NORFLOX Tablets (Norfloxacin + Lactic acid bacillus)

**Black Box Warning**
Serious Adverse Reactions Including Tendinitis, Tendon Rupture, Peripheral Neuropathy, Central Nervous System Effects And Exacerbation Of Myasthenia Gravis
See full prescribing information for complete boxed warning
Fluoroquinolones, including norfloxacin have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:
  o Tendinitis and tendon rupture
  o Peripheral neuropathy
  o Central nervous system effects
Discontinue norfloxacin immediately and avoid the use of fluoroquinolones, including Ciprofloxacin, in patients who experience any of these serious adverse reactions.
Fluoroquinolones, including norfloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid norfloxacin in patients with known history of myasthenia gravis.
Because fluoroquinolones, including norfloxacin, have been associated with serious adverse reactions, reserve norfloxacin for use in patients who have no alternative treatment options for uncomplicated urinary tract infections (including cystitis).
This drug may cause low blood sugar and mental health related side effects.

**Composition**

**NORFLOX 100 DT**
Each uncoated dispersible tablet contains:
Norfloxacin, IP .......... 100 mg
Lactic acid Bacillus ..... $6 \times 10^6$ spores
(Appropriate overages added)
Colours: Titanium Dioxide FCF and Lake Sunset Yellow FCF

**NORFLOX 200 Tablets**
Each film-coated tablet contains:
Norfloxacin, IP .......... 200 mg
Lactic acid Bacillus ..... $6 \times 10^6$ spores
(Appropriate overages added)
Colours: Titanium Dioxide and Lake Sunset Yellow FCF

**NORFLOX 400 Tablets**
Each film-coated tablet contains:
Norfloxacin, IP .......... 400 mg
Lactic acid Bacillus ..... $120 \times 10^6$ spores
(Appropriate overages added)
Colours: Titanium Dioxide and Lake Sunset Yellow FCF
Norfloxacin has in vitro activity against a broad range of Gram-positive and Gram-negative aerobic bacteria. 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 antipseudomonal activity.

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 catalyzed 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). Resistant organisms have emerged during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are as follows:

- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Acinetobacter* spp.
- *Enterococcus* spp.

For this reason, when there is a lack of satisfactory clinical response, repeat culture and susceptibility testing should be done. Nalidixic acid-resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MICs) to norfloxacin than nalidixic acid-susceptible strains. There is generally no cross-resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin may demonstrate activity against indicated organisms resistant to some other antimicrobial agents, including the aminoglycosides, penicillins, cephalosporins, tetracyclines, macrolides, and sulphonamides, including combinations of sulphamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Norfloxacin has in vitro activity against a broad range of gram-positive and gram-negative aerobic bacteria. Norfloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections:

- **Gram-positive Aerobes**
  - *Enterococcus faecalis*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Staphylococcus saprophyticus*
  - *Streptococcus agalactiae*
- **Gram-negative Aerobes**
  - *Citrobacter freundii*
  - *Enterobacter aerogenes*
  - *Enterobacter cloacae*
Escherichia coli
Klebsiella pneumoniae
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens

The following in vitro data are available, but their clinical significance is unknown. Norfloxacin exhibits in vitro MICs of ≤4 μg/mL against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of norfloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-negative Aerobes
Citrobacter diversus
Edwardsiella tarda
Enterobacter agglomerans
Haemophilus ducreyi
Klebsiella oxytoca
Morganella morganii
Providencia alcalifaciens
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Pseudomonas stutzeri
Other
Ureaplasma urealyticum

Norfloxacin is not generally active against obligate anaerobes.
Norfloxacin has not been shown to be active against Treponema pallidum

Pharmacokinetics

In fasting healthy volunteers, at least 30-40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 mg, 400 mg and 800 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8, 1.5 and 2.4 μg/mL are attained approximately 1 hour after dosing. The presence of food and/or dairy products may decrease absorption. The effective half-life of norfloxacin in serum and plasma is 3-4 hours. Steady-state concentrations of norfloxacin will be attained within 2 days of dosing.

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchyma</td>
<td>7.3 μg/g</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.5 μg/g</td>
</tr>
<tr>
<td>Seminal fluid</td>
<td>2.7 μg/mL</td>
</tr>
<tr>
<td>Testicle</td>
<td>1.6 μg/g</td>
</tr>
<tr>
<td>Uterus/Cervix</td>
<td>3.0 μg/g</td>
</tr>
</tbody>
</table>
At 2–3 hours after a single 400 mg dose, urinary concentrations of 200 μg/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 μg/mL for at least 12 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 greater solubility occurring at pHs above and below this value. The serum protein binding of norfloxacin is between 10 and 15%.

Norfloxacin is eliminated through metabolism, biliary excretion, and renal excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to 278, 773, and 82 μg of norfloxacin/g of the faeces were obtained at 12, 24, and 48 hours, respectively. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/min). Within 24 hours of drug administration, 26–32% of the administered dose is recovered in the urine as norfloxacin with an additional 5–8% being recovered in the urine as six active metabolites of lesser antimicrobial potency. Only a small percentage (less than 1%) of the dose is recovered thereafter. Faecal recovery accounts for another 30% of the administered dose. In elderly subjects (average creatinine clearance 91 mL/min/1.73 m²), approximately 22% of the administered dose was recovered in urine, and renal clearance averaged 154 mL/min.

In healthy elderly volunteers (65–75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Following a single 400 mg dose of norfloxacin, a mean (± SD) AUC and C\text{max} of 9.8 (2.83) μg•hr/mL and 2.02 (0.77) μg/mL, respectively, were observed in healthy elderly volunteers. The extent of systemic exposure was slightly higher than that seen in younger adults (AUC, 6.4 μg•hr/mL; C\text{max}, 1.5 μg/mL). Drug absorption appears unaffected. However, the effective half-life of norfloxacin in these elderly subjects was 4 hours.

There is no information on accumulation of norfloxacin with repeated administration in elderly patients. However, no dosage adjustment is required based on age alone. In elderly patients with reduced renal function, the dosage should be adjusted as for other patients with renal impairment.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/min/1.73 m² is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/min/1.73 m², the renal elimination of norfloxacin decreases so that the effective serum half-life is 6.5 hours. In these patients, alteration of dosage is necessary. Drug absorption appears unaffected by decreasing renal function.

### Indications

NORFLOX tablet is indicated for: In the treatment of acute, uncomplicated, complicated, chronic & recurrent urinary tract infections including pyelonephritis, cystitis, urethritis and gonococcal infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to norfloxacin. Therapy with norfloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be given. Repeat culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agents but also on the possible emergence of bacterial resistance.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of norfloxacin and other antibacterial drugs, norfloxacin should be used only to treat or prevent infections that are proven or strongly suspected...
to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**Dosage And Administration**

Norfloxacin tablets should be taken at least 1 hour before, or at least 2 hours after a meal or ingestion of milk and/or other dairy products.

Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution should not be taken within 2 hours of administration of norfloxacin. Norfloxacin tablets should be taken with a glass of water. Patients receiving norfloxacin should be well hydrated.

Disperse the dispersible tablet in a teaspoonful (5 ml) of boiled and cooled water before administration.

<table>
<thead>
<tr>
<th>Normal Renal Function</th>
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Norfloxacin may be used for the treatment of UTIs in patients with renal impairment. In patients with a creatinine clearance rate of 30 mL/min/1.73 m² 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/min/1.73 m².

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.

<table>
<thead>
<tr>
<th>Renal Impairment</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Infection</th>
<th>Description</th>
<th>Unit Dose</th>
<th>Frequency</th>
<th>Duration</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTIs</td>
<td>Uncomplicated UTIs (cystitis) due to <em>Escherichia coli</em>, <em>Klebsiella pneumoniae</em>, or <em>Proteus mirabilis</em></td>
<td>400 mg</td>
<td>q12h</td>
<td>3 days</td>
<td>800 mg</td>
</tr>
<tr>
<td></td>
<td>Uncomplicated UTIs due to other indicated organisms</td>
<td>400 mg</td>
<td>q12h</td>
<td>7–10 days</td>
<td>800 mg</td>
</tr>
<tr>
<td></td>
<td>Complicated UTIs</td>
<td>400 mg</td>
<td>q12h</td>
<td>10–21 days</td>
<td>800 mg</td>
</tr>
<tr>
<td>Sexually Transmitted Diseases</td>
<td>Uncomplicated urethral and cervical gonorrhea caused by Neisseria gonorrhoeae</td>
<td>800 mg</td>
<td>Single dose</td>
<td>1 day</td>
<td>800 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Males:</th>
<th>(weight in kg) \times (140 - age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(72) \times \text{serum creatinine (mg/100 mL)}</td>
</tr>
<tr>
<td>Females:</td>
<td>(0.85) \times \text{(above value)}</td>
</tr>
</tbody>
</table>
Geriatric Use

Elderly patients being treated for UTIs, who have a creatinine clearance of greater than 30 mL/min/1.73 m², should receive the dosages recommended under Normal Renal Function.

Elderly patients being treated for UTIs, who have a creatinine clearance of 30 mL/min/1.73 m² or less, should receive 400 mg once daily as recommended under Renal Impairment.

Contraindications

Norfloxacin is contraindicated in persons with a history of hypersensitivity, tendinitis or tendon rupture associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents.

Warnings And Precautions

Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects

Fluoroquinolones, including norfloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting norfloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. Discontinue norfloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including norfloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Tendinitis and Tendon Rupture

Fluoroquinolones, including norfloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur within hours or days of starting norfloxacin, or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Discontinue norfloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including norfloxacin, in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Peripheral Neuropathy

Fluoroquinolones, including norfloxacin, have been associated with an increased risk of peripheral neuropathy. Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including norfloxacin. Symptoms may occur soon after initiation of norfloxacin and may be irreversible in some patients.
Discontinue norfloxacin immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation, and/or motor strength in order to minimize the development of an irreversible condition. Avoid fluoroquinolones, including norfloxacin, in patients who have previously experienced peripheral neuropathy.

Central Nervous System Effects

Fluoroquinolones, including norfloxacin, have been associated with an increased risk of central nervous system (CNS) effects, including convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychoses. Quinolones may also cause CNS stimulation which may lead to tremors, restlessness, lightheadedness, confusion, and hallucinations. If these reactions occur in patients receiving norfloxacin, the drug should be discontinued and appropriate measures instituted. The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Therefore, until more information becomes available, norfloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors which predispose to seizures.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including norfloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post-marketing serious adverse reactions, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid norfloxacin in patients with known history of myasthenia gravis.

Safety in Children, Adolescents, Nursing mothers, and during Pregnancy

The safety and efficacy of oral norfloxacin in pediatric patients, adolescents (under the age of 18), pregnant women, and nursing mothers have not been established. The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose (on a mg/kg basis), caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Other quinolones also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Other serious and sometimes fatal adverse reactions, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including norfloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: • fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity, and supportive measures should be instituted.

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy, including norfloxacin. Some reactions were accompanied by
cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions. If an allergic reaction to norfloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, including intubation, should be administered as indicated.

Clostridium Difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including norfloxacin and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated. Syphilis Treatment: Norfloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with norfloxacin should have a follow-up serologic test for syphilis after three months.

General

Needle-shaped crystals were found in the urine of some volunteers who received either placebo, 800 mg norfloxacin, or 1600 mg norfloxacin (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 b.i.d., 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. Alteration in dosage regimen is necessary for patients with impaired renal function. Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolone antibiotics after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs. Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6 phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin. Prescribing norfloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Serious Adverse Reactions

Advise patients to stop taking norfloxacin if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug. Inform patients of the following serious adverse reactions that have been associated with norfloxacin or other fluoroquinolone use: Disabling and potentially irreversible serious adverse reactions that may occur together: Inform patients that
disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of norfloxacin and may occur together in the same patient. Inform patients to stop taking norfloxacin immediately if they experience an adverse reaction and to call their healthcare provider.

Tendinitis and Tendon Rupture: instruct patients to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue norfloxacin treatment. The risk of severe tendon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Peripheral Neuropathies: Inform patients that peripheral neuropathies have been associated with the use of norfloxacin, that symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should immediately discontinue norfloxacin and contact their physicians.

Central Nervous System Effects (for example, convulsions, dizziness, light-headedness, increased intracranial pressure): Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including norfloxacin. Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to norfloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct patients to notify their physician if persistent headache with or without blurred vision occurs.

Exacerbation of Myasthenia Gravis: inform patients that fluoroquinolones like norfloxacin may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.

Hypersensitivity Reactions: Inform patients that norfloxacin can cause hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

Hepatotoxicity: Inform patients that severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking norfloxacin. Instruct patients to inform their physician if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.

Diarrhea: Inform patients that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more 8 months after having taken the last dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.

Prolongation of the QT interval: inform patients of the following:
that norfloxacin may cause changes in the electrocardiogram (QTc interval prolongation).
that norfloxacin should be avoided in patients receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents.
that norfloxacin should be used with caution in subjects receiving drugs that affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
to inform their physicians of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia or recent myocardial ischemia.
Photosensitivity/Phototoxicity: Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.

Other Information
Patients should be advised:

- to drink fluids liberally.
- that NORFLOXACIN should be taken at least one hour before or at least two hours after a meal or ingestion of milk and/or other dairy products.
- that multivitamins or other products containing iron or zinc, antacids or Didanosine, chewable/buffered tablets or the pediatric powder for oral solution, should not be taken within the two-hour period before or within the two-hour period after taking norfloxacin.
- that some quinolones may increase the effects of theophylline and/or caffeine
- that convulsions have been reported in patients taking quinolones, including norfloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Patients should be counseled that antibacterial drugs including norfloxacin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When norfloxacin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by norfloxacin or other antibacterial drugs in the future.

Laboratory Tests
As with any potent antibacterial agent, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions

Quinolones, including norfloxacin, have been shown in vitro to inhibit cytochrome (Cy) P1A2. Concomitant use with drugs metabolized 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 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 the dosage of theophylline adjusted as required. Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with norfloxacin. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of oral anticoagulants, including warfarin or its derivatives 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 glyburide (a sulphonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and
The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of norfloxacin in the urinary tract. Multivitamins, or other 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. Didanosine 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. Some quinolones have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of the 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.

**Pregnancy**

**Pregnancy Category C**

Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximum daily total human dose (on a mg/kg basis). At this dose, peak plasma levels obtained in monkeys were approximately 2 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 6-50 times the maximum daily human dose (on a mg/kg basis). There are no adequate and well-controlled studies in pregnant women. Norfloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Lactation**

It is not known whether norfloxacin is excreted in human milk. When a 200-mg dose of norfloxacin was administered to nursing 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 nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Paediatric Use**

The safety and effectiveness of oral norfloxacin in paediatric patients and adolescents below the age of 18 years have not been established. Norfloxacin causes arthropathy in juvenile animals of several animal species.

**Geriatric Use**

Geriatric patients are at increased risk for developing severe tendon disorders, including tendon rupture, when being treated with a fluoroquinolone such as norfloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles’ tendon, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing norfloxacin to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue norfloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur. Of the 340 subjects in one large clinical study of norfloxacin for treatment of UTIs, 103 patients were aged 65 years and
older, 77 of whom were aged 70 years and older; no overall differences in safety and effectiveness were evident between these subjects and younger subjects. In clinical practice, no difference in the type of reported adverse experiences have been observed between the elderly and younger patients except for a possible increased risk of tendon rupture in elderly patients receiving concomitant corticosteroids. In addition, an increased risk for other adverse experiences in some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. A pharmacokinetic study of norfloxacin in elderly volunteers (65 to 75 years of age with normal renal function for their age) was carried out.

In general, elderly patients may be more susceptible to the drug-associated effects of the QTc interval. Therefore, precaution should be taken when using norfloxacin concomitantly with drugs that can result in prolongation of the QTc interval (e.g. class IA or class III anti-arrhythmics) or in patients with risk factors for torsades de pointes (e.g. known QTc prolongation, uncorrected hypokalaemia).

Undesirable Effects

Single-Dose Studies

In clinical trials involving 82 healthy subjects and 228 patients with gonorrhoea, treated with a single dose of norfloxacin, 6.5% reported drug-related adverse experiences. However, the following incidence figures were calculated without reference to drug relationship.

The most common adverse experiences (>1.0%) were: dizziness (2.6%), nausea (2.6%), headache (2.0%), and abdominal cramping (1.6%).

Additional reactions (0.3–1.0%) were anorexia, diarrhoea, hyperhidrosis, asthenia, anal/rectal pain, constipation, dyspepsia, flatulence, tingling of the fingers, and vomiting.

Laboratory adverse changes considered drug-related were reported in 4.5% of patients/subjects. These laboratory changes were increased AST (SGOT) (1.6%), decreased WBCs (1.3%), decreased platelet count (1.0%), increased urine protein (1.0%), decreased haematocrit and haemoglobin (0.6%), and increased eosinophils (0.6%).

Multiple-Dose Studies

In clinical trials involving 52 healthy subjects and 1,980 patients with UTIs or prostatitis treated with multiple doses of norfloxacin, 3.6% reported drug-related adverse experiences. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (>1.0%) were: nausea (4.2%), headache (2.8%), dizziness (1.7%), and asthenia (1.3%).

Additional reactions (0.3–1.0%) were abdominal pain, back pain, constipation, diarrhoea, dry mouth, dyspepsia/heartburn, fever, flatulence, hyperhidrosis, loose stools, pruritus, rash, somnolence, and vomiting.

Less frequent reactions (0.1–0.2%) included abdominal swelling, allergies, anorexia, anxiety, bitter taste, blurred vision, bursitis, chest pain, chills, depression, dysmenorrhoea, oedema, erythema, foot or hand swelling, insomnia, mouth ulcer, myocardial infarction, palpitation, pruritus ani, renal colic, sleep disturbances, and urticaria.

Abnormal laboratory values observed in these patients/subjects were: eosinophilia (1.5%), elevation of ALT (SGPT) (1.4%), decreased WBCs and/or neutrophil count (1.4%), elevation of AST (SGOT) (1.4%), and increased alkaline phosphatase (1.1%). Those occurring less frequently included increased BUN, increased LDH, increased serum creatinine, decreased haematocrit, and glycosuria.
The most frequently reported adverse reaction in postmarketing experience was rash. CNS effects characterized as generalized seizures, myoclonus and tremors have been reported with norfloxacin. Visual disturbances have been reported with drugs in this class. The following additional adverse reactions have been reported since the drug was marketed:

**Hypersensitivity Reactions**
Hypersensitivity reactions have been reported, including anaphylactoid reactions, angio-oedema, dyspnoea, vasculitis, urticaria, arthritis, arthralgia, and myalgia.

**Skin**
Toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, exfoliative dermatitis, photosensitivity/phototoxicity reactions.

**Gastrointestinal**
Pseudomembranous colitis, hepatitis, jaundice, including cholestatic jaundice and elevated liver function tests, pancreatitis (rare), and stomatitis. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.

**Hepatic**
Hepatic failure, including fatal cases.

**Cardiovascular**
On rare occasions, prolonged QTc interval and ventricular arrhythmia, including *torsades de pointes*.

**Renal**
Interstitial nephritis, renal failure.

**Nervous System/Psychiatric**
Peripheral neuropathy, Guillain-Barré syndrome, ataxia, paraesthesia, hypoesthesia, psychic disturbances, including psychotic reactions and confusion.

**Musculoskeletal**
Tendinitis, tendon rupture; exacerbation of myasthenia gravis; elevated creatine kinase (CK).

**Haematologic**
Neutropenia; leucopenia; agranulocytosis; haemolytic anaemia, sometimes associated with glucose-6 phosphate dehydrogenase deficiency; thrombocytopenia.

**Special Senses**
Hearing loss, tinnitus, diplopia, dysgeusia.

Other adverse events reported with quinolones include the following: Agranulocytosis, albuminuria, candiduria, crystalluria, cylindruria, dysphagia, elevation of blood glucose, elevation of serum cholesterol, elevation of serum potassium, elevation of serum triglycerides, haematuria, hepatic necrosis, symptomatic hypoglycaemia, nystagmus, postural hypotension, prolongation of prothrombin time, and vaginal candidiasis.

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below:

- Disturbances in attention
- Disorientation
- Agitation
- Nervousness
- Memory impairment
Serious disturbances in mental abilities called delirium. If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

### Overdosage

No significant lethality was observed in male and female mice and rats at single oral doses up to 4 g/kg. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

### Storage And Handling Instructions

Store in a cool and dry place. Protect from moisture.

### Packaging Information

- NORFLOX 100: Blister pack of 10 dispersible tablets
- NORFLOX 200: Blister pack of 10 tablets
- NORFLOX 400: Blister pack of 10 tablets

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**NORFLOX Tablets**

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