PHYSICIANS CIRCULAR

Tablets
NOROXIN®†
(norfloxacin, USP)

NOROXIN (norfloxacin, USP) is a quinolone carboxylic acid antibacterial agent for oral administration.

MICROBIOLOGY

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

NOROXIN inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level, three specific events were attributed to NOROXIN in *Escherichia 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.

Resistance to norfloxacin due to spontaneous mutation is a rare occurrence (range, 10^{-9} - 10^{-12}). Resistance of the organism has developed during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are the following:

Pseudomonas aeruginosa
Klebsiella pneumoniae
Acinetobacter spp.
Enterococci
Methicillin-resistant *Staphylococcus aureus*

Because of its specific structure, NOROXIN is generally active against organisms that are resistant to other organic acids such as nalidixic, oxolinic, and pipemidic acids, cinoxacin, and flumequine. Organisms resistant to norfloxacin *in vitro* are also resistant to these organic acids. Preliminary studies suggest that norfloxacin-resistant organisms are also generally resistant to pefloxacin, ofloxacin, ciprofloxacin and enoxacin. There is no cross-resistance between norfloxacin and structurally unrelated antibacterial agents such as penicillins, cephalosporins, tetracyclines, macrolides, aminocyclitols and sulfonamides, 2,4 diaminopyrimidines, or combinations thereof (e.g. co-trimoxazole).

Analysis of the overall clinical experience with NOROXIN revealed a high correlation between the results of susceptibility tests conducted *in vitro* and the bacteriological and clinical efficacy of the agent in humans.

NOROXIN is active *in vitro* against the following bacteria:
Bacteria found in urinary tract infections:

<u>Enterobacteriaceae</u>
Citrobacter spp.

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

Pseudomonadaceae
Pseudomonas aeruginosa
Pseudomonas cepacia
Pseudomonas fluorescens
Pseudomonas stutzeri

Other
Flavobacterium spp.

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

Bacteria associated with acute gastroenteritis:

Aeromonas hydrophila
Campylobacter fetus subsp. *jejuni*
Enterotoxigenic *Escherichia coli*
Plesiomonas shigelloides
Salmonella spp.
Salmonella typhi
Shigella spp.
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Vibrio cholerae
Vibrio parahaemolyticus
Yersinia enterocolitica

In addition, NOROXIN is active against *Bacillus cereus, Neisseria gonorrhoeae, Ureaplasma urealyticum, Haemophilus influenzae* and *Haemophilus ducreyi*.

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

INDICATIONS

NOROXIN is a broad-spectrum bactericidal agent indicated for:

The treatment of:

- Upper and lower, complicated and uncomplicated, acute and chronic urinary tract infections. These infections include cystitis, pyelitis, cystopyelitis, pyelonephritis, chronic prostatitis, epididymitis, and those urinary infections associated with urologic surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to NOROXIN.

- Acute bacterial gastroenteritis caused by susceptible organisms.

- Gonococcal urethritis, pharyngitis, proctitis or cervicitis caused by both penicillinase and non-penicillinase producing *Neisseria gonorrhoeae*.

- Typhoid fever.

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

The prophylaxis of:

- Sepsis in patients with profound neutropenia[*]. NOROXIN suppresses the endogenous aerobic bowel flora which may cause sepsis in patients with neutropenia (i.e., patients with leukemia who are receiving chemotherapy).

- Bacterial gastroenteritis.

[*] In clinical trials, profound neutropenia was defined as neutrophil count $\leq 100/mm^3$ for one week or longer.

DOSAGE AND ADMINISTRATION

NOROXIN should be taken with a glass of water at least one hour before or two hours after a meal or milk ingestion. 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.

Susceptibility of the causative organism to NOROXIN should be tested; however, therapy may be initiated before obtaining the results of these tests.

TREATMENT

DIAGNOSIS	DOSAGE	THERAPY DURATION
Urinary Tract Infections	400 mg b.i.d.	7-10 days
Uncomplicated Acute Cystitis	400 mg b.i.d.	3-7 days
Chronic Relapsing Urinary Tract Infection*	400 mg b.i.d.	up to 12 wks.**
Acute Bacterial Gastroenteritis	400 mg b.i.d.	5 days
Acute Gonococcal Urethritis, Pharyngitis, Proctitis or Cervicitis	800 mg	single dose
Typhoid Fever	400 mg t.i.d.	14 days

* If adequate suppression is obtained within the first 4 weeks of therapy, the dose of NOROXIN may be reduced to 400 mg daily.

** For chronic prostatitis, treatment for 4 weeks has been shown to be highly effective.

PROPHYLAXIS

	DOSAGE	THERAPY DURATION
Sepsis of profound neutropenia	400 mg t.i.d.	Duration of profound neutropenia*
Bacterial gastroenteritis	400 mg daily	Starting 24 hrs. prior to arrival and continuing 48 hrs. after departure from endemic areas

*Data for recommending treatment beyond eight weeks are presently not available.

RENAL IMPAIRMENT

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

There are insufficient data on which to have a dosage recommendation for the treatment of gonorrhea in patients with a creatinine clearance of 30 mL/min/1.73m^2 or less.

NOROXIN has not been studied in patients with typhoid fever with a creatinine clearance below 30 mL/min/1.73m^2.

CONTRAINDICATIONS

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

PRECAUTIONS

As with other organic acids, NOROXIN should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures. Convulsions have been reported rarely in patients receiving NOROXIN.

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

As with other quinolones, tendinitis and/or tendon rupture have been observed rarely in patients taking NOROXIN, especially when corticosteroids are taken concomitantly. If a patient develops symptoms of tendinitis and/or tendon rupture, NOROXIN should be discontinued immediately and the patient advised to seek appropriate medical management.

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 NOROXIN. (See Side Effects.)

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

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including NOROXIN, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis”.

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.

<u>RENAL IMPAIRMENT</u>

NOROXIN is suitable for the treatment of patients with renal impairment, however, since NOROXIN is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction (see DOSAGE AND ADMINISTRATION).

PREGNANCY

The safe use of NOROXIN in pregnant women has not been established and, consequently, the benefits of treatment with NOROXIN should be weighed against potential risks. NOROXIN has been detected in cord blood and amniotic fluid.

NURSING MOTHERS

When a 200 mg dose was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low and as many drugs are secreted in human milk, caution should be exercised when NOROXIN is administered to a nursing woman.

CHILDREN

Safety and efficacy in children have not been established; therefore, NOROXIN should not be used in prepubertal children.

DRIVING AND OPERATING MACHINERY

Norfloxacin may 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.

DRUG INTERACTIONS

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

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

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.

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

Elevated serum levels of cyclosporine have been reported with concomitant use 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 anticoagulant, including warfarin or its derivatives and fluindione 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.

Multivitamins, products containing iron or zinc, antacids, sucralfate, or 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 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.

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.

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

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

SIDE EFFECTS

NOROXIN generally is well tolerated. The overall incidence of drug related side effects reported during worldwide clinical trials involving 2346 patients was approximately 3%.

The most common side effects (less than 3% but occurring in >0.1% of the patients) have been gastrointestinal, neuropsychiatric and skin reactions, and include nausea, headache, dizziness, rash, heartburn, abdominal pain/cramps and diarrhea.

In very rare instances (<0.1%), other side effects such as anorexia, sleep disturbances, depression, anxiety/nervousness, irritability, euphoria, disorientation, hallucination, tinnitus and epiphora have been reported.

Abnormal laboratory side effects were rarely observed during clinical trials; however, the following have been reported with an incidence of <0.3%: leukopenia, eosinophilia, neutropenia, thrombocytopenia, elevation of ALT (SGPT), AST (SGOT).

The following additional side effects have been reported since the drug was marketed:

<u>HYPERSENSITIVITY REACTIONS</u>
Hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, vasculitis, urticaria, arthritis, myalgia, arthralgia and interstitial nephritis

<u>SKIN</u>
Photosensitivity
Stevens-Johnson Syndrome

Toxic Epidermal Necrolysis
Exfoliative dermatitis
Erythema multiforme
Pruritus

GASTROINTESTINAL
Pseudomembranous colitis
Pancreatitis (rare)
Hepatitis, jaundice, including cholestatic jaundice and elevated liver function tests

MUSCULOSKELETAL
Tendinitis
Tendon rupture
Exacerbation of myasthenia gravis
Elevated creatine kinase (CK)

NERVOUS SYSTEM/PSYCHIATRIC
Polyneuropathy including Guillain-Barré syndrome
Confusion
Paresthesia
Hypoesthesia
Psychic disturbances including psychotic reactions
Convulsions
Tremors
Myoclonus

HEMATOLOGIC
Agranulocytosis
Hemolytic anemia, sometimes associated with glucose 6 phosphate dehydrogenase deficiency

GENITOURINARY
Vaginal candidiasis

RENAL FUNCTION
Renal failure

SPECIAL SENSES
Dysgeusia
Visual disturbances
Hearing loss

OVERDOSAGE

No specific information is available on the treatment of overdosage with NOROXIN. Adequate hydration must be maintained.

AVAILABILITY

Noroxin Tablets are supplied in blister of 14 tablets (2X 7's). Each tablet contains (norfloxacin, USP) equivalent to 400mg Norfloxacin, USP.