Nifursol *(BAN, USAN, pINN)*

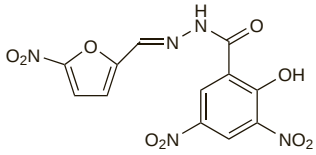
Nifursolum. 3,5-Dinitro-2′-(5-nitrofurfurylidene)salicylohydrazide.

Нифурсол

$C_{12}H_7N_5O_9$ = 365.2.

CAS — 16915-70-1.

ATC Vet — QP51AX05.



Profile

Nifursol is an antiprotozoal used in veterinary practice for the prevention of blackhead (histomoniasis) in poultry.

Nifurtimox *(BAN, rINN)*

Bayer-2502; Nifurtimoxum. Tetrahydro-3-methyl-4-(5-nitrofurfurylideneamino)-1,4-thiazine 1,1-dioxide.

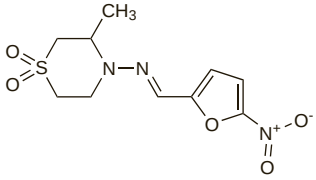
Нифуртимокс

$C_{10}H_{13}N_3O_5S$ = 287.3.

CAS — 23256-30-6.

ATC — P01CC01.

ATC Vet — QP51AC01.



Pharmacopoeias. In *Fr.* and *Int.*

Adverse Effects

Adverse effects are common with nifurtimox and include gastrointestinal effects such as anorexia with loss of weight, abdominal pain, nausea and vomiting, and effects on the nervous system, especially peripheral neuropathy. Psychoses, CNS excitement, insomnia, drowsiness, headache, myalgia, arthralgia, dizziness, and convulsions have also been reported. Skin rashes and other allergic reactions may occur.

Mutagenicity. An increase in chromosomal aberrations has been seen in children given nifurtimox.[1]

1. Gorla NB, *et al.* Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res* 1989; **224:** 263–7.

Pharmacokinetics

Nifurtimox is well absorbed and rapidly metabolised after oral doses.

◊ References.

1. Paulas C, *et al.* Pharmacokinetics of a nitrofuran compound, nifurtimox, in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 454–7.
2. Gonzalez-Martin G, *et al.* The pharmacokinetics of nifurtimox in chronic renal failure. *Eur J Clin Pharmacol* 1992; **42:** 671–3.

Uses and Administration

Nifurtimox is a nitrofuran derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease) due to infection by *Trypanosoma cruzi*, especially the early acute stage of the disease. In African trypanosomiasis it has some activity against *T. brucei gambiense*, the organism responsible for West African sleeping sickness.

Nifurtimox is given orally in 3 to 4 divided doses. It is better tolerated by children than by adults. Treatment for American trypanosomiasis is given for 60 to 120 days (but see below). Doses for adults are 8 to 10 mg/kg daily. Doses for children are: aged 1 to 10 years, 15 to 20 mg/kg daily for 90 days; aged 11 to 16 years, 12.5 to 15 mg/kg daily for 90 days.

Leishmaniasis. Mucocutaneous leishmaniasis of the New World (p.824) is usually treated with pentavalent antimony or, in those who do not respond, with amphotericin B or pentamidine. However, nifurtimox 10 mg/kg daily for a minimum of 4 weeks has been shown to be effective in cases of mucocutaneous leishmaniasis in Colombia and Brazil. Despite this, toxic effects with nifurtimox are common and its role as a second-line drug or with pentavalent antimony has not been established.[1]

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793*, 1990.

African trypanosomiasis. Nifurtimox has been tried as an alternative to melarsoprol or eflornithine in the meningoencephalitic stage of *Trypanosoma brucei gambiense* infection (p.827), but higher doses than those used in American trypanosomiasis are necessary. A good initial response was achieved[1] in 25 patients with nifurtimox 15 mg/kg daily for 60 days, but 3 patients relapsed while still receiving nifurtimox and a further 12 of 19 patients who were followed up relapsed subsequently. An attempt[2] to improve the response by increasing the daily dose even higher to 30 mg/kg for 30 days resulted in substantial toxicity and only a modest improvement in results, with 9 of 25 patients relapsing. However, promising results have been reported[3] from use of oral nifurtimox 15 mg/kg daily for 10 days with eflornithine 400 mg/kg daily intravenously for 7 days.

1. Pepin J, *et al.* An open clinical trial of nifurtimox for arseno-resistant Trypanosoma brucei gambiense sleeping sickness in central Zaire. *Trans R Soc Trop Med Hyg* 1989; **83:** 514–17.
2. Pépin J, *et al.* High-dose nifurtimox for arseno-resistant Trypanosoma brucei gambiense sleeping sickness: an open trial in central Zaire. *Trans R Soc Trop Med Hyg* 1992; **86:** 254–6.
3. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage Trypanosoma brucei gambiense sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; **45:** 1435–42.

American trypanosomiasis. The treatment of American trypanosomiasis (p.827) is generally unsatisfactory, but nifurtimox is of value especially in the acute phase. However, there has been controversy over its ability to cure completely, that is to eradicate all parasites, in chronic disease.[1] Doses recommended by WHO[2,3] are 8 to 10 mg/kg daily in three divided doses for adults, and 15 to 20 mg/kg daily in four divided doses for children. WHO recommends that nifurtimox should be given for 60 or 90 days.[2,3] Some in the USA[4] suggest a 90- to 120-day regimen for adults but nifurtimox is not well tolerated and the experience of other workers[1] suggests that few patients may complete the full course.

1. Gutteridge WE. Existing chemotherapy and its limitations. *Br Med Bull* 1985; **41:** 162–8.
2. 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)
3. WHO. *WHO model formulary.* Geneva: WHO, 2004.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Nimorazole *(BAN, rINN)*

Nimorazol; Nimorazolum; Nitrimidazine. 4-[2-(5-Nitroimidazol-1-yl)ethyl]morpholine.

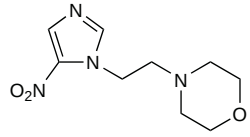
Ниморазол

$C_9H_{14}N_4O_3$ = 226.2.

CAS — 6506-37-2.

ATC — P01AB06.

ATC Vet — QP51AA06.



Pharmacopoeias. In *It.*

Adverse Effects and Precautions

As for Metronidazole, p.837.

Pharmacokinetics

Nimorazole is readily absorbed from the gastrointestinal tract. Peak blood concentrations are achieved within 2 hours, and high concentrations are reported to occur in salivary and vaginal secretions. Trichomonicidal urinary concentrations may persist for up to 48 hours after a dose. It is excreted in the urine together with 2 active metabolites. Unchanged drug and metabolites also appear in breast milk.

Uses and Administration

Nimorazole is a 5-nitroimidazole derivative. It has antimicrobial actions and uses similar to those of metronidazole (p.839).

In the treatment of trichomoniasis, the usual dose of nimorazole is 2 g orally as a single dose with a main meal. It may alternatively be given in a dose of 1 g every 12 hours for three doses, or 250 mg three times daily for 5 to 7 days. In amoebiasis, nimorazole 1 g is given twice daily, usually for 5 to 10 days and in giardiasis a dose of 500 mg is given twice daily, usually for 5 to 7 days.

Nimorazole may also be used in the treatment of acute ulcerative gingivitis in a dose of 500 mg twice daily for 2 days.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Naxogin; Vagarne†; ***Austria:*** Naxogin; ***Belg.:*** Naxogin; ***Braz.:*** Naxogin; ***Chile:*** Naxogin†; ***Ger.:*** Esclama†; ***Rus.:*** Naxogin (Наксоджин).

Multi-ingredient: ***Arg.:*** Vagarne†; ***Braz.:*** Naxogin Composto; ***Chile:*** Naxogin Compositum; Naxogin Dos†; ***Indon.:*** Gynoxa; Naxogin Complex.

Nitazoxanide *(BAN, USAN, rINN)*

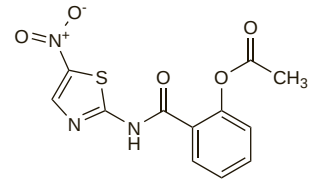
Nitazoxanida; Nitazoxanidum; PH-5776. *N*-(5-Nitro-2-thiazolyl)salicylamide acetate.

Нитазоксанид

$C_{12}H_9N_3O_5S$ = 307.3.

CAS — 55981-09-4.

ATC — P01AX11.



Adverse Effects

The most common adverse effects associated with nitazoxanide are abdominal pain and diarrhoea. Nausea and vomiting, flatulence, and increased appetite have also been reported. Headache may occur. Other reported adverse effects include fever, malaise, pruritus, sweating, dizziness, and rhinitis. Discoloration of urine and of the eyes has been reported rarely. Increased creatinine and liver enzyme values have been noted.

Pharmacokinetics

Nitazoxanide is absorbed from the gastrointestinal tract after oral dosage and is rapidly hydrolysed to an active desacetyl metabolite, tizoxanide. Tizoxanide then partially undergoes conjugation, primarily by glucuronidation. The extent of absorption is enhanced if given with food and peak plasma concentrations of tizoxanide and the glucuronide are seen 1 to 4 hours after an oral dose. The parent drug is not detected in plasma. Tizoxanide is more than 99% bound to plasma proteins. About two-thirds of an oral dose of nitazoxanide is eliminated in the faeces and one-third in the urine; tizoxanide is excreted in the urine, bile, and faeces, while the glucuronide is excreted in only the urine and bile.

Uses and Administration

Nitazoxanide is used for the treatment of cryptosporidiosis and giardiasis in immunocompetent patients. It is given orally and should be taken with food. Doses are 100 mg twice daily for 3 days in those aged 1 to 3 years, 200 mg twice daily for 3 days in those aged 4 to 11 years, and 500 mg twice daily for 3 days in adults. Nitazoxanide has also been tried in a number of other protozoal and helminth infections, particularly in immunocompromised patients, including those with HIV infection. It is also being investigated for the treatment of rotavirus disease and *Clostridium difficile* colitis.

◊ Reviews.

1. Bailey JM, Erramouspe J. Nitazoxanide treatment for giardiasis and cryptosporidiosis in children. *Ann Pharmacother* 2004; **38:** 634–40.
2. Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis* 2005; **40:** 1173–80.
3. Musher DM, *et al.* Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006; **43:** 421–7.
4. Anderson VR, Curran MP. Nitazoxanide: a review of its use in the treatment of gastrointestinal infections. *Drugs* 2007; **67:** 1947–67.

Protozoal infections. As well as its established use in cryptosporidiosis (p.823) and giardiasis (p.824), nitazoxanide has been used in other protozoal infections including intestinal amoebiasis (p.822), blastocytosis (p.823), and microsporidiosis (p.826).

Rotavirus diarrhoea. A randomised double-blind placebo-controlled study[1] in 38 young children (median age 11 months) with confirmed rotavirus diarrhoea found that oral nitazoxanide 7.5 mg/kg twice daily for 3 days significantly reduced the duration of rotavirus disease. The median time to resolution of illness after the first dose was 31 hours for those given nitazoxanide compared with 75 hours for those in the placebo group.

1. Rossignol J-F, *et al.* Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. *Lancet* 2006; **368:** 124–9.

Worm infections. Nitazoxanide has been used in various helminthiases, including ascariasis (p.134), hymenolepiasis (p.136), the liver fluke infection fascioliasis (p.137), and trichuriasis (p.139).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Heliton†; Nixoran; ***Braz.:*** Annita; ***Mex.:*** Bionit; Daxon; Kidonax; Mitafar; NTZ†; Padovan Ton; Paramix; Rosanil; ***USA:*** Alinia; ***Venez.:*** Celectan.

Multi-ingredient: ***Mex.:*** Heliton.

Ornidazole *(USAN, rINN)*

Ornidatsoli; Ornidazol; Ornidazolum; Ro-7-0207. 1-Chloro-3-(2-methyl-5-nitroimidazol-1-yl)propan-2-ol.

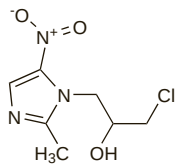
Орнидазол

$C_7H_{10}ClN_3O_3$ = 219.6.

CAS — 16773-42-5.

ATC — G01AF06; J01XD03; P01AB03.

ATC Vet — QG01AF06; QJ01XD03; QP51AA03.



Adverse Effects and Precautions

As for Metronidazole, p.837.

Pharmacokinetics

Ornidazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached within 3 hours. After repeated oral doses of 500 mg every 12 hours, steady-state peak and trough concentrations are 14 and 6 micrograms/mL respectively.

The plasma elimination half-life of ornidazole is 12 to 14 hours. Less than 15% is bound to plasma proteins. It is widely distributed in body tissues and fluids, including the CSF.

Ornidazole is metabolised in the liver and is excreted in the urine, mainly as conjugates and metabolites, and to a lesser extent in the faeces. Biliary excretion may be important in the elimination of ornidazole and its metabolites.

◊ References.

1. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy* 1976; **22:** 19–29.
2. Matheson I, *et al.* Plasma levels after a single oral dose of 1.5 g ornidazole. *Br J Vener Dis* 1977; **53:** 236–9.
3. Schwartz DE, *et al.* Metabolic studies of ornidazole in the rat, in the dog and in man. *Xenobiotica* 1979; **9:** 571–81.
4. Turcant A, *et al.* Pharmacokinetics of ornidazole in neonates and infants after a single intravenous infusion. *Eur J Clin Pharmacol* 1987; **32:** 111–13.
5. Martin C, *et al.* Pharmacokinetics and tissue penetration of a single dose of ornidazole (1,000 milligrams intravenously) for antibiotic prophylaxis in colorectal surgery. *Antimicrob Agents Chemother* 1990; **34:** 1921–4.
6. Bourget P, *et al.* Disposition of ornidazole and its metabolites during pregnancy. *J Antimicrob Chemother* 1995; **35:** 691–6.

Hepatic impairment. The elimination of ornidazole after a single intravenous dose of 500 mg was impaired in 10 patients with severe liver cirrhosis when compared with 10 healthy subjects; mean half-lives were 21.9 hours and 14.1 hours respectively.[1] These results suggested that the interval between doses of ornidazole should be doubled in patients with marked hepatic impairment. The need for dose adjustment was confirmed in further studies of patients with other forms of liver disease.[2,3]

1. Taburet AM, *et al.* Pharmacokinetics of ornidazole in patients with severe liver cirrhosis. *Clin Pharmacol Ther* 1986; **40:** 359–64.
2. Bourget P, *et al.* Ornidazole pharmacokinetics in several hepatic diseases. *J Pharmacol Clin* 1988; **7:** 25–32.
3. Taburet AM, *et al.* Pharmacokinetics of ornidazole in patients with acute viral hepatitis, alcoholic cirrhosis, and extrahepatic cholestasis. *Clin Pharmacol Ther* 1989; **45:** 373–9.

Renal impairment. The half-life of intravenous ornidazole was not prolonged in a study in patients with advanced chronic renal failure, including those on continuous ambulatory peritoneal dialysis, although total plasma clearance was halved; modification of the usual dosage is not necessary in such patients. However, the drug was removed by haemodialysis and ornidazole should be given after the dialysis session rather than before.[1] In another study[2] the systemic availability and total body clearance of ornidazole were unaffected in chronic renal failure; it was considered that an additional dose should be given before haemodialysis to compensate for removal during that procedure.

1. Merdjan H, *et al.* Pharmacokinetics of ornidazole in patients with renal insufficiency; influence of haemodialysis and peritoneal dialysis. *Br J Clin Pharmacol* 1985; **19:** 211–17.
2. Horber FF, *et al.* High haemodialysis clearance of ornidazole in the presence of a negligible renal clearance. *Eur J Clin Pharmacol* 1989; **36:** 389–93.

Uses and Administration

Ornidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p.839) in the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections.

It is given orally after food, or intravenously. Intravenous solutions of ornidazole should be diluted to 5 mg or less per mL and 100 or 200 mL infused over 15 to 30 minutes.

In **amoebiasis**, 500 mg of ornidazole is given orally twice daily for 5 to 10 days; children are given 25 mg/kg as a single daily dose for 5 to 10 days. Patients with amoebic dysentery may be given 1.5 g as a single daily dose for 3 days; the children's dose is 40 mg/kg daily. An alternative regimen for adults over 60 kg is 1 g twice daily for 3 days. In severe amoebic dysentery and amoebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 0.5 to 1 g initially, followed by 500 mg every 12 hours for 3 to 6 days; the children's dose is 20 to 30 mg/kg daily.

In **giardiasis**, 1 or 1.5 g of ornidazole is given orally as a single daily dose for 1 or 2 days; the children's dose is 30 or 40 mg/kg daily.

In **trichomoniasis**, a single oral dose of 1.5 g is given; alternatively, a 5-day oral course of ornidazole 500 mg twice daily may be used. Sexual partners should also be treated. The children's dose is 25 mg/kg as a single dose by mouth.

For the treatment of **anaerobic bacterial infections,** ornidazole is given by intravenous infusion in an initial dose of 0.5 to 1 g, followed by 1 g daily as a single dose or in two divided doses for 5 to 10 days; oral therapy with 500 mg every 12 hours should be substituted as soon as possible. Children may be given 10 mg/kg intravenously every 12 hours for 5 to 10 days.

For the prevention of postoperative anaerobic bacterial infections, 1 g is given by intravenous infusion about 30 minutes before surgery.

Administration in hepatic impairment. In view of the prolonged half-life and reduced clearance of ornidazole reported in patients with hepatic dysfunction (see above), the interval between doses should be doubled in patients with severe hepatic impairment.

Administration in renal impairment. The elimination of ornidazole is reported to be largely unaltered in patients with impaired renal function (see under Pharmacokinetics, above). Dosage adjustment is therefore usually unnecessary, although patients receiving haemodialysis should be given a supplemental dose of ornidazole before dialysis; a supplemental dose of 500 mg should be given if the daily dose is 2 g daily or 250 mg should be given if the daily dose is 1 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Mebaxol; ***Belg.:*** Tiberal; ***Chile:*** Invigan; ***Cz.:*** Avrazor; ***Fr.:*** Tiberal; ***Gr.:*** Betiral†; ***India:*** Giro; Oniz; Ornida; Zil; ***Mex.:*** Danubial†; ***NZ:*** Tiberal; ***Rus.:*** Dazolic (Дазолик); Ornisid (Орнисид); ***Spain:*** Tinerol†; ***Switz.:*** Tiberal; ***Turk.:*** Biteral; Borneral; Ornidone; Ornisid; Ornitop; ***Venez.:*** Tiberal†.

Multi-ingredient: ***India:*** Bidoflox-Oz†; Gatiquin Oz Kit; Levoflox Oz Kit; Ocimix; Orflaz Kit; Ornof; Tariflox Plus.

Paromomycin Sulfate *(rINNM)*

Aminosidin Sulphate; Aminosidine Sulphate; Catenulin Sulphate; Crestomycin Sulphate; Estomycin Sulphate; Hydroxymycin Sulphate; Monomycin A Sulphate; Neomycin E Sulphate; Paromomycin Sulphate *(BANM)*; Paromomycine, Sulfate de; Paromomycini Sulfas; Paucimycin Sulphate; Sulfato de paromomicina. *O*-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-*O*-β-D-ribofuranosyl-(1→5)-*O*-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine sulphate.

Паромомицина Сульфат

$C_{23}H_{45}N_5O_{14}.xH_2SO_4$.

CAS — 59-04-1 (paromomycin); 7542-37-2 (paromomycin); 1263-89-4 (paromomycin sulfate).

ATC — A07AA06.

ATC Vet — QA07AA06.

Pharmacopoeias. In *Chin.*, *Int.*, *It.*, and *US*.
USP 31 (Paromomycin Sulfate). The sulfate salt of an antibiotic substance produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, or a mixture of two or more such salts.
A creamy-white to light yellow, odourless or practically odourless, very hygroscopic powder. It loses not more than 5% of its weight on drying. Very soluble in water; insoluble in alcohol, in chloroform, and in ether. pH of a 3% solution in water is between 5.0 and 7.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Neomycin, p.305.

Effects on the pancreas. Pancreatitis was associated with use of paromomycin during treatment of cryptosporidiosis in a patient with HIV infection.[1]

1. Tan WW, *et al.* Paromomycin-associated pancreatitis in HIV-related cryptosporidiosis. *Ann Pharmacother* 1995; **29:** 22–4.

Interactions

As for Neomycin, p.305.

Antimicrobial Action

Paromomycin is active against various protozoa including *Leishmania* spp., *Entamoeba histolytica*, and *Cryptosporidium* spp. In addition, it has an antibacterial spectrum similar to that of neomycin (p.305). There is cross-resistance between paromomycin and kanamycin, framycetin, neomycin, and streptomycin.

Paromomycin also has anthelmintic properties against tapeworms.

Antimycobacterial activity. References.

1. Kanyok TP, *et al.* Activity of aminosidine (paromomycin) for Mycobacterium tuberculosis and Mycobacterium avium. *J Antimicrob Chemother* 1994; **33:** 323–7.
2. Piersimoni C, *et al.* Bacteriostatic and bactericidal activities of paromomycin against Mycobacterium avium complex isolates. *J Antimicrob Chemother* 1994; **34:** 421–4.
3. Kanyok TP, *et al.* In vivo activity of paromomycin against susceptible and multidrug-resistant Mycobacterium tuberculosis and M. avium complex strains. *Antimicrob Agents Chemother* 1994; **38:** 170–3.

Pharmacokinetics

Paromomycin is poorly absorbed from the gastrointestinal tract and most of the dose is eliminated unchanged in the faeces.

Parenteral administration. References.

1. Kanyok TP, *et al.* Pharmacokinetics of intramuscularly administered aminosidine in healthy subjects. *Antimicrob Agents Chemother* 1997; **41:** 982–6.

Uses and Administration

Paromomycin is an aminoglycoside antibiotic that has been given orally in the treatment of intestinal protozoal infections, including amoebiasis, cryptosporidiosis, and giardiasis. It has also been tried parenterally for visceral, and topically for cutaneous, leishmaniasis. For details of these infections and their treatment, see under Choice of Antiprotozoal, p.822. It has been used in the treatment of tapeworm infection, but it is not the treatment of choice. Like neomycin (p.305), it has been used in the suppression of intestinal flora both pre-operatively and in the management of hepatic encephalopathy.