Nitrofurantoin *(BAN, rINN)*

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

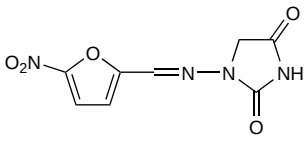
Нитрофурантоин

$C_8H_6N_4O_5$ = 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-

furantoin monohydrate, is available in some countries and is given in a dose of 100 mg twice daily. A usual long-term prophylactic dose is 50 to 100 mg at bedtime.

For details of doses in children, see below.

◊ Reviews.

1. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs* 2001; **61:** 353–64.

Administration in children. In the UK, nitrofurantoin may be given to children aged 3 months to 12 years for the *treatment* of urinary-tract infection in a usual oral dose of 3 mg/kg daily given in 4 divided doses; 1 mg/kg may be given at night for long-term *prophylactic* therapy. However, a systematic review[1] concluded, on the basis of the rather low-grade evidence available, that the adverse effects of nitrofurantoin may outweigh its benefits and render it unacceptable for long-term therapy.

Higher oral doses of 5 to 7 mg/kg daily in 4 divided doses are recommended for the *treatment* of urinary-tract infection in the USA in children aged 1 month and above; for long-term *prophylactic* therapy 1 mg/kg daily given in one or two divided doses is considered adequate.

Older children may be given usual adult doses (see above).

1. Williams GJ, *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/01/08).

Preparations

BP 2008: Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets; ***USP 31:*** Nitrofurantoin Capsules; Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Furadantina; ***Austral.:*** Furadantin; Macrodantin; Ralodantin†; ***Austria:*** Furadantin; ***Belg.:*** Furadantine; ***Braz.:*** Hantina; Macrodantina; Nitrofen; Urogem; ***Canad.:*** Macrobid; Macrodantin†; Novo-Furantoin; ***Chile:*** Macrodantina; Macrosan; Matidan; ***Cz.:*** Furantoin†; Nifurantin†; ***Fin.:*** Nitrofurc; ***Fr.:*** Furadantine; Furadoine; Microdoine; ***Ger.:*** Furadantin; Nifurantin; Nifuretten; Uro-Tablinen; ***Gr.:*** Furolin; ***India:*** Furadantin; ***Irl.:*** Furadantin; Macrobid; Macrodantin; ***Israel:*** Macrodantin†; Uvamin; ***Ital.:*** Furadantin; Furedan; Furil; Macrodantin; Neo-Furadantin; ***Mex.:*** Biofurin; Furadantina; Furitex; Futroken; Macrodantina; Macrofurin; Promac; Suronit; ***Neth.:*** Furabid; Furadantine MC; ***Norw.:*** Furadantin; ***NZ:*** Furadantin; Nifuran; ***Philipp.:*** Macrodantin; ***Pol.:*** Siraliden; ***Port.:*** Furadantina; ***S.Afr.:*** Furadantin; Macrodantin; ***Spain:*** Furantoina; Furobactina; ***Swed.:*** Furadantin; ***Switz.:*** Furadantine; Urodin; Uvamine retard; ***Turk.:*** Piyeloseptyl; ***UK:*** Furadantin; Macrobid; Macrodantin; ***USA:*** Furadantin; Macrobid; Macrodantin; ***Venez.:*** Furadina†; Macrodantina.

Multi-ingredient: ***Arg.:*** Bagociletas con Anestesia; Bagociletas sin Anestesia†; ***Braz.:*** Urofen†; Uropac; ***Ger.:*** Nifurantin B 6; Urospasmon sine†; Urospasmon†; ***India:*** Nephrogesic; ***Mex.:*** Furanton†; ***Turk.:*** Uriseptin.

Nitrofurazone *(BAN)*

Nitrofural *(plNN)*; Furacilinum; Nitrofuraali; Nitrofurál; Nitrofuralis; Nitrofuralum; Nitrofuratsoni; Nitrofurazon; Nitrofurazonum. 5-Nitro-2-furaldehyde semicarbazone.

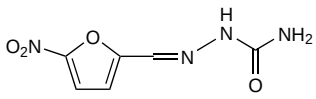
Нитрофурал

$C_6H_6N_4O_4$ = 198.1.

CAS — 59-87-0.

ATC — B05CA03; D08AF01; D09AA03; P01CC02; S01AX04; S02AA02.

ATC Vet — QB05CA03; QD08AF01; QD09AA03; QG01AX90; QP51AC02; QS01AX04; QS02AA02.



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

Ph. Eur. 6.2 (Nitrofural; Nitrofurazone BP 2008). A yellow or brownish-yellow, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.0. Protect from light.

USP 31 (Nitrofurazone). A lemon-yellow, odourless crystalline powder. It darkens slowly on exposure to light. Soluble 1 in 4200 of water, 1 in 590 of alcohol, and 1 in 350 of propylene glycol; practically insoluble in chloroform and in ether; soluble in dimethylformamide; slightly soluble in polyethylene glycol mixtures. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Sterilisation. Autoclaving gauze dressings impregnated with nitrofurazone, as recommended by the US manufacturer, resulted in a greater than 10% loss of the drug.[1] Since the spectroscopic assay used may not distinguish between nitrofurazone and some of its degradation products, the degree of degradation may have been greater than this.

1. Phillips C, Fisher E. Effect of autoclaving on stability of nitrofurazone soluble dressing. *Am J Health-Syst Pharm* 1996; **53:** 1169–71.

Adverse Effects

Sensitisation and generalised allergic skin reactions may be produced by topical nitrofurazone.

Nitrofurazone is a toxic drug when given orally and serious adverse effects include severe peripheral neuropathy; haemolysis may occur in patients with G6PD deficiency. Nitrofurazone in high oral doses is carcinogenic in *rats*.

Precautions

Nitrofurazone is contra-indicated in patients with known hypersensitivity. Preparations containing macrogols should be used with caution in patients with renal impairment since macrogols can be absorbed and their accumulation in such patients may result in symptoms of further impairment.

Oral nitrofurazone should be used with caution in patients with G6PD deficiency because of the risk of haemolysis.

Antimicrobial Action

Nitrofurazone is a nitrofuran derivative with a broad spectrum of antibacterial activity, but with little activity against *Pseudomonas* spp. It also has antitrypanosomal activity.

Uses and Administration

Nitrofurazone is a nitrofuran derivative that is used topically for wounds, burns, ulcers, and skin infections, and for the preparation of surfaces before skin grafting. It is usually applied in a concentration of 0.2% in a water-soluble or water-miscible basis. A solution of nitrofurazone is used for bladder irrigation.

Urinary catheters impregnated with nitrofurazone, to reduce bacterial colonisation and infection, are available in some countries.

Preparations

USP 31: Nitrofurazone Ointment; Nitrofurazone Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Furacin; Ivoran Pilot†; Nitromed; ***Belg.:*** Furacine; ***Braz.:*** Alivioderm†; Caziderm; Cleanbac†; Furacin; Sensiderme; ***Chile:*** Demodek†; Furacin; ***Ger.:*** Furacin-Sol; ***India:*** Furacin; ***Mex.:*** Furacin; Kufro; Nifurol; Probizal; Vulnizol; ***Neth.:*** Furacine; ***Philipp.:*** Furacin; ***Port.:*** Rayonfur; ***S.Afr.:*** Furacin; Furex; Germex; ***Spain:*** Furacin; ***Thai.:*** Bactacin; Mytrocin; Polycin; ***Turk.:*** Dermikolin; Furacin; Furaderm; Furazol; ***USA:*** Furacin†; ***Venez.:*** Furacin; Furfuril; Fuxal; Polifur†.

Multi-ingredient: ***Arg.:*** Fadanasal; Neo Pelvicillin; O-Biol; Vagicural; Vagisan; Vagisan Compuesto; Vislus; ***Braz.:*** Nitrileno; Nitrolerg†; Otodol†; ***India:*** Furacin-S; ***Ital.:*** Furotricina; ***Mex.:*** Madecassol C; Madecassol N; ***Spain:*** Dertrase; ***Thai.:*** Denson.

Nitroxoline *(BAN, plNN)*

Nitroxolina; Nitroxolinum. 5-Nitroquinolin-8-ol.

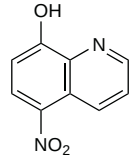
Нитроксолин

$C_9H_6N_2O_3$ = 190.2.

CAS — 4008-48-4.

ATC — J01XX07.

ATC Vet — QJ01XX07.



Profile

Nitroxoline has antibacterial and antifungal properties and is used in the treatment of urinary-tract infections in oral doses ranging from 80 to 250 mg three times daily before food. It has also been given with sulfamethizole.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Nibiol†; ***Ger.:*** Cysto-Saar; ***Rus.:*** 5-Nitrox (5-Нитрокс); 5-Nok (5-Нок); ***S.Afr.:*** Nicene N.

Multi-ingredient: ***Braz.:*** Minazol.

Norfloxacin *(BAN, USAN, rINN)*

AM-715; *N*-Desmethylpefloxacin; MK-366; Norfloksacinas; Norfloksacyna; Norfloksasiini; Norfloksasin; Norfloxacine; Norfloxacino; Norfloxacinum. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

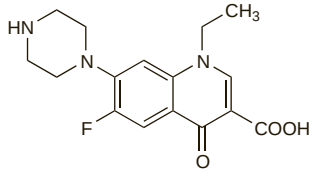
Норфлоксацин

$C_{16}H_{18}FN_3O_3$ = 319.3.

CAS — 70458-96-7.

ATC — J01MA06; S01AX12.

ATC Vet — QJ01MA06; QS01AX12.



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

Ph. Eur. 6.2 (Norfloxacin). A white or pale yellow, hygroscopic, photosensitive, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone. Store in airtight containers. Protect from light.

USP 31 (Norfloxacin). A white to pale yellow crystalline powder. Slightly soluble in water, in alcohol, and in acetone; freely soluble in acetic acid; sparingly soluble in chloroform; practically insoluble in ether; very slightly soluble in ethyl acetate and in methyl alcohol. Store in airtight containers. Protect from light.

Norfloxacin Pivoxil *(BANM, rINNM)*

Norfloxacine, Pivoxil de; Norfloxacini Pivoxil; Norfloxacino pivoxilo. Pivaloyloxymethyl 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

Норфлоксацина Пивоксил

$C_{22}H_{28}FN_3O_5$ = 433.5.

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Interactions

As for Ciprofloxacin, p.246.

Antimicrobial Action

As for Ciprofloxacin, p.246, although norfloxacin is less potent *in vitro*. Norfloxacin is not active against Chlamydiaceae, mycoplasmas, or mycobacteria.

Pharmacokinetics

About 30 to 40% of an oral dose of norfloxacin is absorbed. Peak plasma concentrations of about 1.5 micrograms/mL occur about 1 to 2 hours after a 400-mg oral dose; the presence of food can delay absorption. Norfloxacin is about 14% bound to plasma proteins. It is probably widely distributed, but information is limited. Norfloxacin penetrates well into tissues of the genito-urinary tract. It crosses the placenta. Relatively high concentrations are achieved in bile.

The plasma half-life is 3 to 4 hours and may be prolonged in renal impairment; a value of 6.5 hours or more has been reported when creatinine clearance is below 30 mL/minute per 1.73 m^2. About 30% of a dose is excreted unchanged in the urine within 24 hours, producing high urinary concentrations; norfloxacin is least soluble at a urinary pH of 7.5. Urinary excretion is by tubular secretion and glomerular filtration and is reduced by probenecid, although plasma concentrations of norfloxacin are not generally affected. Some metabolism occurs, possibly in the liver, and several metabolites have been identified in urine, some with antibacterial activity. About 30% of an oral dose is recovered from the faeces.

Uses and Administration

Norfloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.243), but it is generally less potent *in vitro*.

Norfloxacin is used mainly in the treatment of urinary-tract infections (p.199) and for the treatment of gonorrhoea (p.191).

Norfloxacin is given orally at least 1 hour before, or 2 hours after, food or milk.

In urinary-tract infections the usual dose is 400 mg twice daily for 3 to 10 days. Treatment may need to be continued for up to 12 weeks in chronic relapsing urinary-tract infections; it may be possible to reduce the dose to 400 mg once daily if there is an adequate response within the first 4 weeks. A 28-day course of treatment with a dose of 400 mg twice daily should be given for acute or chronic bacterial prostatitis.

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

A single oral dose of 800 mg is given in the treatment of uncomplicated gonorrhoea.

Eye drops containing 0.3% of norfloxacin are used to treat eye infections.

The pivaloyloxymethyl salt of norfloxacin, norfloxacin pivoxil, is also used in some countries.