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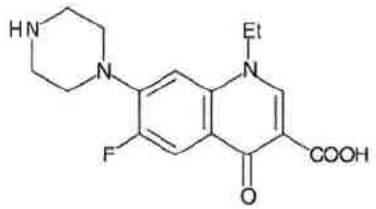
Roxin

PRODUCT INFORMATION

Name of the drug

Norfloxacin. The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34 Cas No.: 70458-96-7

Description

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.

Roxin tablets contain 400 mg of norfloxacin. The tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920. The tablets are gluten free.

Pharmacology

Microbiology
Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter sp., Enterococci.* For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus, Staph. epidermidis, Staph. Saprophyticus.* Gram-negative bacteria including *Citrobacter diversus, C. freundii, Enterobacter*

cloacae, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests
Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology
Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Pharmacokinetics
In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the

administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see Dosage and Administration). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

The serum protein binding of norfloxacin is between 10 and 15%.

Indications

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Contraindications

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials. Children; Pregnancy (see Precautions).

Precautions

Arthropathy

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The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent

lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

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Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

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Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Nervous system

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The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see Adverse Reactions).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Vision disorders

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If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Photosensitivity

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Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

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Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further

increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

~~Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with norfloxacin and other quinolones. Norfloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon.~~

Haemolytic reactions

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Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see Adverse Reactions).

~~Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see Adverse Reactions).~~

Comment [S22.1]: Paragraph moved under heading "Nervous system"

Cardiac disorders

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Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Renal Impairment

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Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Effect on ability to drive or operate machinery

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Norfloxacin may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and coordination.

Carcinogenicity, mutagenicity, impairment of fertility

Information is not available at present on the carcinogenic potential of norfloxacin.

Norfloxacin was tested for mutagenic activity in a number of in vivo and in vitro tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1,000 mg/kg/day. Norfloxacin had no mutagenic activity in vitro in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy (Category B3)

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

Use in children

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in ~~prepubertal~~ children ~~or growing adolescents.~~less than 18 years of age.

~~**Impaired Renal Function**~~

~~Alteration in dosage regimens necessary for patients with impaired renal function (See Dosage and Administration).~~

Comment [S222]: Sentence moved under heading "Renal Impairment".

Information for Patients

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Interactions

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

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Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life. that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Adverse Reactions

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis., Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus., and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis., elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia., visual disturbances, Hearing loss

Causal relationship unknown: A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Dosage and Administration

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see Precautions).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the

duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

Overdosage

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.
In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

Presentation

400 mg Tablets: White, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and "> " on the other.

*Bottle and blister packs of 14.

Sponsor

Aspen Pharma Pty Ltd
34-36 Chandos Street,
St. Leonards NSW 2065
Australia

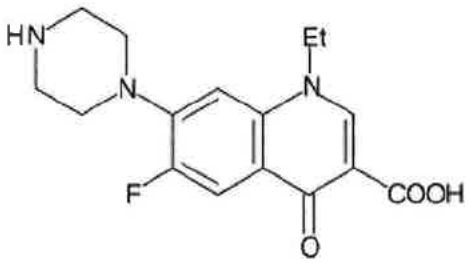
Approved by the Therapeutic Goods Administration on 21 August 2002.
Date of most recent amendment: ~~August 2009~~

Roxin

PRODUCT INFORMATION

Name of the drug

Norfloxacin. The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34 Cas No.: 70458-96-7

Description

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Roxin tablets contain 400 mg of norfloxacin. The tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920. The tablets are gluten free.

Pharmacology

Microbiology
Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter sp., Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus, Staph. epidermidis, Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus, C. freundii, Enterobacter*

cloacae, Escherichia coli, Klebsiella oxytoca, K. pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa. Bacteria found in gastrointestinal infections: *Shigella, E. coli, Salmonella typhi.*

In addition, norfloxacin is active against *Neisseria gonorrhoeae.*

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests
Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology
Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Pharmacokinetics
In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the

administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see Dosage and Administration). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

The serum protein binding of norfloxacin is between 10 and 15%.

Indications

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Contraindications

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials. Children; Pregnancy (see Precautions).

Precautions

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent

lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see Adverse Reactions).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further

increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see Adverse Reactions).

Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Renal Impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Effect on ability to drive or operate machinery

Norfloxacin may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and coordination.

Carcinogenicity, mutagenicity, impairment of fertility

Information is not available at present on the carcinogenic potential of norfloxacin.

Norfloxacin was tested for mutagenic activity in a number of in vivo and in vitro tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1,000 mg/kg/day. Norfloxacin had no mutagenic activity in vitro in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy (Category B3)

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well

controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

Use in children

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Information for Patients

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Interactions

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Adverse Reactions

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.
The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown: A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Dosage and Administration

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see Precautions).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

Overdosage

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.
In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

Presentation

400 mg Tablets: White, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and "> " on the other.

*Bottle and blister packs of 14.

Sponsor

Aspen Pharma Pty Ltd
34-36 Chandos Street,
St. Leonards NSW 2065
Australia

Approved by the Therapeutic Goods Administration on 21 August 2002.
Date of most recent amendment:

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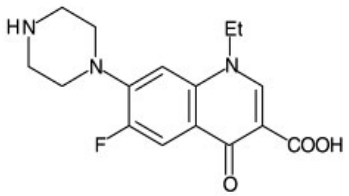
Roxin

PRODUCT INFORMATION

Name of the Medicine

Norfloxacin. The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34 ~~Cas~~ CAS No.: 70458-96-7

Description

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.

Roxin tablets contain 400 mg of norfloxacin. The tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920. The tablets are gluten free.

Pharmacology

Microbiology
Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp.*, *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter*

cloacae, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests
Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology
Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Pharmacokinetics
In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the

administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see DOSAGE AND ADMINISTRATION). Drug absorption appears unaffected by decreasing renal function.

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Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

The serum protein binding of norfloxacin is between 10 and 15%.

Indications

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

Contraindications

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials. Children; Pregnancy (see PRECAUTIONS).

Precautions

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient.

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These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

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Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

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Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be

consulted immediately (see ADVERSE EFFECTS).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see ADVERSE EFFECTS).

Cardiac disorders

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Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy (Category B3)

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

Use in children

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Information for Patients

Patients should be advised to take ~~NOROXIN~~ norfloxacin one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Interactions with Other Medicines

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

Adverse Effects

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.
The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown: A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Dosage and Administration

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see PRECAUTIONS).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

Overdosage

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.
In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

Presentation and Storage Conditions

400 mg Tablets: White, film-coated, convex, oval shaped scored tablet, embossed with "N|F" on one side and "> " on the other.

Bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

Store below 30°C

Name and address of the Sponsor

Arrow Pharma Pty Ltd
15-17 Chapel Street,

Cremorne VIC 3121

Poison Schedule of the Medicine

S4 – Prescription Only Medicine

Date of first inclusion on the Australian Register of Therapeutic Goods (the ARTG)

21 August 2002.

Date of most recent amendment

~~14 March 2017~~TBD

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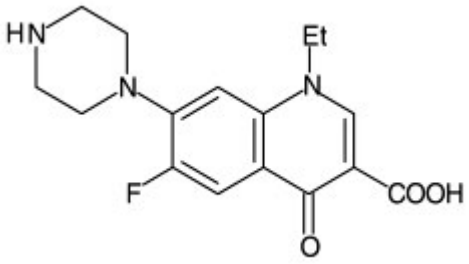
Roxin

PRODUCT INFORMATION

Name of the Medicine

Norfloxacin. The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34 CAS No.: 70458-96-7

Description

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.

Roxin tablets contain 400 mg of norfloxacin. The tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920. The tablets are gluten free.

Pharmacology

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp.*, *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter*

cloacae, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests
Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology
Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Pharmacokinetics
In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the

administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see DOSAGE AND ADMINISTRATION). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

The serum protein binding of norfloxacin is between 10 and 15%.

Indications

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

Contraindications

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials. Children; Pregnancy (see PRECAUTIONS).

Precautions

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient.

These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see ADVERSE EFFECTS).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see ADVERSE EFFECTS).

Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Renal Impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Effect on ability to drive or operate machinery

Norfloxacin may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and coordination.

Carcinogenicity, mutagenicity, impairment of fertility

Information is not available at present on the carcinogenic potential of norfloxacin.

Norfloxacin was tested for mutagenic activity in a number of in vivo and in vitro tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1,000 mg/kg/day. Norfloxacin had no mutagenic activity in vitro in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy (Category B3)

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

Use in children

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Information for Patients

Patients should be advised to take norfloxacin one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

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The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

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Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.
The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown: A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Dosage and Administration

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see PRECAUTIONS).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

Overdosage

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.
In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

Presentation and Storage Conditions

400 mg Tablets: White, film-coated, convex, oval shaped scored tablet, embossed with "N|F" on one side and "> " on the other.

Bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

Store below 30^{O}C

Name and address of the Sponsor

Arrow Pharma Pty Ltd
15-17 Chapel Street,
Cremorne VIC 3121

Poison Schedule of the Medicine

S4 – Prescription Only Medicine

Date of first inclusion on the Australian Register of Therapeutic Goods (the ARTG)

21 August 2002.

Date of most recent amendment

TBD

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AUSTRALIAN PI – ROXIN (NORFLOXACIN) DOSE FORM

1 NAME OF THE MEDICINE

Norfloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXIN tablets contain 400mg of norfloxacin.

Physical and Chemical characteristics:

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.

Excipients:

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ROXIN tablets are white, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and ">" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see **Section 4.4 Special warnings and precaution for use**).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.

Children; Pregnancy (see **Section 4.4 Special warnings and precaution for use and Section 4.6, Fertility, pregnancy and lactation; Pregnancy**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Psychiatric Adverse Reactions

Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased

in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Information for Patients

Patients should be advised to take norfloxacin 1 hour before or 2 hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Use in renal impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by

severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see **Section 4.2 Dose and method of administration**).

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation.

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Norfloxacin may cause dizziness or light-headedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and co-ordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.

In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp*., *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility

test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

Distribution

The serum protein binding of norfloxacin is between 10 and 15%.

Metabolism

Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency.

Excretion

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see **Section 4.2 Dose and method of administration**). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1000 mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was

weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity

Information is not available at present on the carcinogenic potential of norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ROXIN tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

The tablets are gluten free.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30^{O}C

6.5 Nature and contents of container

ROXIN tablets are available in bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

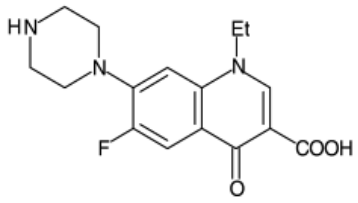
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34

CAS number

CAS No.: 70458-96-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

21 August 2002

10 DATE OF REVISION

~~10 August 2018~~TBC

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
~~n/a~~4.4	~~Reformatting~~Added precautions - Aortic aneurysm and dissection - Dysglycaemia - Psychiatric Adverse Reactions

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AUSTRALIAN PI – ROXIN (NORFLOXACIN) DOSE FORM

1 NAME OF THE MEDICINE

Norfloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXIN tablets contain 400mg of norfloxacin.

Physical and Chemical characteristics:

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.

Excipients:

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ROXIN tablets are white, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and ">" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see **Section 4.4 Special warnings and precaution for use**).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.

Children; Pregnancy (see **Section 4.4 Special warnings and precaution for use and Section 4.6, Fertility, pregnancy and lactation; Pregnancy**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Psychiatric Adverse Reactions

Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased

in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see **Section 4.8 Adverse effects (Undesirable reactions)**).

Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Information for Patients

Patients should be advised to take norfloxacin 1 hour before or 2 hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Use in renal impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by

severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see **Section 4.2 Dose and method of administration**).

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation.

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Norfloxacin may cause dizziness or light-headedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and co-ordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.

In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp*., *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility

test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

Distribution

The serum protein binding of norfloxacin is between 10 and 15%.

Metabolism

Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency.

Excretion

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see **Section 4.2 Dose and method of administration**). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1000 mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was

weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity

Information is not available at present on the carcinogenic potential of norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ROXIN tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

The tablets are gluten free.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30^{O}C

6.5 Nature and contents of container

ROXIN tablets are available in bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

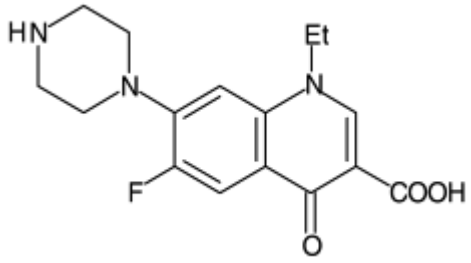
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34

CAS number

CAS No.: 70458-96-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

21 August 2002

10 DATE OF REVISION

TBC

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Added precautions - Aortic aneurysm and dissection - Dysglycaemia - Psychiatric Adverse Reactions

AUSTRALIAN PRODUCT INFORMATION~~I~~ – ROXIN (NORFLOXACIN) ~~DOSE FORM~~TABLETS

Commented [S22 1]: Minor editorial changes in line with the new form for providing PI

1 NAME OF THE MEDICINE

Norfloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXIN tablets contain 400mg of norfloxacin.

~~Physical and Chemical characteristics:~~

Commented [S22 2]: Minor editorial changes in line with the new form for providing PI

~~Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.~~

Commented [S22 3]: Minor editorial changes – text moved to section 6.7 in line with the new form for providing PI

~~Excipients:~~

Commented [S22 4]: Minor editorial changes in line with the new form for providing PI

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

ROXIN tablets are white, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and ">" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see **Section 4.4 Special warnings and precaution for use**).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.

Children; Pregnancy (see **Section 4.4 Special warnings and precaution for use and Section 4.6, Fertility, pregnancy and lactation; Pregnancy**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

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Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

Commented [S22[redacted]6]: Minor editorial changes in line with the new form for providing PI

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

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Psychiatric Adverse Reactions

Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Commented [S22[redacted]8]: SRR change as requested by Signal Investigation Unit

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

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Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased

in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

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Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

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Information for Patients

Patients should be advised to take norfloxacin 1 hour before or 2 hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Use in renal impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by

severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see **Section 4.2 Dose and method of administration**).

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation.

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Norfloxacin may cause dizziness or light-headedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and co-ordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.

In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp*., *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility

test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

Distribution

The serum protein binding of norfloxacin is between 10 and 15%.

Metabolism

Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency.

Excretion

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see **Section 4.2 Dose and method of administration**). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1000 mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was

weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity

Information is not available at present on the carcinogenic potential of norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ROXIN tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

The tablets are gluten free.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30^{O}C

6.5 Nature and contents of container

ROXIN tablets are available in bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.

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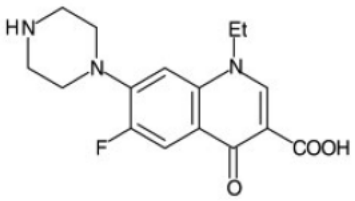
Chemical structure

The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34

CAS number

CAS No.: 70458-96-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

21 August 2002

10 DATE OF REVISION

~~10 August 2018~~TBC

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
~~n/a~~4.4	~~Reformatting~~Added precautions - Aortic aneurysm and dissection - Dysglycaemia - Psychiatric Adverse Reactions
n/a	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION – ROXIN (NORFLOXACIN) TABLETS

1 NAME OF THE MEDICINE

Norfloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXIN tablets contain 400mg of norfloxacin.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

ROXIN tablets are white, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and ">" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression, in adults, of chronic, recurrent urinary tract infection.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine),

chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see **Section 4.4 Special warnings and precaution for use**).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.

Children; Pregnancy (see **Section 4.4 Special warnings and precaution for use and Section 4.6, Fertility, pregnancy and lactation; Pregnancy**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment

with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see **Section 4.8 Adverse effects (Undesirable effects)**).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 Adverse effects (Undesirable effects)**).

Psychiatric Adverse Reactions

Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 Adverse effects (Undesirable effects)**).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling,

inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see **Section 4.8 Adverse effects (Undesirable effects)**).

Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Information for Patients

Patients should be advised to take norfloxacin 1 hour before or 2 hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Use in renal impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see **Section 4.2 Dose and method of administration**).

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin,

because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation.

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Norfloxacin may cause dizziness or light-headedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and co-ordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.

In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp*., *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate”

indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

Distribution

The serum protein binding of norfloxacin is between 10 and 15%.

Metabolism

Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency.

Excretion

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see **Section 4.2 Dose and method of administration**). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1000 mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity

Information is not available at present on the carcinogenic potential of norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ROXIN tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

The tablets are gluten free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{O}C

6.5 NATURE AND CONTENTS OF CONTAINER

ROXIN tablets are available in bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

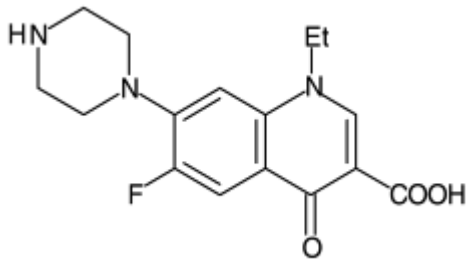
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.

Chemical structure

The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34

CAS number

CAS No.: 70458-96-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

21 August 2002

10 DATE OF REVISION

TBC

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Added precautions - Aortic aneurysm and dissection - Dysglycaemia - Psychiatric Adverse Reactions
n/a	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – ROXIN (NORFLOXACIN) ~~DOSE FORM~~ TABLETS

Commented [S22 1]: Minor editorial changes in line with the new form for providing PI

1 NAME OF THE MEDICINE

Norfloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXIN tablets contain 400mg of norfloxacin.

~~Physical and Chemical characteristics:~~

Commented [S22 2]: Minor editorial changes in line with the new form for providing PI

~~Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.~~

Commented [S22 3]: Minor editorial changes – text moved to section 6.7 in line with the new form for providing PI

~~Excipients:~~

Commented [S22 4]: Minor editorial changes in line with the new form for providing PI

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

ROXIN tablets are white, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and ">" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

~~Suppression, in adults, of chronic, recurrent urinary tract infection.~~

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within two hours of administration of norfloxacin (see **Section 4.4 Special warnings and precaution for use**).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

~~For suppression in chronic, recurrent urinary tract infection, 400 mg twice daily may be administered for four to twelve weeks.~~

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.

Children; Pregnancy (see **Section 4.4 Special warnings and precaution for use and Section 4.6, Fertility, pregnancy and lactation; Pregnancy**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Commented [S22[redacted]5]: SRR change as requested by Signal Investigation Unit

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

Commented [S22[redacted]6]: Minor editorial changes in line with the new form for providing PI

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

Commented [S22[redacted]7]: Minor editorial changes in line with the new form for providing PI

Psychiatric Adverse Reactions

Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

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Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

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Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased

in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see **Section 4.8 Adverse effects (Undesirable ~~reactions~~effects)**).

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Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

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Information for Patients

Patients should be advised to take norfloxacin 1 hour before or 2 hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Use in renal impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by

severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see **Section 4.2 Dose and method of administration**).

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation.

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Norfloxacin may cause dizziness or light-headedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and co-ordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.

In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp*., *Enterococci*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility

test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

Distribution

The serum protein binding of norfloxacin is between 10 and 15%.

Metabolism

Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency.

Excretion

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see **Section 4.2 Dose and method of administration**). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1000 mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was

weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity

Information is not available at present on the carcinogenic potential of norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ROXIN tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

The tablets are gluten free.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30^{O}C

6.5 Nature and contents of container

ROXIN tablets are available in bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.

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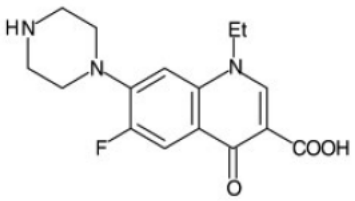
Chemical structure

The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34

CAS number

CAS No.: 70458-96-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

21 August 2002

10 DATE OF REVISION

~~10 August 2018~~TBC

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
~~4.1n/a~~	Deletion of indication "Suppression. in adults of chronic. recurrent urinary tract infection"~~Reformatting~~
4.2	Deletion of dosage instruction for "Suppression. in adults of chronic. recurrent urinary tract infection",
4.4	Added precautions - Aortic aneurysm and dissection - Dysglycaemia Psychiatric Adverse Reactions
n/a	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION – ROXIN (NORFLOXACIN) TABLETS

1 NAME OF THE MEDICINE

Norfloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXIN tablets contain 400mg of norfloxacin.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

ROXIN tablets are white, film-coated, convex, oval shaped scored tablet, embossed with "N | F" on one side and ">" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with complicated and uncomplicated urinary tract infections that are caused by susceptible strains of microorganisms.

Treatment of adults with gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

Note. Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Norfloxacin tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving norfloxacin should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or Videx (didanosine), chewable/ buffered tablets or the paediatric powder for oral solution, should not be taken within

two hours of administration of norfloxacin (see **Section 4.4 Special warnings and precaution for use**).

Urinary tract infection: Normal renal function. The recommended dosage of norfloxacin for the treatment of urinary tract infection is 400 mg twice daily for seven to ten days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400 mg twice daily for three days. In one study of uncomplicated lower urinary tract infections, treatment for seven days resulted in somewhat better eradication rates than treatment for three days.

Maximum total daily dosage should not exceed 800 mg per day.

Impaired renal function: Norfloxacin may be used for the treatment of urinary tract infections in patients with renal insufficiency. In patients with a creatinine clearance rate of 30 mL/minute/1.73 m^2 or less, the recommended dosage is one 400 mg tablet once daily for the duration given above. At this dosage, the urinary concentration exceeds the MICs for most urinary pathogens susceptible to norfloxacin, even when the creatinine clearance is less than 10 mL/minute/1.73 m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

When only the serum creatinine level is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Men:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Women: 0.85 x the value calculated for men

Use in the elderly: Elderly patients with a creatinine clearance of greater than 30 mL/minute/1.73 m^2 should receive the dosages recommended under Normal renal function.

Elderly patients with a creatinine clearance of 30 mL/minute/1.73 m2 or less should receive 400 mg once daily as recommended under 'Impaired renal function'.

Gastrointestinal infection: (Shigellosis, traveller's diarrhoea.) The recommended dosage is 400 mg twice daily for five days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.

Children; Pregnancy (see **Section 4.4 Special warnings and precaution for use and Section 4.6, Fertility, pregnancy and lactation; Pregnancy**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ROXIN, have been associated with disabling and persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Nervous system) and musculoskeletal system (see Effect on tendons).

Reserve fluoroquinolones for proven or suspected infections where alternative agents are ineffective or contraindicated.

Arthropathy

The oral administration of single doses of norfloxacin 100 mg/kg caused lameness in immature dogs. Histological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight bearing joints and other signs of arthropathy in immature animals of various species.

Crystalluria

Needle shaped crystals were found in the urine of some volunteers who received either placebo, norfloxacin 800 mg or norfloxacin 1,600 mg (at or twice the recommended daily dose, respectively) while participating in a double blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Antibiotic-associated colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including norfloxacin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antiobiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Nervous system

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. As with other

organic acids, norfloxacin should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis (see **Section 4.8 Adverse effects (Undesirable effects)**).

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Norfloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 Adverse effects (Undesirable effects)**).

Psychiatric Adverse Reactions

Fluoroquinolones, including norfloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving norfloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 Adverse effects (Undesirable effects)**).

Photosensitivity

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Effect on tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with fluoroquinolone therapy including norfloxacin. This risk is further increased in elderly patients and those treated concurrently with corticosteroids. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued at the first sign of pain, swelling, inflammation, or rupture of a tendon. Patients are advised to inform their health professional, rest the affected limb(s) and refrain from exercise.

Haemolytic reactions

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see **Section 4.8 Adverse effects (Undesirable effects)**).

Cardiac disorders

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking norfloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to norfloxacin has not yet been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalaemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents. Quinolones should also be used with caution in patients using cisapride, erythromycin, antipsychotics, tricyclic antidepressants or have any personal or family history of QTc prolongation.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Information for Patients

Patients should be advised to take norfloxacin 1 hour before or 2 hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

Use in renal impairment

Norfloxacin is suitable for the treatment of patients with renal impairment; however, since norfloxacin is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction. Alteration in dosage regimen is necessary for patients with impaired renal function (see **Section 4.2 Dose and method of administration**).

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore is not to be used in children less than 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use with norfloxacin. Therefore, cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives and phenindione or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glibenclamide (a sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Multivitamins, calcium preparations, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours, of the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Videx (didanosine) chewable/ buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within two hours of, the administration of norfloxacin, because these products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin.

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with norfloxacin and metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 500 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150 mg/kg/day with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100 to 800 mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

Use in lactation.

It is not known whether norfloxacin is excreted in human milk.

When a 200 mg dose of norfloxacin was administered to breastfeeding mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to discontinue the drug at least 24 to 48 hours before restarting breastfeeding, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Norfloxacin may cause dizziness or light-headedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and co-ordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1,127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1 to 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7% and dizziness 1.8%.

Additional reactions (0.3 to 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendinitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1,127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT and AST 1.8%, increased alkaline phosphatase 1.4%, and decreased white blood cell or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine and lactate dehydrogenase (LDH), and decreased haematocrit.

Postmarketing.

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions: These include anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia, interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin: Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central nervous system: Confusion, paraesthesia, polyneuropathy including Guillain-Barre syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver, gastrointestinal: Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice, elevated liver function tests.

Musculoskeletal: Tendinitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK), muscle spasms

Haematological: Agranulocytosis, Thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genitourinary: Vaginal candidiasis.

Renal function: Renal failure.

Metabolic: Dysglycaemia

Special senses: Dysgeusia, visual disturbances, Hearing loss

Causal relationship unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation and asthenia. On very rare occasions, hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema, proteinuria and transient hearing loss have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male and female mice and male and female rats were greater than 4 g/kg.

Treatment.

In the event of acute overdosage, absorption may be decreased by giving active charcoal, the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Norfloxacin has in vitro activity against a broad spectrum of Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to norfloxacin in *Escherichia coli* cells: inhibition of the ATP dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-12} cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following: *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter sp.*, *Enterococci*. For this reason,

when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active in vitro against the following organisms:

Bacteria found in urinary tract infections. Aerobic bacteria: Gram-positive bacteria including *Streptococcus faecalis* (Enterococcus), *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. Saprophyticus*. Gram-negative bacteria including *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*. Bacteria found in gastrointestinal infections: *Shigella*, *E. coli*, *Salmonella typhi*.

In addition, norfloxacin is active against *Neisseria gonorrhoeae*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MIC) to norfloxacin than nalidixic acid susceptible strains. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated.

This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in sites where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Animal Pharmacology

Norfloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50 mg/kg/day. In rats, crystals were reported following doses of 200 mg/kg/day.

Embryo lethality and slight maternotoxicity (vomiting and anorexia) were observed in cynomolgus monkeys at doses of 150 mg/kg/day or higher.

Ocular toxicity, seen with some related drugs, was not observed in any norfloxacin treated animals.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In fasting healthy volunteers, approximately 30 to 40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 and 400 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 microgram/mL are attained approximately one hour after dosing. The presence of food may decrease absorption. The effective half-life of norfloxacin in serum and plasma is three to four hours. Steady-state concentrations of norfloxacin will be attained within two days of dosing.

Distribution

The serum protein binding of norfloxacin is between 10 and 15%.

Metabolism

Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency.

Excretion

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/minute). Within 24 hours of drug administration, 26 to 32% of the administered dose is recovered in the urine as norfloxacin with an additional 5 to 8% being recovered in the urine as six metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400 mg dose, urinary concentrations of 200 microgram/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 microgram/mL for approximately twelve hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/minute/1.73 m2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/minute/1.73 m2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see **Section 4.2 Dose and method of administration**). Drug absorption appears unaffected by decreasing renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is four hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to norfloxacin 278, 773 and 82 microgram/g of faeces were obtained at 12, 24 and 48 hours, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500 to 1000 mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity

Information is not available at present on the carcinogenic potential of norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ROXIN tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

The tablets are gluten free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{O}C

6.5 NATURE AND CONTENTS OF CONTAINER

ROXIN tablets are available in bottle (HDPE) and blister* packs of 2*, 6* and 14 tablets.

*Currently not marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

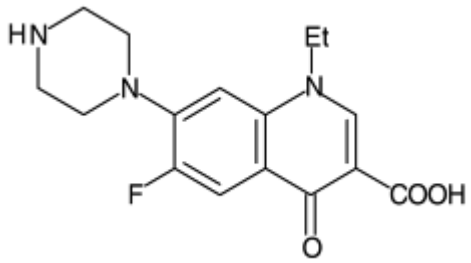
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Norfloxacin is a white to pale yellow crystalline powder. It is freely soluble in glacial acetic acid, and slightly soluble in ethanol, methanol and water.

Chemical structure

The chemical name for norfloxacin is 1-ethyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. Its structural formula is:



$C_{16}H_{18}FN_3O_3$ Molecular weight: 319.34

CAS number

CAS No.: 70458-96-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

21 August 2002

10 DATE OF REVISION

TBC

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Deletion of indication "Suppression, in adults of chronic, recurrent urinary tract infection"
4.2	Deletion of dosage instruction for "Suppression, in adults of chronic, recurrent urinary tract infection"
4.4	Added precautions - Aortic aneurysm and dissection - Dysglycaemia Psychiatric Adverse Reactions
n/a	Minor editorial changes