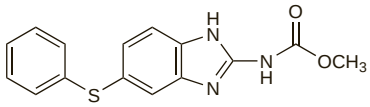
Fenbendazole *(BAN, USAN, rINN)*

Fenbendatsoli; Fenbendazol; Fenbendazolum; Hoe-881V. Methyl 5-phenylthio-1*H*-benzimidazol-2-ylcarbamate.

Фенбендазол

$C_{15}H_{13}N_3O_2S$ = 299.3.
CAS — 43210-67-9.
ATC — P02CA06.
ATC Vet — QP52AC13.



Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.
Ph. Eur. 6.2 (Fenbendazole for Veterinary Use; Fenbendazole BP(Vet) 2008). A white or almost white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Protect from light.
USP 31 (Fenbendazole). A white to off-white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

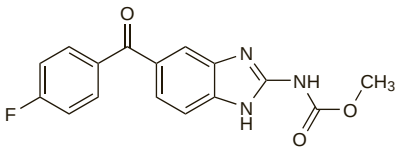
Profile
Fenbendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148). It is used in veterinary medicine.

Flubendazole *(BAN, USAN, rINN)*

Flubendatsoli; Flubendazol; Flubendazolas; Flubendazolum; Fluoromebendazole; R-17889. Methyl 5-(4-fluorobenzoyl)-1*H*-benzimidazol-2-ylcarbamate.

Флубендазол

$C_{16}H_{12}FN_3O_3$ = 313.3.
CAS — 31430-15-6.
ATC — P02CA05.
ATC Vet — QP52AC12.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Flubendazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile
Flubendazole, a benzimidazole carbamate anthelmintic, is an analogue of mebendazole (p.148) and has similar actions and uses.

For the treatment of enterobiasis in adults and children, flubendazole 100 mg is given as a single oral dose, repeated after 2 to 3 weeks. For ascariasis, hookworm infections, and trichuriasis 100 mg is given twice daily for 3 days. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p.134.

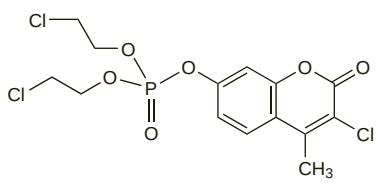
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Flumoxal; ***Fr.:*** Fluvermal; ***Port.:*** Fluvermal; Teniverme; ***Spain:*** Flicum; ***Venez.:*** Fluvermox.

Haloxon *(BAN, rINN)*

Haloxón; Haloxone; Haloxonum. Bis(2-chloroethyl) 3-chloro-4-methylcoumarin-7-yl phosphate.

Галоксон

$C_{14}H_{14}Cl_3O_6P$ = 415.6.
CAS — 321-55-1.
ATC Vet — QP52AB04.



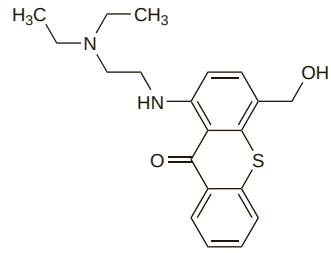
Profile
Haloxon is an organophosphorus compound (see Organophosphorus Insecticides, p.2047) used as an anthelmintic in veterinary medicine.

Hycanthone *(USAN, rINN)*

Hicantona; Hycanthonum; NSC-134434; Win-24933. 1-(2-Diethylaminoethylamino)-4-hydroxymethylthioxanthen-9-one.

Гикантон

$C_{20}H_{24}N_2O_2S$ = 356.5.
CAS — 3105-97-3.



Hycanthone Mesilate *(rINNM)*

Hycanthone, Mésilate d'; Hycanthone Mesylate; Hycanthoni Mesilas; Hydroxylucanthone Methanesulphonate; Mesilato de hicantona.

Гикантона Мезилат

$C_{20}H_{24}N_2O_2S,CH_3SO_3H$ = 452.6.
CAS — 23255-93-8.

Profile
Hycanthone has been used as a schistosomicide in the individual or mass treatment of infection with *Schistosoma haematobium* and *S. mansoni*.

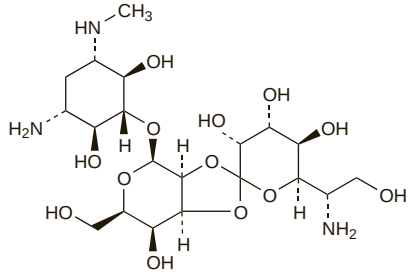
Owing to its toxicity and concern about possible carcinogenicity, mutagenicity, and teratogenicity, hycanthone has been replaced by other drugs such as praziquantel.

Hygromycin B

Higromicina B. *O*-6-Amino-6-deoxy-L-glycero-D-galacto-heptopyranosylidene-(1→2-3)-*O*-β-D-talopyranosyl-(1→5)-2-deoxy-*N*^{3}-methyl-D-streptamine.

Гигромицин Б

$C_{20}H_{37}N_3O_{13}$ = 527.5.



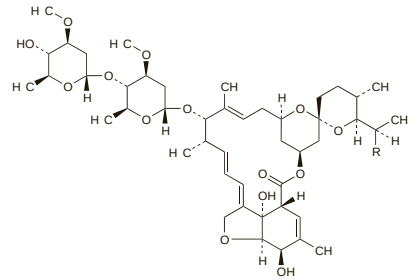
Profile
Hygromycin B is an anthelmintic used in veterinary medicine for nematode infections.

Ivermectin *(BAN, USAN, rINN)*

Ivermectina; Ivermectine; Ivermectinum; Ivermektiini; Ivermektin; Ivermektinas.

Ивермектин

CAS — 70288-86-7 (ivermectin); 70161-11-4 (component B_{1a}); 70209-81-3 (component B_{1b}).
ATC — P02CF01.
ATC Vet — QP54AA01; QS02QA03.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Ivermectin). A mixture of ivermectin component H_2B_{1a} (5-*O*-demethyl-22,23-dihydroavermectin A_{1a}; $C_{48}H_{74}O_{14}$ = 875.1) and ivermectin component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}; $C_{47}H_{72}O_{14}$ = 861.1).
A white or yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.
USP 31 (Ivermectin). A mixture of component H_2B_{1a} (5-*O*-demethyl-22,23-dihydro-avermectin A_{1a}; $C_{48}H_{74}O_{14}$ = 875.1) and component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-avermectin A_{1a}; $C_{47}H_{72}O_{14}$ = 861.1). It may contain small amounts of suitable antoxidant and chelating agents.
A white to yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in petroleum spirit; soluble in acetone and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature of 2° to 8°. Where the use of an antoxidant is allowed, store at 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions
The adverse effects reported with ivermectin in patients with filariasis are generally consistent with a mild Mazzotti reaction arising from its effect on microfilariae. They include fever, pruritus, skin rashes, arthralgia, myalgia, asthenia, orthostatic hypotension, tachycardia, oedema, lymphadenopathy, gastrointestinal symptoms, sore throat, cough, and headache. The effects tend to be transient and if treatment is required they respond to analgesics and antihistamines.

Ivermectin may cause mild ocular irritation. Somnolence, transient eosinophilia, and raised liver enzyme values have also been reported.

Ivermectin is not recommended during pregnancy. Mass treatment is generally withheld from pregnant women (see Pregnancy, below), children under 15 kg, and the seriously ill.

Incidence of adverse effects. Some studies have shown quite a high incidence of adverse effects with ivermectin and have associated the effects with the severity of infection.[1-3] However, in none of these studies were the reactions considered to be life-threatening and only symptomatic treatment was required. The severity, incidence, and duration of adverse reactions was reported to be reduced after repeated annual administration.[4] When larger groups of patients were considered in the Onchocerciasis Control Programme (OCP) in West Africa, a much lower incidence of adverse reactions was seen in patients given ivermectin for the first time[5] and when treatment was repeated a year later that incidence was reduced even further. The results from several studies in this programme[6] showed 93 severe reactions in 50 929 patients (1.83%), most of the reactions being orthostatic hypotension or dizziness (53). In a 3-year randomised, double-blind, controlled study of ivermectin for onchocerciasis control in 572 patients,[7] 3-monthly treatment with the standard dose of 150 micrograms/kg was associated with a reduced risk of adverse reactions, especially oedema, pruritus, and back pain, when compared with the same dose given annually. Higher doses of 400 then 800 micrograms/kg, given either 3-monthly or annually, were associated with subjective ocular problems. Another study[8] found 22 severe reactions in 17 877 patients treated for onchocerciasis in an area also endemic for *Loa loa* infection, and demonstrated a relationship to heavy *L. loa* microfilaraemia. The Mectizan® Expert Committee and the Technical Consultative Committee have reported the incidence of encephalopathy after ivermectin treatment of onchocerciasis in *Loa loa* endemic areas to be less than 1 case in 10 000 treatments[9] and have implemented recommendations for ivermectin mass treatment programmes

of onchocerciasis in areas co-endemic for loiasis to reduce the risk of serious adverse events, especially in areas where the population is ivermectin naive.

Some supervision is considered necessary after doses of ivermectin;[2,6] the OCP recommendation[6] is for resident nurses to monitor patients for a period of 36 hours after treatment, whatever the level of endemicity. However, the incidence of adverse reactions reported after repeated doses appears to be lower than after the first dose and the need for supervision on re-treatment has been questioned.[10]

Neurotoxicity seen in some breeds of *dogs* has not been seen in *cattle* or *horses*[11] and nor was it reported in man in the above studies. Another potential concern was the prolongation of prothrombin times observed in 28 patients given ivermectin,[12] but others have not confirmed this effect[13] or observed any bleeding disorders.[14]

There has been some concern over the use of ivermectin to treat scabies in elderly patients after a report suggesting a possible link to an increased incidence of death among a cohort of 47 patients.[15] It has, however, been argued that no such association has been seen in other populations of elderly patients and that the statistical methods used by the original authors were deficient.[16-18] There was no evidence of an increase in death rate associated with ivermectin in a community-based trial in Papua New Guinea of diethylcarbamazine with or without ivermectin for lymphatic filariasis.[19]

1. Kumaraswami V, *et al.* Ivermectin for the treatment of Wuchereria bancrofti filariasis: efficacy and adverse reactions. *JAMA* 1988; **259:** 3150–3.
2. Rothova A, *et al.* Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989; **i:** 1439–41.
3. Zea-Flores R, *et al.* Adverse reactions after community treatment of onchocerciasis with ivermectin in Guatemala. *Trans R Soc Trop Med Hyg* 1992; **86:** 663–6.
4. Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis: results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 1993; **87:** 313–17.
5. De Sole G, *et al.* Lack of adverse reactions in ivermectin treatment of onchocerciasis. *Lancet* 1990; **335:** 1106–7.
6. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; **67:** 707–19.
7. Kamgno J,*et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; **98:** 496–504.
8. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; **350:** 18–22.
9. The Mectizan Expert Committee and The Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and loiasis. 2004. Available at: http://www.mectizan.org/library/EnglishMECTCCLoaRecs-June04.pdf (accessed 20/09/05)
10. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: adverse reactions after the first five treatment rounds. *Trans R Soc Trop Med Hyg* 1991; **85:** 501–5.
11. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987. Available at: http://libdoc.who.int/trs/WHO_TRS_752_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_752_(part2).pdf (accessed 16/07/08)
12. Homeida MMA, *et al.* Prolongation of prothrombin time with ivermectin. *Lancet* 1988; **i:** 1346–7.
13. Richards FO, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i;** 1139–40.
14. Pacque MC, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i:** 1140.
15. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; **349:** 1144–5.
16. Diazgranados JA, Costa JL. Deaths after ivermectin treatment. *Lancet* 1997; **349:** 1698.
17. Reintjes R, Hoek C. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350:** 215.
18. Coyne PE, Addiss DG. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350:** 215–16.
19. Alexander NDE, *et al.* Absence of ivermectin-associated excess deaths. *Trans R Soc Trop Med Hyg* 1998; **92:** 342.

Breast feeding. Mean ivermectin concentrations in the breast milk of 4 healthy women who had been given a standard dose of ivermectin were 14.13 nanograms/mL.[1] It was felt that in view of this low concentration the precaution of excluding lactating mothers from ivermectin mass treatment programmes should be reconsidered. Some authorities have recommended that ivermectin should not be given to mothers who are breast feeding until the infant is at least one week old. The American Academy of Pediatrics states that, since no adverse effects have been seen in breast-fed infants whose mothers were receiving ivermectin, it may be considered to be usually compatible with breast feeding.[2]

1. Ogbuokiri JE, *et al.* Ivermectin levels in human breast milk. *Eur J Clin Pharmacol* 1994; **46:** 89–90.
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)

Encephalopathy. For information on encephalopathy following Ivermectin treatment of onchocerciasis in *Loa loa* endemic areas, see Incidence of Adverse Effects, above.

Pregnancy. Ivermectin is teratogenic in *animals* and there are no adequate and well controlled studies in human pregnancy. Ivermectin treatment is therefore usually contra-indicated during pregnancy and pregnant women should be excluded from mass treatment schedules with ivermectin. However, women not yet diagnosed as pregnant or unwilling to admit their pregnancy have been treated. An assessment[1] of 203 pregnancy outcomes to women who had taken ivermectin during pregnancy, mostly during the first 12 weeks, found that the rates of major congenital malformation, miscarriage, and still-birth associated with ivermectin were similar to those in untreated mothers. In another study, 110 women also inadvertently given ivermectin during pregnancy experienced a similar lack of adverse effect on pregnancy outcome;[2] it was considered that the precaution of avoiding the use of ivermectin in women notifying a pregnancy should be adequate.

1. Pacqué M, *et al.* Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* 1990; **336:** 1486–9.
2. Chippaux J-P, *et al.* Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg* 1993; **87:** 318.

Pharmacokinetics

Ivermectin is absorbed after oral doses, with peak plasma concentrations being obtained after about 4 hours. Ivermectin is reported to be about 93% bound to plasma proteins and has a plasma elimination half-life of about 12 hours. It undergoes metabolism and is excreted largely as metabolites over a period of about 2 weeks, chiefly in the faeces, with less than 1% appearing in the urine and less than 2% in breast milk (see also Breast Feeding, above).

Uses and Administration

Ivermectin is a semisynthetic derivative of one of the avermectins, a group of macrocyclic lactones produced by *Streptomyces avermitilis*.

It has a microfilaricidal action in onchocerciasis and reduces the microfilarial load without the toxicity seen with diethylcarbamazine. Ivermectin also has a microfilaricidal action in lymphatic filariasis and is used in its management. Ivermectin is active in some other worm infections. It is used in the treatment of strongyloidiasis and has been tried in some *Mansonella* infections. For details of these infections and their treatment, see under Choice of Anthelmintic, p.134, and under the individual headings below.

In the treatment of onchocerciasis, a single oral dose of 3 to 12 mg of ivermectin, based roughly on 150 micrograms/kg for patients weighing more than 15 kg and over 5 years of age, is given annually or every 6 months. This schedule has been adopted for mass treatment in infected areas. No food should be taken for 2 hours before or after the dose.

Ivermectin 200 micrograms/kg as a single dose, or daily on two consecutive days, is used for the treatment of strongyloidiasis.

◊ Reviews.

1. Ottesen EA, Campbell WC. Ivermectin in human medicine. *J Antimicrob Chemother* 1994; **34:** 195–203.
2. Ōmura S. Ivermectin: 25 years and still going strong. *Int J Antimicrob Agents* 2008; **31:** 91–8.

Cutaneous larva migrans. There are some reports[1,2] of ivermectin being effective in the treatment of cutaneous larva migrans (p.135). An oral dose of 200 micrograms/kg daily for 1 to 2 days has been recommended.[3]

1. Caumes E, *et al.* Efficacy of ivermectin in the therapy of cutaneous larva migrans. *Arch Dermatol* 1992; **128:** 994–5.
2. Caumes E, *et al.* A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg* 1993; **49:** 641–4.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Intestinal nematode infections. Ivermectin activity has been seen in man against *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Trichuris trichiura*;[1] although some have failed to detect activity against *Trichuris*,[2] ivermectin given with albendazole has been studied for the treatment of trichuriasis (p.139) and may prove useful. Roundworm expulsion has been reported as a 'side-effect' of ivermectin when used in community-based treatment of onchocerciasis.[3] In a controlled study,[4] single doses of ivermectin 150 or 200 micrograms/kg produced cure rates of 94% in strongyloidiasis (see below) and above 67% in ascariasis, trichuriasis, and enterobiasis. Although some activity has been observed against *Necator americanus*,[1] cure rates for hookworm were considered unsatisfactory.[4]

1. Freedman DO, *et al.* The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 1989; **159:** 1151–3.
2. Whitworth JAG, *et al.* A field study of the effect of ivermectin on intestinal helminths in man. *Trans R Soc Trop Med Hyg* 1991; **85:** 232–4.
3. Whitworth JAG, *et al.* Community-based treatment with ivermectin. *Lancet* 1988; **ii:** 97–8.
4. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; **40:** 304–9.

Loiasis. There is evidence of reduced microfilaraemia after ivermectin treatment[1-5] in patients with loiasis (p.137), but concern exists over its potential for neurotoxicity in patients with a high microfilarial burden.[6,7] Low-dose regimens (about 25 micrograms/kg) have been investigated[8] but did not seem to offer much advantage in reducing neurotoxicity.

1. Martin-Prevel Y, *et al.* Reduction of microfilaraemia with single high-dose of ivermectin in loiasis. *Lancet* 1993; 342: 442.
2. Ranque S, *et al.* Decreased prevalence and intensity of Loa loa infection in a community treated with ivermectin every three months for two years. *Trans R Soc Trop Med Hyg* 1996; **90:** 429–30.
3. Duong TH, *et al.* Reduced Loa loa microfilaria count ten to twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; **91:** 592–3.
4. Gardon J, *et al.* Marked decrease in Loa loa microfilaraemia six and twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; **91:** 593–4.
5. Chippaux J-P, *et al.* Impact of repeated large scale ivermectin treatments on the transmission of Loa loa. *Trans R Soc Trop Med Hyg* 1998; **92:** 454–8.
6. Anonymous. Encephalitis following treatment of loiasis. *WHO Drug Inf* 1991; **5:** 113–14.
7. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; **350:** 18–22.
8. Kamgno J, *et al.* Randomized, controlled, double-blind trial with ivermectin on Loa loa microfilaraemia: efficacy of a low dose (~25 μg/kg) versus current standard dose (150 μg/kg). *Trans R Soc Trop Med Hyg* 2007; **101:** 777–85.

Lymphatic filariasis. Ivermectin is used in the management of lymphatic filariasis (p.137). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single oral dose of ivermectin 150 to 200 micrograms/kg with a single oral dose of albendazole 400 mg given once each year for at least 5 years.

Mansonella infections. The response of *Mansonella* infections (p.137) to ivermectin depends on the species. It may be effective against *Mansonella ozzardi*, but studies in *M. perstans* infection have not shown ivermectin to produce a substantial reduction in microfilaraemia.[1,2] A good response to ivermectin has been reported in infections with *M. streptocerca*.[3,4]

1. Van den Enden E, *et al.* Treatment failure of a single high dose of ivermectin for Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 1993; **87:** 90.
2. Schulz-Key H, *et al.* Efficacy of ivermectin in the treatment of concomitant Mansonella perstans infections in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 1993; **87:** 227–9.
3. Fischer P, *et al.* Treatment of human Mansonella streptocerca infection with ivermectin. *Trop Med Int Health* 1997; **2:** 191–9.
4. Fischer P, *et al.* Long-term suppression of Mansonella streptocerca microfilariae after treatment with ivermectin. *J Infect Dis* 1999; **180:** 1403–5.

Onchocerciasis. Ivermectin has a microfilaricidal action against *Onchocerca volvulus* and is the main drug used in the control of onchocerciasis (p.137). A single oral dose rapidly eliminates microfilariae from the skin, with maximum effect after 1 to 2 months,[1] and gradually eliminates them from the cornea and anterior chamber of the eye.[2] Ivermectin has little effect on the adult worms but does suppress the release of microfilariae from the adult worm for several cycles which accounts for its prolonged activity. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Its action against *O. volvulus* has been attributed to a GABA-agonist effect. Studies have also indicated that ivermectin inhibits the transmission of microfilariae by reducing their uptake from man by the insect vector.[3-6]

Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in community-wide mass treatment programmes in all countries in which onchocerciasis is endemic, where it is given at a standard dose of 150 micrograms/kg once or twice a year to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg, and those unable to walk or otherwise seriously ill.[7] The adult worms live for about 15 years, therefore treatment will need to be continued for many years. Several studies have confirmed the long-term safety and efficacy of such programmes.[8-12] Studies have reported that increasing the frequency of the standard doses of ivermectin to every 3 or 6 months appears to increase efficacy compared with annual treatments[13,14] and that 3-monthly regimens may also reduce risk of adverse effects.[14,15] No additional benefit was noted by increasing the dose of ivermectin to 400 or 800 micrograms/kg given either 3-monthly or annually.

In non-endemic areas, repeated doses may be necessary to reduce recurrence; a study in the UK found that patients given three doses at monthly intervals had fewer relapses at 6 months than patients who received a single dose, but relapses were nevertheless seen in 50% of patients at 12 months.[16]

The ocular microfilarial load can be safely reduced by ivermectin[2,17] and early lesions of the anterior segment of the eye have improved.[17] A reduction in the incidence[18] and progression[19] of optic nerve damage has also been reported, but the effect on posterior segment disease is less certain.[20] A systematic review of 5 placebo-controlled studies, with data from 3810 individuals, found no statistically significant difference between ivermectin and placebo groups for preventing visual acuity loss.[21] Improvements in skin lesions have been reported.[22]

1. Basáñez MG, *et al.* Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8:** 310–22.
2. Newland HS, *et al.* Effect of single-dose ivermectin therapy on human Onchocerca volvulus infection with onchocercal ocular involvement. *Br J Ophthalmol* 1988; **72:** 561–9.
3. Taylor HR, *et al.* Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science* 1990; **250:** 116–18.
4. Trpis M, *et al.* Effect of mass treatment of a human population with ivermectin on transmission of Onchocerca volvulus by Simulium yahense in Liberia, West Africa. *Am J Trop Med Hyg* 1990; **42:** 148–56.
5. Chavasse DC, *et al.* Low level ivermectin coverage and the transmission of onchocerciasis. *Trans R Soc Trop Med Hyg* 1995; **89:** 534–7.
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Scabies and pediculosis. Scabies (p.2035) is usually treated with a topically applied acaricide. However, a single oral dose of ivermectin has been reported to be effective.[1,2] In a study of 11 patients with uncomplicated scabies, a single oral dose of ivermectin 200 micrograms/kg was effective in curing infection after 4 weeks. In a group of 11 patients, also infected with HIV, scabies was cured in 8 after 2 weeks.[1] Two of the remaining 3 patients received a second dose of ivermectin which cured the scabies infection by the fourth week. A single oral dose of ivermectin 150 micrograms/kg was partially effective in an outbreak of scabies in 1153 Tanzanian patients.[3] Crusted (Norwegian) scabies has also been reported to be effectively treated by a single oral dose of 12 mg of ivermectin in addition to topical application of 3% salicylic acid ointment in 2 patients; the treatment was effective in under one week.[2] A single oral dose of ivermectin 200 micrograms/kg was effective for crusted scabies in a 2-year-old infant who had contracted the disease following long-term corticosteroid use.[4]

Ivermectin has also been investigated[5] as a possible treatment for pediculosis (p.2034) although, again, topically applied insecticides are the usual method of control. A study *in vitro* and in *animals* showed that ivermectin killed nymphs and females of the human body louse (*Pediculus humanus humanus*). Ivermectin was known to be effective against other louse species that infect a range of *animals*.[6]

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6. Mumcuoglu KY, *et al.* Systemic activity of ivermectin on the human body louse (Anoplura: Pediculidae). *J Med Entomol* 1990; **27:** 72–5.

Strongyloidiasis. Ivermectin is effective in the treatment of strongyloidiasis (p.138) and is considered by some authorities to be the drug of choice.

References.

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Trichostrongyliasis. For mention of the use of ivermectin in *Trichostrongylus* infections, see p.139.

Preparations

USP 31: Ivermectin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dermopero; Securo; ***Austral.:*** Stromectol; ***Braz.:*** Ivermec†; Leverctin; Revectina; Vermectil; ***Fr.:*** Mectizan; Stromectol; ***Jpn:*** Stromectol; ***Mex.:*** Ivexterm; ***Neth.:*** Stromectol; ***NZ:*** Stromectol; ***USA:*** Mectizan; Stromectol.

Levamisole *(BAN, rINN)*

Levamisol; Lévamisole; Levamisoli; Levamisolum; Levamizol. (*S*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*][1,3]thiazole.

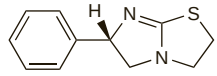
Левамизол

$C_{11}H_{12}N_2S$ = 204.3.

CAS — 14769-73-4.

ATC — P02CE01.

ATC Vet — QP52AE01.



Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.
Ph. Eur. 6.2 (Levamisole for Veterinary Use; Levamisole BP(Vet) 2008). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Levamisole Hydrochloride *(BANM, USAN, rINNM)*

Cloridrato de Levamizol; Hidrocloruro de levamisol; ICI-59623; Lévamisole, chlorhydrate de; Levamisol-hydrochlorid; Levamisol-hydroklorid; Levamisoli hydrochloridum; Levamisolihydrokloridi; Levamizol-hidroklorid; Levamizolio hidrochloridas; Lewamizolu chlorowodorek; NSC-177023; R-12564; RP-20605; *l*-Tetramisole Hydrochloride; *l*-Tetramisole Hydrochloride.

Левамизола Гидрохлорид

$C_{11}H_{12}N_2S,HCl$ = 240.8.

CAS — 16595-80-5.

ATC — P02CE01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Levamisole Hydrochloride). A white to almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane. A 5% solution in water has a pH of 3.0 to 4.5. Protect from light.
USP 31 (Levamisole Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 4.5. Protect from light.

Adverse Effects

When given in single doses for the treatment of ascariasis or other worm infections, levamisole is generally well tolerated and adverse effects are usually limited to nausea, vomiting, diarrhoea, abdominal pain, dizziness, and headache.

When levamisole is used as an immunostimulant and given for longer periods, adverse effects are more frequent and diverse and, in common with other immunomodulators, may sometimes result from exacerbation of the primary underlying disease. Adverse effects associated especially with the more prolonged use of levamisole have included: hypersensitivity reactions such as fever, a flu-like syndrome, arthralgia, muscle pain, skin rashes, and cutaneous vasculitis; CNS effects including headache, insomnia, dizziness, and convulsions; haematological abnormalities such as agranulocytosis, leucopenia, and thrombocytopenia; and gastrointestinal disturbances, including an abnormal taste in the mouth.

Incidence of adverse effects. In a review[1] (by the manufacturers) of 46 controlled studies in which 2635 cancer patients received adjuvant levamisole treatment, most patients received levamisole on 3 consecutive days every 2 weeks (1102 patients) or on 2 consecutive days every week (1156 patients), usually in a daily dose of 150 mg. Levamisole caused several adverse effects, such as skin rash, nausea, vomiting, and a metallic or bitter taste in the mouth, which although troublesome were relatively trivial and often regressed during therapy or disappeared on cessation of therapy. A total of 38 patients developed agranulocytosis and of these 36 had received weekly treatment. Several contracted possible life-threatening infections and 2 died of septic shock.

1. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; **5:** 1–9.

Effects on the endocrine system. Rechallenge confirmed that levamisole was responsible for inappropriate antidiuretic hormone syndrome in a patient receiving levamisole with fluorouracil.[1]

1. Tweedy CR, *et al.* Levamisole-induced syndrome of inappropriate antidiuretic hormone. *N Engl J Med* 1992; **326:** 1164.

Effects on the liver. Elevated aspartate aminotransferase concentrations in 2 of 11 patients given levamisole for recurrent pyoderma suggested liver toxicity, a very rarely occurring adverse effect.[1] In a later report, liver enzyme concentrations were raised in a 14-year-old boy treated with levamisole for minimal change nephrotic syndrome.[2]

1. Papageorgiou P, *et al.* Levamisole in chronic pyoderma. *J Clin Lab Immunol* 1982; **8:** 121–7.
2. Bulugahapitiya DTD. Liver toxicity in a nephrotic patient treated with levamisole. *Arch Dis Child* 1997; **76:** 289.

Effects on the nervous system. Reports[1,2] of inflammatory leukoencephalopathy were associated with the use of fluorouracil and levamisole in 4 patients being treated for adenocarcinoma of the colon. Active demyelination was demonstrated in 2 patients.[1] Clinical improvement occurred when chemotherapy was stopped; 3 patients were treated with corticosteroids.[1] A similar syndrome has been reported in a patient with a history of hepatitis C given levamisole alone.[3]

1. Hook CC, *et al.* Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. *Ann Neurol* 1992; **31:** 262–7.
2. Kimmel DW, Schutt AJ. Multifocal leukoencephalopathy: occurrence during 5-fluorouracil and levamisole therapy and resolution after discontinuation of chemotherapy. *Mayo Clin Proc* 1993; **68:** 363–5.
3. Lucia P, *et al.* Multifocal leucoencephalopathy induced by levamisole. *Lancet* 1996; **348:** 1450.

Precautions

The use of levamisole should be avoided in patients with pre-existing blood disorders. Patients given levamisole with fluorouracil should undergo appropriate monitoring of haematological and hepatic function.

Rheumatoid arthritis. The presence of HLA B27 in seropositive rheumatoid arthritis is an important predisposing factor to the development of agranulocytosis with levamisole; it is recommended that the use of levamisole in this group should be avoided.[1]

1. Mielants H, Veys EM. A study of the hematological side effects of levamisole in rheumatoid arthritis with recommendations. *J Rheumatol* 1978; **5** (suppl 4): 77–83.

Sjögren's syndrome. The appearance of adverse effects in 9 of 10 patients with rheumatoid arthritis and Sjögren's syndrome while being treated with levamisole led to abandonment of the study.[1] Levamisole should be given with caution, if at all, to patients with Sjögren's syndrome.

1. Balint G, *et al.* Sjögren's syndrome: a contraindication to levamisole treatment? *BMJ* 1977; **2:** 1386–7.

Interactions

Alcohol. US licensed product information states that levamisole can produce a disulfiram-like reaction with *alcohol.*

Anticoagulants. For an increase in the activity of *warfarin* when given with levamisole and fluorouracil, see Interactions, Levamisole, under Warfarin, p.1431.