

DATA SHEET

NORFLOXACIN

Norfloxacin (Ph. Eur./BP)

Presentation

White oval shaped, film coated tablets with 'CD' engraved on one side and bisect line on the other side.

Each tablet contains 400 mg of norfloxacin.

Uses

Actions

Microbiology: NORFLOXACIN is a broad spectrum fluoroquinolone antibiotic with 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 of norfloxacin.

NORFLOXACIN is a bactericidal, inhibiting the bacterial deoxyribonucleic acid synthesis. At the molecular level, three specific events were attributed to NORFLOXACIN in *Escherichia coli* cells: inhibition of the ATP-dependent DNA supercoiling reaction catalysed by DNA gyrase; inhibition of the relaxation of supercoiled DNA; promotion of double-stranded DNA breakage.

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

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

Because of its specific structure, NORFLOXACIN is generally active against organisms that are resistant to other organic acids such as nalidixic, oxolinic, and pipemidic acids, cinoxacin, and flumequine. Organisms resistant to norfloxacin *in vitro* are also resistant to these organic acids. Preliminary studies suggest that norfloxacin-resistant organisms are also generally resistant to pefloxacin, ofloxacin, ciprofloxacin and enoxacin. There is 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 (eg. cotrimoxazole).

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

NORFLOXACIN is active *in vitro* against the following bacteria:

BACTERIA FOUND IN URINARY TRACT INFECTIONS:

Enterobacteriaceae:

- Citrobacter spp.
- *Citrobacter 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 GASTRO-ENTERITIS

- *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, NORFLOXACIN is active against *Bacillus cereus*, *Neisseria gonorrhoeae*, *Ureaplasma urealyticum*, *Haemophilus influenzae* and *Haemophilus ducreyi*.

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

SUSCEPTIBILITY TESTING

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

Category	Zone Diameter (mm)	MIC (µg/ml)
Susceptible	≥ 17	≤ 4
Intermediate	13-16	8
Resistant	≤ 12	≥ 16

Table 1.

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

Neisseria gonorrhoeae and organisms isolated from tissue are considered susceptible to NORFLOXACIN if the zone diameter is ≥ 21mm or MIC ≤ 1µg/ml.

Pharmacokinetics

NORFLOXACIN is rapidly absorbed following oral administration. In healthy volunteers at least 30-40% of an oral dose of NORFLOXACIN is absorbed. This results in a serum concentration of 1.5 µg/ml being attained approximately one hour after administration of a 400 mg dose. Mean serum half-life is 3-4 hours and is independent of dose.

Table 2 shows the mean concentrations of norfloxacin in various fluids and tissues measured 1 to 4 hours post-dose after two 400 mg doses, unless otherwise indicated:

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 feces were obtained at 12, 24, and 48 hours, respectively.

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
Gallbladder tissue	1.8 µg/g *
Bile	6.9 µg/ml (after two 200 mg doses)

* Measured 4-6 hours after one 400 mg dose

Table 2.

Renal excretion occurs by both glomerular filtration and net tubular secretion, as evidenced by the high rate of renal clearance (approx 275 ml/min). After a single 400 mg dose, urinary concentrations reach a value of 200 µg/ml or more in healthy volunteers and remain above 30 µg/ml for at least 12 hours. In the first 24 hours, 33 % - 48 % of the medicine is recovered in the urine.

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 compared to the normal population. Medicine absorption appears unaffected. However, the effective half life of norfloxacin in these elderly subjects is 4 hours.

Following a single 400 mg dose of norfloxacin, the disposition of the medicine in patients with creatinine clearance greater than 30 ml/min/1.73 m² is similar to that of healthy volunteers. In patients with creatinine clearance less than 30 ml/min/1.73 m², the renal elimination of norfloxacin decreases significantly. The effective serum half-life is approximately 8 hours. Medicine absorption appears unaffected by decreasing renal function.

Norfloxacin exists in the urine as norfloxacin and six active metabolites of lesser antimicrobial potency. The parent compound accounts for over 70% of total excretion. The bactericidal potency of NORFLOXACIN is not affected by the pH of urine.

The protein binding is less than 15 %.

Peak serum levels of NORFLOXACIN are slightly lower when administered with food than when given fasting.

Indications

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

Upper and lower, complicated and uncomplicated, acute 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 NORFLOXACIN.

Acute bacterial gastroenteritis caused by susceptible organisms.

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

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

Dosage and Administration

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

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

Treatment: (See Table 3)

Diagnosis	Dosage	Therapy Duration
Urinary tract infections	400 mg twice a day	7-10 days
Uncomplicated acute cystitis	400 mg twice a day	3-7 days
Chronic prostatitis	400 mg twice a day	4 weeks
Acute bacterial gastroenteritis	400 mg twice a day	5 days
Acute gonococcal urethritis, pharyngitis, proctitis or cervicitis	800 mg	Single dose

Table 3

Renal Impairment: NORFLOXACIN is suitable for the treatment of patients with renal insufficiency. In studies involving patients whose creatinine clearance was less than 30ml/min/1.73m², 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 10ml/min/1.73m², compared to patients with creatinine clearance of 10-30 ml/min/1.73m². 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 MIC's for most pathogens sensitive to norfloxacin.

There are insufficient data on which to have a dosage recommendation for the treatment of gonorrhoea in patients with a creatinine clearance of 30 ml/min/1.73 m² or less.

Contraindications

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

NORFLOXACIN should not be used in prepubertal children.

Warnings and Precautions

As with other organic acids, NORFLOXACIN should be used with caution in individuals with a history of convulsions or known factors that predispose to seizures. Convulsions have been reported rarely in patients receiving NORFLOXACIN, however, a causal relationship to NORFLOXACIN has not been established.

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

- Norfloxacin may cause tendonitis or tendon rupture.
- The risk of tendonitis or tendon rupture is increased in patients: over the age of 60 years; on concomitant systemic steroid therapy; or who have received a kidney, heart or lung transplant.
- Norfloxacin should not be used in patients with a history of fluoroquinolone associated tendonopathy.
- Tendonitis and tendon rupture risk is present during use and for 6 months following use of fluoroquinolones such as Norfloxacin.
- Prescribers should advise patients that at the first sign of tendon pain, inflammation or tendon rupture, to stop taking Norfloxacin, avoid exercise or use of the affected area and immediately contact their doctor.

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who have taken quinolone agents, including NORFLOXACIN (*see Adverse Effects*).

Renal Impairment: NORFLOXACIN is suitable for the treatment of patients with renal impairment, however since NORFLOXACIN is primarily excreted by the kidney, urinary levels may be significantly compromised by severe renal dysfunction (see Dosage and Administration).

Pregnancy: Category B3 The safe use of NORFLOXACIN in pregnant women has not been established and, consequently, the benefits of treatment with NORFLOXACIN should be weighed against potential risks. NORFLOXACIN 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 medicines are secreted in human milk, caution should be exercised when NORFLOXACIN is administered to a nursing woman.

Children: Safety and efficacy in children have not been established; therefore, NORFLOXACIN should not be used in prepubertal children (*see Animal Toxicology*).

Animal Toxicology: Norfloxacin and related medicines have been shown to cause arthropathy in immature animals of most species tested. The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage.

Related medicines (eg. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Dogs six months or older were not susceptible to these changes.

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

Although NORFLOXACIN was not teratogenic in cynomolgus monkeys, at several times the therapeutic human dosage an increased percentage of embryonic losses was observed.

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

Driving and operating machinery: Norfloxacin is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery. Care should, however, be exercised until the effect of norfloxacin on the patient is known.

Adverse Effects

NORFLOXACIN generally is well tolerated. The overall incidence of medicine 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 diarrhoea.

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%, leucopenia, eosinophilia, neutropenia, thrombocytopenia, elevation of ALAT (SGPT), ASAT (SGOT).

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

Hypersensitivity Reactions including anaphylaxis, interstitial nephritis, angioedema, vasculitis, urticaria, arthritis, myalgia and arthralgia.

Skin:

- Photosensitivity
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Exfoliative dermatitis
- Erythema multiforme
- Pruritus

Gastrointestinal:

- Pseudomembranous colitis
- Pancreatitis (rare)
- Hepatitis, including elevated liver function tests

Musculoskeletal:

- Tendinitis
- Tendon rupture
- Possible exacerbation of myasthenia gravis

Nervous System/Psychiatric:

- Polyneuropathy including Guillain-Barre Syndrome
- Confusion
- Paraesthesia
- Psychic disturbances including psychotic reactions

Hematologic:

- Hemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency

Genitourinary:

- Vaginal candidiasis

Adverse Effects, Causal Relationship Unknown: A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation, convulsive disorders, asthenia/fatigue, somnolence, constipation and flatulence. On very rare occasions hypertonia, renal failure, dyspnea, ataxia, dysarthria, dysphasia, hemophthalmia, nystagmus, periorbital erythema, fever, vomiting, dry mouth, visual disturbances, transient hearing loss, and hypoglycemia have been reported.

Without establishing a causal relationship, the following have also been reported: increased serum creatinine, proteinuria, increased BUN, and decreased hematocrit.

Interactions

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

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

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

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

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

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

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

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

Overdosage

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

Pharmaceutical Precautions

Protect from light and moisture. Store below 25 °C. Shelf life 2 years.

Medicine Classification

Prescription Medicine.

Package Quantities

14 tablets.

Further Information

Norfloxacin is chemically described as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperaziny)-3-quinolinecarboxylic acid. Its empirical formula is $C_{16}H_{18}FN_3O_3$.

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