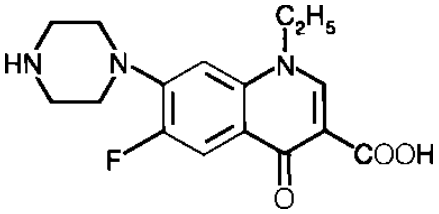
NOROXIN®
(norfloxacin, MSD)

Tablets

NAME OF THE MEDICINE

Norfloxacin

NOROXIN (norfloxacin, MSD) is a synthetic antibacterial agent for oral administration. Norfloxacin, a fluoroquinolone, is: 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid. Its empirical formula is C_{16} H_{18} FN_3 O_3 and the structural formula is:



CAS No: 70458-96-7

DESCRIPTION

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

Norfloxacin, a fluoroquinolone, differs from quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position. Examples of antibacterial drugs which are quinolones include nalidixic acid and cinoxacin.

Each tablet of NOROXIN contains 400 mg of norfloxacin and the following inactive ingredients: cellulose - microcrystalline, croscarmellose sodium, magnesium stearate, hydroxypropylcellulose, hypromellose, titanium dioxide and carnauba wax.

CLINICAL PHARMACOLOGY

In fasting healthy volunteers, approximately 30-40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200mg and 400mg. At the respective doses, mean peak serum and plasma concentrations of 0.8 and 1.5 mcg/mL are attained approximately one hour after dosing. The presence of food 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.

The absorbed norfloxacin is eliminated mainly through renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275mL/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 metabolites of considerably less antimicrobial potency. However, urinary recovery may occasionally be very low. Only a small percentage (less than 1%) of the dose is recovered thereafter.

Two to three hours after a single 400mg dose, urinary concentrations of 200mcg/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30mcg/mL for approximately 12 hours following a 400mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5 with solubility increasing at pHs above and below this value.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30mL/min/1.73m^2 is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30mL/min/1.73m^2, the renal elimination of norfloxacin decreases so that the effective serum half-life is 8.6 to 11.5 hours. In these patients, alteration of dosage is necessary (see DOSAGE AND ADMINISTRATION). Drug absorption appears unaffected by decreasing renal function.

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. Drug absorption appears unaffected. The effective half-life of norfloxacin in these elderly subjects is 4 hours.

Faecal recovery accounts for another 30% of the administered dose. This represents the unabsorbed drug along with a small contribution through biliary excretion. After a single 400mg dose of norfloxacin, mean antimicrobial activities equivalent to 278, 773, and 82 mcg of norfloxacin/g of faeces were obtained at 12, 24, and 48 hours, respectively.

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

ANIMAL PHARMACOLOGY

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

Crystalluria has occurred in laboratory animals tested with norfloxacin. In dogs, needle shaped drug crystals were seen in the urine at doses of 50mg/kg/day. In rats, crystals were reported following doses of 200mg/kg/day.

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

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

Microbiology

Norfloxacin has *in vitro* activity against a broad spectrum of gram-negative and some gram-positive aerobic bacteria. 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 catalysed 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 *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-12} cells). 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 species
Enterococci

For this reason, when there is a lack of satisfactory clinical response, culture and susceptibility testing should be repeated.

Norfloxacin is active *in vitro* against the following organisms:

1) Bacteria found in urinary tract infections:

Aerobic Bacteria

Gram-positive bacteria including:
Streptococcus faecalis (enterococcus)
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus

Gram-negative bacteria including:
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

2) Bacteria found in gastrointestinal infections:
Shigella
E.coli
Salmonella typhi

In addition, norfloxacin is active against *Neisseria gonorrhoea*.

Norfloxacin is not generally active against obligate anaerobes.

Nalidixic acid resistant organisms are generally susceptible to norfloxacin *in vitro*; however, these organisms may have higher MICs to norfloxacin than nalidixic acid susceptible strains. There is generally no cross-resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin often demonstrates activity against indicated organisms resistant to the aminoglycosides (including gentamicin), penicillins, cephalosporins, tetracyclines, macrolides, and sulphonamides, including combinations of sulphamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Susceptibility Tests

Quantitative methods that require measurement of zone diameters give precise estimates of bacterial susceptibility. One such procedure has been recommended for use with discs to test susceptibility to norfloxacin.

Reports from the laboratory giving results of the standard single disc susceptibility test with a 10mcg norfloxacin disc should be interpreted according to the following criteria.

Susceptible organisms produce zones of 13mm or greater, indicating that the test organism is likely to respond to therapy.

Resistant organisms produce zones of 12mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered susceptible if the MIC value for norfloxacin is equal to or less than 16mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 32mcg/mL.

The standardised quality control procedure requires use of control organisms. The 10mcg norfloxacin disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC	Zone Size Range
E. coli	25922	28 - 35 mm
P. aeruginosa	27853	22 - 29 mm
S. aureus	25923	17 - 28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC	MIC (mcg/mL)
E. coli	25922	0.03 - 0.125
S. aureus	29213	0.5 - 2.0
S. faecalis	29212	2.0 - 8.0
P. aeruginosa	27853	1.0 - 4.0

Based on urinary concentrations of norfloxacin achieved in man, breakpoint criteria have been established as listed below.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Susceptible	$\geq$13	$\leq$16
Resistant	$\leq$12	$\geq$32

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

INDICATIONS

Treatment

NOROXIN is indicated for the treatment of adults with:

- complicated and uncomplicated urinary tract infections that are caused by susceptible strains of micro-organisms.

- gastrointestinal infections, in particular shigellosis and traveller's diarrhoea.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during treatment if clinical response warrants.

Suppression

NOROXIN is indicated for the suppression, in adults, of chronic, recurrent urinary tract infection.

CONTRAINDICATIONS

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

Norfloxacin should not be used in children or pregnant women.

PRECAUTIONS

The oral administration of single doses of norfloxacin 100mg/kg caused lameness in immature dogs. Histological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs (e.g. nalidixic acid and cinoxacin) also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Needle shaped crystals were found in the urine of some volunteers who received either placebo, 800mg norfloxacin, or 1600mg 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 400mg 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.

Antibiotic associated pseudomembranous colitis has been reported with nearly all antibiotics including norfloxacin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, eg, opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Convulsions have been reported rarely in patients receiving norfloxacin. 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.

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.

Tendinitis, Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with norfloxacin and other quinolones. Norfloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon and the patient advised to seek appropriate medical management.

Rarely, haemolytic 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 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 norfloxacin, in patients with myasthenia gravis (see ADVERSE EFFECTS).

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmias. 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 yet 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 hypokalaemia, 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.

Renal Impairment

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. Alteration in dosage regimen is necessary for patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Effects on Fertility

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

Use in Pregnancy (Category B3)

Norfloxacin has been shown to produce embryonic loss in cynomolgus monkeys when given in doses of 150mg/kg/day with peak plasma levels that are 2 to 3 times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 100-800mg/kg/day. There were no adequate and well controlled studies in pregnant women. Since norfloxacin, like other drugs in this class, causes arthropathy in immature animals, it should not be used in pregnant women.

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

When a 200mg dose of norfloxacin was administered to nursing mothers, norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because of the potential for serious adverse reactions from norfloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug at least 24-48 hours before re-starting breast feeding, taking into account the importance of the drug to the mother.

Paediatric Use
As with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals. The safety of norfloxacin in children has not been adequately explored and therefore norfloxacin is not to be used in children less than 18 years of age.

Genotoxicity
Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at 500-1000mg/kg/day. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Carcinogenicity
Information is not available at present on the carcinogenic potential of norfloxacin.

Driving and Operating machinery
NOROXIN may cause dizziness or lightheadedness; therefore, patients should know how they react to norfloxacin before they operate a vehicle or machinery or engage in activities requiring mental alertness and coordination.

Information for Patients

Patients should be advised to take NOROXIN one hour before or two hours after a meal. Patients should also be advised to drink fluids liberally and not to take antacids concomitantly or within 2 hours after dosing.

INTERACTIONS WITH OTHER MEDICINES

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 antagonise the antibacterial effect of norfloxacin in the urinary tract.

Quinolones, including norfloxacin, have been shown *in vitro* to inhibit CYP1A2. Concomitant use with drugs metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

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.

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 drugs are used concomitantly.

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

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.

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

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.

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

ADVERSE EFFECTS

In clinical trials, norfloxacin was generally well tolerated.

The incidence of subjects reporting drug related adverse experiences in clinical trials involving 1127 subjects was 3.4%. However, the overall incidence was 10.7% and the figures below were calculated without reference to drug relationship. Most adverse reactions occur within the first few days of therapy.

The most common adverse experiences (1% - 3%) were either gastrointestinal or neurological: nausea 2.8%, headache 2.7%, and dizziness 1.8%.

Additional reactions (0.3% - 1%) were: fatigue, rash, abdominal pain, dyspepsia, somnolence, depression, insomnia, constipation, flatulence, and heartburn.

Less frequent reactions included: dry mouth, diarrhoea, fever, vomiting, erythema, euphoria, anxiety, irritability, hallucinations, altered taste, vaginal swelling and tendonitis.

Visual disturbances have been reported with drugs in this class.

Abnormal laboratory values observed in these 1127 subjects in clinical trials were eosinophilia 1.8%, elevation of ALT (SGPT) and AST (SGOT) 1.8%, increased alkaline phosphatase 1.4%, and decreased WBC or neutrophil count 1.2%. Those occurring less frequently included increased serum urea, serum creatinine, and LDH, and decreased haematocrit.

Post Marketing

The following additional adverse effects have been reported since the drug was marketed.

Hypersensitivity reactions
Hypersensitivity reactions have been reported including anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia and interstitial nephritis, Drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Skin
Photosensitivity, Steven-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, and leukocytoclastic vasculitis.

Central Nervous System
Confusion, paraesthesia, polyneuropathy including Guillain-Barré syndrome, hypoesthesia, psychic disturbances including psychotic reactions, convulsions, tremors and myoclonus.

Liver and Gastro Intestinal Tract
Pseudomembranous colitis, pancreatitis (rare), hepatitis, including jaundice and cholestatic jaundice and elevated liver function tests.

Musculoskeletal
Tendonitis, tendon rupture, exacerbation of myasthenia gravis, elevated creatine kinase (CK)

Haematological
Agranulocytosis, thrombocytopenia, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency

Genitourinary
Vaginal candidiasis

Renal Function
Renal failure

Special Senses
Dysgeusia, visual disturbances, Hearing loss, Retinal detachment

Adverse Effects, Causal Relationship Unknown

A definite causal relationship could not be established with regard to the following adverse effects: conjunctivitis, eye pain/irritation, asthenia, and increased BUN. On very rare occasions, prolonged QTc interval and ventricular arrhythmia (including torsades de pointes), hypertonia, ataxia, dysarthria, dysphasia, haemophthalmia, nystagmus, periorbital erythema and, proteinuria have been reported.

DOSAGE AND ADMINISTRATION

NOROXIN tablets should be taken one hour before or two hours after a meal with a glass of water. Patients receiving NOROXIN should be well hydrated. Multivitamins, other products containing iron or zinc, antacids containing magnesium and aluminum, sucralfate or VIDEX (didanosine), chewable/buffered tablets or the paediatric powder for oral solution, should not be taken within 2 hours of administration of NOROXIN (see PRECAUTIONS).

Urinary Tract Infection

Normal Renal Function

The recommended dosage of NOROXIN for the treatment of urinary tract infection is 400mg twice daily for 7 to 10 days.

For uncomplicated lower urinary tract infections, the recommended dosage is 400mg twice daily for 3 days. In one study of uncomplicated lower urinary tract infections, treatment for 7 days resulted in somewhat better eradication rates than treatment for 3 days.

For suppression in chronic recurrent urinary tract infection, 400mg twice daily may be administered for 4 to 12 weeks.

Maximum total daily dosage should not exceed 800mg per day.

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 30mL/min/1.73m^2 or less, the recommended dosage is one 400mg 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 10mL/min/1.73m^2. However, such patients should be observed carefully for adverse effects due to possible drug retention.

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.

$$\text{Males:} = \frac{(\text{weight in kg}) \times (140 - \text{age})}{(72) \times \text{serum creatinine (mmol/L)}} \times 0.0885$$

$$\text{Females:} = (0.85) \times (\text{above value})$$

Elderly

Elderly patients with a creatinine clearance of greater than 30mL/min/1.73m^2 should receive the dosages recommended under Normal Renal Function.

Elderly patients with a creatinine clearance of 30mL/min/1.73m^2 or less should receive 400mg once daily as recommended under Renal Impairment.

Gastrointestinal Infection (Shigellosis, Traveller's Diarrhoea)

The recommended dosage is 400mg twice daily for five days.

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied by inducing vomiting, and the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

NOROXIN 400mg is supplied as white, oval, biconvex tablets scored on one side and embossed "MSD705" on the other, in PVC/PVDC/Aluminium blister packs of 6 and 14.

Storage

NOROXIN tablets should be stored in a tightly-closed container below 30^{o}C.

NAME AND ADDRESS OF THE SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY. LIMITED
54-68 Ferndell Street, South Granville, NSW 2142

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

DATE OF FIRST INCLUSION IN THE ARTG:

Date approved by the TGA: 9 September, 1990

DATE OF MOST RECENT AMENDMENT:

Date of latest amendment: 6 June 2012