PRODUCT MONOGRAPH

^{Pr}TEVA–NORFLOXACIN

norfloxacin Tablets USP
400 mg

Antibacterial Agent

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Revision:
October 12, 2018

Submission Control No: 218542

PRODUCT MONOGRAPH

TEVA-NORFLOXACIN
Norfloxacin Tablets, USP
400 mg

THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTIONS AND CLINICAL PHARMACOLOGY

TEVA-NORFLOXACIN (norfloxacin) is a quinolone carboxylic acid antibacterial agent for oral administration. Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal.

At the molecular level, three specific actions have been attributed to norfloxacin in the inhibition of *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.

A comparative, two-way single dose bioavailability study was performed on two norfloxacin 400 mg tablet formulations, TEVA-NORFLOXACIN (norfloxacin) and Noroxin®. The pharmacokinetic data calculated for norfloxacin in the TEVA-NORFLOXACIN and Noroxin® tablet formulations is tabulated below:

	Geometric mean Arithmetic mean (C.V.)		
	TEVA-NORFLOXACIN 1 x 400 mg	Noroxin®** 1 x 400 mg	Ratio of Geometric Means (%)
AUC_T (ng·h/mL)	5669 5787 (21)	5467 5753 (29)	103
AUC_I (ng·h/mL)	5986 6113 (21)	5789 6082 (29)	103
C_{max} (ng/mL)	1048 1069 (21)	958 1018 (31)	109
T_{max}* (h)	1.35 (0.72)	1.42 (0.48)	-
$T_{1/2}$* (h)	5.10 (0.41)	5.17 (0.47)	-
*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation). **Noroxin® (Merck, Sharp and Dohme Canada, Canada)			

INDICATIONS AND CLINICAL USE

The treatment of upper and lower urinary tract infections, specifically complicated and uncomplicated cystitis, pyelitis and pyelonephritis caused by susceptible strains of the following microorganisms:

Escherichia coli
Klebsiella pneumonia
unspecified Klebsiella spp.
unspecified Enterobacter spp.
unspecified Citrobacter spp.
Proteus mirabilis
Staphylococcus aureus
Streptococcus faecalis
Pseudomonas aeruginosa

In cases of uncomplicated acute bacterial cystitis, limit the use of TEVA-NORFLOXACIN (norfloxacin) to circumstances where no other treatment options are available. A urine culture should be obtained prior to treatment to ensure norfloxacin susceptibility.

The treatment of adults with gonococcal urethritis, or cervicitis due to penicillinase-producing and non-penicillinase producing Neisseria gonorrhoeae.

Limit the use of TEVA-NORFLOXACIN (norfloxacin) to patients where no other treatment options exist AND where norfloxacin susceptibility is demonstrated, OR norfloxacin susceptibility is highly likely, typically greater than or equal to 95%, based on local susceptibility patterns.

Appropriate culture and susceptibility studies should be carried out prior to initiation of therapy with TEVA-NORFLOXACIN (norfloxacin) and if clinically indicated during treatment. Therapy may be initiated before obtaining results of these tests (see MICROBIOLOGY), however, modification of such treatment may be required once the results become available.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEVA-NORFLOXACIN (norfloxacin) and other antibacterial drugs, TEVA-NORFLOXACIN (norfloxacin) should be used only to treat 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

TEVA-NORFLOXACIN (norfloxacin) is contraindicated in patients with known hypersensitivity to

norfloxacin, to any component of this product or to other quinolone antibacterial agents.

WARNINGS

Serious Warning and Precautions
Fluoroquinolones, including TEVA-NORFLOXACIN, have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.

The safety of TEVA-NORFLOXACIN (norfloxacin) in children is unknown. TEVA-NORFLOXACIN should not be given to patients in whom epiphyseal closure has not occurred. In two animal species (dogs and rabbits) in which norfloxacin was administered to young animals, lameness and lesions (i.e., blister formation and eventual erosion) of the articular cartilage of the weight bearing joints were observed. In young dogs, this occurred following a single dose several times the recommended human dose. These changes were not observed in dogs 6 months of age or older. Similar changes in animals have been observed with other structurally related drugs.

TEVA-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.

If vision disorder occurs in association with the use of TEVA-NORFLOXACIN, consult an eye specialist immediately. A modest increase in risk of developing retinal detachment was found in association with the use of fluoroquinolones in some observational studies; however, a causal relationship to the drug has not been clearly established.

The safety of TEVA-NORFLOXACIN in the treatment of infections in pregnant women is not established.

PRECAUTIONS

General

TEVA-NORFLOXACIN (norfloxacin) should be used with caution in patients with a history of convulsions.

During therapy with TEVA-NORFLOXACIN, patients should be reminded to drink sufficient amounts of fluids to maintain adequate hydration in order to avoid possible development of crystalluria.

As with other quinolones, tendinitis and/or tendon rupture have been observed rarely in patients taking norfloxacin, especially when corticosteroids are taken concomitantly. If a patient develops symptoms of tendinitis and/or tendon rupture, norfloxacin 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 norfloxacin (see ADVERSE REACTIONS).

Photosensitivity reactions have been observed in patients exposed to sunlight while receiving quinolone antibiotics. While taking TEVA-NORFLOXACIN, excessive exposure to sunlight should be avoided and therapy discontinued if photosensitivity should occur.

Use in Obstetrics

The safety of use of TEVA-NORFLOXACIN in the treatment of infections in pregnant women is not established; consider its use only if the anticipated benefits to the mother justify the potential risks to the fetus. Following a single dose of 200 mg norfloxacin, concentrations in umbilical cord serum ranged from non detectable levels to 0.5 mg/L and in amniotic fluid from non detectable levels to 0.92 mg/L. The pharmacokinetics of norfloxacin in pregnant patients have not been investigated.

Reproduction studies have been carried out in the mouse, rat, rabbit, and monkey. Norfloxacin did not show any teratogenic effects in these studies. In the monkey, however, an increased incidence of embryonic loss has been observed at a dosage of 10 times the human dose which results in peak plasma levels approximately 2 to 3 times that in humans. In the rabbit, embryonic loss was observed when norfloxacin was given by the oral route but not by the subcutaneous route. The clinical significance of the study results observed in rabbits and monkeys is not known (see TOXICOLOGY) .

Nursing Mothers

Norfloxacin was not detected in human milk following a single 200 mg dose. However, because this dose was low (half the recommended single dose) and as many drugs are secreted in human milk, caution should be exercised if TEVA-NORFLOXACIN is to be administered to a nursing woman.

Elderly

Alterations in dosage are not recommended (see DOSAGE AND ADMINISTRATION and HUMAN PHARMACOLOGY). When norfloxacin was administered to 4 females and 2 males, 67 to 74 years old, with normal renal function for their age, [i.e., creatinine clearance of 91 ± 14 mL/min/1.73 m^2 (1.52 ± 0.2 mL/s/1.73 m^2)], the plasma half-life of the drug was only slightly prolonged.

Drug Interactions

Since urinary excretion of norfloxacin is diminished by concomitant administration of probenecid, TEVA-NORFLOXACIN should not be administered concomitantly with probenecid.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline-related adverse reactions 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 norfloxacin. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

TEVA-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 TEVA-NORFLOXACIN because they may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Norfloxacin has 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.

Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Renal Impairment

Since norfloxacin is eliminated primarily by the kidney, TEVA-NORFLOXACIN should be used with caution and at a reduced dosage in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). TEVA-NORFLOXACIN is not recommended for anuric patients.

There is 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 (0.5 mL/s/1.73m^2) or less.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing TEVA-NORFLOXACIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

ADVERSE REACTIONS

Norfloxacin is generally well tolerated. In controlled clinical trials involving 1,528 patients, the overall incidence of drug-related adverse reactions was approximately 3%.

The following adverse reactions were reported.

GASTROINTESTINAL SYSTEM	Incidence (%)
Nausea	2.0
Dyspepsia	0.3
Flatulence	0.3
Heartburn	0.3
Abdominal pain	0.3
Vomiting	0.2
Diarrhea	0.2
Anorexia	0.1
NERVOUS SYSTEM	
Headache	1.6
Dizziness/Lightheadedness	1.2
Drowsiness	<1.0
Mood alterations	<1.0
Anxiety disorders	2 cases
Depression	4 cases
Disorientation	1 case
Dream abnormalities	1 case
Euphoria	2 cases
Explosive personality disorder	1 case
Hallucinations	1 case
Irritability	1 case
Nervousness	2 cases
Paresthesia	<1.0
Visual disturbances	<0.1
Epiphora	1 case
GASTROINTESTINAL SYSTEM	
Insomnia	<0.4
MUSCULOSKELETAL SYSTEM	
Tendinitis	0.1
Arthralgia	0.1
HYPERSENSITIVITY REACTIONS	
Rash	0.4
Erythema	0.2
Urticaria	0.1
Pruritus	0.1

The following additional adverse reactions have been reported since the drug was marketed:

Musculoskeletal System: tendon rupture, possible exacerbation of myasthenia gravis.

Body as a Whole/Site Unspecific: asthenia/fatigue.

Hypersensitivity reactions: anaphylaxis, interstitial nephritis, angioedema, vasculitis, urticaria, arthritis, myalgia.

Ocular: conjunctivitis, eye pain/irritation.

Skin: photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus.

Gastrointestinal: constipation, flatulence, pseudomembranous colitis, pancreatitis (rare), hepatitis.

Nervous System/Psychiatric: convulsions, confusion, paresthesia, polyneuropathy including Guillain-Barré syndrome, psychic disturbances including psychotic reactions, somnolence.

Hematologic: hemolytic anemia, thrombocytopenia.

Special Senses: tinnitus.

Genitourinary: vaginal candidiasis.

Laboratory: abnormal adverse reactions observed rarely in clinical trials include leukopenia, eosinophilia, neutropenia, proteinuria and elevation of ALAT (SGPT), ASAT (SGOT), alkaline phosphatase, bilirubin, increased BUN, serum creatinine, and LDH, and decreased hematocrit.
On very rare occasions, the following have been reported: hypertonia, renal failure, dyspnea, ataxia, dysarthria, dysphasia, hemophthalmia, nystagmus, periorbital erythema, fever, dry mouth and transient hearing loss.

Others:
Although the following adverse reactions were not observed in these clinical trials with norfloxacin, they have been reported following treatment with other quinolone antibacterial agents:

- hemolytic anemia in patients with latent or actual defects in glucose-6-phosphate dehydrogenase (G6PD) activity;
- overbrightness of light, change in colour perception, difficulty in focusing, decrease in visual acuity and double vision;
- restlessness;

- bullae;
- palpitation;
- soreness of the gums;
- joint stiffness;
- swelling of the extremities;
- metallic taste;
- toxic psychosis (rare);
- perineal burning;
- vertigo;
- edema;
- cholestasis;
- metabolic acidosis;
- (signs and symptoms of increased intracranial pressure in infants and children which usually disappeared rapidly with no sequelae when treatment was discontinued).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There has not been any case of overdose with TEVA-NORFLOXACIN (norfloxacin) reported to date; consequently neither the signs nor the symptoms of overdosage have been identified.

In the event of recent 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 should be maintained to avoid the possible development of crystalluria. Norfloxacin is not dialysable.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of TEVA-NORFLOXACIN (norfloxacin) for urinary tract infections is one 400 mg tablet twice a day taken with a glass of water at least 1 hour before, or 2 hours after a meal or milk ingestion for 7 to 10 days.

For women with uncomplicated acute cystitis, the duration of therapy can be reduced to three (3) days.

For adults with gonococcal urethritis or cervicitis, the recommended dosage of TEVA-NORFLOXACIN is two 400 mg tablets (800 mg) given as a single dose.

Elderly

The recommended dosage of TEVA-NORFLOXACIN in elderly patients with normal renal function for their age is the same as given for adults above.

Impaired Renal Function

TEVA-NORFLOXACIN may be used in the treatment of patients with renal insufficiency who do not require hemodialysis.

In patients with a glomerular filtration rate of less than 30 mL/min/1.73 m^2 (0.50 mL/s/1.73 m^2) but greater than 6.6 mL/min/1.73 m^2 (0.11 mL/s/1.73 m^2) the recommended dose is one 400 mg tablet once daily (see PRECAUTIONS).

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: $$\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/100 mL)}}$$

Females: 0.85 x above value.

To convert to international units multiply result by 0.01667.

The administration of TEVA-NORFLOXACIN to anuric patients is not recommended.

Children

The safety and efficacy of TEVA-NORFLOXACIN in prepubertal children have not been established. TEVA-NORFLOXACIN should not be used in patients in whom epiphyseal closure has not occurred (see WARNINGS).

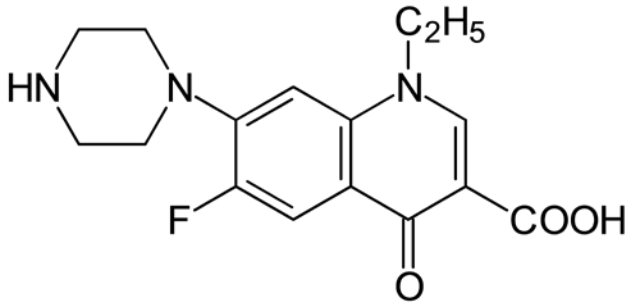
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: norfloxacin

Chemical Name: 1-ethyl-6-fluoro-1,4 dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid.

Structural Formula:



Molecular formula: $C_{16}H_{18}FN_3O_3$

Molecular weight: 319.34 g/mol

Description: Norfloxacin is an odourless, white to pale yellow crystalline powder with a bitter taste and a melting point of 220°-224°C. It is freely soluble in glacial acetic acid; sparingly soluble in dichloromethane; slightly soluble in acetone and chloroform; very slightly soluble in ethanol, methanol, ethyl acetate and benzene; and practically insoluble in water. Solubility in water is minimal between pH 6.0 to 10. Dissociation constants are: pKa_1=6.3 and pKa_2=8.8.

Composition

Each TEVA-NORFLOXACIN 400 mg Tablet contains 400 mg norfloxacin. Non-medicinal ingredients: croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triethyl citrate, polyethylene glycol and talc.

Stability and storage recommendations

Bottles of TEVA-NORFLOXACIN should be stored between 15°C and 30°C. Keep bottles tightly closed. Unit dose packages should be stored between 15°C and 25°C and protected from high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA–NORFLOXACIN (norfloxacin) 400 mg tablets are biconvex, scored film coated tablets engraved with **N|N** on one side and **400** on the other.

Available in bottles of 100, 500, and 1000 and in boxes of 100 as unit dose strips.

MICROBIOLOGY

The *in vitro* activity of norfloxacin against clinical isolates of gram-positive and gram-negative aerobic bacteria is shown in Table 1. Susceptibility was determined by both agar and broth dilution tests, pH 7.1-7.4, using inoculum sizes ranging from 10^4 to 10^5 colony-forming units (cfu) per ml. Norfloxacin lacks useful activity against Actinomyces spp., Fusobacterium spp., Bacteroides spp., and Clostridium spp., other than C. perfringens.

The minimal inhibitory concentrations (MICs) of norfloxacin against aerobic bacteria are not significantly affected by culture medium composition or by changes in inoculum size in the range 10^3 to 10^6 cfu/spot (Table 2). In one study with 37 enterobacteria in Mueller-Hinton agar, increases in MIC values of norfloxacin at 10^8 cfu/spot were 2- to 4-fold higher than at 10^6 cfu/spot.

MICs of 4- and 33-fold higher were seen when representative enterobacteria were tested simultaneously in Diagnostic Sensitivity Test (DST) agar at pH 5.5 (MIC range= 0.12 to 32 mg/L), and at pH 7.2 (MIC = 0.015 to 4). This reduction in antibacterial activity suggests a pH effect (Table 2). In pooled human urine agar at pH 6.5, the observed MICs ranged from 0.06 to 16 mg/L. The magnesium content of urine could account for the reduced activity of norfloxacin and other quinolones in pooled human urine agar.

Generally, minimal bactericidal concentrations (MBCs) for norfloxacin are 1 to 4 times the MICs against susceptible bacteria. At these concentrations, norfloxacin is bactericidal, even with bacteria in their stationary phase of growth.

TABLE 1: CUMULATIVE PERCENT OF STRAINS INHIBITED AT THE INDICATED CONCENTRATION OF NORFLOXACIN																		
Organism	Number of strains	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Achromobacter xylosoxidans	(30)											3	7	13		37	60	73
Acinetobacter calcoaceticus	(122)								1	7	20	38	62	91	96	100		
Alcaligenes faecalis	(23)											4		9	22	70	91	
Citrobacter freundii	(27)					26	48	74	93	96	100							
Citrobacter spp.	(15)						60		80	87		100						
Enterobacter cloacae	(76)					3	28	50	92	96		97	100					
Enterobacter spp.	(67)						33	55	87	91	96	97	100					
Escherichia coli	(417)					0.5	47	77	93	95	97	99	99	100				
Klebsiella pneumoniae	(50)						6	30	64	84	88	94	98	100				
Klebsiella spp.	(138)						24	56	77	84	95	99	99	100				
Morganella morganii	(52)					2	25	79	87		94	100						
Neisseria gonorrheae	(589)*	0.5	2	14	56	82	95	99	99	99				100				
Proteus mirabilis	(115)						51	63	74	93	100							
Proteus vulgaris	(58)					10	26	67	93	98		100						
Proteus spp., indole+	(10)						90	100										
Proteus Spp	(27)							52	93	100								
Providencia rettgeri	(111)					10	23	43	66	74	80	85	87	93	100			
Providencia stuartii	(16)				6	32	63	76	82	88		94			100			
Providencia spp.	(20)							80	85	95	95	100						
Pseudomonas aeruginosa	(245)							1	8	36	64	84	92	98		100		
Pseudomonas cepacia	(17)												6		71	100		
Pseudomonas maltophilia	(43)												2	9	49	84	95	100
Pseudomonas spp.	(112)							10	12	58	81	86	90	96	99	100		
Salmonella spp.	(11)						55		91		100							
Serratia marcescens	(87)							6	44	67	79	85	90	93	99	100		
Serratia spp.	(20)						15	95	100									
Shigella spp.	(3)								100[x]									
Staphylococcus aureus	(111)							1	2	8	42	76	95	99	100			
Staphylococcus epidermis	(75)							3	15	41	81	95	97	100				
Staphylococcus saprophyticus	(15)								13	13	87	100						
Streptococcus agalactiae	(10)										10	90	100					
Streptococcus bovis	(15)								20	20	33	53	80	87	100			
Streptococcus faecalis	(67)										3	52	91	100				
Ureaplasma urealyticum	(20)												15	50	90	100		

*includes 303 penicillinase-producing strains

[x]Only three strains

TABLE 2: EFFECT OF CULTURE MEDIUM COMPOSITION, pH, AND INOCULUM SIZE ON ANTIBACTERIAL ACTIVITY OF NORFLOXACIN

		MIC (mg/L)										
		Culture Medium[a]				pH[b]			Inoculum Size (cfu)[c]			
Organism/Strain		TSA	NA	MH	BHI	6	7	8	10^3	10^4	10^5	10^6
Staphylococcus aureus	2868	0.125	1.0	0.5	2	4	2	1	2	2	2	2
Escherichia coli	4391	0.03	0.06	0.06	0.06	1	0.06	0.06	0.03	0.03	0.03	0.03
Klebsiella pneumoniae	4005	0.06	0.06	0.06	0.06	ND	ND	ND	0.03	0.06	0.06	0.06
Escherichia coli	4392	0.25	0.25	0.25	0.5	8	0.5	0.25	0.5	0.25	0.25	0.5
Proteus mirabilis	3125	0.125	0.25	0.125	0.25	2	0.5	0.125	0.03	0.125	0.03	0.125
Serratia marcescens	2854	0.25	0.5	0.125	0.25	ND	ND	ND	0.125	0.125	0.06	0.125
Pseudomonas aeruginosa	2835	1	1	1	2	4	1.0	0.5	1	1	0.5	0.5

[a] TSA = trypticase soy agar (BBL); NA = nutrient agar (Difco); MH = Mueller Hinton agar (BBL); BHI = brain heart infusion (Difco); 10^6 cfu, pH 7.3

[b] Trypticase soy broth, 10^5 cfu/mL; ND = not done

[c] TSA (BBL), pH 7.3

Development of Resistance

A progressive increase in MIC of norfloxacin was demonstrated in five bacterial isolates by daily passage in subinhibitory concentrations of drug (Table 3). Cross-resistance with other quinolone antibacterial agents has also been observed.

TABLE 3: COMPARATIVE NORFLOXACIN MIC OF PARENT AND DERIVATIVE STRAINS

Organism/Strain		Norfloxacin MICs (mg/L)*		
		Parent Strain	R3	R5
Escherichia coli	2891	0.25	0.25	0.5
Klebsiella Pneumoniae	4354	0.25	4	8
Proteus vulgaris	2829	0.25	0.5	4
Pseudomonas aeruginosa	2835	0.5	2	8
Staphylococcus aureus	4310	1	4	32

*Broth dilution test, inoculum 10^6 cfu/mL, trypticase soy broth.

R3 = parent strain after 3 transfers.

R5 = parent strain after 5 transfers.

The frequency with which resistant mutants arise varies among genera (Table 4), is greatest for *P. aeruginosa* and least for *E. coli*. In concentrations within two dilutions of the MIC, mutants of *P. aeruginosa* can be isolated rather frequently (10^{-4} to 10^{-6}), whereas those of *E. coli* are relatively uncommon (10^{-8}). Increasing amounts of norfloxacin resulted in lower frequency of mutants (Table 4).

TABLE 4: FREQUENCY OF NORFLOXACIN—RESISTANT MUTANTS AMONG VARIOUS SPECIES OF ENTEROBACTERIACEAE, *PSEUDOMONAS AERUGINOSA, AND STAPHYLOCOCCUS AUREUS*

		Norfloxacin MICs (mg/L)*		
Organism/Strain		0.15	0.45	1.5
Escherichia coli	3773	1.1×10^{-8}	ND	ND
Klebsiella oxytoca	4007	7.5×10^{-7}	1.5×10^{-7}	ND
Klebsiella pneumoniae	3972	2.2×10^{-7}	5.1×10^{-8}	ND
Enterobacter cloacae	301	2.3×10^{-8}	ND	ND
Serratia marcescens	1581	4.6×10^{-7}	2.8×10^{-7}	1.3×10^{-9}
Citrobacter freundii	2301	5.0×10^{-8}	ND	ND
Proteus vulgaris	J 17	1.2×10^{-6}	ND	ND
Morganella morganii	2481	1.3×10^{-7}	ND	ND

		Norfloxacin MICs (mg/L)		
Organism/Strain		2	8	24
Pseudomonas aeruginosa	1404	8.9×10^{-5}	7.3×10^{-9}	ND
Pseudomonas aeruginosa	976	4.6×10^{-7}	ND	ND
Pseudomonas aeruginosa	526	1.3×10^{-6}	ND	ND
Pseudomonas aeruginosa	380	ND	ND	ND
Pseudomonas aeruginosa	133	4.6×10^{-4}	ND	ND
Pseudomonas aeruginosa	89	5.4×10^{-7}	ND	ND
Staphylococcus aureus	51	ND	ND	—
Staphylococcus aureus	105	ND	ND	—
Staphylococcus aureus	137	4.1×10^{-9}	ND	—

*Overnight cultures in trypticase soy broth (Oxoid) were plated in 10– and 100–fold dilutions on CLED agar (Oxoid) containing various concentrations of norfloxacin.

ND = not detectable, frequency of resistant mutants < 10^{-10}.

Nalidixic acid-resistant urinary isolates have been reported to demonstrate higher MICs to norfloxacin than nalidixic acid-susceptible strains. In one study, nalidixic acid-resistant strains of enterobacteria (MIC ≥ 128 mg/L) showed an MIC range for norfloxacin of 0.06-16 mg/L (Table 5), or 4-16 times that for the nalidixic acid-susceptible strains tested (MIC range of 0.015-1.0 mg/L). Thus, induced resistance to nalidixic acid was associated with cross-resistance to norfloxacin.

TABLE 5: NORFLOXACIN MICs AGAINST NALIDIXIC ACID–SUSCEPTIBLE AND RESISTANT URINARY ENTEROBACTERIA

Organisms (# of strains tested)	MIC Range (mg/L)*
Nalidixic acid–susceptible[a] (59)	
DST agar (Oxoid) (pH 7.2)	0.015 – 0.12
urine agar (pH 6.5)	0.06 – 1.0
Nalidixic acid–resistant[b] (44)	
DST agar (pH 7.2)	0.06 – 4.0
urine agar (pH 6.5)	0.25 – 16.0

*The inoculum was applied with a multipoint inoculator, at approximately 10^2 cfu/spot.
[a]MIC ≤ 32 mg/L
[b]MIC ≥ 128 mg/L

Nalidixic acid-resistant organisms were inhibited by norfloxacin at a concentration of 16 mg/L or less for approximately 90% of the isolates investigated. Norfloxacin is active *in vitro* against Enterobacteriaceae and nonfermentative gram-negative bacilli (Pseudomonas aeruginosa, Acinetobacter spp.) resistant to ampicillin, carbenicillin, trimethoprim and aminoglycosides. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Susceptibility Testing

The standard disc (1-3) susceptibility test [formerly, Kirby-Bauer] (using the 10 mcg norfloxacin disc of 6 mm diameter) or dilution susceptibility should be used.

Organisms should be tested with norfloxacin discs, since norfloxacin has been shown by *in vitro* tests to be active against genera and strains of bacteria known to be or determined to be resistant when nalidixic acid discs are used.

TABLE 6: INTERPRETATION OF SUSCEPTIBILITY CRITERIA OF NORFLOXACIN (FOR MILD OR MODERATE INFECTIONS OF THE URINARY TRACT)

	Zone Diameter (10 mcg norfloxacin disc) (mm)	Approximate MIC Correlation (mcg/ml)
Susceptible	≥17	≤4
Intermediate	13-16	8
Resistant	≤12	≥16

These susceptibility criteria apply only to organisms isolated from urine (urinary tract). There is a lack of clinical data to indicate if these same susceptibility criteria will be appropriate for the treatment of severe urinary tract infections suitable for oral therapy.

Proposed control limits for monitoring susceptibility tests are given in Table 7.

TABLE 7: CONTROL LIMITS FOR MONITORING NORFLOXACIN SUSCEPTIBILITY TESTS

Organism	Zone Diameter (mm)	MIC (mcg/ml)
E.coli ATCC*25922	28-35	0.03 - 0.12
S. aureus ATCC* 25923	17-28	-
S. aureus ATCC* 29213	-	0.5-2.0
S. faecalis ATCC*29212	-	2.0-8.0
P. aeruginosa ATCC*27853	22-29	1.0-4.0

*Trademark of American Type Culture Collection

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Central Nervous System

Norfloxacin (0.1-1.0 g/kg p.o.) showed no significant influences on behavior or in various pharmacological tests of central nervous system activity in either mice or rats. Similarly, norfloxacin (10 mg/kg i.v.) produced no changes in the central nervous system of rabbits implanted with recording electrodes.

Peripheral Nervous System

Intravenous administration of norfloxacin (10 mg/kg) modestly reduced (30%) contractions of

the cat nictitating membrane elicited by both pre- and post-ganglionic nerve stimulation. Nerve stimulated contractions of the rabbit tibialis muscle, however, were unaffected by similar doses of norfloxacin.

Using *in vitro* smooth muscle preparations (guinea pig ileum and trachea), norfloxacin (100-300 mg/L) exhibited no anticholinergic, antiserotonergic or antihistaminergic activity. Likewise, norfloxacin did not alter the intrinsic muscle tone of the above preparations. In the isolated rat vas deferens, norfloxacin did alter responses to norepinephrine (slightly enhancing low concentrations and reducing high concentrations) though no alteration in epinephrine responses were observed in the guinea pig ileum and trachea. Norfloxacin (100 mg/L) slightly reduced the amplitude of spontaneous contractions of the pregnant and nonpregnant rat uterus and rabbit ileum *in vitro*. However, *in vivo* norfloxacin (10 mg/kg i.v.) was without significant effect on spontaneous contractions of the stomach, intestine, bladder and uterus of rabbits. Similarly, gastrointestinal motility in mice was unaffected by 1.0 g/kg p.o. of norfloxacin.

Cardiovascular and Respiratory Systems

Norfloxacin (1.0 mg bolus) slightly increased (10 ± 3%) coronary flow and decreased heart rate (7 ± 2%) while modestly depressing contractile force (45 ± 4%) of isolated, perfused guinea pig hearts. In the isolated rabbit ear artery, a similar 1 mg bolus of norfloxacin produced a weak, transient decrease followed by an increase in blood flow. *In vivo*, norfloxacin administered intravenously increased by about 20% the respiratory rate in urethane anesthetized rabbits (30 mg norfloxacin/kg) and barbiturate anesthetized dogs (10 mg norfloxacin/kg). In these animals blood pressure tended to be reduced without significant changes in heart rate. The decrease of blood pressure in rabbits (approximately 15%) and particularly dogs, was marked by considerable animal variation (3/6 dogs had decreases of 90-100 mmHg). Infusion of norfloxacin (180 mg/hour i.v.) produced an elevation in the respiratory rate (60% increase) with a decrease (about 10%) in blood pressure and no change in heart rate in dogs. In urethane anesthetized rats, a reduction of about 20% in blood pressure was caused by norfloxacin (200 mg/kg i.v.). This reduction was inhibited by diphenhydramine but unaffected by atropine, propranolol or phentolamine. Oral administration of norfloxacin (1.0 g/kg) did not alter the blood pressure of unanesthetized rats.

Other Systems

Norfloxacin (1.0 g/kg p.o.) did not change blood sugar levels or coagulation time in rats and did not exhibit any anti-inflammatory activity in rats. Similarly, norfloxacin (300 mg/kg p.o.) was unable to prevent cold stress-induced ulcers in rats. Subcutaneous administration of norfloxacin (200 mg/kg) significantly reduced by about 90% gastric acid secretion while doses as high as 1.0 g/kg p.o. failed to alter bile secretion in rats. Norfloxacin (1.0 g/kg p.o.) significantly reduced urinary volume (30% decrease) over 24 hours and reduced urinary Na^+ excretion (ca. 25%) and significantly increased urinary K^+ excretion (ca. 30%) over this time period. None of these effects were observed at doses of 100 mg/kg p.o.

Animal Pharmacokinetics

The absorption, distribution, and excretion of norfloxacin has been studied in rats, dogs,

monkeys, mice and rabbits. Absorption is rapid in all species following oral administration, ranging from 10-12% in rats, mice and rabbits to 20-25% in monkeys and 70% in beagle dogs. Serum levels of norfloxacin measured for 0.5 to 4 hours after oral drug administration to monkeys (25 mg/kg) ranged from 0.3 to 2.35 mcg/mL. In rats, dogs and monkeys, 8%, 39%, and 17% of respective oral doses of norfloxacin were excreted in urine, chiefly as unchanged drug (>75%), but also as various combinations of six metabolites, all with modifications in the piperazine ring.

HUMAN PHARMACOLOGY

Pharmacokinetics

In 15 healthy fasting male volunteers aged 22 to 52 years (mean age: 34.1 $\pm$ 9.2 years), the mean peak serum concentrations of norfloxacin was 0.8 $\pm$ 0.3 (0.4-1.5) and 1.5 $\pm$ 0.6 (0.6-2.7) mg/L occurring within 1-1.5 hours of oral administration of 200 mg and 400 mg doses, respectively.

The mean elimination half-life of norfloxacin was approximately 3 hours. Therefore, as was noted in another group of 26 healthy male (23) and female (3) volunteers aged 19 to 50 years (mean: 28.6 ± 9.1 years), norfloxacin regimens of 400 mg given every 12 hours produced slight accumulation.

Theoretically it could be expected that steady-state concentrations will be attained after 2 days of recommended dosage.

Pharmacokinetic information for healthy normal volunteers is given in Table 9.

Excretion and Metabolism

Following oral administration to 15 healthy fasting male volunteers, aged 22 to 52 years (mean: 34.1 ± 9.2 years), 25% to 30% of a norfloxacin dose was recovered unchanged in urine within 48 hours (see Table 8).

TABLE 8: MEAN URINARY EXCRETION OF NORFLOXACIN

	Hours After Administration									
	0–1	**1–2**	**2–3**	**3–4**	**4–6**	**6–8**	**8–12**	**12–24**	**24–48**	**Total**
	Urine Concentration, □g/mL (±S.D.)									
200 mg dose	37.7 (31.3)	139.1 (159.9)	65.7 (88.3)	44.5 (54.8)	19.1 (10.7)	19.2 (9.9)	16.5 (10.5)	7.3 (6.4)	1.0 (1.7)	—
400 mg dose	38.6 (206.0)	392.7 (302.0)	244.6 (300.9)	141.0 (182.9)	57.0 (60.5)	42.2 (26.4)	36.0 (24.1)	13.7 (9.9)	1.5 (2.0)	—
400 mg dose elderly	100.6 (100.8)	154.1 (85.1)	148.3 (74.0)	67.8 (77.5)	101.8 (59.5)	43.0 (23.1)	30.5 (11.0)	12.8 (7.0)	— —	—
	Amount Excreted, mg (±S.D.)									
200 mg dose	3.2 (2.4)	14.2 (6.6)	8.2 (2.6)	5.0 (2.0)	6.5 (3.7)	3.9 (1.6)	5.0 (3.3)	5.3 (3.2)	0.9 (1.3)	52.2 (18.6)
400 mg dose	7.5 (6.4)	22.6 (9.9)	19.7 (12.9)	12.5 (6.6)	14.2 (6.4)	8.8 (3.4)	10.2 (4.3)	8.3 (4.3)	1.3 (1.8)	105.1 (36.2)
400 mg dose elderly	9.0 (3.3)	19.0 (9.0)	16.0 (9.0)	6.3 (3.7)	8.7 (5.9)	8.3 (7.1)	8.7 (4.2)	7.1 (3.2)	— —	83.2 (31.6)

During the same period of time, an additional 8 to 10% of the dose was recovered as 6 metabolites with modifications on the piperazine ring. The 2 major metabolites are the 3-oxo-piperazinyl derivative and the 7-ethylenediamine derivative. The 3-oxo-piperazinyl predominates and no glucuronide conjugates were detected. Norfloxacin and these metabolites were detected in bile. The concentration of norfloxacin in bile was 5 mcg/mL collected 1 to 2 hours after oral administration of a 200 mg dose to 1 patient with choledocholithiasis. A similar distribution ratio of the same 6 metabolites was in both bile and urine. These data suggest that 30-40% of an oral dose of norfloxacin is absorbed. After a single 400 mg dose, mean antimicrobial activities equivalent to 164 ±202, 338 ± 220, 632 ± 688, and 126 ± 123 mcg of norfloxacin/g of feces were recovered over 0 to 12, 12 to 24, 24 to 36, and 36 to 48 hours, respectively.

Renal excretion of norfloxacin occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance 275 ± 71 mL/min (range: 161 - 424) [4.58 ± 1.18 mL/s range: 2.68 - 7.07)].

Two to three hours after a single 400 mg dose, mean urinary concentrations of 200 mg/L or more were obtained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 mg/L for at least 12 hours following a 400 mg dose (see Table 8).

Factors Influencing the Pharmacokinetics

Food: Food slightly reduces the absorption of norfloxacin as evidenced by a reduction of approximately 30% in peak serum concentration and of approximately 35% in peak urine concentration.

Age (elderly): In 4 females and 2 males, 67 to 74 years old with normal renal function for their age i.e., creatinine clearance 91±14 mL/min./l.73 m^2 (1.52 ± 0.23 mL/s./l.73 m^2) norfloxacin was eliminated more slowly because of their slightly decreased renal function causing a small increase in plasma concentrations of drug.

Approximately 22% of the dose was recovered unchanged in urine (see Table 8). The renal clearance of drug was 154 mL/min (2.57 mL/s). The maximum plasma concentration was approximately 2 mg/L, occurring 1.3 hours after drug administration. The plasma half-life of norfloxacin in these individuals was 4 hours (see Table 9).

TABLE 9: COMPARISON OF PHARMACOKINETIC PARAMETERS BETWEEN HEALTHY ELDERLY VOLUNTEERS AND HEALTHY YOUNGER VOLUNTEERS FOLLOWING A SINGLE 400 MG ORAL DOSE

Parameter	Elderly Volunteers	Younger Volunteers
C_{max}, mg/L	2.0 (±0.8)	1.5 (±0.6)
T_{max}, hr	1.3 (±0.4)	1.0 (±0.4)
Half-life, hr	3.9	3.2
Total (AUC), mg.hr/L	9.8 (±2.8)	6.6 (±3.3)
Renal clearance, mL/min	154 (±16)	299 (±95)
Renal clearance, mL/s	2.57 (±0.27)	4.98 (±1.58)
%-Dose Urinary Recovery	22 (±7)	27 (±9)

Impaired Renal Function: Excretion of norfloxacin in patients with creatinine clearance (C_{cr}) greater than 30 mL/min/1.73 m^2 (0.50 mL/s/1.73 m^2), was similar to that of healthy volunteers. In patients with C_{cr} less than 30 mL/min/1.73 m^2 (0.50 mL/s/1.73 m^2) but greater than 6.6 mL/min/1.73 m^2 (0.11 mL/s/1.73 m^2), less than 10% of an oral dose was excreted in urine. The mean elimination half-life of norfloxacin in serum increased to 6.5 hours in these patients (see Table 10).

TABLE 10: MEAN PHARMACOKINETIC PARAMETERS FOR NORFLOXACIN FOLLOWING A SINGLE 400 MG ORAL DOSE IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH VARYING DEGREES OF RENAL INSUFFICIENCY

Group	Creatinine Clearance (mL/min/1.73 $m^{2)}$ [mL/s/1.73 m^2]	C_{max} (mg/L)	T_{max} (hr)	Half-Life (hr)*	Total (AUC) (mg.hr/L	Renal Clearance (mL/min)	% Dose Urinary Recovery
I	≥90 [≥1.5]	1.51 (±0.56)	1.4 (0.4)	3.47	6.94 (2.73)	297.2 (117.4)	28.2 (12.8)
II	31-89 [0.52-1.48]	1.91 (0.71)	1.3 (0.4)	3.38	9.53 (2.47)	264.5 (83.2)	35.3 (9.2)
III	10-30 [0.17-0.50]	1.70 (0.43)	1.8 (1.1)	6.57	24.01 (13.49)	17.8 (4.4)	6.7 (4.1)
IV	6.6-9 [0.11-0.15]	1.70 (0.92)	1.8 (1.2)	6.40	16.46 (14.52)	14.7 (8.4)	2.4 (1.1)

*Harmonic mean

Probenecid: The 12-hour urinary excretion of norfloxacin following a 200 mg dose was diminished from 28% of the dose to 14% of the dose by the coadministration of probenecid.

Serum Protein Binding: At a serum concentration of 2.5 mg/L, the human serum protein binding is 10 to 15%.

Tissue Concentrations: Concurrent norfloxacin concentrations in serum, tissues and body fluids are given in Table 11.

TABLE 11: NORFLOXACIN CONCENTRATIONS IN HUMAN TISSUES AND BODY FLUIDS

				Concentration (±S.D.)	
Tissue/Fluid	No. of Subjects	Dose of norfloxacin (mg)	Sampling time (hr after dose)	Tissue/Fluid (mg/L or mg/kg)	Serum µg/mL
Liver	2	200	2	3.40	0.10
				1.66	0.52
Gall Bladder	2	200	2.5	<0.2	-
				0.48	-
Gall Bladder Bile	2	200	2	0.15	0.10
				4.46	0.52
	20	400	2	10.3 (±2.7)	1.25 (±0.3)
Bile in Common bile duct	2	200	2.5	0.41	-
				4.19	-
	20	400	2	8.8 (±1.4)	1.25 (±0.3)
Bile	1	100	4	3.16	0.65
			6	5.68	0.48
	3	400	2	0.13-0.70	0.18-1.2
			3	2.72-6.0	0.53-1.1
			4	2.60-4.20	0.6-0.83
			6	1.4-2.5	0.30-0.70
Prostate	15	800+	3-4	0.93 (±0.66)	1.17 (±0.55)
	10	800*	1-2	<0.25-4.65	<0.25-5.30
Kidney**	3	800*	2	16.2	4.30
			3	15.1	4.00
			6.5	3.9	0.32

+ One 400 mg tablet at time zero the evening before surgery and again 11 hr later

* One 400 mg tablet given between 21hr and 22hr the night before surgery and a second 400 mg tablet one hour before surgery.

** The serum levels in 2 out of 3 patients were higher than expected and consequently kidney concentrations may also have been higher than expected

TOXICOLOGY

Acute Toxicity

SPECIES	SEX	ROUTE	LD_{50} mg/kg (95% confidence limit)
Mouse	Male	p.o.	> 4,000
Mouse	Male	Subcutaneous	> 1,500
Mouse	Male	Intramuscular	470 (405-545)
Mouse	Male	Intravenous	220 (209-232)
Mouse	Female	p.o.	> 4,000
Mouse	Female	Subcutaneous	> 1,500
Mouse	Female	Intramuscular	480 (429-538)
Mouse	Female	Intravenous	237 (226-248)
Rat	Male	p.o.	> 4,000
Rat	Male	Subcutaneous	> 1,500
Rat	Male	Intramuscular	> 500
Rat	Male	Intravenous	270 (233-313)
Rat	Female	p.o.	> 4,000
Rat	Female	Subcutaneous	> 1,500
Rat	Female	Intramuscular	> 500
Rat	Female	Intravenous	245 (211-284)

The six metabolites were also tested orally for their acute toxicity in rats and mice. The LD_{50} values were estimated to be greater than 2000 mg/kg.

Subacute Toxicity Studies

One month oral toxicity studies were carried out in rats (250, 500 and 1000 mg/kg/day, 10 males and 10 females per group), dogs (50, 100 and 200 mg/kg/day, one male and one female per group; or 25, 50 and 100 mg/kg b.i.d., 6 days per week, 3 males and 3 females per group) and monkeys (25, 50, 100 mg/kg, b.i.d., 6 days per week, 2 males per group). In all studies, similar size groups served as controls and received sterile distilled water.

A slight increase in urinary potassium excretion was seen in female rats dosed at 500 and 1000 mg/kg/day. There was, however, no concurrent decrease in serum potassium level. A slight enlargement of cecum was observed in 3 of 10 male rats at 1000 mg/kg/day. Liver glucose-6-phosphatase activity was slightly increased at all dose levels in the dog study in which norfloxacin was given at doses of 25, 50 or 100 mg/kg b.i.d.

Chronic Toxicity Studies

A six-month oral toxicity study in rats at norfloxacin doses of 0, 125, 250 and 500 mg/kg/day (10 rats/sex/group) revealed only minimal effects as evidenced by slight body weight retardation in male rats in the 250 and 500 mg/kg/day groups.

A similar study was carried out in rats (15 rats/sex/group) at norfloxacin doses of 0, 50, 200 and 600 mg/kg/day orally. There was a slight, but not statistically significant, decrease in body weight gain at 600 mg/kg/day in males. In addition, crystalluria consisting of the dihydrate and the magnesium salt of norfloxacin occurred in rats from the 200 and 600 mg/kg/day groups. The crystalluria was most frequent in males given 600 mg/kg/day. A high incidence of cecal enlargement was seen at all dose levels. Gray feces were observed in all treated groups and a very slight but statistically significant decrease in serum proteins was observed in males dosed at 600 mg/kg/day.

Four chronic oral toxicity studies were performed to evaluate the potential toxicity of norfloxacin in dogs following chronic administration for 20 weeks to 13 months. The doses used were: 0, 25, 50 and 100/200 mg/kg/day (the dose was increased due to lack of drug-induced effect, 6 days per week, 4 males and 4 females per group); 0, 50, 150 and 300 mg/kg/day (7 days per week, 3 males and 3 females per group); 0, 25, 50 and 100 mg/kg/day (7 days per week, 1 male and 1 female per group); 0, 50, 100 and 150 mg/kg/day (7 days per week, 4 males and 4 females per group). Crystalluria was evident in one of these studies where dogs were given the drug at 50, 150 and 300 mg/kg/day for 26 weeks. The incidence was dose related. Four dogs, (1 and 3 in the 150 mg and 300 mg/kg/day dosage groups respectively), were found dead or were sacrificed due to urinary obstruction from drug crystals. It was postulated that crystalluria in dogs and rats is the result of low solubility of norfloxacin in alkaline urine. This was supported by the observation of a significant decrease in the incidence of crystalluria and the absence of urinary obstruction in dogs in a separate study at 50, 150 and 300 mg/kg/day orally to 3 dogs/sex/group for three months where the urine was acidified by the administration of ammonium chloride. The pH after urine acidification was generally 6.0 or below whereas the urinary pH of dogs where drug crystals were formed was between 6.86 and 8.28.

Other frequently observed changes in the 150 and 300 mg/kg/day groups consisted of a dose-related incidence of emesis, grey or clay-coloured feces (due to unabsorbed drug) and retardation of body weight gain. There were also changes in the hematologic and serum biochemical parameters (leukocytosis, elevated serum urea nitrogen and creatinine) that are compatible with uremia and pyelonephritis secondary to intrarenal or urethral obstruction.

REPRODUCTION STUDIES

Fertility

The effect of norfloxacin on fertility was assessed in male and female mice. Norfloxacin was administered orally at dosage levels of 0, 125, 250, 500 mg/kg/day (20 per sex per group) for 61 days before mating and during mating to male mice and for 15 days before mating until the sixth day of pregnancy to female mice. There were no treatment-related effects on the reproductive performances of the adults or differences in growth and characteristics of the fetuses.

TERATOLOGY

In mice, oral doses of 0, 125, 250 or 500 mg/kg/day (31 mice/group) given on days 6 to 15 of gestation did not have any adverse effect on the pregnant mother or F_1 or F_2 fetuses.

In rats, oral doses of 0, 50, 200 or 800 mg/kg/day (administered b.i.d. to 20 rats/group) given on days 6 to 17 of gestation did not adversely affect the progress or outcome of pregnancy.

Rabbits

In an oral teratology study, rabbits were given 0, 25, 50 or 100 mg/kg/day of norfloxacin orally (12 or 13 rabbits per group) from day 6 to 18 of gestation. In this study, rabbits in the 100 mg/kg/day group showed decreased activity, reduced appetite, diarrhea and reduced body weight gain. Embryotoxicity (i.e., abortion and fetal resorption) was also observed at this dosage level. An additional study comparing the maternal and fetal toxicity of norfloxacin administered orally at doses of 100 mg/kg/day with that administered subcutaneously at doses of 20 mg/kg/day (which resulted in approximately 5-fold higher maximum plasma drug levels) was carried out. There was no evidence of embryotoxicity in the group that received norfloxacin at a dose of 20 mg/kg/day by the subcutaneous route. This suggested that the embryotoxicity of norfloxacin in rabbits did not correlate with drug levels in blood.

Monkeys

In an oral teratology study in cynomolgus monkeys, norfloxacin was given at doses of 0, 50, 100, 150 or 300/200 mg/kg/day (the dose was reduced because of emesis) in single or divided doses from days 20 to 50 gestation. There were at least 10 female monkeys in each group. Doses of 200 mg/kg/day and greater were maternotoxic and produced vomiting, reduced appetite, and body weight loss. In the 150 and 300/200 mg/kg/day groups, 3 of 10 and 11 of 16 monkeys lost their embryos. There was no evidence of a teratogenic effect in surviving fetuses. Doses of 100 mg/kg/day did not result in any increase in embryonic losses relative to controls.

Gestation and Postnatal Development

The effect of norfloxacin during the gestation and postnatal period was studied in mice at doses of 0, 125, 250 and 500 mg/kg/day (21 mice per group). Female mice were dosed orally from day 15 of gestation to day 21 postpartum. No significant difference was observed with newborn of the treated groups as compared to controls.

Mutagenicity

Norfloxacin was negative in a dominant lethal test in mice (300 or 800 mg/kg administered as a single dose), an *in vivo* chromosome aberration test in rats (1000 mg/kg/day for 38 days) and hamsters (250 or 500 mg/kg, one dose), and various *in vitro* genotoxicity studies including an Ames test, chromosomal aberration test, sister chromatid exchange assay, unscheduled DNA

synthesis assay and V-79 mammalian cell mutagenesis assay. Norfloxacin was weakly positive in a test for DNA repair (rec assay), however, this was considered to be of questionable biological significance since a more sensitive test for DNA repair (V-79 mammalian cell mutagenesis assay) was negative.

Carcinogenicity

A 19-month chronic oral toxicity study was done in rats (50 per sex per group). The rats were autopsied after a 12 to 14 week withdrawal period. Norfloxacin was given in the diet at 0.05 or 0.2% in the feed. The estimated drug intake was 18-35 mg/kg/day for the low dose group and 70-140 mg/kg/day for the high-dose group. No drug related neoplastic changes were reported as compared to control animals. The highest dose was below the maximum tolerated dose (approximately 600 mg/kg/day).

Special Toxicity Studies

Arthopathy

Three to five month old dogs were treated orally with norfloxacin for seven days at doses of 0, 30, 60, 100, 250 or 500 mg/kg/day or for 99 days at a dose of 0 or 200 mg/kg/day (2 or 3 dogs per group). Similarly, 8-10 week old rabbits were treated orally for seven days at 0, 250 or 300 mg/kg/day or for 21 days at 0, 100 or 150 mg/kg/day (5-11 rabbits/group). Nalidixic acid (30, 60 and 100 mg/kg/day) and pipemidic acid (30, 60, 100, 200 and 500 mg/kg/day) were used as positive controls. Clinical signs of lameness appeared from the second day in dogs given doses greater than 60 mg/kg/day of norfloxacin and persisted through the duration of the seven day study. Similar signs of lameness were seen in dogs given oral doses greater than 30 mg/kg/day of nalidixic acid and pipemidic acid. No clinical signs of lameness were seen in rabbits treated with any of these test compounds. In dogs, lameness was associated with joint lesions that were characterized by increased amount of synovial fluid and blister formation and sometimes erosions on the articular cartilage. There was recovery from clinical signs within six to eight weeks after initiation of the study, but lesions remained. In the rabbits, there was blister formation on the articular cartilage at doses of 250 mg/kg/day or greater for seven days. There were no clinical signs of lameness.

The arthropathogenic effects of norfloxacin were limited to young animals. There was no evidence of lameness or gross changes in the joints of dogs that were 8 to 10 months of age at the start of the study and given oral doses of norfloxacin up to 100 to 150 mg/kg/day for 22 weeks to 13 months.

Antigenicity

Antigenicity of norfloxacin was studied by examining its potential to induce delayed hypersensitivity and anaphylactic reaction in guinea pigs (0.8% and 0.5% respectively) and specific antibodies in rabbits (30 mg/ml - 1 ml, 2 injections). Norfloxacin elicited no delayed

hypersensitivity reaction on the skin of guinea pigs. Anaphylactic reaction was not observed in guinea pigs sensitized with norfloxacin alone or a mixture of norfloxacin and Freund's complete adjuvant. Serum from guinea pigs sensitized with norfloxacin failed to induce passive cutaneous anaphylaxis in recipient guinea pigs. Specific antibodies against norfloxacin were not detected in sera of rabbits immunized with norfloxacin conjugated with bovine gammaglobulin and Freund's complete adjuvant.

Retina

No evidence of retinal toxicity was seen in cats given oral doses up to 200 mg/kg/day for two weeks as measured by electroretinogram and histopathology.

Auditory System

Norfloxacin administered to rats at a rate of 500 mg/kg/day orally for six months did not have any adverse effect on the auditory or vestibular function or on the histology of the organ of Corti.

REFERENCES

1. Abiko T, Ishihama A, Ogawa N, et al. Phase I. Study on AM-715. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 136-145.

2. Barry AL, Jones RN. Cross-resistance among cinoxacin, ciprofloxacin, DJ-6783, enoxacin, nalidixic acid, norfloxacin and oxolinic acid after *in vitro* selection of resistant populations. Antimicrob Ag Chemother 1984; 25: 775-777.

3. Bauernfeind A, Petermuller C. *In vitro* activity of ciprofloxacin, norfloxacin and nalidixic acid. Eur J Clin Microbiol1983; 2:111-115.

4. Bergeron MG, Thabet M, Roy R, Lessard C, Foucault P. Norfloxacin penetration into human renal and prostatic tissue. Antimicrob Ag Chemother 1985; 28 (2): 349-350.

5. Body BA, Fromtling RA, Shadomy S, Shadomy HJ. *In vitro* antibacterial activity of norfloxacin compared with eight other antimicrobial agents. Eur J Clin Microbiol 1983; 2: 230-234.

6. Bologna M, Vaggi L, Flammini D, Carlucci G, Forchetti CM. Norfloxacin in prostatitis: correlation between HPLC tissue concentrations and clinical results. Drugs Exptl Clin Res 1985; 11 (2): 95-100.

7. Boppano VK, Swanson BN. Determination of norfloxacin, a new nalidixic acid analog, in human serum and urine by high-performance liquid chromatography. Antimicrob Ag Chemother 1982; 21: 808-810.

8. Carver PL, Fekety R. The quinolones expanded choices and individual differences. Consultant 1988; 28: 59-67.

9. Corigliano BE, Appleman MD, Haseltine PNR, Leedom JM. Comparative *in vitro* activities of norfloxacin (MK-0366) and six commonly used antimicrobial agents against 199 urinary isolates showing various degrees of antibiotic resistance. Diagn Microbiol Infect Dis 1984; 2: 101-106.

10. Cullman W, Stieglitz M, Baars B, Opferkuch W. Comparative evaluation of recently developed quinolone compounds -with a note on the frequency of resistance mutants. Chemotherapy (Basel) 1985; 31: 19-28.

11. Davies Bl, Maesen FPV. Drug interactions with quinolones. Rev Inf Dis 1989; II (Supp.5): S1083-1090.

12. Downs J, Andriole VT, Ryan JL. *In vitro* activity of MK-0366 against clinical urinary pathogens including gentamicin - resistant Pseudomonas aeruginosa. Antimicrob Ag

Chemother 1982; 21: 670-672.

13. Dubreuil L, Devos J, Romond C, Bryskier A. Susceptibility of obligate anaerobes to ofloxacin, pefloxacin, enoxacin and norfloxacin. Pathol Biol (Paris) 1985; 33: 421-425.

14. Duckworth GJ, Williams JD. Frequency of appearance of resistant variants to norfloxacin and nalidixic acid. J Antimicrob Chemother 1984; 13 (Suppl B): 33-38.

15. Edwards OJ, Bowles SK, Svensson CK, Rybak MJ. Inhibition of drug metabolism by quinolone antibiotics. Clin Pharmacokinet 1988; 15: 194-204.

16. Fromtling RA, Abruzzo GK, Gadebusch HH, *In vitro* effect of pH and glucose concentration on the antibacterial activity of norfloxacin in urine. Meth Find Exptl Clin Pharmacol1984; 6: 737-741.

17. Gadebusch HH, Koupal LR, Celozzi E, et al. Norfloxacin (MK-0366, AM-715), a new orally absorbed synthetic compound for the treatment of bacterial infections. Current Chemotherapy and Immunotherapy (Proc 12th ICC) 1982; Vol. 1, 351-353.

18. Gadebusch HH, Shungu DL, Weinberg E, Chung Sk. Comparison of the antibacterial activity of norfloxacin (MK-0366, AM-715), a new organic acid, with that of other orally absorbed chemotherapeutic agents. Infection 1982; 10: 41-44.

19. Goto S, Ogawa M, Kaneko Y, et al. The *in vitro* and *in vivo* antibacterial activities and serum levels of AM-715, a new quinolinecarboxylic acid. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 12-26.

20. Greenwood D, Osman M, Goodwin J, Cowlishaw WA, Slack R. Norfloxacin: activity against urinary tract pathogens and factors influencing the emergence of resistance. J Antimicrob Chemother 1984; 13: 315-323.

21. Haase D, Urias B, Harding G, Ronald A. Comparative *in vitro* activity of norfloxacin against urinary tract pathogens. Eur J Clin Microbial 1983; 2: 235-241.

22. Harder SS, Staib AH, Beer C, et al. 4-quinolones inhibit biotransformation of caffeine. Eur J Clin Pharmacal 1988; 35: 651-659.

23. Husson MO, Izard D, Leclerc H. Comparative *in vitro* antibacterial activity of norfloxacin versus four other quinolone derivatives. Drugs Exptl Clin Res 1984; 10: 315-319.

24. Irikura T, Suzuki H, Sugimoto T. Reproduction studies of AM-715 in mice, I. Fertility study. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 886-894.

25. Irikura T, Suzuki H, Sugimoto T. Reproduction studies of AM-715 in mice, II. Teratology study. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 895-914.

26. Irikura T, Suzuki H, Sugimoto T. Reproduction studies of AM-715 in Mice, III. Perinatal and post-natal study. Chemotherapy 1981; 29 (Suppl. 4): 915-931.

27. Ito A, Hirai K, Inoue M, Koga H, Suzue S, Irikura T, Mitsuhashi S. *In vitro* antibacterial activity of AM-715, a new nalidixic acid analog. Antimicrob Ag Chemother 1980; 17: 103-108.

28. Ito A, Shindo K, Matsumura E, et al. Clinical evaluation on AM-715 in the field of internal medicine. Chemotherapy (Tokyo) 1981; 29 (Suppl .4): 284-292.

29. Jones RN, Barry AL. Norfloxacin (MK-0366, AM-715): *in vitro* activity and cross resistance with other organic acids including quality control limits for disk diffusion testing. Diagn Microbiol Infect Dis 1983; 1: 165-172.

30. Kato Y, Saitoh A, Ishikawa K, et al. Studies of AM-715, a new synthetic antibacterial agent. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 146-156.

31. Khan MY, Gruninger RP, Nelson SM, Klicker RE. Comparative *in vitro* activity of norfloxacin (MK-0366) and ten other oral antimicrobial agents against urinary bacterial isolates. Antimicrob Ag Chemother 1982; 21: 848-851.

32. King A, Warren C, Shannon K, Phillips I. *In vitro* antibacterial activity of norfloxacin (MK-0366). Antimicrob Ag Chemother 1982; 21: 604-607.

33. Kiriyama T, Okada K, Okabe T, et al. A phase II study of AM-715 on acute simple cystitis and complicated urinary tract infection. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 531-545.

34. Koga H, Itoh A, Murayama S, Suzue S, Irikura T. Structure-activity relationships of antibacterial 6, 7 - and 7, 8 - Disubstituted 1 - Alkyl - 1,4 - Dihydro - -Oxoquinoline - 3 - carboxylic acids. J Med Chem 1980; 23: 1358-1363.

35. Leigh DA, Smith EC, Marriner J. Comparative study using norfloxacin and amoxicillin in the treatment of complicated urinary tract infections in geriatric patients. J Antimicrobial Chemother 1984; 13 (Suppl. B): 79-83.

36. Matsuoka K, Eto K, Sakai Y, et al. Clinical experience of AM-715 on urinary tract infection. Chemotherapy (Tokyo) 1981; 29 (Suppl . 4): 622-630.

37. Naide Y, Fujita T, Okishio N, et al. Clinical and pharmacological evaluation of AM-715 for application to urogenital infections. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 475-496.

38. Nakatsu H, Hatachi K, Fujii M, et al. Fundamental and clinical studies of AM-715 in complicated urinary tract infections. Chemotherapy 1981; 29 (Suppl. 4): 578-586.

39. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests - fourth edition. Approved standard, M2-A4. National Committee for Clinical Laboratory Standards, Villanova, PA. 1990; 10(7).

40. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Second edition approved standard, M7-A2. National Committee for Clinical Laboratory Standards, Villanova, PA. 1990; 10(8).

41. Neu HC. Effects of cations upon the activity of quinolone agents. In: Shah PM, ed. Quinolone Bulletin: reports on gyrase inhibitors. M.I. Publications, Frankfurt, 1985.

42. Neu HC, Labthavikul P. *In vitro* activity of norfloxacin, a quinolinecarboxalic acid, compared with that of β-lactams, aminoglycosides and trimethoprim. Antimicrob Ag Chemother 1982; 22: 23-27.

43. Newsom SWB. The antimicrobial spectrum of norfloxacin. J Antimicrob Chemother 1984; 13 (Suppl. B): 25-31.

44. Newsom SWB, Mathews J, Amphlett M, Warren RE. Norfloxacin and the antibacterial γ pyridone β carboxylic acids. J Antimicrob Chemother 1982; 10: 25-30.

45. Nix DE, Wilton JH, Ronald B, et al. Inhibition of norfloxacin absorption by antacids. Antimicrob Agents Chemother 1990; 34(3): 432-435.

46. Noyes M, Polk RE. Norfloxacin and absorption of magnesium-aluminum. Ann Intern Med 1988; 168-169.

47. Okayama K, Kanzaki R, Hayakawa M, et al. Basic and clinical studies on AM-715. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 259-283.

48. Ozaki T, Uchida H, Irikura T. Studies on the metabolism of AM-715 in humans by high-performance liquid chromatography. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 128-135.

49. Parpia SH, Nix DE, Hejmanowski LG, et al. Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob Agents Chemother 1989; 33(1): 99-102.

50. Polk RE. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med 1989; 87 (Suppl SA): 76S-81S.

51. Prince RA. Fluoroquinolone-drug interactions: an overview. Antimicrob Newsletter 1989; 6(12): 93-99.

52. Ratcliffe NT, Smith JT. Mechanism of reduced activity of 4-quinolone agents in urine. Fortschritte der Antimikrobiellen und Antineoplasticken Chemotherapie 1984; 3: 563-569.

53. Saito T, Yamada Y, Arai T. Studies on AM-715: biliary excretion, tissue concentration of the liver and the gallbladder wall, and clinical evaluation in surgical field. Chemotherapy 1981; 29(Suppl. 4): 631-638.

54. Sanders CC, Sanders WE Jr, Goering RV, Werner V. Selection of multiple antibiotic resistance by quinolones, β-lactams, and aminoglycosides with special reference to cross-resistance between unrelated drug classes. Antimicrob Ag Chemother 1984; 26: 797-801.

55. Sato K, Matsuura Y, Inoue M, Une T, Osada Y, Ogawa H, Mitsuhashi S. *In vitro* and *in vivo* activity of DL-8280, a new oxazine derivative. Antimicrob Ag Chemother 1982; 22: 548-553.

56. Sawae Y, Okada K. Laboratory and clinical studies on AM-715. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 388-395.

57. Shimada J, Yamaji T, Ueda Y, et al. Mechanism of renal excretion of AM-715, a new quinolocarboxylic acid derivative, in rabbits, dogs and humans. Antimicrob Agents Chemother 1983; 23: 1-7.

58. Shimura H, Yamamoto H, Igimi H, et al. Fundamental and clinical studies of norfloxacin (AM-715) in biliary tract infection. Chemotherapy 1983; 31: 351-367.

59. Shungu DL, Weinberg E, Gadebusch HH. Tentative interpretive standards for disk diffusion susceptibility testing with norfloxacin (MK-0366, AM-715). Antimicrobial Ag Chemother 1983; 23: 256-260.

60. Simon C, Lindner U. *In vitro* activity of norfloxacin against *Mycoplasma hominis* and *Ureaplasma urealyticum*. Eur J Clin Microbial 1983; 2: 479-480.

61. Speranza V, Fiocca F, Basoli A, Lezoche E. Norfloxacin treatment of biliary-tract infections. G ltal Chemioter 1984; 31: 149-152.

62. Stein GE. The 4-quinolone antibiotics: past, present and future. Pharmacotherapy 1988; 8: 301-314.

63. Stille W, Ostner KH. Nitrofurantoin-nalidixic acid antagonism. Klin Wochenschr 1966; 44: 155-156.

64. Takahashi H, Koboyashi Y, Fujimori I. Clinical study on AM-715. Chemotherapy (Tokyo) 1981; 29 (Suppl. 4): 293-298.

65. Thomson DJ, Menkis AH, McKenzie FM. Norfloxacin-cyclosporine interaction. Transplantation 1988; 46: 312-313.

66. Wang C, Sabbaj J, Corrado M, Hoagland V. World-wide clinical experience with norfloxacin: efficacy and safety. Scand J Infect Dis 1986; Suppl. 48: 81-89.

67. Westwood GPC, Hooper WL. Antagonism of oxolinic acid by nitrofurantoin (letter). Lancet 1975; 1: 460.

68. Yamamoto Y, Ihara T, Shimura H. Laboratory and clinical investigations of AM-715 in surgical field. Chemotherapy 1981; 29 (Suppl. 4): 663-668.

69. A comparative two-way, single-dose bioavailability study of norfloxacin 400 mg tablets in fasting volunteers. Completed November 1996. Data on file at Tev Canada Limited.

70. PrNORFLOXACIN Product Monograph by AA Pharma Inc. Control number 212191, date of revision: February 07, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr] TEVA-NORFLOXACIN
Norfloxacin Tablets, USP

Read this carefully before you start taking **TEVA-NORFLOXACIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-NORFLOXACIN**.

Serious Warnings and Precautions

Fluoroquinolones, including TEVA-NORFLOXACIN, are associated with disabling and long lasting effects such as:

- **tendonitis (inflamed tendon), tendon rupture.**
- **peripheral neuropathy (problems in the nerves).**
- **problems in the brain such as seizures, psychoses, confusion and other symptoms.**

See SIDE EFFECTS AND WHAT TO DO ABOUT THEM of the Patient Medication Information section for further information and symptoms.

Talk to your doctor to see if this medication is suitable for you.

What is TEVA-NORFLOXACIN used for?
- Norfloxacin is an antibiotic used to treat:

- infection of the urinary tract.
- bacterial infection (*Neisseria gonorrhea*) of:
    - the urethra (tube from the bladder to the penis or vaginal opening).
    - or cervix (lower part of the uterus).

Antibacterial drugs like TEVA-NORFLOXACIN treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, NORFLOXACIN should be used exactly as directed. Misuse or overuse of TEVA-NORFLOXACIN could lead to the growth of bacteria that will not be killed by TEVA-NORFLOXACIN (resistance).
This means that TEVA-NORFLOXACIN may not work for you in the future. Do not share your medicine.

How does TEVA-NORFLOXACIN work?
Norfloxacin works by:

- preventing the bacterial DNA from working, thereby preventing growth.
- kills bacteria.

What are the ingredients in TEVA-NORFLOXACIN?
Medicinal ingredients: Norfloxacin
Non-medicinal ingredients: croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triethyl citrate, polyethylene glycol and talc.

TEVA-NORFLOXACIN comes in the following dosage forms:
Tablets 400 mg

Do not use TEVA-NORFLOXACIN if:
- You are allergic to norfloxacin, or any ingredients in this product or any other quinolone antibacterial agents

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-NORFLOXACIN. Talk about any health conditions or problems you may have, including if you:
- have had seizures.
- have had tendon problems after using of quinolone antibiotics.
- have kidney disease.
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed.
- are taking any other prescription or non-prescription products.

Other warnings you should know about:
- If vision is affected with the use of TEVA-NORFLOXACIN, talk to your eye specialist immediately.
- Avoid excessive exposure to the sun when taking TEVA-NORFLOXACIN. Photosensitivity skin reactions can occur with symptoms such as inflamed red skin, hives, rash, itchiness and blisters. Talk to your doctor if this occurs.
- you have defects in the glucose-6-phosphate dehydrogenase enzyme. Using quinolone antibiotics, such as TEVA-NORFLOXACIN, can rarely destroy blood cells. Discuss with your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-NORFLOXACIN:
- Probenecid (gout medication).
- Theophylline (lung disease medication).
- Cyclosporine (skin and joint pain medication).
- Oral anticoagulant warfarin or its derivatives (blood thinner medication).
- Multivitamins.
- Products containing iron or zinc.
- Antacids (heartburn and indigestion medication).

- Sucralfate (intestinal disease medication).
- Caffeine.
- Nitrofurantoin (urinary tract infection medication).

How to take TEVA-NORFLOXACIN:

- Take this medicine exactly as directed by your physician. **Do not stop even if you feel better. Stopping too soon may cause your symptoms to return.**
- It is best to take the tablet with **a full glass of water,** one hour **before,** or two hours **after** eating a meal or drinking milk.
- Drink plenty of liquids every day during TEVA-NORFLOXACIN treatment (e.g. water or juice) to avoid potential side effects (e.g. crystalluria- cloudy urine).
- TEVA-NORFLOXACIN should not be taken within two hours of taking iron, zinc supplements or multivitamins containing them.

Usual dose:

Adults

The recommended dosage of TEVA-NORFLOXACIN for urinary tract infections is one 400 mg tablet twice a day for 7 to 10 days.

For women with a mild urinary tract infection, the recommend dosage can be decreased to 3 days.

For adults with gonococcal infection of the urethra or cervix, the recommended dosage of TEVA-NORFLOXACIN is two 400 mg tablets (800 mg) given as a single dose.

Elderly

The recommended dosage of TEVA-NORFLOXACIN in elderly patients with normal renal function for their age is the same as given for adults above.

Overdose:

If you think you have taken too much TEVA-NORFLOXACIN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take the next recommended dose as scheduled. **Do not double the dose to make up for the missed dose.** If you happen to take too many tablets by accident, contact your physician or pharmacist immediately.

What are the possible side effects from using TEVA-NORFLOXACIN?
These are not all the possible side effects you may have when taking TEVA-NORFLOXACIN. If you have a side effect not shown here, contact your doctor.
Stop taking TEVA-NORFLOXACIN and contact your doctor right away if:

a) You have pain, swelling or rupture of your tendon and:
- rest
- avoid physical exercise

Fluoroquinolones, like TEVA-NORFLOXACIN, have been associated with these effects.

b) You have problems in your nerves (neuropathy) with symptoms such as:
- pain, burning, tingling, numbness or weakness

Fluoroquinolones, like TEVA-NORFLOXACIN, have been associated with this condition.

Fluoroquinolones, like TEVA-NORFLOXACIN, have been associated with effects such as:
- confusion, tremors, headache.
- seeing things, depression, agitation.
- difficulty sleeping, anxiety, nervousness and suicidal thoughts.
-

Contact your doctor right away if you have suicidal thoughts.

Common side effects that may occur include:
- nausea, headache and dizziness

Other side effects that may occur include:
- rash, itching, muscle pain
- vomiting, upset stomach, diarrhea, constipation
- poor appetite

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
NOT KNOWN			
allergic reactions with symptoms: swelling of the face, lips throat, hives, difficulty breathing			√
pancreatitis (inflamed pancreas) with symptoms: abdominal pain, nausea, vomiting			√
destruction of red blood cells (hemolytic anemia) with symptoms: fatigue, shortness of breath, yellowing of skin and			√

eyes			
lower blood platelets (thrombocytopenia) with symptoms: increased bleeding (nose bleeds) bruising or red/purple spots on the skin			√
serious skin reactions with symptoms: widespread blisters on skin, mouth and nose, peeling skin			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffectcanada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature 15°C to 30°C
- Store your tablets in a tightly closed container, away from direct light, and out of damp places such as the bathroom or kitchen.

Keep out of reach and sight of children.

If you want more information about TEVA-NORFLOXACIN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9.

Last Revised: October 12, 2018