AVELOX®
(moxifloxacin hydrochloride) Tablets
AVELOX® I.V.
(moxifloxacin hydrochloride in sodium chloride injection)

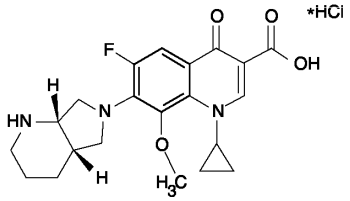
08918409, R.XX 08/08

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

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

DESCRIPTION

AVELOX (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as AVELOX Tablets for oral administration and as AVELOX I.V. for intravenous administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular weight of 437.9. Its empirical formula is $C_{21}H_{24}FN_3O_4$ *HCl and its chemical structure is as follows:



AVELOX Tablets are available as film-coated tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin). The inactive ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and ferric oxide.

AVELOX I.V. is available in ready-to-use 250 mL latex-free flexibags as a sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin) with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The color does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, USP, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

CLINICAL PHARMACOLOGY

Absorption

Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The

absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin. Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally are summarized below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48 ± 2.7	12.7 ± 1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	

* Range of means from different studies

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given by 1 hour I.V. infusion are summarized below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose I.V.			
Healthy young male/female (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)			
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2		
< 65 years (n = 58)	4.6 ± 4.2		
≥ 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients** (n = 107)			
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
≥ 65 years (n = 55)	4.7 ± 2.7		

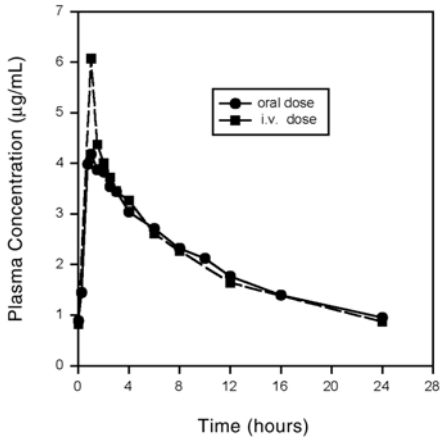
* Range of means from different studies

** Expected C_{max} (concentration obtained around the time of the end of the infusion)

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state

is achieved after at least three days with a 400 mg once daily regimen.

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Distribution

Moxifloxacin is approximately 30-50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg. Moxifloxacin is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, subcutaneous tissue, skeletal muscle, and abdominal tissues and fluids following oral or intravenous administration of 400 mg. Moxifloxacin concentrations measured post-dose in various tissues and fluids following a 400 mg oral or I.V. dose are summarized in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Tissues and the Corresponding Plasma Concentrations After a Single 400 mg Oral or Intravenous Dose [§]

Tissue or Fluid	N	Plasma Concentration (µg/mL)	Tissue or Fluid Concentration (µg/mL or µg/g)	Tissue Plasma Ratio:
Respiratory				
Alveolar Macrophages	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10
Bronchial Mucosa	8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial Lining Fluid	5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus				
Maxillary Sinus Mucosa	4	3.7 ± 1.1[†]	7.6 ± 1.7	2 ± 0.3
Anterior Ethmoid Mucosa	3	3.7 ± 1.1[†]	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	3.7 ± 1.1[†]	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal				

Blister Fluid	5	3.0 ± 0.5‡	2.6 ± 0.9	0.9 ± 0.2
Subcutaneous Tissue	6	2.3 ± 0.4#	0.9 ± 0.3*	0.4 ± 0.6
Skeletal Muscle	6	2.3 ± 0.4#	0.9 ± 0.2*	0.4 ± 0.1
Intra-Abdominal				
Abdominal tissue	8	2.9 ± 0.5	7.6 ± 2.0	2.7 ± 0.8
Abdominal exudate	10	2.3 ± 0.5	3.5±1.2	1.6 ± 0.7
Abscess fluid	6	2.7 ± 0.7	2.3 ±1.5	0.8±0.4

§ all moxifloxacin concentrations were measured 3 hours after a single 400 mg dose, except the abdominal tissue and exudate concentrations which were measured at 2 hours post-dose and the sinus concentrations which were measured 3 hours post-dose after 5 days of dosing.

† N = 5

‡N = 7

#N = 12

* Reflects only non-protein bound concentrations of drug.

Metabolism

Approximately 52% of an oral or intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral or intravenous dose is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

In vitro studies with cytochrome (CYP) P450 enzymes indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

Excretion

Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2 L/hr and 2.6 ± 0.5 L/hr, respectively.

Special Populations

Geriatric

Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and 17 young (8 male; 9 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics. In 16 healthy male volunteers (8 young; 8 elderly) given a single 200 mg dose of oral moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was not statistically different between young and elderly males and elimination half-life was unchanged. No dosage adjustment is necessary based on age. In large phase III studies, the concentrations around the time of the end of the infusion in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients.

Pediatric

The pharmacokinetics of moxifloxacin in pediatric subjects have not been studied.

Gender

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. There are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration.

A 400 mg single dose study was conducted in 18 young males and females. The comparison of moxifloxacin pharmacokinetics in this study (9 young females and 9 young males) showed no differences in AUC or C_{max} due to gender. Dosage adjustments based on gender are not necessary.

Race

Steady-state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians, with a mean C_{max} of 4.1 µg/mL, an AUC_{24} of 47 µg•h/mL, and an elimination half-life of 14 hours, following 400 mg p.o. daily.

Renal Insufficiency

The pharmacokinetic parameters of moxifloxacin are not significantly altered in mild, moderate, severe, or end-stage renal disease. No dosage adjustment is necessary in patients with renal impairment, including those patients requiring hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).

In a single oral dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin were reduced by 21% and 28% in the patients with moderate ($CL_{CR} \geq 30$ and ≤ 60 mL/min) and severe ($CL_{CR} < 30$ mL/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients was increased by 13%. In the moderate and severe renally impaired patients, the mean AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and 1.4-fold (ranging up to 2.5-fold), respectively.

The pharmacokinetics of single dose and multiple dose moxifloxacin were studied in patients with $CL_{CR} < 20$ mL/min on either hemodialysis or continuous ambulatory peritoneal dialysis (8 HD, 8 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin in these HD and CAPD patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of moxifloxacin were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5 to 3, compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal disease including those undergoing HD and CAPD has not been studied.

Oral administration of 400 mg QD moxifloxacin for 7 days to patients on HD or CAPD produced mean systemic exposure (AUC_{ss}) to moxifloxacin similar to that generally seen in healthy volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Both HD and CAPD removed only small amounts of moxifloxacin from the body (approximately 9% by HD, and 3% by CAPD). HD and CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

Hepatic Insufficiency

In 400 mg single oral dose studies in 6 patients with mild (Child Pugh Class A), and 10 patients with moderate (Child Pugh Class B), hepatic insufficiency, moxifloxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of controls.

The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8-fold) in the mild and moderate groups, respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See **DOSAGE AND ADMINISTRATION.**)

Photosensitivity Potential

A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32 healthy volunteers (8 per group) demonstrated that moxifloxacin does not show phototoxicity in comparison to placebo. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo. In this study, the MED measured for both doses of moxifloxacin were not significantly different from placebo, while lomefloxacin significantly lowered the MED. (See **PRECAUTIONS, Information for Patients.**)

It is difficult to ascribe relative photosensitivity/phototoxicity among various fluoroquinolones during actual patient use because other factors play a role in determining a subject's susceptibility to this adverse event such as: a patient's skin pigmentation, frequency and duration of sun and artificial ultraviolet light (UV) exposure, wearing of sunscreen and protective clothing, the use of other concomitant drugs and the dosage and duration of fluoroquinolone therapy (See **ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports).**

Drug-drug Interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole, theophylline, warfarin, digoxin, atenolol, probenecid, morphine, oral contraceptives, ranitidine, glyburide, calcium, iron, and antacids has been evaluated. There was no clinically significant effect of moxifloxacin on itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives, or glyburide kinetics. Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of moxifloxacin. These results and the data from *in vitro* studies suggest that moxifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 enzymes.

As with all other quinolones, iron and antacids significantly reduced bioavailability of moxifloxacin.

Itraconazole: In a study involving 11 healthy volunteers, there was no significant effect of itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the pharmacokinetics of moxifloxacin (a single 400 mg dose given on the 7th day of itraconazole dosing). In addition, moxifloxacin was shown not to affect the pharmacokinetics of itraconazole.

Theophylline: No significant effect of moxifloxacin (200 mg every twelve hours for 3 days) on the pharmacokinetics of theophylline (400 mg every twelve hours for 3 days) was detected in a study involving 12 healthy volunteers. In addition, theophylline was not shown to affect the pharmacokinetics of moxifloxacin. The effect of co-administration of a 400 mg dose of moxifloxacin with theophylline has not been studied, but it is not expected to be clinically significant based on *in vitro* metabolic data showing that moxifloxacin does not inhibit the CYP1A2 isoenzyme.

Warfarin: No significant effect of moxifloxacin (400 mg once daily for eight days) on the pharmacokinetics of R- and S-warfarin (25 mg single dose of warfarin sodium on the fifth day) was detected in a study involving 24 healthy volunteers. No significant change in prothrombin time was observed. (See **PRECAUTIONS, Drug Interactions.**)

Digoxin: No significant effect of moxifloxacin (400 mg once daily for two days) on digoxin (0.6 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The mean digoxin C_{max} increased by about 50% during the distribution phase of digoxin. This transient increase in digoxin C_{max} is not viewed to be clinically significant. Moxifloxacin pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for moxifloxacin or digoxin is required when these drugs are administered concomitantly.

Atenolol: In a crossover study involving 24 healthy volunteers (12 male; 12 female), the mean atenolol AUC following a single oral dose of 50 mg atenolol with placebo was similar to that observed when atenolol was given concomitantly with a single 400 mg oral dose of moxifloxacin. The mean C_{max} of single dose atenolol decreased by about 10% following co-administration with a single dose of moxifloxacin.

Morphine: No significant effect of morphine sulfate (a single 10 mg intramuscular dose) on the mean AUC and C_{max} of moxifloxacin (400 mg single dose) was observed in a study of 20 healthy male and female volunteers.

Oral Contraceptives: A placebo-controlled study in 29 healthy female subjects showed that moxifloxacin 400 mg daily for 7 days did not interfere with the hormonal suppression of oral contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered contraceptive agents.

Probenecid: Probenecid (500 mg twice daily for two days) did not alter the renal clearance and total amount of moxifloxacin (400 mg single dose) excreted renally in a study of 12 healthy volunteers.

Ranitidine: No significant effect of ranitidine (150 mg twice daily for three days as pretreatment) on the pharmacokinetics of moxifloxacin (400 mg single dose) was detected in a study involving 10 healthy volunteers.

Antidiabetic agents: In diabetics, glyburide (2.5 mg once daily for two weeks pretreatment and for five days concurrently) mean AUC and C_{max} were 12% and 21% lower, respectively, when taken with moxifloxacin (400 mg once daily for five days) in comparison to placebo. Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin in comparison to those taking glyburide alone, suggesting no interference by moxifloxacin on the activity of glyburide. These interaction results are not viewed as clinically significant.

Calcium: Twelve healthy volunteers were administered concomitant moxifloxacin (single 400 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement) followed by an additional two doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no significant effect on the mean AUC of moxifloxacin. The mean C_{max} was slightly reduced and the

time to maximum plasma concentration was prolonged when moxifloxacin was given with calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours). These differences are not considered to be clinically significant.

Antacids: When moxifloxacin (single 400 mg tablet dose) was administered two hours before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there was a 26%, 60% and 23% reduction in the mean AUC of moxifloxacin, respectively. Moxifloxacin should be taken at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or VIDEX® (didanosine) chewable/ buffered tablets or the pediatric powder for oral solution. (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND ADMINISTRATION.**)

Iron: When moxifloxacin tablets were administered concomitantly with iron (ferrous sulfate 100 mg once daily for two days), the mean AUC and C_{max} of moxifloxacin was reduced by 39% and 59%, respectively. Moxifloxacin should only be taken more than 4 hours before or 8 hours after iron products. (See **PRECAUTIONS, Drug Interactions** and **DOSAGE AND ADMINISTRATION.**)

Electrocardiogram: Prolongation of the QT interval in the ECG has been observed in some patients receiving moxifloxacin. Following oral dosing with 400 mg of moxifloxacin the mean (± SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6 msec (± 26) (n = 787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 msec (± 24) on Day 1 (n = 69) and 3 msec (± 29) on Day 3 (n = 290). (See **WARNINGS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with high doses of intravenous (I.V.) moxifloxacin in dogs. Therefore, moxifloxacin should be avoided with Class IA and Class III antiarrhythmics. (See **ANIMAL PHARMACOLOGY, WARNINGS,** and **PRECAUTIONS.**)

MICROBIOLOGY

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin and other quinolones. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

In vitro resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency of between 1.8×10^{-9} to $< 1 \times 10^{-11}$ for Gram-positive bacteria.

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic Gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus anginosus
Streptococcus constellatus
Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]*)
Streptococcus pyogenes

* MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 μg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic Gram-negative microorganisms

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

Anaerobic microorganisms

Bacteroides fragilis
Bacteroides thetaiotaomicron
Clostridium perfringens
Peptostreptococcus species

Other microorganisms

Chlamydia pneumoniae
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**
Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 μg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
Streptococcus viridans group

Aerobic Gram-negative microorganisms

Citrobacter freundii
Klebsiella oxytoca
Legionella pneumophila

Anaerobic microorganisms

Fusobacterium species

Prevotella species

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and methicillin-susceptible *Staphylococcus aureus*:

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [a]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* species including *Streptococcus pneumoniae* [b] and *Enterococcus faecalis*:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard moxifloxacin powder should provide the following MIC values:

Microorganism		MIC (µg/mL)
Enterococcus faecalis	ATCC 29212	0.06 - 0.5

Escherichia coli	ATCC 25922	0.008 - 0.06
Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Staphylococcus aureus	ATCC 29213	0.015 - 0.06
Streptococcus pneumoniae	ATCC 49619[d]	0.06 - 0.25

[c]This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[d]This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg moxifloxacin to test the susceptibility of microorganisms to moxifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg moxifloxacin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing Enterobacteriaceae and methicillin-susceptible *Staphylococcus aureus*:

Zone Diameter (mm)	Interpretation	
≥ 19	Susceptible	(S)
16 – 18	Intermediate	(I)
≤ 15	Resistant	(R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[e]*:*

Zone Diameter (mm)	Interpretation	
≥ 18	Susceptible	(S)

[e] This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[2].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* species including *Streptococcus pneumoniae* [f] and *Enterococcus faecalis*:

Zone Diameter (mm)	Interpretation	
≥ 18	Susceptible	(S)
15 – 17	Intermediate	(I)
≤ 14	Resistant	(R)

[f]These interpretive standards are applicable only to disk diffusion tests using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for moxifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg moxifloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)

Escherichia coli	ATCC 25922	28 – 35
Haemophilus influenzae	ATCC 49247[g]	31 – 39
Staphylococcus aureus	ATCC 25923	28 – 35
Streptococcus pneumoniae	ATCC 49619[h]	25 – 31

[g] These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)[2].

[h] These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Anaerobic Techniques: For anaerobic bacteria, the susceptibility to moxifloxacin as MICs can be determined by standardized procedures[3] such as reference agar dilution methods[i]. The MICs obtained should be interpreted according to the following criteria:

MIC (ug/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

[i] This interpretive standard is applicable to reference agar dilution susceptibility tests using *Brucella* agar supplemented with hemin, vitamin K_1 and 5% laked sheep blood.

Acceptable ranges of MICs (ug/mL) for control strains for reference agar dilution testing [j]:

Microorganism		MIC (ug/mL)
Bacteroides fragilis	ATCC 25285	0.12-0.5
Bacteroides thetaiotaomicron	ATCC 29741	1-4
Eubacterium lentum	ATCC 43055	0.12-0.5

[j] These quality control ranges are applicable to reference agar dilution tests using *Brucella* agar supplemented with hemin, vitamin K_1 and 5% laked sheep blood.

INDICATIONS AND USAGE

AVELOX Tablets and I.V. are indicated for the treatment of adults (≥ 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION** for specific recommendations. In addition, for I.V. use see **PRECAUTIONS, Geriatric Use.**)

Acute Bacterial Sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*

Acute Bacterial Exacerbation of Chronic Bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-susceptible *Staphylococcus aureus,* or *Moraxella catarrhalis.*

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant strains*), *Haemophilus influenzae, Moraxella catarrhalis,* methicillin-susceptible *Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae,* or *Chlamydia pneumoniae.*

* MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 μg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Uncomplicated Skin and Skin Structure Infections caused by methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*.

Complicated Intra-Abdominal Infections including polymicrobial infections such as abscess caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides thetaiotaomicron*, or *Peptostreptococcus* species.

Complicated Skin and Skin Structure Infections caused by methicillin-susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae* (See **Clinical Studies**).

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with AVELOX may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AVELOX and other antibacterial drugs, AVELOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Moxifloxacin is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

Tendinopathy and Tendon Rupture: Fluoroquinolones, including AVELOX, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. AVELOX should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

THE SAFETY AND EFFECTIVENESS OF MOXIFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PRECAUTIONS-PEDIATRIC USE, PREGNANCY AND NURSING MOTHERS

SUBSECTIONS.)

QT prolongation: Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 9,200 patients in controlled clinical studies, including 223 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 moxifloxacin tablet treated patients in a post-marketing observational study in which ECGs were not performed. (See **CLINICAL PHARMACOLOGY, Electrocardiogram.** For I.V. use, see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS, Geriatric Use.**)

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY.**)

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving moxifloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold. (See **PRECAUTIONS: General, Information for Patients,** and **ADVERSE REACTIONS.**)

Hypersensitivity reactions: Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including moxifloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Moxifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, may be administered as indicated.

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones,

including AVELOX. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AVELOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones.

PRECAUTIONS

General: Quinolones may cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS** and **Information for Patients.**)

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolone antibiotics after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (See **ADVERSE REACTIONS** and **ADVERSE REACTIONS/ Post-Marketing Adverse Event Reports**).

Prescribing AVELOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the

development of drug-resistant bacteria.

Information for Patients:

To assure safe and effective use of moxifloxacin, the following information and instructions should be communicated to the patient when appropriate:

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue AVELOX treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- that antibacterial drugs including AVELOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AVELOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AVELOX or other antibacterial drugs in the future.
- that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.
- to inform their physician of any other medications when taken concurrently with moxifloxacin, including over-the-counter medications.
- to contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.
- that moxifloxacin tablets may be taken with or without meals, and to drink fluids liberally.
- that moxifloxacin tablets should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate, or VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug Interactions.**)
- that moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and

discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician (see **CLINICAL PHARMACOLOGY/ Photosensitivity Potential**).

- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.
- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions:

Antacids, Sucralfate, Metal Cations, Multivitamins: Quinolones form chelates with alkaline earth and transition metal cations. Oral administration of quinolones with antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before or 8 hours after these agents. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **DOSAGE AND ADMINISTRATION.**)

No clinically significant drug-drug interactions between itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives or glyburide have been observed with moxifloxacin. Itraconazole, theophylline, digoxin, probenecid, morphine, ranitidine, and calcium have been shown not to significantly alter the pharmacokinetics of moxifloxacin. (See **CLINICAL PHARMACOLOGY.**)

Warfarin: No significant effect of moxifloxacin on R- and S-warfarin was detected in a clinical study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in the presence of moxifloxacin. Quinolones, including moxifloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives.

Drugs metabolized by Cytochrome P450 enzymes: *In vitro* studies with cytochrome P450 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (e.g. midazolam, cyclosporine, warfarin, theophylline).

Nonsteroidal anti-inflammatory drugs (NSAIDs): Although not observed with moxifloxacin in preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions. (See **WARNINGS.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed.

Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 12 times the maximum recommended human dose based on body surface area (mg/m^2), or at intravenous doses as high as 45 mg/kg/day, approximately equal to the maximum recommended human dose based on body surface area (mg/m^2). At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

Pregnancy: Teratogenic Effects. Pregnancy Category C:

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose based on systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 80 mg/kg/day (approximately 2 times the maximum recommended human dose based on body surface area (mg/m^2)) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day. Intravenous administration of 20 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon systemic exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body weights and delayed fetal skeletal ossification. When rib and vertebral malformations were combined, there was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose included mortality, abortions, marked reduction of food consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when pregnant cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival. Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.

Since there are no adequate or well-controlled studies in pregnant women, moxifloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin may also be excreted in human milk. Because of the potential for serious adverse reactions in infants who are nursing from mothers taking moxifloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Moxifloxacin causes arthropathy in juvenile animals. (See **WARNINGS.**)

Geriatric Use:

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as AVELOX. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing AVELOX to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue AVELOX and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

In controlled multiple-dose clinical trials, 23% of patients receiving oral moxifloxacin were greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The clinical trial data demonstrate that there is no difference in the safety and efficacy of oral

moxifloxacin in patients aged 65 or older compared to younger adults.
In trials of intravenous use, 42% of moxifloxacin patients were greater than or equal to 65 years of age, and 23% were greater than or equal to 75 years of age. The clinical trial data demonstrate that the safety of intravenous moxifloxacin in patients aged 65 or older was similar to that of comparator-treated patients. In general, elderly patients may be more susceptible to drug-associated effects of the QT interval. Therefore, AVELOX should be avoided in patients taking drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

Clinical efficacy trials enrolled over 9,200 moxifloxacin orally and intravenously treated patients, of whom over 8,600 patients received the 400 mg dose. Most adverse events reported in moxifloxacin trials were described as mild to moderate in severity and required no treatment. Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 2.9% of orally treated patients and 6.3 % of sequentially (intravenous followed by oral) treated patients. The latter studies were conducted in community acquired pneumonia and complicated skin and skin structure infections and complicated intra-abdominal infections with, in general, a sicker patient population compared to the tablet studies.
Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 2% of moxifloxacin treated patients were: nausea (6%), diarrhea (5%), dizziness (2%).
Additional clinically relevant uncommon events, judged by investigators to be at least possibly drug-related, that occurred in greater than or equal to 0.1% and less than 2% of moxifloxacin treated patients were:

BODY AS A WHOLE: abdominal pain, headache, asthenia, injection site reaction (including phlebitis), malaise, moniliasis, pain, allergic reaction
CARDIOVASCULAR: tachycardia, palpitation, vasodilation, QT interval prolonged
DIGESTIVE: vomiting, abnormal liver function test, dyspepsia, dry mouth, flatulence, oral moniliasis, constipation, GGTP increased, anorexia, stomatitis, glossitis
HEMIC AND LYMPHATIC: leukopenia, eosinophilia, prothrombin decrease (prothrombin time prolonged/International Normalized Ratio (INR) increased), thrombocythemia
METABOLIC AND NUTRITIONAL: lactic dehydrogenase increased, amylase increased
MUSCULOSKELETAL: arthralgia, myalgia
NERVOUS SYSTEM: insomnia, nervousness, vertigo, somnolence, anxiety, tremor
SKIN/APPENDAGES: rash (maculopapular, purpuric, pustular), pruritus, sweating, urticaria
SPECIAL SENSES: taste perversion
UROGENITAL: vaginal moniliasis, vaginitis

Additional clinically relevant rare events, judged by investigators to be at least possibly drug-related, that occurred in less than 0.1% of moxifloxacin treated patients were:
abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation, back pain, chest pain, confusion, convulsions, depersonalization, depression, dysphagia, dyspnea, ECG abnormal, emotional lability, face edema, gastritis, gastrointestinal disorder, hallucinations, hyperglycemia, hyperlipidemia, hypertension, hypertonia, hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic), kidney function abnormal, lab test abnormal (not specified), leg pain, paraesthesia, parosmia, pelvic pain, peripheral edema, photosensitivity/phototoxicity reactions, pseudomembranous colitis, prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR) decreased), sleep disorders, speech disorders, supraventricular tachycardia, syncope, taste loss,

tendon disorder, thinking abnormal, thrombocytopenia, thromboplastin decrease, tinnitus, tongue discoloration, ventricular tachycardia

Post-Marketing Adverse Event Reports:

Additional adverse events have been reported from worldwide post-marketing experience with moxifloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events, some of them life-threatening, include anaphylactic reaction, anaphylactic shock, angioedema (including laryngeal edema), hepatic failure, including fatal cases, hepatitis (predominantly cholestatic), photosensitivity/phototoxicity reaction (see **PRECAUTIONS)**, psychotic reaction, Stevens-Johnson syndrome, tendon rupture, toxic epidermal necrolysis, and ventricular tachyarrhythmias (including in very rare cases cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions).

LABORATORY CHANGES

Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in ≥ 2% of patients and at an incidence greater than in controls included: increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin, bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose, pO_2, bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities were caused by the drug or the underlying condition being treated.

OVERDOSAGE

Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient should be carefully observed and given supportive treatment. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure. About 3% and 9% of the dose of moxifloxacin, as well as about 2% and 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and hemodialysis, respectively.

Single oral moxifloxacin doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was 100 mg/kg. Toxic signs after administration of a single high dose of moxifloxacin to these animals included CNS and gastrointestinal effects such as decreased activity, somnolence, tremor, convulsions, vomiting and diarrhea.

DOSAGE AND ADMINISTRATION

The dose of AVELOX is 400 mg (orally or as an intravenous infusion) once every 24 hours. The duration of therapy depends on the type of infection as described below.

Infection *	Daily Dose	Duration
Acute Bacterial Sinusitis	400 mg	10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5 days
Community Acquired Pneumonia	400 mg	7-14 days
Uncomplicated Skin and Skin Structure Infections	400 mg	7 days
Complicated Skin and Skin Structure Infections	400 mg	7 – 21 days
Complicated Intra-Abdominal Infections	400 mg	5-14 days

* due to the designated pathogens (See **INDICATIONS AND USAGE.**). For I.V. use see **Precautions, Geriatric Use.**

For Complicated Intra-Abdominal Infections, therapy should usually be initiated with the intravenous formulation.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with AVELOX I.V. may be switched to AVELOX Tablets when clinically indicated at the discretion of the physician.

Oral doses of moxifloxacin should be administered at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug Interactions.**)

Impaired Renal Function

No dosage adjustment is required in renally impaired patients, including those on either hemodialysis or continuous ambulatory peritoneal dialysis.

Impaired Hepatic Function

No dosage adjustment is required in patients with mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in patients with severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See **CLINICAL PHARMACOLOGY, Hepatic Insufficiency.**)

AVELOX I.V. should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

AVELOX I.V. should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to AVELOX I.V. or infused simultaneously through the same intravenous line. If the same

intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the "piggyback" method of administration is used, the line should be flushed before and after infusion of AVELOX I.V. with an infusion solution compatible with AVELOX I.V. as well as with other drug(s) administered via this common line.

AVELOX I.V. is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP	Sterile Water for Injection, USP
1M Sodium Chloride Injection	10% Dextrose for Injection, USP
5% Dextrose Injection, USP	Lactated Ringer's for Injection

Preparation for administration of AVELOX I.V. injection premix in flexible containers:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin from an appropriate transfer set (e.g. one that does not require excessive force, such as ISO compatible administration set) into port with a gentle twisting motion until pin is firmly seated.

NOTE: Refer to complete directions that have been provided with the administration set.

HOW SUPPLIED

Tablets

AVELOX (moxifloxacin hydrochloride) Tablets are available as oblong, dull red film-coated tablets containing 400 mg moxifloxacin.

The tablet is coded with the word "BAYER" on one side and "M400" on the reverse side.

Package	NDC Code
Bottles of 30:	0085-1733-01
Unit Dose Pack of 50:	0085-1733-02
ABC Pack of 5:	0085-1733-03

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Avoid high humidity.

Intravenous Solution – Premix Bags

AVELOX I.V. (moxifloxacin hydrochloride in sodium chloride injection) is available in ready-to-use 250 mL latex-free flexible bags containing 400 mg of moxifloxacin in 0.8% saline. NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.

Package	NDC Code
250 mL flexible container	0085-1737-01

Parenteral drug products should be inspected visually for particulate matter prior to administration. Samples containing visible particulates should not be used.

Since the premix flexible containers are for single-use only, any unused portion should be discarded.

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

DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile dogs oral doses of moxifloxacin ≥ 30 mg/kg/day (approximately 1.5 times the maximum recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy. There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and 500 mg/kg/day, respectively.

Unlike some other members of the quinolone class, crystalluria was not observed in 6 month repeat dose studies in rats and monkeys with moxifloxacin.

No ocular toxicity was observed in a 13 week oral repeat dose study in dogs with a moxifloxacin dose of 60 mg/kg/day. Ocular toxicity was not observed in 6 month repeat dose studies in rats and monkeys (daily oral doses up to 500 mg/kg and 135 mg/kg, respectively). In beagle dogs, electroretinographic (ERG) changes were observed in a 2 week study at oral doses of 60 and 90 mg/kg/day. Histopathological changes were observed in the retina from one of four dogs at 90 mg/kg/day, a dose associated with mortality in this study.

Some quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs). Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (e.g., seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen.

In dog studies, at plasma concentrations about five times the human therapeutic level, a QT-prolonging effect of moxifloxacin was found. Electrophysiological *in vitro* studies suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism. In dogs, the combined infusion of sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation than that induced by the same dose (30 mg/kg) of moxifloxacin alone.

In a local tolerability study performed in dogs, no signs of local intolerability were seen when moxifloxacin was administered intravenously. After intra-arterial injection, inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis

AVELOX Tablets (400 mg once daily for five days) were evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in a large, randomized, double-blind, controlled clinical trial conducted in the US. This study compared AVELOX with clarithromycin (500 mg twice daily for 10 days) and enrolled 629 patients. The primary endpoint for this trial was clinical success at 7-17 days post-therapy. The clinical success for AVELOX was 89% (222/250) compared to 89% (224/251) for clarithromycin.

The following outcomes are the clinical success rates at the follow-up visit for the clinically evaluable patient groups by pathogen:

PATHOGEN	AVELOX		Clarithromycin	
Streptococcus pneumoniae	16/16	(100%)	20/23	(87%)
Haemophilus influenzae	33/37	(89%)	36/41	(88%)
Haemophilus parainfluenzae	16/16	(100%)	14/14	(100%)
Moraxella catarrhalis	29/34	(85%)	24/24	(100%)
Staphylococcus aureus	15/16	(94%)	6/8	(75%)
Klebsiella pneumoniae	18/20	(90%)	10/11	(91%)

The microbiological eradication rates (eradication plus presumed eradication) in AVELOX treated patients were *Streptococcus pneumoniae* 100%, *Haemophilus influenzae* 89%, *Haemophilus parainfluenzae* 100%, *Moraxella catarrhalis* 85%, *Staphylococcus aureus* 94%, and *Klebsiella pneumoniae* 85%.

Community Acquired Pneumonia

A large, randomized, double-blind, controlled clinical trial was conducted in the US to compare the efficacy of AVELOX Tablets (400 mg once daily) to that of high-dose clarithromycin (500 mg twice daily) in the treatment of patients with clinically and radiologically documented community acquired pneumonia. This study enrolled 474 patients (382 of whom were valid for the primary efficacy analysis conducted at the 14 - 35 day follow-up visit). Clinical success for clinically evaluable patients was 95% (184/194) for AVELOX and 95% (178/188) for high dose clarithromycin.

A large, randomized, double-blind, controlled trial was conducted in the US and Canada to compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days to an IV/PO fluoroquinolone control (trovafloxacin or levofloxacin) in the treatment of patients with clinically and radiologically documented community acquired pneumonia. This study enrolled 516 patients, 362 of whom were valid for the primary efficacy analysis conducted at the 7-30 day post-therapy visit. The clinical success rate was 86% (157/182) for AVELOX therapy and 89% (161/180) for the fluoroquinolone comparators.

An open-label ex-US study that enrolled 628 patients compared AVELOX to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The intravenous formulations of the comparators are not FDA approved. The clinical success rate at Day 5-7 (the primary efficacy timepoint) for AVELOX therapy was 93% (241/258) and demonstrated superiority to amoxicillin/clavulanate ± clarithromycin (85%, 239/280) [95% C.I. 2.9%, 13.2%]. The clinical success rate at the 21-28 days post-therapy visit for AVELOX was 84% (216/258), which also demonstrated superiority to the comparators (74%, 208/280) [95% C.I. 2.6%, 16.3%].

The clinical success rates by pathogen across four CAP studies are presented below:

Clinical Success Rates By Pathogen (Pooled CAP Studies)

PATHOGEN	AVELOX	
Streptococcus pneumoniae	80/85	(94%)
Staphylococcus aureus	17/20	(85%)
Klebsiella pneumoniae	11/12	(92%)
Haemophilus influenzae	56/61	(92%)
Chlamydia pneumoniae	119/128	(93%)
Mycoplasma pneumoniae	73/76	(96%)
Moraxella catarrhalis	11/12	(92%)

Community Acquired Pneumonia caused by Multi-Drug Resistant *Streptococcus pneumoniae* (MDRSP)*

Avelox was effective in the treatment of community acquired pneumonia (CAP) caused by multi-drug resistant *Streptococcus pneumoniae* MDRSP* isolates. Of 37 microbiologically evaluable patients with MDRSP isolates, 35 patients (95%) achieved clinical and bacteriological success post-therapy. The clinical and bacteriological success rates based on the number of patients treated are shown in the table below.

* MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (MIC $\geq$ 2 μg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Clinical and Bacteriological Success Rates for Moxifloxacin-Treated MDRSP CAP Patients (Population: Valid for Efficacy):

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N [a]	%	n/N [b]	%
Penicillin-resistant	21/21	100%*	21/21	100%*
2nd generation cephalosporin-resistant	25/26	96%*	25/26	96%*
Macrolide-resistant **	22/23	96%	22/23	96%
Trimethoprim/sulfamethoxazole-resistant	28/30	93%	28/30	93%
Tetracycline-resistant	17/18	94%	17/18	94%

[a] n = number of patients successfully treated; N = number of patients with MDRSP (from a total of 37 patients)

[b] n = number of patients successfully treated (presumed eradication or eradication); N = number of patients with MDRSP (from a total of 37 patients)

* One patient had a respiratory isolate that was resistant to penicillin and cefuroxime but a blood isolate that was intermediate to penicillin and cefuroxime. The patient is included in the database based on the respiratory isolate.

**Azithromycin, clarithromycin, and erythromycin were the macrolide antimicrobials tested.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in the table below:

S. pneumoniae with MDRSP	Clinical Success	Bacteriological Eradication Rate
Resistant to 2 antimicrobials	12/13 (92.3 %)	12/13 (92.3 %)
Resistant to 3 antimicrobials	10/11 (90.9 %)*	10/11 (90.9 %)*
Resistant to 4 antimicrobials	6/6 (100%)	6/6 (100%)
Resistant to 5 antimicrobials	7/7 (100%)*	7/7 (100%)*
Bacteremia with MDRSP	9/9 (100%)	9/9 (100%)

* One patient had a respiratory isolate resistant to 5 antimicrobials and a blood isolate resistant to 3 antimicrobials. The patient was included in the category resistant to 5 antimicrobials.

Acute Bacterial Sinusitis

In a large, controlled double-blind study conducted in the US, AVELOX Tablets (400 mg once daily for ten days) were compared with cefuroxime axetil (250 mg twice daily for ten days) for the treatment of acute bacterial sinusitis. The trial included 457 patients valid for the primary efficacy determination. Clinical success (cure plus improvement) at the 7 to 21 day post-therapy test of cure visit was 90% for AVELOX and 89% for cefuroxime.

An additional non-comparative study was conducted to gather bacteriological data and to evaluate microbiological eradication in adult patients treated with AVELOX 400 mg once daily for seven days. All patients (n = 336) underwent antral puncture in this study. Clinical success rates and eradication/ presumed eradication rates at the 21 to 37 day follow-up visit were 97% (29 out of 30) for *Streptococcus pneumoniae,* 83% (15 out of 18) for *Moraxella catarrhalis,* and 80% (24 out of 30) for *Haemophilus influenzae.*

Uncomplicated Skin and Skin Structure Infections

A randomized, double-blind, controlled clinical trial conducted in the US compared the efficacy of AVELOX 400 mg once daily for seven days with cephalexin HCl 500 mg three times daily for seven days. The percentage of patients treated for uncomplicated abscesses was 30%, furuncles 8%, cellulitis 16%, impetigo 20%, and other skin infections 26%. Adjunctive procedures (incision and drainage or debridement) were performed on 17% of the AVELOX treated patients and 14% of the comparator treated patients. Clinical success rates in evaluable patients were 89% (108/122) for AVELOX and 91% (110/121) for cephalexin HCl.

Complicated Skin and Skin Structure Infections

Two randomized, active controlled trials of cSSSI were performed. A double-blind trial was conducted primarily in North America to compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days to an IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of patients with cSSSI. This study enrolled 617 patients, 335 of which were valid for the primary efficacy analysis. A second open-label International study compared AVELOX 400 mg QD for 7-21 days to sequential IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of patients with cSSSI. This study enrolled 804 patients, 632 of which were valid for the primary efficacy analysis. Surgical incision and drainage or debridement was performed on 55% of the moxifloxacin treated and 53% of the comparator treated patients in these studies and formed an integral part of therapy for this indication. Success rates varied with the type of diagnosis ranging from 61% in patients with infected ulcers to 90% in patients with complicated erysipelas. These rates were similar to those seen with comparator drugs. The overall success rates in the evaluable patients and the clinical success by pathogen are shown below:

Overall Clinical Success Rates in Patients with Complicated Skin and Skin Structure Infections

Study	Moxifloxacin n/ N (%)	Comparator n/N (%)	95% Confidence Interval
North America	125/162 (77.2%)	141/173 (81.5%)	-14.4%, 2%
International	254/315 (80.6%)	268/317 (84.5%)	-9.4%, 2.2%

Clinical Success Rates by Pathogen in Patients with Complicated Skin and Skin Structure Infections

Pathogen	Moxifloxacin n/ N (%)	Comparator n/N (%)
Staphylococcus aureus (methicillin-susceptible strains) *	106/129 (82.2%)	120/137 (87.6%)
Escherichia coli	31/38 (81.6 %)	28/33 (84.8 %)
Klebsiella pneumoniae	11/12 (91.7 %)	7/10 (70%)
Enterobacter cloacae	9/11 (81.8%)	4/7 (57.1%)

* methicillin susceptibility was only determined in the North American Study

Complicated Intra-Abdominal Infections

Two randomized, active controlled trials of cIAI were performed. A double-blind trial was conducted primarily in North America to compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 5-14 days to IV/ piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of patients with cIAI, including peritonitis, abscesses, appendicitis with perforation, and bowel perforation. This study enrolled 681 patients, 379 of which were considered clinically evaluable. A second open-label international study compared AVELOX 400 mg QD for 5-14 days to IV ceftriaxone plus IV metronidazole followed by PO amoxicillin/clavulanic acid in the treatment of patients with cIAI. This study enrolled 595 patients, 511 of which were considered clinically evaluable. The clinically evaluable population consisted of subjects with a surgically confirmed complicated infection, at least 5 days of treatment and a 25-50 day follow-up assessment for patients at the Test of Cure visit. The overall clinical success rates in the clinically evaluable patients are shown below:

Clinical Success Rates in Patients with Complicated Intra-Abdominal Infections

Study	Moxifloxacin n/ N (%)	Comparator n/N (%)	95% Confidence Interval
North America (overall)	146/183 (79.8 %)	153/196 (78.1 %)	-7.4%,9.3%
Abscess	40/57 (70.2 %)	49/63 (77.8 %) *	NA [a]
Non-abscess	106/126 (84.1 %)	104/133 (78.2 %)	NA
International (overall)	199/246 (80.9 %)	218/265 (82.3 %)	-8.9 %,4.2%
Abscess	73/93 (78.5 %)	86/99 (86.9 %)	NA
Non-abscess	126/153 (82.4 %)	132/166 (79.5 %)	NA

* excludes 2 patients who required additional surgery within the first 48 hours.

[a] NA - not applicable

REFERENCES: 1. Clinical and Laboratory Standards Institute, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Sixth Edition. Approved Standard CLSI Document M7-A6, Vol. 23, No. 2, CLSI, Wayne, PA, January, 2003.

2. Clinical and Laboratory Standards Institute, Performance Standards for Antimicrobial Disk Susceptibility Tests-Eighth Edition. Approved Standard CLSI Document M2-A8, Vol. 23, No. 1, CLSI, Wayne, PA, January, 2003.

3. Clinical and Laboratory Standards Institute, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard CLSI Document M11-A6, Vol. 24, No. 2, CLSI, Wayne, PA, 2004.

Manufactured by:

Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Avelox Tablets made in Germany

Avelox I.V. made in Germany

or

Avelox I.V. made in Norway by
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Distributed by:

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Rx Only

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MEDICATION GUIDE

AVELOX® (*AV-eh-locks)*
(moxifloxacin hydrochloride)
Tablets

AVELOX® I.V. (*AV-eh-locks)*
(moxifloxacin hydrochloride in sodium chloride injection)

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

What is the most important information I should know about AVELOX?
AVELOX belongs to a class of antibiotics called fluoroquinolones. AVELOX can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take AVELOX.

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

- Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
  - hear or feel a snap or pop in a tendon area
  - bruising right after an injury in a tendon area
  - unable to move the affected area or bear weight
- See the section "**What are the possible side effects of AVELOX?**" for more information about side effects.

What is AVELOX?
AVELOX is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by certain germs called bacteria in adults 18 years or older. It is not known if AVELOX is safe and works in people under 18 years of age. Children have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems while taking fluoroquinolone antibiotic medicines.

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

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

Who should not take AVELOX?
Do not take AVELOX if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or if you are allergic to any of the ingredients in AVELOX. Ask your healthcare provider if you are not sure. See the list of ingredients in AVELOX at the end of this Medication Guide.

What should I tell my healthcare provider before taking AVELOX?
See **"What is the most important information I should know about AVELOX?"**
Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation"
- have low blood potassium (hypokalemia)
- have a slow heart beat (bradycardia)
- have a history of seizures
- have kidney problems
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if AVELOX will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if AVELOX passes into breast milk. You and your healthcare provider should decide whether you will take AVELOX or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal and dietary supplements. AVELOX and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take AVELOX or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "**What are the possible side effects of AVELOX?**".
- a blood thinner (warfarin, Coumadin, Jantoven)
- a medicine to control your heart rate or rhythm (antiarrhythmics). See "**What are the possible side effects of AVELOX?**"
- an anti-psychotic medicine
- a tricyclic antidepressant
- erythromycin
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See "**What is the most important information I should know about AVELOX?**"
- Certain medicines may keep AVELOX from working correctly. Take AVELOX either 4 hours before or 8 hours after taking these products:
  - an antacid or multivitamin, or other product that has magnesium, aluminum, iron, or zinc
  - sucralfate (Carafate)
  - didanosine (Videx®, Videx® EC)

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

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

How should I take AVELOX?

- Take AVELOX once a day exactly as prescribed by your healthcare provider.
- Take AVELOX at about the same time each day.
- AVELOX Tablets should be swallowed.
- AVELOX can be taken with or without food.
- Drink plenty of fluids while taking AVELOX.
- AVELOX I.V. is given to you by intravenous (I.V.) infusion into your vein slowly, over 60 minutes, as prescribed by your healthcare provider.
- Do not skip any doses, or stop taking AVELOX even if you begin to feel better, until you finish your prescribed treatment, unless**:**
  - you have tendon effects (see "**What is the most important information I should know about AVELOX?**"),
  - you have a serious allergic reaction (see "**What are the possible side effects of AVELOX?**"), or
  - your healthcare provider tells you to stop.
- This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to AVELOX. If this happens, AVELOX and other antibiotic medicines may not work in the future.

- If you miss a dose of AVELOX, take it as soon as you remember. Do not take more than 1 dose of AVELOX in one day.
- If you take too much, call your healthcare provider or get medical help immediately.

What should I avoid while taking AVELOX?

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

What are the possible side effects of AVELOX?

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

Other serious side effects of AVELOX include:

- **Central Nervous System Effects**
  Seizures have been reported in people who take fluoroquinolone antibiotics including AVELOX. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking AVELOX will change your risk of having a seizure. Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of AVELOX. Talk to your healthcare provider right away if you have any of these side effects, or other changes in mood or behavior:
    - feeling dizzy
    - seizures
    - hear voices, see things, or sense things that are not there (hallucinations)
    - feel restless
    - tremors
    - feel anxious or nervous
    - confusion
    - depression
    - trouble sleeping
    - feel more suspicious (paranoia)
    - suicidal thought or acts
    - nightmares
- **Serious allergic reactions**
  Allergic reactions can happen in people taking fluoroquinolones, including AVELOX, even after only one dose. Stop taking AVELOX and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
    - hives
    - trouble breathing or swallowing
    - swelling of the lips, tongue, face
    - throat tightness, hoarseness
    - rapid heartbeat

- faint
- yellowing of the skin or eyes. Stop taking AVELOX and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to AVELOX (a liver problem).

- **Skin rash.** Skin rash may happen in people taking AVELOX, even after only one dose. Stop taking AVELOX at the first sign of a skin rash and call your healthcare provider. Skin rash may be sign of a more serious reaction to AVELOX.
- **Serious heart rhythm changes** (QT prolongation and torsade de pointes)
  Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. Avelox may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:
  - who are elderly
  - with a family history of prolonged QT interval,
  - with low blood potassium (hypokalemia),
  - who take certain medicines to control heart rhythm (antiarrhythmics)
- **Intestine infection (Pseudomembranous colitis)**
  Pseudomembranous colitis can happen with most antibiotics, including AVELOX. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage (Peripheral Neuropathy)**
  Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including AVELOX. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
  - pain
  - burning
  - tingling
  - numbness
  - weakness

  AVELOX may need to be stopped to prevent permanent nerve damage.
- **Sensitivity to sunlight (photosensitivity)**
  See "**What should I avoid while taking AVELOX?**"

The most common side effects of AVELOX include nausea and diarrhea.

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

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

How should I store AVELOX?
AVELOX Tablets

- Store AVELOX 59–86°F (15–30°C)
- Keep AVELOX away from moisture (humidity)

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

General Information about AVELOX

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

This Medication Guide summarizes the most important information about AVELOX. If you would like more information about AVELOX, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AVELOX that is written for healthcare professionals. For more information go to www.AVELOX.com or call 1-800-526-4099.

What are the ingredients in AVELOX?

- AVELOX Tablets:
  - Active ingredient: moxifloxacin hydrochloride
  - Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and ferric oxide.
- AVELOX I.V.:
  - Active ingredient: moxifloxacin hydrochloride
  - Inactive ingredients: sodium chloride, USP, water for injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

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Manufactured by:

Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Avelox Tablets made in Germany
Avelox I.V. made in Germany
or
Avelox I.V. made in Norway by
Fresenius Kabi Norge AS
NO-1753 Halden, Norway

Distributed by:

Schering Corporation
Kenilworth, NJ 07033

Rx Only

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