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.
6. Boussinesq M, *et al.* Onchocerca volvulus: striking decrease in transmission in the Vina valley (Cameroon) after eight annual large scale ivermectin treatments. *Trans R Soc Trop Med Hyg* 1997; **91:** 82–6.
7. Pond B. Distribution of ivermectin by health workers. *Lancet* 1990; **335:** 1539.
8. 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.
9. Pacqué M, *et al.* Safety of and compliance with community-based ivermectin therapy. *Lancet* 1990; **335:** 1377–80.
10. Pacqué M, *et al.* Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. *J Infect Dis* 1991; **163:** 381–5.
11. Steel C, *et al.* Immunologic responses to repeated ivermectin treatment in patients with onchocerciasis. *J Infect Dis* 1991; **164:** 581–7.
12. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: clinical and parasitological responses to four doses given at six-monthly interval. *Trans R Soc Trop Med Hyg* 1992; **86:** 277–80.
13. Greene BM, *et al.* A comparison of 6-, 12-, and 24-monthly dosing with ivermectin for treatment of onchocerciasis. *J Infect Dis* 1991; **163:** 376–80.
14. Gardon J,*et al.* Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* 2002; **360:** 203–10.
15. 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.
16. Churchill DR, *et al.* A trial of a three-dose regimen of ivermectin for the treatment of patients with onchocerciasis in the UK. *Trans R Soc Trop Med Hyg* 1994; **88:** 242.
17. Dadzie KY, *et al.* Changes in ocular onchocerciasis after two rounds of community-based ivermectin treatment in a holo-endemic onchocerciasis focus. *Trans R Soc Trop Med Hyg* 1991; **85:** 267–71.
18. Abiose A, *et al.* Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet* 1993; **341:** 130–4.
19. Cousens SN, *et al.* Impact of annual dosing with ivermectin on progression of onchocercal visual field loss. *Bull WHO* 1997; **75:** 229–36.
20. Whitworth JAG, *et al.* Effects of repeated doses of ivermectin on ocular onchocerciasis: community-based trial in Sierra Lione. *Lancet* 1991; **338:** 1100–1103.
21. Ejere H, *et al.* Ivermectin for onchocercal eye disease (river blindness). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 29/07/07).
22. Pacqué M, *et al.* Improvements in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 1991; **90:** 590–4.

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]

1. Meinking TL, *et al.* The treatment of scabies with ivermectin. *N Engl J Med* 1995; **333:** 26–30.
2. Aubin F, Humbert P. Ivermectin for crusted (Norwegian) scabies. *N Engl J Med* 1995; **332:** 612.
3. Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol* 2000; **143:** 520–3.
4. Marlière V, *et al.* Crusted (Norwegian) scabies induced by use of topical corticosteroids and treated successfully with ivermectin. *J Pediatr* 1999; **135:** 122–4.
5. Foucault C, *et al.* Oral ivermectin in the treatment of body lice. *J Infect Dis* 2006; **193:** 474–6.
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.

1. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; **40:** 304–9.
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3. Lyagoubi M, *et al.* Chronic persistent strongyloidiasis cured by ivermectin. *Trans R Soc Trop Med Hyg* 1992; **86:** 541.
4. Datry A, *et al.* Treatment of Strongyloides stercoralis infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg* 1994; **88:** 344–5.
5. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; **169:** 1076–9.
6. Marti H, *et al.* A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg* 1996; **55:** 477–81.
7. Igual-Adell R, *et al.* Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother* 2004; **5:** 2615–9.

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.

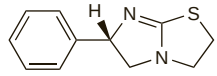
Левамизол

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