9.

Effects on the kidneys. Sodium stibogluconate given for 10 days to 16 young men with cutaneous leishmaniasis had no apparent adverse effect on glomerular or tubular renal function.[1] However, evidence of renal tubular dysfunction has been reported in patients with mucocutaneous leishmaniasis given meglumine antimonate or sodium stibogluconate for 30 days or more[2] and acute renal failure has occurred in patients both with,[3] and without,[4] pre-existing renal impairment, the latter resulting in death.

1. Joliffe DS. Nephrotoxicity of pentavalent antimonials. *Lancet* 1985; **i:** 584.
2. Veiga JPR, *et al.* Renal tubular dysfunction in patients with mucocutaneous leishmaniasis treated with pentavalent antimonials. *Lancet* 1983; **ii:** 569.
3. Balzan M, Fenech F. Acute renal failure in visceral leishmaniasis treated with sodium stibogluconate. *Trans R Soc Trop Med Hyg* 1992; **86:** 515–16.
4. Rodrigues MLO, *et al.* Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 33–7.

Effects on the liver. WHO has reported that when serious adverse effects occur with sodium stibogluconate they usually involve the liver or the heart.[1] There have been reports of disturbed liver function[2,3] in patients given sodium stibogluconate, although there has also been a report[4] that signs of altered liver function, which may be a feature of visceral leishmaniasis, improved during treatment with sodium stibogluconate.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 17/07/08)
2. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii:** 13–16.
3. Hepburn NC, *et al.* Hepatotoxicity of sodium stibogluconate in leishmaniasis. *Lancet* 1993; **342:** 238–9.
4. Misbahuddin M, *et al.* Stibogluconate for leishmaniasis. *Lancet* 1993; **342:** 804.

Effects on the musculoskeletal system. Arthralgia is common with pentavalent antimony compounds. It is usually dose-dependent[1] but a patient has been described who experienced symptoms early in treatment.[2] Palindromic arthropathy with effusion was associated with sodium stibogluconate treatment in another patient.[3]

1. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii:** 13–16.
2. Castro C, *et al.* Severe arthralgia, not related to dose, associated with pentavalent antimonial therapy for mucosal leishmaniasis. *Trans R Soc Trop Med Hyg* 1990; **84:** 362.
3. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; **21:** 107–10.

Effects on the nervous system. Peripheral neuropathy developed in a patient about 8 days after starting therapy with sodium stibogluconate.[1] The symptoms were generally reversible when treatment was stopped (after 17 days), although there was some slight persistent hypoaesthesia in the toes. An interaction with a single dose of amitriptyline, taken on the second day of stibogluconate therapy, seemed unlikely but could not be ruled out.

1. Brummitt CF, *et al.* Reversible peripheral neuropathy associated with sodium stibogluconate therapy for American cutaneous leishmaniasis. *Clin Infect Dis* 1996; **22:** 878–9.

Effects on the pancreas. Pancreatitis has been associated with sodium stibogluconate treatment.[1-3] Withdrawing treatment usually resulted in resolution of pancreatitis.

1. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; **21:** 107–10.
2. Gasser RA, *et al.* Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis* 1994; **18:** 83–90.
3. Domingo P, *et al.* Treatment of Indian kala-azar with pentavalent antimony. *Lancet* 1995; **345:** 584–5.

Pharmacokinetics

The pentavalent antimony compounds are poorly absorbed from the gastrointestinal tract. After intravenous doses an initial distribution phase is followed by biexponential elimination by the kidneys. The elimination half-life of the initial phase is about 1.7 hours and that of the slow terminal phase is about 33 hours. The corresponding half-lives after intramuscular doses are reported to be 2 hours and 766 hours respectively. The slow elimination phase may reflect reduction to trivalent antimony. Accumulation occurs on daily use and maximum tissue concentrations may not be reached for 7 days or more. Antimony has been detected in breast milk (see Breast Feeding, above).

◊ References.

1. Rees PH, *et al.* Renal clearance of pentavalent antimony (sodium stibogluconate). *Lancet* 1980; **ii:** 226–9.
2. Chulay JD, *et al.* Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. *Trans R Soc Trop Med Hyg* 1988; **82:** 69–72.
3. Al Jaser M, *et al.* Pharmacokinetics of antimony in patients treated with sodium stibogluconate for cutaneous leishmaniasis. *Pharm Res* 1995; **12:** 113–16.

Uses and Administration

Pentavalent antimony, as sodium stibogluconate or meglumine antimonate, is used as first-line treatment for all forms of leishmaniasis except *Leishmania aethiopica* infections.

For systemic use, sodium stibogluconate is given by intramuscular or intravenous injection as a solution containing the equivalent of pentavalent antimony 100 mg/mL. Intramuscular injection is generally preferable. Intravenous injections must be given very slowly (over at least 5 minutes) and preferably through a fine needle to avoid thrombophlebitis; as with trivalent antimony compounds, they should be stopped immediately if coughing, vomiting, or substernal pain occurs. Meglumine antimonate is given by deep intramuscular injection as a solution containing the equivalent of pentavalent antimony 85 mg/mL. Doses are expressed in terms of the equivalent amount of pentavalent antimony.

Local variations exist in treatment schedules but WHO recommends the following regimens:

- In **visceral leishmaniasis**, initial treatment is based on daily intramuscular injection of pentavalent antimony 20 mg/kg to a maximum of 850 mg (but see below) for at least 20 days. The length of treatment varies from one endemic area to another, but is continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals. Patients who relapse are re-treated at the same dose.
- Early non-inflamed lesions of **cutaneous leishmaniasis** due to all forms of *Leishmania* except *L. aethiopica*, *L. amazonensis*, and *L. braziliensis* may be treated by infiltration with intralesional injections of 1 to 3 mL of sodium stibogluconate or meglumine antimonate (about 100 to 300 mg of pentavalent antimony), repeated once or twice if necessary at intervals of 1 to 2 days. Systemic therapy with intramuscular pentavalent antimony 10 to 20 mg/kg daily is given if the lesions are more severe and continued until a few days after clinical and parasitological cure is achieved.

  Cutaneous leishmaniasis due to *L. aethiopica* is not responsive to antimonials at conventional doses. In cutaneous leishmaniasis due to *L. braziliensis*, prolonged systemic treatment with intramuscular pentavalent antimony 20 mg/kg daily for a minimum of 4 weeks is indicated. Similar doses are required for **diffuse cutaneous leishmaniasis** due to *L. amazonensis* and are continued for several months after clinical improvement occurs. Relapses should be expected until immunity develops.
- In **mucocutaneous leishmaniasis**, daily doses of intramuscular pentavalent antimony 20 mg/kg are given for a minimum of 4 weeks; if the response is poor, 10 to 15 mg/kg may be given every 12 hours for the same period. Relapses are well known and have generally been associated with inadequate or interrupted treatment; they are treated with the same drug given for at least twice as long as the original treatment. Only when that fails should alternative treatment be given.

Leishmaniasis. The main treatment for leishmaniasis (p.824) is a pentavalent antimony compound such as sodium stibogluconate. Higher doses of antimony compounds than those recommended by WHO (see above) have been tried in order to overcome the unresponsiveness of leishmaniasis to therapy. In the USA, the use of 20 mg/kg daily of pentavalent antimony has been recommended, without restriction to an 850-mg maximum daily dose.[1,2] At 20 mg/kg daily the most common adverse effects are musculoskeletal disorders, elevated liver enzyme values, and T-wave changes on the ECG, and the CDC recommends that the ECG, blood chemistry, and blood count should be monitored throughout therapy if resources permit.[1] Severe cardiotoxicity is rare at this dose but fatal cardiac toxicity has been reported with doses of up to 60 mg/kg daily (see under Effects on the Heart, above). Drug-resistant strains of *Leishmania infantum* have been associated with unresponsiveness to treatment with meglumine antimonate.[3] It was suggested[4] that the use of suboptimal doses may be increasing the prevalence of drug-resistant strains of the parasite. However, low doses of antimony compounds (5 mg/kg daily for 30 days) have produced long-term cure in patients with cutaneous *L. braziliensis* infection followed for up to 10 years.[5]

INTRALESIONAL ADMINISTRATION. Intralesional infiltration of 3 doses of sodium stibogluconate on alternate days or once weekly was more effective than daily treatment in a study of 96 patients in Saudi Arabia.[6] Local infiltration of meglumine antimonate in usual doses of 150 to 900 mg (maximum 1500 mg) once each week for up to 6 weeks produced microbiological and clinical cures in all of 45 patients in Italy with cutaneous leishmaniasis.[7]

1. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg* 1992; **46:** 296–306.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. Faraut-Gambarelli F, *et al.* In vitro and in vivo resistance of Leishmania infantum to meglumine antimoniate: a study of 37 strains collected from patients with visceral leishmaniasis. *Antimicrob Agents Chemother* 1997; **41:** 827–30.
4. Grogl M, *et al.* Drug resistance in leishmaniasis: its implication in systemic chemotherapy of cutaneous and mucocutaneous disease. *Am J Trop Med Hyg* 1992; **47:** 117–26.
5. Oliveira-Neto MP, *et al.* A low-dose antimony treatment in 159 patients with American cutaneous leishmaniasis: extensive follow-up studies (up to 10 years). *Am J Trop Med Hyg* 1997; **57:** 651–5.
6. Tallab TM, *et al.* Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate. *Int J Dermatol* 1996; **35:** 594–7.
7. Aste N, *et al.* Intralesional treatment of cutaneous leishmaniasis with meglumine antimoniate. *Br J Dermatol* 1998; **138:** 370–1.

Preparations

BP 2008: Sodium Stibogluconate Injection.

Proprietary Preparations (details are given in Part 3)
Braz.: Glucantime; ***Fr.:*** Glucantime; ***Israel:*** Pentostam; ***Ital.:*** Glucantim†; ***Spain:*** Glucantime; ***UK:*** Pentostam; ***Venez.:*** Glucantime.

Atovaquone *(BAN, USAN, rINN)*

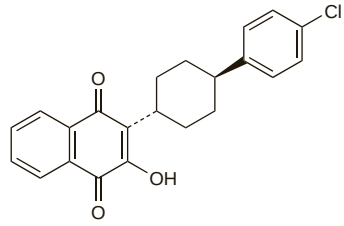
Atovacuona; Atovakon; Atovakvon; Atovakvoni; Atovaquonum; BW-A566C; BW-566C; BW-566C80; 566C; 566C80. 2-[*trans*-4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

Атовахон

$C_{22}H_{19}O_3Cl$ = 366.8.

CAS — 95233-18-4.

ATC — P01AX06.



Pharmacopoeias. In *US.*
USP 31 (Atovaquone). A yellow powder. Insoluble in water; slightly soluble in alcohol, in butanediol, in ethyl acetate, in glycerol, in octanol, and in macrogol 200; sparingly soluble in acetone, in di-*n*butyl adipate, in dimethyl sulfoxide, and in macrogol 400; soluble in chloroform; freely soluble in *N*-methyl-2-pyrrolidone and in tetrahydrofuran; very slightly soluble in 0.1N sodium hydroxide. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Adverse reactions to atovaquone include skin rashes, headache, fever, insomnia, and gastrointestinal effects such as nausea, diarrhoea, and vomiting. Raised liver enzyme values, hyponatraemia, and haematological disturbances such as anaemia and neutropenia may occur occasionally. Atovaquone should be avoided in patients with gastrointestinal disorders that may limit absorption of the drug.

Effects on the skin. Stevens-Johnson syndrome has been reported[1] in a patient taking atovaquone with proguanil.

1. 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 17/07/08)

Interactions

Use of atovaquone with either metoclopramide, tetracycline, or rifampicin (and possibly also rifabutin) may result in decreases in plasma-atovaquone concentrations. Other drugs which have produced small reductions in plasma-atovaquone concentrations include aciclovir, antidiarrhoeals, benzodiazepines, cephalosporins, laxatives, opioids, and paracetamol.

Atovaquone is reported to decrease the metabolism of zidovudine resulting in moderate increases in zidovudine plasma concentrations. A decrease in trough concentrations of indinavir, and in the area under the indinavir time-concentration curve has been reported when atovaquone was also given. Small decreases in the plasma concentrations of co-trimoxazole have been noted in patients taking atovaquone. There is a theoretical possibility that atovaquone could displace other highly protein-bound drugs from plasma-protein binding sites.

Pharmacokinetics

Atovaquone is poorly absorbed from the gastrointestinal tract after oral doses; bioavailability is especially poor in patients with AIDS. Bioavailability from commercial oral liquid formulations is better than from tablets and can be further improved if taken with food, particularly meals with a high fat content. Atovaquone is more than 99% bound to plasma proteins and has a long plasma half-life of 2 to 3 days, thought to be due to enterohepatic recycling. It is excreted almost exclusively in faeces as unchanged drug.

◊ References.

1. Hughes WT, *et al.* Safety and pharmacokinetics of 566C80, a hydroxynaphthoquinone with anti-Pneumocystis carinii activity: a phase I study in human immunodeficiency virus (HIV)-infected men. *J Infect Dis* 1991; **163:** 843–8.
2. Rolan PE, *et al.* Examination of some factors responsible for a food-induced increase in absorption of atovaquone. *Br J Clin Pharmacol* 1994; **37:** 13–20.
3. Dixon R, *et al.* Single-dose and steady-state pharmacokinetics of a novel microfluidized suspension of atovaquone in human immunodeficiency virus-seropositive patients. *Antimicrob Agents Chemother* 1996; **40:** 556–60.
4. Hussein Z, *et al.* Population pharmacokinetics of atovaquone in patients with acute malaria caused by Plasmodium falciparum. *Clin Pharmacol Ther* 1997; **61:** 518–30.
5. Rolan PE, *et al.* Disposition of atovaquone in humans. *Antimicrob Agents Chemother* 1997; **41:** 1319–21.