It is mainly active against Gram-positive aerobes. Most strains of staphylococci (including meticillin-resistant and multiply-resistant *Staph. aureus*) and streptococci are susceptible *in vitro*, although the enterococci are relatively resistant. Mupirocin is also active against *Listeria monocytogenes* and *Erysipelothrix rhusiopathiae*. The Gram-negative organisms are generally insensitive, but *Haemophilus influenzae*, *Neisseria* spp. and a few others are sensitive. Anaerobic organisms, both Gram-positive and Gram-negative, are generally resistant, and activity against fungi is low. Mupirocin is more active *in vitro* at acid pH than in alkaline conditions.

Naturally resistant strains of *Staph. aureus* occur rarely but resistance, including high-level plasmid-mediated transferable resistance, has emerged, particularly during long-term use. There has been some concern that inappropriate prescribing of mupirocin has led to this steadily increasing resistance.

Activity against fungi. Activity of mupirocin 2% *in vitro* against *Candida albicans* was comparable to that of other commonly used topical antifungals. Although MICs were considerably in excess of those reported for susceptible bacteria, clinical responses in 10 patients suggested that adequate concentrations of mupirocin were achieved after topical application.[1]

1. Rode H, *et al.* Efficacy of mupirocin in cutaneous candidiasis. *Lancet* 1991; **338:** 578.

Resistance. References.

1. Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. *J Antimicrob Chemother* 1998; **41:** 11–18.
2. Schmitz F-J, *et al.* The prevalence of low- and high-level mupirocin resistance in staphylococci from 19 European hospitals. *J Antimicrob Chemother* 1998; **42:** 489–95.
3. Upton A, *et al.* Mupirocin and Staphylococcus aureus: a recent paradigm of emerging antibiotic resistance. *J Antimicrob Chemother* 2003; **51:** 613–17.
4. Kresken M, *et al.* Prevalence of mupirocin resistance in clinical isolates of Staphylococcus aureus and Staphylococcus epidermidis: results of the Antimicrobial Resistance Surveillance Study of the Paul-Ehrlich-Society for Chemotherapy, 2001. *Int J Antimicrob Agents* 2004; **23:** 577–81.
5. Walker ES, *et al.* A decline in mupirocin resistance in methicillin-resistant Staphylococcus aureus accompanied administrative control of prescriptions. *J Clin Microbiol* 2004; **42:** 2792–5.
6. Wertheim HF, *et al.* Mupirocin prophylaxis against nosocomial Staphylococcus aureus infections in nonsurgical patients: a randomized study. *Ann Intern Med* 2004; **140:** 419–25.
7. Kallen AJ, *et al.* Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005; **26:** 916–22.
8. Unemura Y, *et al.* Impact of prophylactic mupirocin for radical esophagectomy. *J Infect Chemother* 2006; **12:** 257–63.
9. Sit D, *et al.* Prophylactic intranasal mupirocin ointment in the treatment of peritonitis in continuous ambulatory peritoneal dialysis patients. *Adv Therapy* 2007; **24:** 387–93.

Pharmacokinetics

Only very small amounts of topically applied mupirocin are absorbed into the systemic circulation where it is rapidly metabolised to monic acid which is excreted in the urine.

Uses and Administration

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens*. It is applied topically as a 2% ointment in a macrogol base, or as a cream containing mupirocin calcium equivalent to 2% mupirocin, in the treatment of various bacterial skin infections. These preparations should be applied up to 3 times daily for up to 10 days; treatment should be re-evaluated if there is no response after 3 to 5 days. They are not suitable for application to mucous membranes, and therefore a nasal ointment containing mupirocin calcium equivalent to 2% mupirocin in a paraffin basis is used for eradication of the nasal carriage of *Staphylococcus aureus*, particularly epidemic meticillin-resistant strains. The nasal ointment should be applied into each nostril 2 or 3 times daily for a maximum of 7 days.

For further details of skin infections and staphylococcal infections and their treatment, see under Choice of Antibacterial, p.194.

◊ References.

1. Roth VR, *et al.* Should we routinely use mupirocin to prevent staphylococcal infections? *Infect Control Hosp Epidemiol* 2000; **21:** 745–9.
2. Perl TM, *et al.* Mupirocin and the Risk of Staphylococcus Aureus Study Team. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med* 2002; **346:** 1871–7.
3. Takahashi S, *et al.* The preventive effects of mupirocin against nasotracheal intubation-related bacterial carriage. *Anesth Analg* 2003; **97:** 222–5.
4. Laupland KB, Conly JM. Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. *Clin Infect Dis* 2003; **37:** 933–8.
5. Tacconelli E, *et al.* Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. *Clin Infect Dis* 2003; **37:** 1629–38.

Preparations

BP 2008: Mupirocin Ointment;
USP 31: Mupirocin Cream; Mupirocin Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Bactroban; Mupax; Mupirox; Paldar; Vidox; ***Austral.:*** Bactroban; ***Austria:*** Bactroban; ***Belg.:*** Bactroban; ***Braz.:*** Bacrocin; Bactocin; Bactroban; Bactroneo; ***Canad.:*** Bactroban; ***Chile:*** Bactroban; Bantix; Ultrabiotic; Underan; ***Cz.:*** Bactroban; ***Denm.:*** Bactroban; ***Fin.:*** Bactroban; ***Fr.:*** Bactroban; Mupiderm; ***Ger.:*** InfectoPyoderm; Turixin; ***Gr.:*** Bactroban; Bactrocine; Hevronaz; Micoban; Mupider; Mupiran; Veltion; ***Hong Kong:*** Bactroban; ***Hung.:*** Bactroban; ***India:*** Bactroban; Supirocin; ***Indon.:*** Bactoderm; Bactroban; Pibaksin; ***Irl.:*** Bactroban; ***Israel:*** Bactoderm†; Bactroban; ***Ital.:*** Bactroban; Mupiskin; ***Jpn:*** Bactroban; ***Malaysia:*** Bactroban; Muprin; ***Mex.:*** Bactroban; Sinpebac; ***Neth.:*** Bactroban; ***NZ:*** Bactroban; ***Philipp.:*** Bactifree; Bactroban; Foskina; ***Pol.:*** Bactroban; Mupirox; ***Port.:*** Bactroban; ***Rus.:*** Bactroban (Бактробан); ***S.Afr.:*** Bactroban; ***Singapore:*** Bactroban; Supirocin; ***Spain:*** Bactroban; Plasimine; ***Swed.:*** Bactroban; ***Switz.:*** Bactroban; ***Thai.:*** Bactex; Bactroban; Muporin; ***Turk.:*** Bactroban; ***UK:*** Bactroban; ***USA:*** Bactroban; Centany; ***Venez.:*** Bactroban; Bactrobandos†.

Multi-ingredient: ***India:*** Supirocin-B.

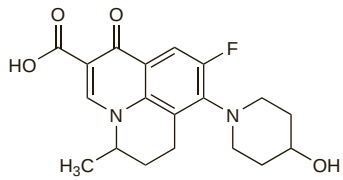
Nadifloxacin *(BAN, rINN)*

Jinofloxacin; Nadifloxacine; Nadifloxacino; Nadifloxacinum; OPC-7251. (±)-9-Fluoro-6,7-dihydro-8-(4-hydroxypiperidino)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

Надифлоксацин

$C_{19}H_{21}FN_2O_4$ = 360.4.

CAS — 124858-35-1.



Profile

Nadifloxacin is a fluoroquinolone antibacterial used in topical treatment of acne. It is applied twice daily as a 1% cream or ointment.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Nadixa; ***Gr.:*** Nadixa; ***India:*** Nadiflox; ***Indon.:*** Acuatim; ***Jpn:*** Acuatim; ***Mex.:*** Nadixa†; ***Port.:*** Nadixa.

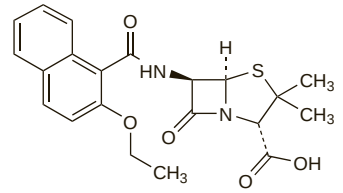
Nafcillin Sodium *(BANM, USAN, rINNM)*

Nafcilina sódica; Nafcilline Sodique; Nafcillinnatrium; Nafcillinum Natricum; Nafsilliininatrium; Natrii Nafcillinum; Wy-3277. Sodium (6*R*)-6-(2-ethoxy-1-naphthamido)penicillanate monohydrate.

Натрий Нафциллин

$C_{21}H_{21}N_2NaO_5S,H_2O$ = 454.5.

CAS — 147-52-4 (nafcillin); 985-16-0 (anhydrous nafcillin sodium); 7177-50-6 (nafcillin sodium monohydrate).



(nafcillin)

Pharmacopoeias. In *US*.
USP 31 (Nafcillin Sodium). A white to yellowish-white powder having not more than a slight characteristic odour. Freely soluble in water and in chloroform; soluble in alcohol. pH of a 3% solution in water is between 5.0 and 7.0. Store in airtight containers.

Incompatibility. Nafcillin sodium has been reported to be incompatible with aminoglycosides and a number of other antibacterials. It has also been reported to be incompatible with acidic and alkaline drugs.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Thrombophlebitis may occur when nafcillin is given by intravenous injection, and tissue damage has been reported on extravasation.

Effects on the kidneys. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; **26:** 985–90.
2. Guharoy SR, *et al.* Suspected nafcillin-induced interstitial nephritis. *Ann Pharmacother* 1993; **27:** 170–3.
3. Hoppes T, *et al.* Four cases of nafcillin-associated acute interstitial nephritis in one institution. *Nat Clin Pract Nephrol* 2007; **3:** 456–61.

Effects on the liver. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; **26**: 985–90.
2. Presti ME, *et al.* Nafcillin-associated hepatotoxicity: report of a case and review of the literature. *Dig Dis Sci* 1996; **41:** 180–4.

Sodium content. Each g of nafcillin sodium contains about 2.2 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Ciclosporin. For the effect of nafcillin on ciclosporin, see p.1825.

Warfarin. For the effect of nafcillin on warfarin, see p.1428.

Antimicrobial Action

As for Flucloxacillin, p.277.

Pharmacokinetics

Nafcillin is incompletely and irregularly absorbed from the gastrointestinal tract, especially when given after food. After intramuscular injection it is absorbed more reliably, an injection of 0.5 to 1 g producing peak plasma concentrations of 5 to 8 micrograms/mL within about 0.5 to 1 hour. Up to 90% of nafcillin in the circulation is bound to plasma proteins. Nafcillin has been reported to have a plasma half-life of about 0.5 to 1.5 hours. The half-life is prolonged in neonates.

Nafcillin crosses the placenta into the fetal circulation and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Nafcillin is distributed into pleural and synovial fluids and into bone.

Nafcillin differs from most other penicillins in that it is largely inactivated by hepatic metabolism. It is excreted via the bile although some reabsorption takes place in the small intestine. Only about 10% of a dose given orally before food, and about 30% of a dose given intramuscularly, is excreted in the urine.

Plasma concentrations are enhanced by probenecid.

Uses and Administration

Nafcillin is a penicillinase-resistant penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

It is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of nafcillin; 1.1 g of nafcillin sodium is equivalent to about 1 g of nafcillin. Nafcillin sodium may be given intravenously by slow injection over 5 to 10 minutes or by slow infusion over at least 30 to 60 minutes; usual adult doses are 0.5 to 1 g of nafcillin every 4 hours, although it is usually recommended that it be used for not more than 24 to 48 hours because of the risk of thrombophlebitis. It has also been given by intramuscular injection in a dose of 500 mg of nafcillin every 4 to 6 hours.

Nafcillin sodium has also been given orally but other penicillinase-resistant penicillins are preferred.

Preparations

USP 31: Nafcillin for Injection; Nafcillin Injection; Nafcillin Sodium Capsules; Nafcillin Sodium for Oral Solution; Nafcillin Sodium Tablets.

Nalidixic Acid *(BAN, USAN, rINN)*

Acide nalidixique; Ácido nalidíxico; Acidum nalidixicum; Kwas nalidyksowy; Kyselina nalidixová; Nalidiksiinihappo; Nalidiksik Asit; Nalidikso rūgštis; Nalidixinic Acid; Nalidixinsyra; Nalidixsav; NSC-82174; Win-18320. 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

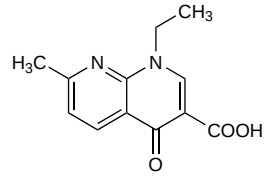
Налидиксовая Кислота

$C_{12}H_{12}N_2O_3$ = 232.2.

CAS — 389-08-2.

ATC — J01MB02.

ATC Vet — QJ01MB02.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Nalidixic Acid). An almost white or pale yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 31 (Nalidixic Acid). A white to very pale yellow, odourless crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 910 of alcohol and 1 in 29 of chloroform; slightly soluble in acetone, in methyl alcohol, and in toluene; soluble in dichloromethane and in solutions of fixed alkali hydroxides and carbonates. Store in airtight containers.

Adverse Effects

The most frequent adverse reactions to nalidixic acid involve the gastrointestinal tract, skin, and CNS. Gastrointestinal effects have been reported in about 8% of patients and include nausea, vomiting, diarrhoea, and abdominal pain.

Adverse effects on the skin include photosensitivity reactions with erythema and bullous eruptions, allergic rashes, urticaria, and pruritus. Erythema multiforme and Stevens-Johnson syndrome have been reported rarely. Eosinophilia, fever, angioedema, and, rarely, anaphylactoid reactions have occurred.

Neurological effects include visual disturbances, headache, dizziness or vertigo, drowsiness, and sometimes confusion, depression, excitement, and hallucinations. Toxic psychoses or convulsions have occurred, especially after large doses; convulsions are most likely in patients with predisposing factors such as cerebral arteriosclerosis or epilepsy. There have been reports of intracranial hypertension, especially in infants and young children, and also of metabolic acidosis.

Peripheral neuropathies, muscular weakness, and myalgia are occasional adverse effects. Sixth cranial nerve palsy has been reported rarely.

Arthralgia has been reported (degenerative changes in weight-bearing joints of young *animals* are documented). Tendon damage has occasionally been associated with nalidixic acid and related compounds, the fluoroquinolones (see Effects on the Musculoskeletal System, under Ciprofloxacin, p.244).

Cholestatic jaundice, thrombocytopenia, and leucopenia have occurred rarely, as has haemolytic anaemia in patients who may or may not have G6PD deficiency. There have been isolated reports of fatal auto-immune haemolytic anaemia in elderly patients.

Precautions

Nalidixic acid is contra-indicated in patients with a history of convulsive disorders and in those with severe renal impairment. It should be given with care to patients with hepatic or moderate renal impairment, severe cerebral arteriosclerosis, or G6PD deficiency. Blood counts and renal and hepatic function should be monitored if treatment continues for more than 2 weeks.

It should be avoided in infants less than 3 months old. Since nalidixic acid and related antimicrobials have been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these compounds should not generally be used in patients aged under 18 years, pregnant women, or during breast feeding (but see also below) unless the benefits outweigh the risks. Treatment should be stopped if symptoms of neuropathy or arthralgia occur. Tendon damage may occur rarely and treatment should be stopped if patients experience tendon pain, inflammation, or rupture.

Exposure to strong sunlight or sunlamps should be avoided during treatment with nalidixic acid.

Nalidixic acid may cause false-positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics[1] states that nalidixic acid is usually compatible with breast feeding, although haemolytic anaemia has been reported[2] in a breast-fed infant, with no evidence of G6PD deficiency, whose mother had received nalidixic acid.

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 27/05/04)
2. Belton EM, Jones RV. Haemolytic anaemia due to nalidixic acid. *Lancet* 1965; **ii:** 691.

Porphyria. Nalidixic acid has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The absorption of nalidixic acid is reduced by sucralfate, and divalent and trivalent cations such as aluminium, calcium, iron, magnesium, and zinc, and therefore use of nalidixic acid with antacids, iron preparations, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. It is recommended that such products should not be given within 2 hours before or after nalidixic acid.

The excretion of nalidixic acid is reduced and plasma concentrations increased by probenecid. Other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline have been shown to antagonise the action of nalidixic acid *in vitro* and should not be used together.

Fatal haemorrhagic enterocolitis has been associated with the use of nalidixic acid and high-dose intravenous melphalan in children; use with other alkylating antineoplastics is also contra-indicated. There is a possible risk of increased nephrotoxicity when nalidixic acid is given with ciclosporin.

Nalidixic acid is reported to enhance the effect of oral anticoagulants such as warfarin (see p.1428); this may be due in part to displacement of anticoagulant from its plasma binding sites. The dose of anticoagulant may need to be reduced.

The effect of some quinolone antibacterials on xanthines is discussed under Caffeine, p.1117, and Theophylline, p.1143.

Convulsions may be precipitated by the use of some quinolones with NSAIDs (see Analgesics, under Interactions of Ciprofloxacin, p.246), although this has not been reported with nalidixic acid.

Antimicrobial Action

Nalidixic acid is considered to act by interfering with the replication of bacterial DNA, probably by inhibiting DNA gyrase (topoisomerase) activity. It is active against Gram-negative bacteria including *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Salmonella* spp., and *Shigella* spp., and is usually bactericidal. *Pseudomonas aeruginosa*, Gram-positive bacteria, and anaerobes are not generally susceptible.

Bacterial resistance may develop rapidly, sometimes within a few days of commencing treatment, but it does not appear to be transferable or R-plasmid mediated (see also below). Cross-resistance occurs with oxolinic acid and cinoxacin.

The antibacterial activity of nalidixic acid is not significantly affected by differences in urinary pH. Antagonism between nalidixic acid and other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline has been shown *in vitro*.

Resistance. Bacterial plasmid-mediated resistance to quinolones had not been seen by the late 1980s.[1] A report[2] of such resistance to nalidixic acid in *Shigella dysenteriae* responsible for an epidemic of shigellosis in Bangladesh in 1987, was questioned at the time.[3] On reinspection of the data, chromosomal mutation rather than plasmid-mediated resistance was confirmed as the mechanism responsible so far for resistance to quinolones.[1] Subsequent data[4] in an isolate of *Klebsiella pneumoniae* has, however, suggested that plasma-mediated resistance to quinolones may be possible.

1. Courvalin P. Plasmid-mediated 4-quinolone resistance: a real or apparent absence? *Antimicrob Agents Chemother* 1990; **34:** 681–4.
2. Munshi MH, *et al.* Plasmid-mediated resistance to nalidixic acid in Shigella dysenteriae type 1. *Lancet* 1987; **ii:** 419–21.
3. Crumplin GC. Plasmid-mediated resistance to nalidixic acid and new 4-quinolones? *Lancet* 1987; **ii:** 854–5.
4. Martínez-Martínez L, *et al.* Quinolone resistance from a transferable plasmid. *Lancet* 1998; **351:** 797–9.

Pharmacokinetics

Nalidixic acid is rapidly and almost completely absorbed from the gastrointestinal tract, and peak plasma concentrations of 20 to 40 micrograms/mL have been reported 1 to 2 hours after a 1-g oral dose. Plasma half-lives of about 1 to 2.5 hours have been reported (but see below).

Nalidixic acid is partially metabolised to hydroxynalidixic acid, which has antibacterial activity similar to that of nalidixic acid and accounts for about 30% of active drug in the blood. About 93% of nalidixic acid and 63% of hydroxynalidixic acid are bound to plasma proteins. Both nalidixic acid and hydroxynalidixic acid are rapidly metabolised to inactive glucuronide and dicarboxylic acid derivatives; the major inactive metabolite 7-carboxynalidixic acid is usually only detected in urine.

Nalidixic acid and its metabolites are excreted rapidly in the urine, nearly all of a dose being eliminated within 24 hours. More than 80% of the drug excreted in the urine is as inactive metabolites, but peak urinary concentrations of active drug averaging about 150 to 200 micrograms/mL are achieved 3 to 4 hours after a single 1-g dose. Hydroxynalidixic acid accounts for about 80 to 85% of activity in the urine. Urinary excretion is reduced by probenecid. About 4% of a dose is excreted in the faeces.

Traces of nalidixic acid are distributed into breast milk and appear to cross the placenta.

◊ Although a plasma half-life of 1 to 2.5 hours is generally cited for nalidixic acid, values of 6 to 7 hours have been reported for active drug (nalidixic acid and hydroxynalidixic acid) after using more specific and sensitive assay techniques and longer sampling periods than previously.[1]

The elimination rate of nalidixic acid appears to be not markedly altered by renal impairment, but the elimination of hydroxynalidixic acid is significantly reduced. 7-Carboxynalidixic acid has appeared in the plasma of patients with renal impairment.[2] Plasma concentrations of active drug were higher and the half-life prolonged in elderly subjects.[3]

1. Ferry N, *et al.* Nalidixic acid kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1981; **29:** 695–8.
2. Cuisinaud G, *et al.* Nalidixic acid kinetics in renal insufficiency. *Br J Clin Pharmacol* 1982; **14:** 489–93.
3. Barbeau G, Belanger P-M. Pharmacokinetics of nalidixic acid in old and young volunteers. *J Clin Pharmacol* 1982; **22:** 490–6.

Uses and Administration

Nalidixic acid is a 4-quinolone antibacterial used in the treatment of uncomplicated lower urinary-tract infections due to Gram-negative bacteria other than *Pseudomonas* spp. (p.199). It has also been used to treat shigellosis (bacillary dysentery) (p.173).

The usual dose is about 4 g daily in 4 divided oral doses for 7 to 14 days in acute infections, reducing thereafter to half this dose in chronic infections. Since bacterial resistance may develop rapidly it has been suggested that if treatment with nalidixic acid has not resulted in a negative urine culture within 48 hours another antimicrobial should be used.

For details of reduced doses in renal impairment, see below.

For details of doses in infants and children, see below.

Although the antibacterial activity of nalidixic acid does not appear to be influenced by urinary pH, the use of sodium bicarbonate or sodium citrate does increase the concentration of active drug in the urine. Commercial preparations containing nalidixic acid, sodium bicarbonate, and sodium citrate have been used in some countries.

It is also used with the analgesic phenazopyridine.

Administration in children. Although nalidixic acid is not generally recommended for use in patients under 18 years of age, it is licensed in both the UK and the USA for infants and children over 3 months of age. The usual oral dose is 55 to 60 mg/kg daily in 4 divided doses for at least 7 days, reducing thereafter to about 30 mg/kg daily in 4 divided doses for prolonged treatment (but see Precautions, above).

In addition, the *BNFC* suggests that a dose of 30 mg/kg daily in 2 divided doses may be given for prophylaxis of urinary-tract infections.

Administration in renal impairment. In the UK, some products of nalidixic acid have been licensed for use at half the usual dose in patients with a creatinine clearance below 20 mL/minute (the *BNFC* suggests a similar reduction in children with creatinine clearance 20 mL/minute per 1.73 m^2 or less). However, other licensed product information does not include this information and suggests that nalidixic acid should not be used in patients with severe renal impairment.

Preparations

BP 2008: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets; ***USP 31:*** Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets.

Proprietary Preparations (details are given in Part 3) ***Arg.:*** Nalidix†; Wintomylon†; ***Braz.:*** Naluril; Wintomylon; ***Canad.:*** NegGram†; ***Chile:*** Wintomylon†; ***Fr.:*** Negram†; ***Gr.:*** Nal-acid†; ***Hong Kong:*** Wintomylon; ***Hung.:*** Nevigramon; ***India:*** Diarlop; Gramoneg; Negadix; ***Indon.:*** Urineg; ***Irl.:*** Negram; ***Israel:*** NegGram†; ***Ital.:*** Betaxina†; Nalidixin†; Naligram†; NegGram†; Uri-Flor; ***Mex.:*** A-N-Dix; Acidix; Fardixon†; Kamilon; Nalix; Pronal Dix; Seltomylon†; Urlix†; Uronalin; Wintomylon; ***Pol.:*** Nevigramon; ***Port.:*** Wintomilon†; ***Rus.:*** Negram (Нерам); ***S.Afr.:*** Puromylon; Winlomylon; ***UK:*** Negram†; Uriben; ***USA:*** NegGram.

Multi-ingredient: ***Irl.:*** Mictral†; ***Mex.:*** Azo-Uronalin; Azo-Wintomylon; Azogen; Nalixone; Naxilan-Plus; Pirifur.

Neomycin *(BAN, rINN)*

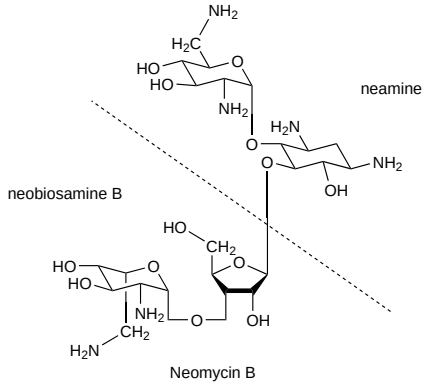
Neomicina; Néomycine; Neomycinum; Neomysiini.

Неомицин

CAS — 1404-04-2 (neomycin); 3947-65-7 (neomycin A); 119-04-0 (neomycin B); 66-86-4 (neomycin C).

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.



Neomycin B

Description. A mixture of 2 isomers, neomycin B ($C_{23}H_{46}N_6O_{13}$ = 614.6) and neomycin C ($C_{23}H_{46}N_6O_{13}$ = 614.6) with neomycin A (neamine, $C_{12}H_{26}N_4O_6$ = 322.4); neomycins B and C are glycoside esters of neamine and neobiosamines B and C. Framycetin (p.279) consists of neomycin B.

Neomycin Sulfate *(rINNM)*

Fradiomycin Sulfate; Neomicino sulfatas; Neomicin-szulfát; Neomisin Sülfat; Neomycin Sulphate *(BANM)*; Néomycine, sulfate de; Neomycini sulfas; Neomycinsulfat; Neomycin-sulfát; Neomycyny siarczan; Neomysiinisulfaatti; Sulfato de neomicina.

Неомицина Сульфат

CAS — 1405-10-3.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

NOTE. NEO is a code approved by the BP 2008 for use on single unit doses of eye drops containing neomycin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Neomycin Sulphate). A mixture of the sulfates of substances produced by the growth of certain selected strains of *Streptomyces fradiae*, the main component being the sulfate of neomycin B. The potency is not less than 680 units/mg, calculated with reference to the dried substance. A white or yellowish-white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

USP 31 (Neomycin Sulfate). The sulfate salt of a kind of neomycin, an antibacterial substance produced by the growth of *Streptomyces fradiae* (Streptomycetaceae), or a mixture of two or more such salts. It has a potency equivalent to not less than 600 micrograms of neomycin per mg, calculated on the dried basis. A white to slightly yellow powder, or cryodesiccated solid. It is odourless or practically so, and is hygroscopic. Soluble 1 in 1 of water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether. pH of a solution in water containing the equivalent of neomycin 3.3% is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Neomycin Undecenoate *(BANM)*

Neomycin Undecylenate *(USAN, rINNM)*; Néomycine, Undécylénate de; Neomycini Undecylenas; Undecilenato de neomicina. The 10-undecenoate salt of neomycin.

Неомицина Ундецилената

CAS — 1406-04-8.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

Adverse Effects and Treatment

As for Gentamicin Sulfate, p.282.

Neomycin has particularly potent nephrotoxic and ototoxic properties and so is generally no longer given parenterally. However, sufficient may be absorbed after use by other routes (e.g. orally, instillation into cavities or open wounds, or topical application to damaged skin), to produce irreversible partial or total deafness. The effect is dose-related and is enhanced by renal impairment. Nephrotoxic effects may also occur.

When given orally in large doses, neomycin causes nausea, vomiting, and diarrhoea. Prolonged oral use may cause a malabsorption syndrome with steatorrhoea and diarrhoea which can be very severe. Superinfection may occur, especially with prolonged treatment.

Neomycin has a neuromuscular-blocking action similar to, but stronger than, that of other aminoglycosides, and respiratory depression and arrest has followed the intraperitoneal instillation of neomycin. Fatalities have occurred.

Hypersensitivity reactions, such as rashes, pruritus, and sometimes drug fever or even anaphylaxis, during local treatment with neomycin and may be masked by the combined use of a corticosteroid. Cross-sensitivity with other aminoglycosides may occur.

Precautions

As for Gentamicin Sulfate, p.283. Parenteral use of neomycin, or its use for irrigation of wounds or serous cavities such as the peritoneum, is no longer recommended.

Neomycin is contra-indicated for intestinal disinfection when an obstruction is present, in patients with a known history of allergy to aminoglycosides, and in infants under 1 year. It should be used with great care in patients with renal or hepatic impairment, or with neuromuscular disorders, and in those with impaired hearing. The topical use of neomycin in patients with extensive skin damage or perforated tympanic membranes may result in deafness.

Prolonged local use should be avoided as it may lead to skin sensitisation and possible cross-sensitivity to other aminoglycosides.

Hypersensitivity and vaccination. Neomycin was thought to be responsible for a hypersensitivity reaction[1] in a child given measles, mumps, and rubella vaccine containing neomycin 25 micrograms. However, there is also a report of successful vaccination with measles, mumps, and rubella vaccine in a neomycin-sensitive child.[2] Although the vaccine may contain small amounts of neomycin or kanamycin, and sensitivity to either is considered a contra-indication to its use, it is only rarely necessary to withhold it once appropriate expert advice has been taken. There is little logic to intradermal testing since test solutions contain 4 to 40 times as much neomycin as the vaccine.[2]

1. Kwittken PL, *et al.* MMR vaccine and neomycin allergy. *Am J Dis Child* 1993; **147:** 128–9.
2. Elliman D, Dhanraj B. Safe MMR vaccination despite neomycin allergy. *Lancet* 1991; **337:** 365.

Interactions

As for Gentamicin Sulfate, p.283. Absorption after oral or local use may be sufficient to produce interactions with other drugs given systemically.

Neomycin orally has been reported to impair the absorption of other drugs including phenoxymethylpenicillin, digoxin, and methotrexate; the efficacy of oral contraceptives might be reduced. The effects of acarbose may be enhanced by oral neomycin.

Antimicrobial Action

Neomycin has a mode of action and spectrum of activity similar to that of gentamicin (p.283) but it lacks activity against *Pseudomonas aeruginosa.* It is reported to be active against *Mycobacterium tuberculosis.*

Because of its extensive topical use, resistance has been reported to be relatively widespread, notably among staphylococci, and some *Salmonella*, *Shigella*, and *Escherichia coli* strains. Cross-resistance with kanamycin, framycetin, and paromomycin occurs.

Pharmacokinetics

Neomycin is poorly absorbed from the gastrointestinal tract, about 97% of an oral dose being excreted unchanged in the faeces. Doses of 3 g orally produce peak plasma concentrations of up to 4 micrograms/mL and absorption is similar after an enema. Absorption may be increased in conditions which damage or inflame the mucosa. Absorption has also been reported to occur from the peritoneum, respiratory tract, bladder, wounds, and inflamed skin.

Once neomycin is absorbed it is rapidly excreted by the kidneys in active form. It has been reported to have a half-life of 2 to 3 hours.

Uses and Administration

Neomycin is an aminoglycoside antibiotic used topically in the treatment of infections of the skin, ear, and eye due to susceptible staphylococci and other organisms. Most preparations contain the sulfate, but neomycin undecenoate is also used. Neomycin is often used with another antibacterial such as bacitracin, colistin, gramicidin, or polymyxin B. Such combinations have been used topically in the eye before ophthalmic surgery for infection prophylaxis and, with propamidine isetionate, in the treatment of acanthamoeba keratitis (p.822). A cream containing neomycin sulfate and chlorhexidine hydrochloride has been used for application to the nostrils in the treatment of staphylococcal nasal carriers (p.195) but, as with other topical antibacterial preparations, development of resistance may be a problem. Neomycin is often used with topical corticosteroids, but such preparations should be used with caution because of the risk that signs of resistant infection may be suppressed. Care must also be taken where there is skin trauma because of the risk of increased absorption and toxicity (see Adverse Effects, above). For details of bacterial skin infections and their treatment, see p.194.

Because neomycin sulfate is poorly absorbed from the gastrointestinal tract, it has been given orally for bowel preparation before abdominal surgery, often with erythromycin (p.195). Neomycin sulfate is also used with other antibacterials and antifungals in the selective decontamination of the digestive tract in patients in intensive care (p.175).

Neomycin is rarely used in the treatment of existing gastrointestinal infections. Although it has been used in the treatment of diarrhoea due to infection with enteropathogenic *Escherichia coli* (EPEC) (p.173), the use of neomycin in children with acute diarrhoea is generally not recommended.

Neomycin sulfate may be given orally to patients with incipient hepatic encephalopathy (p.1697) to reduce the flora of the gastrointestinal tract.

Neomycin has lipid regulating properties and has occasionally been given orally in the treatment of hyperlipidaemias (see below). It has also been used for the irri-