Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Netilmicin Sulphate). A substance obtained by synthesis from sisomicin. The potency is not less than 650 units/mg, calculated with reference to the dried substance. A white or yellowish-white, very hygroscopic, powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.
USP 31 (Netilmicin Sulfate). The potency is equivalent to not less than 595 micrograms of netilmicin per milligram, calculated on the dried basis. A white to pale yellowish-white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. pH of a solution in water containing the equivalent of netilmicin 4% is between 3.5 and 5.5. Store in airtight containers. Protect from moisture.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including netilmicin, with beta lactams, see under Gentamicin Sulfate, p.282. Netilmicin is also reported to be incompatible with furosemide, heparin, and vitamin B complex.

Adverse Effects, Treatment, and Precautions
As for Gentamicin Sulfate, p.282. Some studies suggest that netilmicin is less nephrotoxic and ototoxic than gentamicin or tobramycin, although others have not found any significant differences in their toxicity.

It has been suggested that peak plasma concentrations of netilmicin should not exceed 12 micrograms/mL for prolonged therapy, and troughs should be below 2 micrograms/mL.

Effects on the cardiovascular system. Severe hypotension was associated with netilmicin in a patient undergoing artificial ventilation.[1] Hypotensive episodes were of short duration and coincided with netilmicin injection. They almost disappeared when sedation was stopped.

1. Rygnestad T. Severe hypotension associated with netilmicin treatment. *BMJ* 1997; **315:** 31.

Interactions
As for Gentamicin Sulfate, p.283.

Antimicrobial Action
As for Gentamicin Sulfate, p.283. It is active against a similar range of organisms although it is also reported to have some activity against *Nocardia*. It may be somewhat less effective against *Pseudomonas aeruginosa*. It is not degraded by all of the enzymes responsible for aminoglycoside resistance, and may be active against some strains resistant to gentamicin or tobramycin, but this is less marked than with amikacin: for example, gentamicin-resistant *Providencia*, *Pseudomonas*, and *Serratia* are usually also netilmicin-resistant. Between about 5 and 20% of Gram-negative isolates are reported to be resistant to netilmicin.

Pharmacokinetics
As for Gentamicin Sulfate, p.284.

After intramuscular injection of netilmicin, peak plasma concentrations are achieved within 0.5 to 1 hour, and concentrations of about 7 micrograms/mL have been reported following doses of 2 mg/kg; similar concentrations are obtained after intravenous infusion of the same dose over 1 hour. Peak concentrations after rapid intravenous injection may transiently be 2 or 3 times higher than those following infusion. Standard, once-daily doses may produce transient peak concentrations of 20 to 30 micrograms/mL. In multiple dosing studies, netilmicin in usual doses every 12 hours produced steady-state concentrations on the second day which were less than 20% higher than those seen after the first dose.

The half-life of netilmicin is usually 2.0 to 2.5 hours. About 80% of a dose is excreted in the urine within 24 hours.

Uses and Administration
Netilmicin is a semisynthetic aminoglycoside antibiotic with actions and uses similar to those of gentamicin (p.284). It may be used as an alternative to amikacin (p.201) in the treatment of infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. As with gentamicin, netilmicin may be used with penicillins and with cephalosporins; the injections should be given separately.

Netilmicin is given as the sulfate but doses are expressed in terms of the equivalent amount of base; 1.5 g of netilmicin sulfate is equivalent to about 1 g of netilmicin. It is usually given intramuscularly in doses of 4 to 6 mg/kg daily as a single dose; alternatively, it may be given in equally divided doses every 8 or 12 hours; for the control of life-threatening infections, up to 7.5 mg/kg may be given daily in divided doses every 8 hours for short periods. In the management of urinary-tract infections, a single daily dose of 150 mg for 5 days may be given; for complicated urinary-tract infections, 3 to 4 mg/kg daily in divided doses every 12 hours has been given. A single dose of 300 mg has been licensed for gonorrhoea (p.191).

The same doses may be given by slow intravenous injection over 3 to 5 minutes or infused intravenously over 0.5 to 2 hours in 50 to 200 mL of infusion fluid; proportionately less fluid should be given to children.

Treatment with netilmicin is usually given for 7 to 14 days. Peak plasma concentrations below 12 micrograms/mL and troughs below 2 micrograms/mL have been recommended for divided daily dose regimens.

Dosage recommendations in infants and children vary somewhat. One regimen is 7.5 to 9 mg/kg daily in infants and neonates older than 1 week, and 6 to 7.5 mg/kg daily in older children, both given in divided doses every 8 hours. Premature infants and neonates less than 1 week old may be given 6 mg/kg daily in divided doses every 12 hours. An alternative regimen is 4 to 6.5 mg/kg daily in neonates less than 6 weeks of age, in divided doses every 12 hours, and 5.5 to 8 mg/kg daily in divided doses every 8 or 12 hours in older infants and children.

Dosage should be adjusted in all patients according to plasma-netilmicin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284.

Preparations
USP 31: Netilmicin Sulfate Injection.

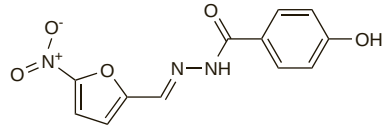
Proprietary Preparations (details are given in Part 3)
Arg.: Netira†; ***Austral.:*** Netromycin†; ***Austria:*** Certomycin; ***Belg.:*** Netromycine†; ***Braz.:*** Netromicina; ***Canad.:*** Netromycin†; ***Cz.:*** Netromycine; Nettacin; ***Denm.:*** Netilyn†; ***Fin.:*** Netilyn; ***Fr.:*** Netromicine; ***Ger.:*** Certomycin; ***Gr.:*** Netromycin; Zaby; ***Hong Kong:*** Netromycin; ***Hung.:*** Netromycine; ***India:*** Netromycin; Netspan; ***Indon.:*** Netromycin; ***Irl.:*** Netillin†; ***Ital.:*** Nettacin; Nettavisc; Zetamicin; ***Malaysia:*** Netromycin; ***Mex.:*** Neticin†; Netromicina; ***Neth.:*** Netromycine; ***Norw.:*** Netilyn; ***NZ:*** Netromycin†; ***Philipp.:*** Keunmixin; Netromycin; ***Pol.:*** Netromycine; ***Port.:*** Netromicina; Tilcin; ***S.Afr.:*** Netromycin; ***Spain:*** Netrocin†; ***Swed.:*** Netilyn; ***Switz.:*** Netromycine; ***Thai.:*** Bactrocin; Nelin; Netil; Netromycin; ***Turk.:*** Netira; Netromycine; ***UK:*** Netillin†; ***Venez.:*** Netromicina.

Multi-ingredient: ***Ital.:*** Netildex.

Nifuroxazide *(rINN)*
Nifuroksatsidi; Nifuroksazid; Nifuroksazidas; Nifuroxazid; Nifuroxazida; Nifuroxazidum. 2′-(5-Nitrofurfurylidene)-4-hydroxybenzohydrazide.

Нифуроксазид

$C_{12}H_9N_3O_5$ = 275.2.
CAS — 965-52-6.
ATC — A07AX03.
ATC Vet — QA07AX03.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Nifuroxazide). A bright yellow crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Profile
Nifuroxazide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It is given orally in a dose of 800 mg daily in divided doses in the treatment of colitis and diarrhoea.

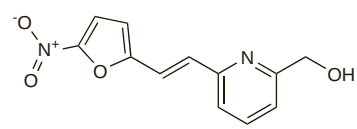
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Bacifurane†; Ercefuryl; ***Braz.:*** Passifuril; ***Chile:*** Diarfin†; ***Cz.:*** Ercefuryl; ***Fr.:*** Bacterix; Bifix; Diafuryl; Ediston; Ercefuryl; Erceryl; Lumifurex; Panfurex; Septidiaryl; ***Gr.:*** Ercefuryl; ***Hong Kong:*** Ercefuryl; Panfurex; ***Indon.:*** Fuzide; Nifudiar; Nifural; ***Ital.:*** Diarret†; ***Mex.:*** Akabar; Diarim†; Eskapar; Topron; ***Philipp.:*** Ercefuryl; ***Rus.:*** Enterofuryl (Энтерофурил); ***Singapore:*** Niraben; ***Thai.:*** Debby†; Ercefuryl; Erfuzide; ***Turk.:*** Diafuryl; Durisal; Endosin; Ercefuryl; Erfulyn; Furil; Nifuryl; Nufro.

Multi-ingredient: ***Chile:*** Diaren; Diarfin†; Enterol Con Nifuroxacida; Imecol; Liracol; Nifurat†; Testisan; ***Mex.:*** Dia-Par Compuesto; Eskapar Compuesto.

Nifurpirinol *(USAN, rINN)*
Furpirinol; Nifurpirinolum; P-7138.

Нифурпиринол

$C_{12}H_{10}N_2O_4$ = 246.2.
CAS — 13411-16-0.

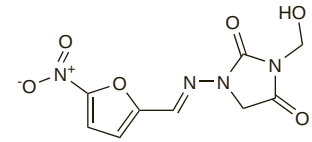


Profile
Nifurpirinol is a nitrofuran antimicrobial used in veterinary medicine for the treatment of bacterial and fungal infections in ornamental fish.

Nifurtoinol *(rINN)*
Hydroxymethylnitrofurantoin; Nifurtoïnol; Nifurtoinolum. 3-Hydroxymethyl-1-(5-nitrofurfurylideneamino)hydantoin.

Нифуртоинол

$C_9H_8N_4O_6$ = 268.2.
CAS — 1088-92-2.
ATC — J01XE02.
ATC Vet — QJ01XE02.



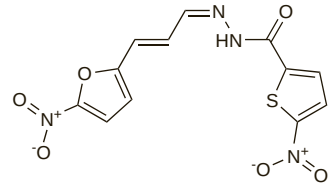
Profile
Nifurtoinol is a nitrofuran antibacterial with properties similar to those of nitrofurantoin (below) and is used in the treatment of urinary-tract infections. It is given orally in doses of up to 300 mg daily in divided doses.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Urfadyn PL.

Nifurzide *(rINN)*
Nifurzida; Nifurzidum. 5-Nitro-2-thiophenecarboxylic acid [3-(5-nitro-2-furyl)allylidene]hydrazide.

Нифурзид

$C_{12}H_8N_4O_6S$ = 336.3.
CAS — 39978-42-2.
ATC — A07AX04.
ATC Vet — QA07AX04.



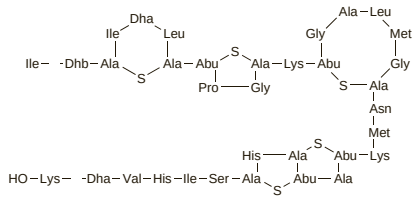
Profile
Nifurzide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It has been given orally in the treatment of diarrhoea.

Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Ricridene†.

Nisin
E234; Nisina.

Низин

CAS — 1414-45-5.



Abu = α-aminobutyric acid
Dha = dehydroalanine
Dhb = dehydrobutyrine

Profile
Nisin is a polypeptide antibacterial produced by *Lactococcus lactis* (*Streptococcus lactis*). It is used as a food preservative.

It has been investigated for the treatment of various infections, including those caused by *Helicobacter pylori* and *Clostridium difficile*.

Nitrofurantoin *(BAN, rINN)*

Furadoninum; Nitrofurantoiini; Nitrofurantoína; Nitrofurantoina; Nitrofurantoinas; Nitrofurantoïne; Nitrofurantoinum. 1-(5-Nitrofurfurylideneamino)hydantoin; 1-(5-Nitrofurfurylideneamino)imidazolidine-2,4-dione.

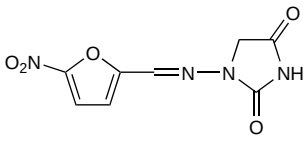
Нитрофурантоин

$C_8H_6N_4O_5$ = 238.2.

CAS — 67-20-9 (anhydrous nitrofurantoin); 17140-81-7 (nitrofurantoin monohydrate).

ATC — J01XE01.

ATC Vet — QJ01XE01.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Int. and *US* specify anhydrous or monohydrate.

Ph. Eur. 6.2 (Nitrofurantoin). A yellow, odourless or almost odourless, crystalline powder or crystals. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store at a temperature not exceeding 25°. Protect from light.

USP 31 (Nitrofurantoin). It is anhydrous or contains one molecule of water of hydration. Lemon-yellow, odourless crystals or fine powder. Nitrofurantoin and its solutions are discoloured by alkalis and by exposure to light, and are decomposed on contact with metals other than stainless steel or aluminium. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store in airtight containers. Protect from light.

Adverse Effects

The estimated incidence of adverse effects with nitrofurantoin has varied enormously, but may be around 10% overall; an incidence of serious reactions of about 0.001% for pulmonary, and 0.0007% for neurological reactions has been suggested. The most common adverse effects of nitrofurantoin involve the gastrointestinal tract. They are dose-related and generally include nausea, vomiting, and anorexia; abdominal pain and diarrhoea occur less frequently. It has been reported that adverse effects on the gastrointestinal tract are less common when nitrofurantoin is given in a macrocrystalline form or with food.

Neurological adverse effects include headache, drowsiness, vertigo, dizziness, nystagmus, and benign intracranial hypertension. Severe and sometimes irreversible peripheral neuropathy has developed, particularly in patients with renal impairment and in those given prolonged therapy.

Hypersensitivity reactions such as skin rashes, urticaria, pruritus, fever, sialadenitis, and angioedema may occur. Anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pancreatitis, a lupus-like syndrome, myalgia, and arthralgia have also been reported. Patients with a history of asthma may experience acute asthmatic attacks.

Acute pulmonary sensitivity reactions characterised by sudden onset of fever, chills, eosinophilia, cough, chest pain, dyspnoea, pulmonary infiltration or consolidation, and pleural effusion may occur within hours to a few days of beginning therapy, but they usually resolve on stopping treatment.

Subacute or chronic pulmonary symptoms including interstitial pneumonitis and pulmonary fibrosis may develop more insidiously in patients on long-term therapy and the latter are not always reversible, particularly if therapy is continued after onset of symptoms.

Hepatotoxicity including cholestatic jaundice, hepatitis, and hepatic necrosis may develop rarely, particularly in women, and may represent a hypersensitivity reaction. Other adverse effects include megaloblastic anaemia, leucopenia, granulocytopenia or agranulocytosis, thrombocytopenia, aplastic anaemia, and haemolytic anaemia in persons with a genetic G6PD deficiency. Transient alopecia has been reported.

Nitrofurantoin may cause a brownish discoloration of the urine.

There is limited evidence from *animal* studies that nitrofurantoin may be carcinogenic, although this has not been shown conclusively in humans.

◊ References.

1. Koch-Weser J, *et al.* Adverse reactions to sulfisoxazole, sulfamethoxazole, and nitrofurantoin: manifestations and specific reaction rates during 2118 courses of therapy. *Arch Intern Med* 1971; **128:** 399–404.
2. Holmberg L, *et al.* Adverse reactions to nitrofurantoin: analysis of 921 reports. *Am J Med* 1980; **69:** 733–8.
3. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. *BMJ* 1982; **284:** 1440–2.
4. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* 1985; **19:** 540–7.
5. Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol (Baltimore)* 2004; **172:** 448–53.

Effects on the lungs. References[1,2] to pulmonary toxicity associated with long-term nitrofurantoin treatment.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Pulmonary toxicity with long-term nitrofurantoin. *Aust Adverse Drug React Bull* 2004; **23:** 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.htm (accessed 11/01/08)
2. Mendez JL, *et al.* Chronic nitrofurantoin-induced lung disease. *Mayo Clin Proc* 2005; **80:** 1298–1302.

Precautions

Nitrofurantoin should not be given to patients with renal impairment since antibacterial concentrations in the urine may not be attained and toxic concentrations in the plasma can occur. Nitrofurantoin is also contra-indicated in patients known to be hypersensitive to nitrofurans, in those with G6PD deficiency, and in infants (in the UK it is contra-indicated below 3 months of age, though the USA permits use from 1 month old).

Nitrofurantoin should be used with care in the elderly, who may be at increased risk of toxicity, particularly acute pulmonary reactions. All patients undergoing prolonged therapy should be monitored for changes in pulmonary function, and the drug withdrawn at the first signs of pulmonary damage. Care is required in patients with pre-existing pulmonary, hepatic, neurological, or allergic disorders, and in those with conditions (such as anaemia, diabetes mellitus, electrolyte imbalance, debility, or vitamin B deficiency) which may predispose to peripheral neuropathy. Nitrofurantoin should be withdrawn if signs of peripheral neuropathy develop. Although hepatic reactions such as hepatitis, cholestatic jaundice, and hepatic necrosis rarely occur, fatalities have been reported. Patients should be monitored, and the drug stopped immediately if hepatitis occurs.

Nitrofurantoin may cause false positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics considers that, although nitrofurantoin is excreted into breast milk, it is usually compatible with breast feeding, but caution is necessary in breast-fed infants with G6PD deficiency.[1] The *BNFC* suggests that the amount ingested may be enough to produce haemolysis in G6PD-deficient infants; it recommends that nitrofurantoin should be avoided in mothers who are breast feeding.

1. 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 11/01/08)

Porphyria. Nitrofurantoin has been associated with acute attacks of porphyria and is considered to be unsafe in porphyric patients.

Pregnancy. Licensed product information contraindicates the use of nitrofurantoin in pregnant patients at term (38 to 42 weeks' of gestation), or during labour and delivery, because of the possibility of producing haemolytic anaemia in the neonate.

Interactions

Nitrofurantoin and the quinolone antibacterials are antagonistic *in vitro* but the clinical significance is unknown. The antibacterial activity of nitrofurantoin may be decreased in the presence of carbonic anhydrase inhibitors and other drugs that alkalinise the urine.

Probenecid or sulfinpyrazone should not be given with nitrofurantoin as they may reduce its excretion. Magnesium trisilicate may reduce the absorption of nitrofurantoin but it is not clear whether this applies to other antacids.

Antiepileptics. For reference to the effect of nitrofurantoin on *phenytoin*, see p.498.

Antifungals. An elderly patient who had been taking nitrofurantoin daily for 5 years developed combined hepatic and pulmonary toxicity 2 months after also starting *fluconazole* therapy.[1] Although either drug may have caused the hepatic toxicity, possible pharmacokinetic changes induced by an interaction with fluconazole may have precipitated the nitrofurantoin-induced pulmonary toxicity.

1. Linnebur SA, Parnes BL. Pulmonary and hepatic toxicity due to nitrofurantoin and fluconazole treatment. *Ann Pharmacother* 2004; **38:** 612–16.

Hormonal contraceptives. For mention of a possible decrease in contraceptive efficacy when nitrofurantoin was used with oral contraceptives, see under Hormonal Contraceptives, p.2068.

Antimicrobial Action

Nitrofurantoin is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens. The mode of action is uncertain but appears to depend on the formation of reactive intermediates by reduction; this process occurs more efficiently in bacterial than in mammalian cells.

It is effective against the enterococci *in vitro*, as well as various other Gram-positive species including staphylococci, streptococci, and corynebacteria, although this is of little clinical significance. Most strains of *Escherichia coli* are particularly sensitive to nitrofurantoin but *Enterobacter* and *Klebsiella* spp. are less susceptible and some may be resistant. *Pseudomonas aeruginosa* is resistant as are most strains of *Proteus* spp.

Nitrofurantoin is most active in acid urine, and if the pH exceeds 8 most of the antibacterial activity is lost. Resistance rarely develops during nitrofurantoin treatment but may occur during prolonged treatment. Plasmid-encoded resistance has been reported in *E. coli*. Resistance may be due to the loss of nitrofuran reductases which generate the active intermediates.

Pharmacokinetics

Nitrofurantoin is readily absorbed from the gastrointestinal tract. The absorption rate is dependent on crystal size. The macrocrystalline form has slower dissolution and absorption rates, produces lower serum concentrations than the microcrystalline form, and takes longer to achieve peak concentrations in the urine. The presence of food in the gastrointestinal tract may increase the bioavailability of nitrofurantoin and prolong the duration of therapeutic urinary concentrations. Preparations of nitrofurantoin from different sources may not be bioequivalent, and care may be necessary if changing from one brand to another.

On absorption, concentrations in blood and body tissues are low because of rapid elimination, and antibacterial concentrations are not achieved. Nitrofurantoin crosses the placenta and the blood-brain barrier and traces have been detected in breast milk. There is some disagreement about the degree of protein binding, and although figures of up to about 60% are quoted by some sources, others suggest that the figure should be as much as 90%. The plasma half-life is reported to range from 0.3 to 1 hour.

Nitrofurantoin is metabolised in the liver and most body tissues while about 30 to 40% of a dose is excreted rapidly in the urine as unchanged nitrofurantoin. Some tubular reabsorption may occur in acid urine. Average doses give a concentration of 50 to 200 micrograms/mL in the urine in patients with normal renal function.

Uses and Administration

Nitrofurantoin is a nitrofuran antibacterial that is used in the treatment of uncomplicated lower urinary-tract infections (p.199), including prophylaxis or long-term suppressive therapy in recurrent infection.

It is given orally, in a usual dose of 50 to 100 mg four times daily, with food or milk. Treatment is usually continued for 7 days. A dual-release formulation, consisting of macrocrystalline nitrofurantoin and nitro-