TABLETS

NOROXIN®

(NORFLOXACIN)

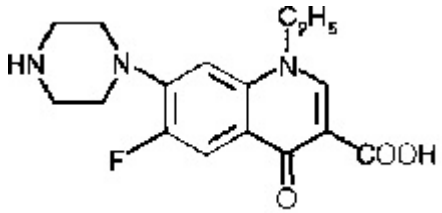
WARNING:
Fluoroquinolones, including NOROXIN, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see WARNINGS).

Fluoroquinolones, including NOROXIN, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid NOROXIN in patients with known history of myasthenia gravis (see WARNINGS).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NOROXIN® and other antibacterial drugs, NOROXIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

NOROXIN (Norfloxacin) is a synthetic, broad-spectrum antibacterial agent for oral administration. Norfloxacin, a fluoroquinolone, is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{16}H_{18}FN_3O_3$ and the structural formula is:



Norfloxacin is a white to pale yellow crystalline powder with a molecular weight of 319.34 and a melting point of about 221°C. It is freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.

NOROXIN is available in 400-mg tablets. Each tablet contains the following inactive ingredients: cellulose, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, and titanium dioxide.

Norfloxacin, a fluoroquinolone, differs from non-fluorinated quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position.

CLINICAL PHARMACOLOGY

In fasting healthy volunteers, at least 30-40% of an oral dose of NOROXIN 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 one 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 two days of dosing.

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, the mean (± SD) AUC and C_{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 and C_{max} 1.5 μg/mL). Drug absorption appears unaffected. However, the effective half-life of norfloxacin in these elderly subjects is 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 (see DOSAGE AND ADMINISTRATION, *Renal Impairment*).

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/min/1.73 m^2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/min/1.73 m^2, 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 (see DOSAGE AND ADMINISTRATION). Drug absorption appears unaffected by decreasing renal function.

Norfloxacin is eliminated through metabolism, biliary excretion, and renal excretion. After a single 400-mg dose of NOROXIN, mean antimicrobial activities equivalent to 278, 773, and 82 μg of norfloxacin/g of feces 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 to 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. Fecal recovery accounts for another 30% of the administered dose. In elderly subjects (average creatinine clearance 91 mL/min/1.73 m^2) approximately 22% of the administered dose was recovered in urine and renal clearance averaged 154 mL/min.

Two to three 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%.

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

Renal Parenchyma	7.3 μg/g
Prostate	2.5 μg/g
Seminal Fluid	2.7 μg/mL
Testicle	1.6 μg/g
Uterus/Cervix	3.0 μg/g
Vagina	4.3 μg/g
Fallopian Tube	1.9 μg/g
Bile	6.9 μg/mL (after two 200-mg doses)

Microbiology

Mechanism of Action

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

1) inhibition of the ATP-dependent DNA supercoiling reaction catalyzed by DNA gyrase,
2) inhibition of the relaxation of supercoiled DNA,
3) promotion of double-stranded DNA breakage.

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.

Drug Resistance

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 the following:

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 sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Activity *in vitro* and *in vivo*

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 as described in the **INDICATIONS AND USAGE** section.

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

NOROXIN is not generally active against obligate anaerobes.

Norfloxacin has not been shown to be active against *Treponema pallidum* (see WARNINGS).

Susceptibility Tests

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method{1} (broth, agar, or microdilution) or equivalent with standardized inoculum concentrations and standardized concentrations of norfloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure{2} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-μg norfloxacin to test the susceptibility of microorganisms to norfloxacin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-μg norfloxacin disk should be interpreted according to the criteria outlined in Table 1. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for norfloxacin.

Table 1: Susceptibility Interpretive Criteria for Norfloxacin

MIC (μg/mL)			Zone Diameter (mm)		
S	I	R	S	I	R

≤4	8	≥16	≥17	13-16	≤12

These interpretative criteria apply only to isolates from urinary tract infections. There are no established norfloxacin interpretive criteria for *Neisseria gonorrhoeae* or organisms isolated from other infection sites.

S=Susceptible, I=Intermediate, and R=Resistant

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 considered 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 situations 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.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard norfloxacin powder should provide the MIC values outlined in Table 2. For the diffusion techniques, the 10-μg norfloxacin disk should provide the zone diameters outlined in Table 2.

Table 2: Quality Control for Susceptibility Testing

Strains	MIC Range (μg/mL)	Zone Diameter (mm)
Enterococcus faecalis (ATCC 29212)	2 – 8	Not applicable
Escherichia coli (ATCC 25922)	0.03 – 0.12	28 – 35
P. aeruginosa (ATCC 27853)	1 – 4	22 – 29
Staphylococcus aureus (ATCC 29213)	0.5 – 2	Not applicable
Staphylococcus aureus (ATCC 25923)	Not applicable	17 – 28

INDICATIONS AND USAGE

NOROXIN is indicated for the treatment of adults with the following infections caused by susceptible strains of the designated microorganisms:

Urinary tract infections

Uncomplicated urinary tract infections (including cystitis) due to *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Citrobacter freundii*[1], *Enterobacter aerogenes*[1], *Enterobacter cloacae*[1], *Proteus vulgaris*[1], *Staphylococcus aureus*[1], or *Streptococcus agalactiae*[1].

Complicated urinary tract infections due to *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, or *Serratia marcescens*[1].

[1] Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Sexually transmitted diseases (see WARNINGS)

Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*.

Prostatitis

Prostatitis due to *Escherichia coli*.

(See DOSAGE AND ADMINISTRATION for appropriate dosing instructions.)

Penicillinase production should have no effect on norfloxacin activity.

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 NOROXIN and other antibacterial drugs, NOROXIN 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.

CONTRAINDICATIONS

NOROXIN (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

Tendinopathy and Tendon Rupture: Fluoroquinolones, including NOROXIN, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, 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. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. NOROXIN should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. 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.

Exacerbation of Myasthenia Gravis: Fluoroquinolones, including NOROXIN, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid NOROXIN in patients with known history of myasthenia gravis. (See PRECAUTIONS, *Information for Patients* and ADVERSE REACTIONS, Post-Marketing, *Musculoskeletal*.)

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. (See PRECAUTIONS, *Pediatric Use*, *Pregnancy*, and *Nursing Mothers* subsections.) The oral administration of single doses

of norfloxacin, 6 times[2] 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 (see ANIMAL PHARMACOLOGY).

Central Nervous System Effects/Disorders: Convulsions have been reported in patients receiving norfloxacin. Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychoses have been reported in patients receiving drugs in this class. Quinolones may also cause central nervous system (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 (see ADVERSE REACTIONS).

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including NOROXIN. 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.

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including NOROXIN. 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 (see PRECAUTIONS, *Information for Patients* and ADVERSE REACTIONS).

Clostridium Difficile Associated Diarrhea: Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including NOROXIN 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.

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[2] Based on a patient weight of 50 kg.

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. Norfloxacin should be discontinued 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..

*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.

PRECAUTIONS

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 (see DOSAGE AND ADMINISTRATION).

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 (see ADVERSE REACTIONS, *Post-Marketing*).

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 (see ADVERSE REACTIONS).

Prescribing NOROXIN 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.

Information for Patients

Patients should be advised:

— 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 NOROXIN 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.

— that fluoroquinolones like NOROXIN 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.

— 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.

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— to inform their physicians of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia or recent myocardial ischemia.
— that peripheral neuropathies have been associated with norfloxacin use,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.
— 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 Videx®[3] (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 (see PRECAUTIONS, *Drug Interactions*).
— that norfloxacin can cause dizziness and lightheadedness and, therefore, patients should know how they react to norfloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination.
— that norfloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
— that photosensitivity/phototoxicity has been reported in patients receiving quinolones. 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.
— that some quinolones may increase the effects of theophylline and/or caffeine (see PRECAUTIONS, *Drug Interactions*).
— 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.
— that diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting the treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including NOROXIN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When NOROXIN 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 NOROXIN 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 CYP1A2. 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.

[3] Registered trademark of Bristol-Myers Squibb Company

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 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 sulfonylurea agent) has, on rare occasions, resulted in severe hypoglycemia. 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 norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of NOROXIN 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.

Videx® (Didanosine) chewable/buffered tablets or the pediatric 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, NOROXIN should be used with caution in individuals receiving NSAIDS concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No increase in neoplastic changes was observed with norfloxacin as compared to controls in a study in rats, lasting up to 96 weeks at doses 8-9 times[2] the usual human dose (on a mg/kg basis).

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 doses 30-60 times[2] the usual human dose (on a mg/kg basis). Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test, Chinese hamster fibroblasts 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 30 times[2] the usual human dose (on a mg/kg basis).

Pregnancy

Teratogenic Effects. Pregnancy Category C. Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times[2] 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[2] the maximum daily human dose (on a mg/kg basis). There are, however, 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 fetus.

Nursing Mothers

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

When a 200-mg dose of NOROXIN 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.

Pediatric Use

The safety and effectiveness of oral norfloxacin in pediatric patients and adolescents below the age of 18 years have not been established. Norfloxacin causes arthropathy in juvenile animals of several animal species. (See WARNINGS and ANIMAL PHARMACOLOGY.)

Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as NOROXIN. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, 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 NOROXIN to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue NOROXIN and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (see Boxed Warning; WARNINGS; and ADVERSE REACTIONS, *Post-Marketing*).

Of the 340 subjects in one large clinical study of NOROXIN for treatment of urinary tract infections, 103 patients were 65 and older, 77 of whom were 70 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 (see WARNINGS). In addition, increased risk for other adverse experiences in some older individuals cannot be ruled out (see ADVERSE REACTIONS).

This drug is known to be substantially excreted by the kidney, 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 (see DOSAGE AND ADMINISTRATION).

A pharmacokinetic study of NOROXIN in elderly volunteers (65 to 75 years of age with normal renal function for their age) was carried out (see CLINICAL PHARMACOLOGY).

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

ADVERSE REACTIONS

Single-Dose Studies

In clinical trials involving 82 healthy subjects and 228 patients with gonorrhea, 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, diarrhea, 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 WBC (1.3%), decreased platelet count (1.0%), increased urine protein (1.0%), decreased hematocrit and hemoglobin (0.6%), and increased eosinophils (0.6%).

Multiple-Dose Studies

In clinical trials involving 52 healthy subjects and 1980 patients with urinary tract infections 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, diarrhea, 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, dysmenorrhea, edema, 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 WBC 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 hematocrit, and glycosuria.

Post-Marketing

The most frequently reported adverse reaction in post-marketing experience is rash.

CNS effects characterized as generalized seizures, myoclonus and tremors have been reported with NOROXIN (see WARNINGS). 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, angioedema, dyspnea, vasculitis, urticaria, arthritis, arthralgia and myalgia (see WARNINGS).

Skin

Toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, exfoliative dermatitis, photosensitivity/phototoxicity reactions (see PRECAUTIONS), leukocytoclastic vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Gastrointestinal

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

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 that may be irreversible, Guillain-Barré syndrome, ataxia, paresthesia, hypoesthesia, psychic disturbances including psychotic reactions and confusion.

Musculoskeletal

Tendinitis, tendon rupture; exacerbation of myasthenia gravis (see WARNINGS, *Exacerbation of myasthenia gravis*); elevated creatine kinase (CK), muscle spasms.

Hematologic

Neutropenia; leukopenia; agranulocytosis; hemolytic anemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency; thrombocytopenia.

Special Senses

Hearing loss, tinnitus, diplopia, dysgeusia. uveitis

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

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.

DOSAGE AND ADMINISTRATION

Tablets NOROXIN 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. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminum, sucralfate, or Videx® (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution, should not be taken within 2 hours of administration of norfloxacin. Tablets NOROXIN should be taken with a glass of water. Patients receiving NOROXIN should be well hydrated (see PRECAUTIONS).

Normal Renal Function

The recommended daily dose of NOROXIN is as described in the following chart:

Infection	Description	Unit Dose	Frequency	Duration	Daily Dose
Urinary Tract	Uncomplicated UTI's (cystitis) due to *E. coli*, *K. pneumoniae*, or *P. mirabilis*	400 mg	q12h	3 days	800 mg
	Uncomplicated UTI's due to other indicated organisms	400 mg	q12h	7-10 days	800 mg
	Complicated UTI's	400 mg	q12h	10-21 days	800 mg
Sexually Transmitted Diseases	Uncomplicated Gonorrhea	800 mg	single dose	1 day	800 mg
Prostatitis	Acute or Chronic	400 mg	q12h	28 days	800 mg

Renal Impairment

NOROXIN 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/min/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/min/1.73 m^2.

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.

Males: $$\frac{\text{(weight in kg)} \times \text{(140 – age)}}{\text{(72)} \times \text{serum creatinine (mg/100 mL)}}$$

Females: (0.85) × (above value)

Elderly

Elderly patients being treated for urinary tract infections who have a creatinine clearance of greater than 30 mL/min/1.73 m^2 should receive the dosages recommended under *Normal Renal Function*.

Elderly patients being treated for urinary tract infections who have a creatinine clearance of 30 mL/min/1.73 m^2 or less should receive 400 mg once daily as recommended under *Renal Impairment*.

HOW SUPPLIED

No. 8338 — Tablets NOROXIN 400 mg are white to off-white, oval shaped, film-coated tablets, coded 705 on one side and plain on the other. They are supplied as follows:

NDC 0006-0705-20 unit of use bottles of 20.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

ANIMAL PHARMACOLOGY

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

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.

REFERENCES

1. Clinical and Laboratory Standards Institute, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - Eighth edition, Approved Standard CLSI Document M7-A8, Vol. 29, No. 2, CLSI, Wayne, PA, 2009.
2. Clinical and Laboratory Standards Institute, Performance standards for antimicrobial disk susceptibility tests - Tenth edition, Approved Standard CLSI Document M2-A10, Vol. 29, No. 1, CLSI, Wayne, PA, 2009.

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MEDICATION GUIDE

NOROXIN® [nor-AHK-sin]
(norfloxacin)
Tablets

Read the Medication Guide that comes with NOROXIN® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about NOROXIN?

NOROXIN belongs to a class of antibiotics called fluoroquinolones. NOROXIN can cause side effects that may be serious or even cause death. If you develop any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take NOROXIN.

1. **Tendon rupture or swelling of the tendon (tendinitis)**
   - **Tendon problems can happen in people of all ages who take NOROXIN.** Tendons are tough cords of tissue that connect muscle to bones. Symptoms of tendon problems may include:
     - Pain, swelling, tears and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.
   - **The risk of getting tendon problems while you take NOROXIN is higher if you:**
     - are over 60 years of age
     - are taking steroids (corticosteroids)
     - have had a kidney, heart or lung transplant
   - **Tendon problems can happen in people who do not have the above risk factors when they take NOROXIN. Other reasons that can increase your risk of tendon problems can include:**
     - physical activity or exercise
     - kidney failure
     - tendon problems in the past, such as in people with rheumatoid arthritis (RA)
   - **Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation.** Stop taking NOROXIN until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons.
   - **Talk to your healthcare provider about the risk of tendon rupture with continued use of NOROXIN.** You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
   - **Tendon rupture can happen while you are taking or after you have finished taking NOROXIN.** Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
   - **Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:**
     - hear or feel a snap or pop in a tendon area
     - bruising right after an incident in a tendon area
     - unable to move the affected area or bear weight

2. **Worsening of myasthenia gravis (a disease which causes muscle weakness)**
   Fluoroquinolones like NOROXIN may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section "What are the possible side effects of NOROXIN?" for more information about side effects.

What is NOROXIN?

NOROXIN is a fluoroquinolone antibiotic medicine used in adults to treat certain infections caused by certain germs called bacteria. It is not known if NOROXIN is safe and works in children under 18 years of age. Children have a higher chance of getting bone and joint (musculoskeletal) problems while taking NOROXIN.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics including NOROXIN do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking NOROXIN.

Who should not take NOROXIN?

Do not take NOROXIN if you:

- have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in NOROXIN. Ask your healthcare provider if you are not sure. See the list of ingredients in NOROXIN at the end of this Medication Guide.
- have had tendinitis or tendon rupture with the use of NOROXIN or another fluoroquinolone antibiotic.

What should I tell my healthcare provider before taking NOROXIN?

See "**What is the most important information I should know about NOROXIN?**"

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QTc prolongation"
- have low potassium (hypokalemia)
- have a slow heartbeat called bradycardia
- have a history of seizures
- have kidney problems. You may need a lower dose of NOROXIN if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if NOROXIN will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if NOROXIN passes into breast milk. You and your healthcare provider should decide whether you will take NOROXIN or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal and dietary supplements. NOROXIN and other medicines[1] can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take NOROXIN or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "**What are the possible side effects of NOROXIN?**"
- glyburide (Micronase, Glynase, Diabeta, Glucovance). See "**What are the possible side effects of NOROXIN?**"
- a blood thinner (warfarin, Coumadin, Jantoven)
- a medicine to control your heart rate or rhythm (antiarrhythmics). See "**What are the possible side effects of NOROXIN?**"
- an anti-psychotic medicine
- a tricyclic antidepressant
- erythromycin
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury.
- probenecid (Probalan, Col-probenecid)
- cyclosporine (Gengraf, Sandimmune, Neoral)
- products that contain caffeine
- clozapine (Fazaclo ODT, Clozaril)
- ropinirole (Requip, Requip XL)
- tacrine (Cognex)
- tizanidine (Zanaflex)
- theophylline (Theo-24, Elixophyllin, Theochron, Uniphyl, Theolair)
- cisapride (Propulsid)
- certain medicines may keep NOROXIN from working correctly. Take NOROXIN either 2 hours before or 2 hours after taking these products:
  - an antacid, multivitamin or other product that has iron or zinc
  - sucralfate (Carafate)
  - didanosine (Videx, Videx EC)

- You should not take the medicine nitrofurantoin (Furadantin, Macrodantin, Macrobid) while taking NOROXIN.

Ask your healthcare provider if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take NOROXIN?

- Take NOROXIN exactly as prescribed by your healthcare provider.
- NOROXIN is usually taken every 12 hours for patients with normal kidney function.
- Take NOROXIN with a glass of water.
- Drink plenty of fluids while taking NOROXIN.
- Take NOROXIN at least one hour before or 2 hours after a meal or having milk or other dairy products.

[1] Other brands listed are the trademarks of their respective owners and are not trademarks of Merck Sharp & Dohme Corp.

- Do not skip any doses, or stop taking NOROXIN even if you begin to feel better, until you finish your prescribed treatment, unless:
  - you have tendon effects (see "**What is the most important information I should know about NOROXIN?**"),
  - you have a serious allergic reaction (see "**What are the possible side effects of NOROXIN?**"), or
  - your healthcare provider tells you to stop. This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to NOROXIN. If this happens, NOROXIN and other antibiotic medicines may not work in the future.
- If you miss a dose of NOROXIN, take it as soon as you remember. Do not take two doses of NOROXIN at the same time. Do not take more than 2 doses of NOROXIN in one day.
- If you take too much, call your healthcare provider or get medical help immediately.

What should I avoid while taking NOROXIN?

- NOROXIN can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how NOROXIN affects you.
- Avoid sunlamps and tanning beds, and try to limit your time in the sun. NOROXIN can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking NOROXIN, call your healthcare provider right away. You should use sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of NOROXIN?

NOROXIN can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about NOROXIN?**"

Other serious side effects of NOROXIN include:

- **Central Nervous System Effects.** Seizures have been reported in people who take fluoroquinolone antibiotics including NOROXIN. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking NOROXIN will change your risk of having a seizure.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of NOROXIN. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:
  - feel lightheaded
  - seizures
  - hear voices, see things, or sense things that are not there (hallucinations)
  - feel restless
  - tremors
  - feel anxious or nervous
  - confusion
  - feel more suspicious (paranoia)

- **Serious allergic reactions.** Allergic reactions can happen in people who take fluoroquinolones, including NOROXIN, even after only one dose. Stop taking NOROXIN and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - throat tightness, hoarseness

- rapid heartbeat
- faint
- skin rash accompanied by fever and feeling unwell
- yellowing of the skin or eyes. Stop taking NOROXIN and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to NOROXIN (a liver problem).

- **Skin rash.** Skin rash may happen in people taking NOROXIN, even after only one dose. Stop taking NOROXIN at the first sign of a skin rash and call your healthcare provider. Skin rash may be sign of a more serious reaction to NOROXIN.

- **Serious heart rhythm changes (QTc prolongation and torsade de pointes).** Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. NOROXIN may cause a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:
  - who are elderly
  - with a family history of prolonged QTc interval
  - with low blood potassium (hypokalemia)
  - who take certain medicines to control heart rhythm (antiarrhythmics)

- **Intestine infection (Pseudomembranous colitis).** Pseudomembranous colitis can happen with most antibiotics, including NOROXIN. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Changes in sensation and nerve damage (Peripheral Neuropathy).** Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including NOROXIN. Stop NOROXIN and talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
  - pain
  - burning
  - tingling
  - numbness
  - weakness

  The nerve damage may be permanent.

- **Low blood sugar (hypoglycemia).** People taking NOROXIN and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar while taking NOROXIN. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity).** See "**What should I avoid while taking NOROXIN?**"

The most common side effects of NOROXIN include:
- dizziness
- nausea
- diarrhea
- heartburn
- headache
- stomach (abdominal) cramping
- weakness

- changes in certain liver function tests

These are not all the possible side effects of NOROXIN. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NOROXIN?

Store between 59-86°F (15-30°C).
Keep container closed tightly.

Keep NOROXIN and all medicines out of the reach of children.

General Information about NOROXIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NOROXIN for a condition for which it is not prescribed. Do not give NOROXIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about NOROXIN. If you would like more information about NOROXIN, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NOROXIN that is written for healthcare professionals. For more information call 1-800-622-4477.

What are the ingredients in NOROXIN?

Active ingredient: norfloxacin

Inactive ingredients: cellulose, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate and titanium dioxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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