

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME


Arrow – Norfloxacin

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of norfloxacin.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

White, film-coated, convex, oval-shaped scored tablet, embossed with "N/F" on one side and '  ' on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Norfloxacin is a broad-spectrum bactericidal agent indicated for the treatment of:

- upper and lower, complicated and uncomplicated acute urinary tract infections including cystitis, pyelitis, cystopyelitis, pyelonephritis, chronic prostatitis, epididymitis, and those urinary infections associated with urologic surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to norfloxacin;
- acute bacterial gastroenteritis caused by susceptible organisms;
- gonococcal urethritis pharyngitis, proctitis or cervicitis caused by both penicillinase and non-penicillinase producing *Neisseria gonorrhoeae*.

Infections caused by multiply-resistant organisms have been successfully treated with the usual doses of norfloxacin.

### 4.2 Dose and method of administration

#### Dose

#### *Adults*

Susceptibility of the causative organism to norfloxacin should be tested prior to and during treatment if clinical response warrants. However, therapy may be initiated before obtaining the results of these tests. Maximum total daily dosage should not exceed 800 mg/day.

Diagnosis	Dosage	Therapy Duration
Urinary tract infections	400 mg twice daily	7 - 10 days
Uncomplicated acute cystitis	400 mg twice daily	3 - 7 days
Chronic prostatitis	400 mg twice daily	4 weeks
Acute bacterial gastroenteritis (shigellosis, traveller's diarrhoea)	400 mg twice daily	5 days
Acute gonococcal urethritis, pharyngitis, proctitis or cervicitis	800 mg	single dose

## **Special Populations**

### *Dosage in patients with impaired renal function*

Arrow - Norfloxacin is suitable for the treatment of patients with renal insufficiency. In studies involving patients whose creatinine clearance was less than 30 mL/minute/1.73 m<sup>2</sup>, but who did not require haemodialysis, the plasma half-life of norfloxacin was approximately 8 hours. Clinical studies showed that there was no difference in the mean half-life of norfloxacin in patients with creatinine clearance of less than 10 mL/minute/1.73 m<sup>2</sup>, compared to patients with creatinine clearance of 10 to 30 mL/minute/1.73 m<sup>2</sup>. Hence, for these patients, the recommended dose is one 400 mg tablet once daily. At this dosage, concentrations in appropriate body tissues or fluids exceed the MICs for most urinary pathogens sensitive to norfloxacin.

There are insufficient data on which to have a dosage recommendation for the treatment of gonorrhoea in patients with a creatinine clearance of 30 mL/minute/1.73 m<sup>2</sup> or less.

### **Method of administration**

Arrow - Norfloxacin should be taken with a glass of water at least one hour before or two hours after a meal or milk ingestion. Patients receiving norfloxacin should drink fluids liberally to be well hydrated. Multivitamins, products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate, or didanosine (tablets and solution) should not be taken concomitantly or within 2 hours after dosing norfloxacin (see section 4.5 Interactions with other medicines and other forms of interaction).

### **4.3 Contraindications**

Arrow - Norfloxacin should not be used in:

- patients with known hypersensitivity to norfloxacin, any chemically related quinoline antibacterials or any component of this product (see section 5.1 Pharmacodynamic properties);
- patients with a history of fluoroquinolone associated tendinopathy (see section 4.4 Special warnings and precautions for use);
- pre-pubertal children;
- pregnant women.

### **4.4 Special warnings and precautions for use**

Fluoroquinolones have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.

#### **Tendonitis and tendon rupture**

Norfloxacin should not be used in patients with a present or past injury, inflammation or rupture of the Achilles tendon (see section 4.3 Contraindications and section 4.8 Undesirable effects).

Tendonitis and/or tendon rupture (particularly Achilles tendon) may occur with quinolone antibiotics. The risk of tendonitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

On the appearance of tendon pain or signs of inflammation of the Achilles tendon, treatment with norfloxacin must be discontinued immediately and the patient treated accordingly. Corticosteroids should not be used if signs of tendinopathy occur.

### **Peripheral Neuropathy**

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including norfloxacin. Symptoms may occur soon after initiation of norfloxacin and may be irreversible.

Patients under treatment with norfloxacin should be advised to inform their doctor if symptoms of neuropathy such as pain, burning, tingling, numbness or weakness or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation develop.

Norfloxacin should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy and the patient should be changed to a non-fluoroquinolone antibiotic.

### **Hypersensitivity reactions**

Norfloxacin can cause serious, potentially fatal hypersensitivity reactions (anaphylactic and anaphylactoid reactions), occasionally following the initial dose (see section 4.8 Undesirable effects). Patients should be advised to discontinue treatment immediately if experiencing such reactions and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

### **Crystalluria**

In case of prolonged treatment, the occurrence of crystalluria should be monitored. While crystalluria is not expected to occur under normal conditions, with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the intake of sufficient fluids should be guaranteed to ensure a proper state of hydration and adequate urinary output.

### **Pseudomembranous colitis**

The occurrence of severe and persistent diarrhoea during or after therapy may be an evidence for rarely observed pseudomembranous colitis. In such cases, therapy must be stopped immediately and a suitable therapy (e.g. vancomycin, 4 x 250 mg by oral route) has to be started. Drugs inhibiting peristalsis are contraindicated.

### **Use in patients with epilepsy and other CNS disorders**

Norfloxacin should only be used if there is an overwhelming clinical need in patients with known epilepsy or disorders which lower the seizure threshold. Convulsions have been reported in rare cases in patients receiving norfloxacin. Norfloxacin may lead to exacerbation and aggravation of the symptoms in patients with known or suspected psychiatric disorders, hallucinations and/or confusion.

In case of convulsive seizures, treatment with norfloxacin should be discontinued.

### **Photosensitivity**

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving fluoroquinolones. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

### **G6PD-(Glucose-6-phosphate-dehydrogenase) deficiency**

In patients with latent or actual glucose-6-phosphate dehydrogenase deficiency, quinolone class haemolytic reactions are possible.

### **Use in patients with myasthenia gravis**

Norfloxacin can exacerbate the symptoms of myasthenia gravis which may result in life-threatening weakness of the respiratory muscles. Adequate counter measures should be taken at any sign of respiratory distress.

### **Cardiac disorders**

Caution should be taken when using fluoroquinolones, including norfloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including norfloxacin, in these populations (see section 4.2 Dose and method of administration, section 4.5 Interaction with other medicines and other forms of interaction, section 4.8 Undesirable effects and section 4.9 Overdose).

### **Aortic aneurysm and dissection**

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.

### **Use in renal impairment**

In patients with severe renal impairment, the risk/benefit ratio of using norfloxacin should be carefully weighed for the individual (see section 4.2 Dose and method of administration). The urinary concentration of norfloxacin may be reduced in patients with severely impaired renal function as norfloxacin is predominantly excreted via the kidneys.

### **Cholestatic hepatitis**

Cholestatic hepatitis is commonly reported with norfloxacin (see section 4.8 Undesirable effects).

Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

### **Vision disorders**

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

### **Dysglycaemia**

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8 Undesirable effects), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

## **4.5 Interaction with other medicines and other forms of interaction**

### *Drugs known to prolong QT interval*

Norfloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4 Special warnings and precautions for use).

### *Probenecid*

Co-administration of probenecid does not affect serum concentrations of norfloxacin, but urinary excretion of the drug diminishes.

### *Nitrofurantoin*

As with other organic acid antibacterials, antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

### *Medicines metabolised by CYP 1A2*

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.

### *Theophylline*

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

### *Caffeine*

The metabolism of caffeine has been shown to be inhibited by quinolones and also by norfloxacin. This can result in delayed elimination and prolonged plasma half-life of caffeine. During treatment with norfloxacin, the ingestion of caffeine-containing medications (eg. certain analgesics) should be avoided where possible.

### *Cyclosporin*

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

### *Warfarin and other coumarin oral anticoagulants*

Quinolones, including norfloxacin, may enhance the effects of oral anticoagulants including warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation parameters should be closely monitored.

### *Fenbufen*

On the basis of animal studies, concomitant administration of quinolones and fenbufen can cause seizures. Co-administration of quinolones and fenbufen should therefore be avoided.

### *Mycophenolic acid, mycophenolate mofetil*

A decreased bioavailability of mycophenolic acid has been found in healthy volunteers who received combination treatment with norfloxacin and metronidazole.

### *Glibenclamide*

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

### *Other interactions*

Multivitamins, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within 2 hours of, the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Oral nutritional solutions and dairy products (milk or milk products such as yoghurt) reduce the absorption of norfloxacin. Arrow - Norfloxacin should therefore be taken at least 1 hour before or 2 hours after such products.

Didanosine (*Videx*) chewable buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within 2 hours of, the administration of norfloxacin, because these products may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of stimulation of central nervous system and convulsive seizures. Arrow - Norfloxacin should be used with caution in individuals receiving NSAIDs concomitantly.

Animal data have shown that quinolones in combination with fenbufen can lead to seizures. Concomitant administration of quinolones and fenbufen should be avoided.

#### **4.6 Fertility, pregnancy and lactation**

##### **Use in pregnancy (Category B3)**

Pregnant women should not be prescribed norfloxacin as there are insufficient findings on safety of use in these groups of subjects and, on the basis of results from animal studies, damage to the articular cartilage in the immature organism cannot completely be excluded. Animal studies has not shown any evidence of teratogenic effects. Norfloxacin passes into umbilical blood and amniotic fluid.

##### **Use in lactation**

It is generally known that quinolones pass into mother's milk. In case of treatment of breast-feeding mothers with norfloxacin, breast feeding must be stopped.

##### **Fertility**

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

##### **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, norfloxacin is not to be used in pre-pubertal children or growing adolescents (see section 4.3 Contraindications and section 5.3 Preclinical safety data).

#### **4.7 Effects on ability to drive and use machines**

Norfloxacin may alter a patient's reactivity so that the ability to drive, operate machinery or work without firm support is impaired, especially at the start of treatment, on increasing dosage or when switching medication and in conjunction with alcohol.

#### **4.8 Undesirable effects**

##### **List of adverse reactions**

The frequencies of adverse events are ranked according to the following: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

##### *Blood and lymphatic system disorders*

Uncommon: Leucopenia, neutropenia, eosinophilia, thrombocytopenia, reduced haematocrit, prolongation of prothrombin time

Rare: Haemolytic anaemia, sometimes associated with Glucose-6-phosphate-dehydrogenase deficiency

##### *Immune system disorders*

Rare: Anaphylactic/anaphylactoid reactions (see section 4.4 Special warnings and precautions for use).

Not known: Hypersensitivity

*Metabolism and nutrition disorders*

Rare: Decreased appetite

Not known: Hypoglycaemic coma (see section 4.4 Special warnings and precautions for use).

*Psychiatric disorders\**

Rare: Changes of mood, depression, feeling of anxiety, nervousness, irritability, euphoria, disorientation, hallucinations, confusion, mental disorder, psychotic disorder, insomnia, sleep disorder

*Nervous system disorders\**

Uncommon: Headache, dizziness and drowsiness

Rare: Paresthesia, polyneuropathy including Guillain-Barré syndrome and seizures, and possible exacerbation of myasthenia gravis (see section 4.4 Special warnings and precautions for use)

*Eye disorders\**

Rare: Visual disturbance, increased lacrimation

*Ear and labyrinth disorders\**

Rare: Tinnitus

*Cardiac disorders\*\**

Not known: Tachycardia; ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see sections 4.4 Special warnings and precautions for use and 4.9 Overdose).

*Vascular disorders\*\**

Rare: Vasculitis

*Gastrointestinal disorders*

Uncommon: Abdominal pain and cramps, dyspepsia, diarrhoea and nausea

Rare: Vomiting, pseudomembranous colitis (see section 4.4 Special warnings and precautions for use), pancreatitis

*Hepatobiliary disorders*

Common: Cholestatic hepatitis (see section 4.4 Special warnings and precautions for use), hepatitis.

Uncommon: Elevation of ALT (SGOT), AST (SGPT) and alkaline phosphatase.

Not known: Jaundice

*Skin and subcutaneous tissue disorders*

Uncommon: Rash

Rare: Skin reactions, exfoliative dermatitis, toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme (Stevens-Johnson syndrome), photosensitivity (see section 4.4 Special warnings and precautions for use"), pruritus, urticaria, angioedema, petechiae, bullous haemorrhagic dermatosis

*Musculoskeletal and connective tissue disorders\**

Common: Rhabdomyolysis

Rare: Tendinitis, tendosynovitis (see section 4.4 Special warnings and precautions for use), myalgia, arthralgia, arthritis

Very rare: Rupture of tendons (e.g. Achilles tendon) (see section 4.4 Special warnings and precautions for use)

#### *Renal and urinary disorders*

Uncommon: Crystalluria

Rare: Tubulointerstitial nephritis

#### *Reproductive system and breast disorders*

Rare: Vaginal candidiasis

#### *General disorders and administration site conditions\**

Rare: Fatigue

#### *Investigations*

Uncommon: Haemotocrit decreased, prothrombin time prolonged, aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased

\* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4 Special warnings and precautions for use).

\*\* Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4 Special warnings and precautions for use).

### **Description of selected adverse reactions**

Photosensitivity has been observed in patients who, during ongoing therapy with quinolone-like medications, have been extensively exposed to sunlight or sunbeds (phototoxic reactions, photosensitisation with vesiculation, redness, swelling and discoloration) (see section 4.4 Special warnings and precautions for use).

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (<https://nzphvc.otago.ac.nz/reporting/>).

### **4.9 Overdose**

In the event of acute overdosage, symptomatic treatment should be implemented.

The stomach should be emptied by induced vomiting or by gastric lavage. The patient should be carefully observed and given symptomatic and supportive treatment as required. Adequate hydration must be maintained to prevent crystalluria. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

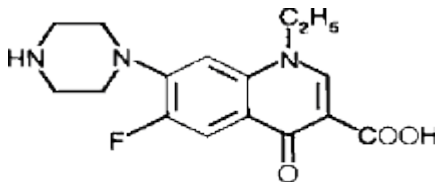


## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, Fluoroquinolones; ATC code: J01MA06

The chemical name for 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid. Its structural formula is:



C<sub>16</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub>      Molecular weight: 319.34      CAS: 70458-96-7

Norfloxacin is a synthetic fluoroquinolone, differs from quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position. It is a white to pale yellow crystalline powder, freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.

Norfloxacin has a broad spectrum of antibacterial activity against Gram-negative and some Gram-positive aerobic pathogens. The fluorine atom at the 6 position provides increased potency against Gram-negative organisms and the piperazine moiety at the 7 position is responsible for anti-pseudomonal activity.

#### Microbiology

Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level, three specific events were attributed to norfloxacin in *Escherichia coli* cells:

1. inhibition of the ATP-dependent DNA supercoiling reaction catalysed by DNA gyrase;
2. inhibition of the relaxation of supercoiled DNA; and
3. promotion of double-stranded DNA breakage.

Resistance to norfloxacin due to spontaneous mutation is a rare occurrence (range from 10<sup>-9</sup> to 10<sup>-12</sup> cells). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients being treated. Organisms in which development of resistance is greatest are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter spp.*, *Enterococci* and *Methicillin-resistant Staphylococcus aureus*. For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Because of its specific structure, norfloxacin is generally active against organisms that are resistant to other organic acids such as nalidixic, oxolinic, and pipemidic acids, cinoxacin and flumequine. Organisms resistant to norfloxacin *in vitro* are also resistant to these organic acids. Preliminary studies suggest that norfloxacin-resistant organisms are also generally resistant to pefloxacin, ofloxacin, ciprofloxacin and enoxacin. There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to aminoglycosides (including gentamicin), aminocyclitols (spectinomycin), penicillins, cephalosporins, tetracyclines, macrolides, sulfonamides (including combinations of sulfamethoxazole and trimethoprim), and 2,4-diaminopyrimidines.

Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Analysis of the overall clinical experience with norfloxacin revealed a high correlation between the results of susceptibility tests conducted *in vitro* and the bacteriological and clinical efficacy of the agent in humans. Norfloxacin is active *in vitro* against the following bacteria:

### **Bacteria found in urinary tract infections**

#### *Enterobacteriaceae*

Citrobacter spp.; Citrobacter koseri (formerly known as Citrobacter diversus); Citrobacter freundii; Edwardsiella tarda; Enterobacter spp.; Enterobacter aerogenes; Enterobacter agglomerans; Enterobacter cloacae; Escherichia coli; Hafnia alvei; Klebsiella spp.; Klebsiella oxytoca; Klebsiella pneumoniae; Morganella morganii; Proteus spp. (indole positive); Proteus mirabilis; Proteus vulgaris; Providencia spp.; Providencia rettgeri; Providencia stuartii; Serratia spp.; Serratia marcescens.

#### *Pseudomonadaceae*

Pseudomonas aeruginosa; Pseudomonas cepacia; Pseudomonas fluorescens; Pseudomonas stutzeri.

#### *Gram-positive cocci*

Enterococcus faecalis; Group G streptococci; Staphylococcus spp.; Staphylococcus Coag. Negative; Staphylococcus aureus (including penicillinase-producing and most methicillin-resistant strains); Staphylococcus epidermidis; Staphylococcus saprophyticus; Streptococcus agalactiae; Viridans group streptococci.

#### *Other*

Flavobacterium spp.

### **Bacteria associated with acute gastroenteritis**

Aeromonas hydrophila; Campylobacter foetus subsp. Jejuni; enterotoxigenic Escherichia coli; Plesiomonas shigelloides; Salmonella spp.; Salmonella typhi; Shigella spp.; Shigella boydii; Shigella dysenteriae; Shigella flexneri; Shigella sonnei; Vibrio cholerae; Vibrio parahemolyticus; Yersinia enterocolitica.

### **Other bacteria**

Norfloxacin is active against Bacillus cereus, Neisseria gonorrhoeae, Ureaplasma urealyticum, Haemophilus influenzae and Haemophilus ducreyi.

Norfloxacin is not active against anaerobes, including Actinomyces spp., Fusobacterium spp. Bacteroides spp. and Clostridium spp. other than C. perfringens.

### **Susceptibility testing**

The FDA standardised disc (formerly, Kirby-Bauer) technique of antibiotic susceptibility testing is recommended using a 10 mcg disc of 6 mm diameter.

<b>Category</b>	<b>Zone Diameter (mm)</b>	<b>MIC (mcg/mL)</b>
Susceptible	> 17	< 4
Intermediate	13 - 16	8
Resistant	< 12	> 16

MIC = Minimum inhibitory concentration

These susceptibility criteria apply only to organisms isolated from urine (urinary tract) and faeces (gastrointestinal tract).

*Neisseria gonorrhoeae* and organisms isolated from tissues are considered susceptible to norfloxacin if the zone diameter is > 21 mm or minimum inhibitory concentration (MIC) < 1 mcg/mL.

Norfloxacin susceptibility test results should not be used to predict susceptibility to other less potent quinoline antibacterial agents such as nalidixic acid.

Following a single 400 mg dose of norfloxacin, the disposition of the drug in patients with creatinine clearance greater than 30 mL/minute/1.73 m<sup>2</sup> is similar to that of healthy volunteers. In patients with creatinine clearance less than 30 mL/minute/1.73 m<sup>2</sup>, the renal elimination of norfloxacin decreases significantly. The effective serum half-life in these patients is approximately 8 hours. Thus, alteration of dosage is necessary (see section 4.2 Dose and method of administration). Norfloxacin absorption appears, however, 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. The effective half-life of norfloxacin in these elderly subjects is 4 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 278, 773 and 82 mcg norfloxacin/g faeces were obtained at 12, 24 and 48 hours, respectively.

## **5.2 Pharmacokinetic properties**

### Absorption

Norfloxacin is rapidly absorbed following oral administration. In healthy volunteers, at least 30 to 40% of an oral dose of norfloxacin is absorbed. This results in a serum concentration of 1.5 mcg/mL being attained approximately 1 hour after administration of a 400 mg dose. Peak serum levels of norfloxacin are slightly lower when administered with food than when given fasting. Mean serum half-life is 3 to 4 hours and is independent of dose. Steady-state concentrations of norfloxacin will be attained within 2 days of dosing.

### Distribution

The following are the mean concentrations of norfloxacin in various fluids and tissues measured 1 to 4 hours after two 400 mg doses, unless otherwise indicated:

Renal parenchyma 7.3 mcg/g

Prostate 2.5 mcg/g

Seminal fluid 2.7 mcg/mL

Testicle 1.6 mcg/g

Uterus/cervix 3.0 mcg/g

Vagina 4.3 mcg/g

Fallopian tube 1.9 mcg/g

Gallbladder tissue 1.8 mcg/g (measured 4 to 6 hours after one 400 mg dose)

Bile 6.9 mcg/mL (after two 200 mg doses).

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

Two to three hours after a single 400 mg dose, urinary concentrations reach a value of 200 or more mcg/mL in healthy volunteers and remain above 30 mcg/mL for at least 12 hours. While the bactericidal potency of norfloxacin is not affected by the pH of urine, the urinary pH may affect its solubility. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

### Metabolism and Elimination

Norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and net tubular secretion, as evidenced by the high rate of renal clearance (approximately 275 mL/minute). In the first 24 hours, 33 to 48% is recovered in the urine as norfloxacin. Six active

metabolites of norfloxacin (5 to 8%) of lesser antimicrobial potency are also recovered in the urine. The parent compound accounts for over 70% of total excretion.

### **5.3 Preclinical safety data**

No information is available on the carcinogenic potential of norfloxacin.

No significant lethality was observed in male and female mice and rats at single oral doses up to 4 g/kg.

#### **Animal toxicology**

Norfloxacin and related medicines have been shown to cause arthropathy in immature animals of most species tested. The oral administration of single doses of 100 mg/kg norfloxacin, six times the recommended human clinical dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage.

Related medicines (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. Dogs 6 months or older were not susceptible to these changes.

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle-shaped 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.

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

Teratology studies in mice and rats and fertility studies in mice at oral doses of 30 to 50 times the usual dose for humans did not reveal teratogenic or foetal toxic effects. Embryotoxicity was observed in rabbits at doses of 100 mg/kg/day. This was secondary to maternal toxicity and it is a non-specific antimicrobial effect in the rabbit due to an unusual sensitivity to antibiotic induced changes in the gut microflora.

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.

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

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).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry AMB OY-B-28920.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

Blister pack: 18 months

Bottle: 24 months

### **6.4 Special precautions for storage**

Blister pack: Store at or below 30°C.

Bottle: Store at or below 25°C.

### **6.5 Nature and contents of container**

Blister packs. Pack size of 6 tablets.

Bottles. Pack size of 100 tablets.

**Not all pack types or pack sizes may be marketed.**

### **6.6 Special precautions for disposal**

No special requirements for disposal.

## **7. MEDICINE SCHEDULE**

Prescription Medicine

## **8. SPONSOR**

Teva Pharma (New Zealand) Limited

PO Box 128 244

Remuera

Auckland 1541

Telephone: 0800 800 097

## **9. DATE OF FIRST APPROVAL**

13 October 2005

## **10. DATE OF REVISION OF THE TEXT**

9 November 2020

## **SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
4.4, 4.5, 4.8 & 4.9	Safety information aligned with Company Core Safety Information No. 308/11/10/20.