PRODUCT MONOGRAPH

PrAVELOX®

Moxifloxacin tablets

400 mg

(as moxifloxacin hydrochloride)

PrAVELOX® I.V.

Moxifloxacin injection

400 mg/250 mL (1.6 mg/mL)

(as moxifloxacin hydrochloride)

Antibacterial Agent

Manufactured by:
Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario
L4W 5R6
www.bayer.ca

Date of Revision:
February 18, 2020

Submission Control No: 233350

Table of Contents

PrAVELOX®

Moxifloxacin tablets
400 mg
(as moxifloxacin hydrochloride)

PrAVELOX® I.V.

Moxifloxacin injection
400 mg/250 mL (1.6 mg/mL)
(as moxifloxacin hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablet, 400 mg (as moxifloxacin hydrochloride)	lactose monohydrate *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*
Intravenous	intravenous solution, 400 mg/250 mL (as moxifloxacin hydrochloride)	*For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

AVELOX (moxifloxacin hydrochloride) is indicated for the treatment of adults (≥18 years of age) with the following bacterial infections caused by susceptible strains of the designated microorganisms for which treatment is appropriate.

Oral Administration

Respiratory Tract Infections

Acute bacterial sinusitis caused by:
Haemophilus influenzae
Moraxella catarrhalis
Streptococcus pneumoniae

Restrict the use of AVELOX to settings where no other treatment options exist, and the clinical presentation meets the diagnostic criteria for acute bacterial sinusitis.[1]

[1] Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Desrosiers et al. Allergy, Asthma & Clinical Immunology 2011, 7:2.

Acute bacterial exacerbation of chronic bronchitis caused by:
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Staphylococcus aureus
Streptococcus pneumoniae

AVELOX should not be prescribed to patients with acute bacterial exacerbations of simple/uncomplicated chronic obstructive pulmonary disease (ie. patients who have chronic obstructive pulmonary disease without underlying risk factors).[2]

AVELOX is not indicated for acute bronchitis.

Community acquired pneumonia of mild to moderate severity caused by:
Chlamydia pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Mycoplasma pneumoniae
Streptococcus pneumoniae (including Multi-drug resistant strains)

> Multi-Drug Resistant Streptococcus pneumoniae (MDRSP) are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime axetil), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Intravenous Administration

Sequential Intravenous/Oral Administration

Intravenous administration is recommended when it offers a route of administration advantageous to the patient (e.g., severe infection or the patient cannot tolerate the oral dosage form, at the discretion of the physician).

Community acquired pneumonia in hospitalized patients caused by:
Chlamydia pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae (including Multi-drug resistant strains)

> Multi-Drug Resistant Streptococcus pneumoniae (MDRSP) are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime axetil), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Complicated intra-abdominal infections due to polymicrobial and monomicrobial infections caused by:

[2] Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. O'Donnell et al. Can Respir J 2008; lS(Suppl A):1A-8A.

Bacteroides fragilis*
Bacteroides thetaiotaomicron
Clostridium perfringens
Enterococcus faecalis (Vancomycin sensitive strains only; many strains are only moderately susceptible)
Escherichia coli
Proteus mirabilis
Streptococcus anginosus
* Increasing resistance of *B. fragilis* to fluoroquinolones including moxifloxacin has been reported.

Complicated skin and skin structure infections in hospitalized patients caused by:

Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Staphylococcus aureus (methicillin-susceptible strains)

Appropriate culture and susceptibility tests should be performed before treatment with AVELOX in order to isolate and identify organisms causing the infection and to determine their susceptibility to moxifloxacin. Therapy with AVELOX may be initiated while awaiting the results of these tests; once results become available, appropriate therapy should be continued. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent, but also on the possible emergence of bacterial resistance. The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance patterns is desirable, particularly when treating severe infections.

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 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.

Pediatrics (<18 years of age)

AVELOX is not recommended for children under the age of 18 years (see **WARNINGS AND PRECAUTIONS**, **TOXICOLOGY**).

Geriatrics (≥65 years of age)

Clinical trial data demonstrate that there is no significant difference in the safety of AVELOX in patients aged 65 or older. Dosage adjustments based on age are not necessary (see **ACTION AND CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

- Patients who are hypersensitive to AVELOX (moxifloxacin hydrochloride) or other fluoroquinolone antibacterial agents (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS**).
- Patients who are hypersensitive to any ingredient in the formulation or component of the container (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Fluoroquinolones, including AVELOX (moxifloxacin hydrochloride), have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.
- AVELOX has been shown to prolong the QT interval of the electrocardiogram in some patients (see **WARNINGS AND PRECAUTIONS: Cardiovascular: QT Interval Prolongation**).
- Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy, including AVELOX (see **WARNINGS AND PRECAUTIONS**: **Hypersensitivity**).
- 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 AND PRECAUTIONS**: **Musculoskeletal**).
- Fluoroquinolones, including AVELOX, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid AVELOX in patients with a known history of myasthenia gravis (see **WARNINGS AND PRECAUTIONS**: **Musculoskeletal**).
- Seizures and toxic psychoses may occur with fluoroquinolone therapy. Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychoses have been reported in patients receiving fluoroquinolones, including AVELOX. AVELOX should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold (see **WARNINGS AND PRECAUTIONS**: Central Nervous System Effects).
- Cases of fulminant hepatitis potentially leading to liver failure (including fatal case) have been reported with AVELOX (see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary**).

Carcinogenesis and Mutagenesis

From the results of animal studies, there is no evidence to suggest that AVELOX is carcinogenic or mutagenic (see **TOXICOLOGY**).

Cardiovascular

QT Interval Prolongation

AVELOX 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 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 and the potential risk.

Sotalol, a Class III antiarrhythmic, has been shown to increase the QTc interval when combined with high doses of intravenous AVELOX in dogs (see **DETAILED PHARMACOLOGY**).

Pharmacokinetic studies between moxifloxacin hydrochloride and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants have not been performed. An additive effect of AVELOX and these drugs cannot be excluded, therefore AVELOX should be used with caution when given concurrently with these drugs.

The effect of AVELOX on patients with congenital prolongation of the QT interval has not been studied, but it is expected that these individuals may be more susceptible to drug-induced QT prolongation. AVELOX should be used with caution in patients with ongoing proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left-ventricular ejection fraction or previous history of symptomatic arrhythmias.

The magnitude of QT prolongation may increase with the infusion rate and with increasing plasma concentrations of the drug. Therefore, the recommended duration of infusion (60 minutes) should not be shortened and the recommended dose should not be exceeded (see DOSAGE AND ADMINISTRATION).

QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsades de Pointes. It has been observed with drugs that prolong the QT interval (including moxifloxacin) that females may be at greater risk compared to males for developing Torsades de Pointes because women tend to have a longer baseline QT interval compared to men. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

In 787 patients with paired valid ECGs in Phase III clinical trials, the mean±SD prolongation of the QTc interval after **oral** dosing with AVELOX 400 mg was 6±26 msec. In patients with paired valid ECGs in Phase III clinical trials, the mean±SD prolongation of the QTc interval within 0-4 hours after a one hour **infusion** of intravenous moxifloxacin hydrochloride 400 mg was 9±24 msec (Day 1; n=176) and 3±29 msec (Day 3; n=290) (see **ACTION AND CLINICAL PHARMACOLOGY**, **DETAILED PHARMACOLOGY**).

No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with AVELOX treatment in clinical trials involving over 4000 patients. However, certain predisposing conditions may increase the risk for ventricular arrhythmias.

When intravenous therapy is initiated, patients should be appropriately monitored. If signs of cardiac arrhythmia occur during treatment with AVELOX, treatment should be stopped and an ECG should be performed.

AVELOX should be used with caution in patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded.

To assure safe and effective use of AVELOX, patients should be advised of the following information and instructions when appropriate:

- that AVELOX may produce changes in the electrocardiogram (QTc interval prolongation)
- that AVELOX should be avoided if they are currently receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents
- that AVELOX 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, clinically relevant heart failure with reduced left-ventricular ejection fraction or previous history of symptomatic arrhythmias
- to contact their physician if they experience palpitations or fainting spells while taking AVELOX
- to inform their physician of any other medications being taken concurrently with AVELOX, including over-the-counter medications.

Atrial Fibrillation

Twenty-five patients from the moxifloxacin hydrochloride clinical datapool (7284 patients) had an episode of atrial fibrillation. In 4 of these patients the relationship between the event and moxifloxacin hydrochloride therapy was assessed as possible, though in each case it could also be explained by pre-existing cardiac disease. There was one episode of atrial fibrillation observed in patients who received a comparator agent (3994 patients).

Aortic Aneurysm and Aortic Dissection

Epidemiologic studies report an increased risk of aortic aneurysm and aortic dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors for aortic aneurysm and aortic dissection (e.g., Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, atherosclerosis).

In case of sudden severe abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Chondrotoxic Effects

As with other members of the fluoroquinolone class, moxifloxacin has caused arthropathy and/or chondrodysplasia in immature dogs. The significance of these findings to humans is unknown (see **ACTION AND CLINICAL PHARMACOLOGY**, **DETAILED PHARMACOLOGY**).

Endocrine and Metabolism

Blood Glucose Disturbances

Fluoroquinolones, including AVELOX, have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. SEVERE CASES OF HYPOGLYCEMIA RESULTING IN COMA OR DEATH HAVE BEEN REPORTED. If a hypoglycemic reaction occurs, discontinue AVELOX immediately and initiate appropriate therapy (see **ADVERSE REACTIONS** and **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Gastrointestinal

Clostridium difficile-Associated Disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including AVELOX (see **ADVERSE REACTIONS**). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases.

Hepatic/Biliary

In 400 mg single dose studies in 6 patients with mild (Child Pugh Class A) and 10 patients with moderate (Child Pugh Class B) hepatic insufficiency, oral moxifloxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of that in 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of that in controls. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for patients with mild or moderate hepatic insufficiency (Child Pugh Classes A and B). Due to limited clinical data, the use of moxifloxacin is not recommended for patients with severe hepatic insufficiency (Child Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY**, **DOSAGE AND ADMINISTRATION**).

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin. Patients should be advised to discontinue treatment and contact their

doctor immediately if they develop signs and symptoms of hepatitis (including abdominal pain, anorexia, jaundice, dark urine, pale stools, pruritus).

Hypersensitivity

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy, including AVELOX.

There have been occasional reports of fatal hypersensitivity and/or anaphylactic reactions observed with fluoroquinolone therapy. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

AVELOX should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with all antibiotics, including moxifloxacin. 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 (see **CONTRAINDICATIONS**, **ADVERSE REACTIONS**).

Musculoskeletal

Myasthenia gravis

Fluoroquinolones, including AVELOX, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid AVELOX in patients with a known history of myasthenia gravis (see **ADVERSE REACTIONS**).

Tendinitis and Tendon Rupture

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with fluoroquinolone therapy, including AVELOX, even within the first 48 hours of treatment. Rupture of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving fluoroquinolones, including AVELOX (see **ADVERSE REACTIONS**). AVELOX should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. 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-fluoroquinolone antimicrobial drug.

AVELOX should not be used in patients with a history of tendon disease/disorder related to previous fluoroquinolone treatment.

Central Nervous System Effects

Psychiatric Adverse Reactions

Fluoroquinolones, including AVELOX, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychoses, hallucinations, or paranoia; depression, or suicidal thoughts; anxiety, agitation, restlessness, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; and memory impairment. Cases of attempted or completed suicide have been reported, especially in patients with a medical history of depression, or an underlying risk factor for depression. These reactions may occur following the first dose. If these reactions occur in patients receiving AVELOX, discontinue AVELOX and institute appropriate measures (see **ADVERSE REACTIONS**).

Central Nervous System Adverse Reactions

Fluoroquinolones, including AVELOX, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (including pseudotumor cerebri), tremors, and light-headedness. As with other fluoroquinolones, AVELOX should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). If these reactions occur in patients receiving AVELOX, discontinue AVELOX immediately and institute appropriate measures (see **ADVERSE REACTIONS**).

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 fluoroquinolones including AVELOX.

Patients under treatment with AVELOX should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see **ADVERSE REACTIONS** - **Post-Market Adverse Drug Reactions**).

Renal

The pharmacokinetic parameters of AVELOX are not significantly altered by mild, moderate, or severe renal impairment. No dosage adjustment is necessary in patients with renal impairment, including patients on chronic dialysis, i.e., hemodialysis or continuous ambulatory peritoneal dialysis. In clinical studies, as renal function decreased, mean exposure (AUC) to the glucuronide conjugate (M2) increased by a factor of 2.8 (Cl_{cr}<30 mL/min), 7.5 (hemodialysis) and 13.3 (continuous ambulatory peritoneal dialysis).

The sulfate and glucuronide conjugates are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal impairment has not been studied (see **ACTION AND CLINICAL PHARMACOLOGY**, **DOSAGE AND ADMINISTRATION**).

Susceptibility/Resistance

Development of Drug-Resistant bacteria

AVELOX is not recommended for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see **ACTION AND CLINICAL PHARMACOLOGY** - **Pharmacodynamics**).

Because of the widespread and rising prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* infections, monotherapy with AVELOX should be avoided in patients with pelvic inflammatory disease, unless fluoroquinolone-resistant *N. gonorrhoeae* can be excluded. If fluoroquinolone-resistant *N. gonorrhoeae* cannot be excluded, the addition of an appropriate antibiotic which is regularly active against *N. gonorrhoeae* (eg, a cephalosporin) to empirical AVELOX therapy should be considered.

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

Skin

Phototoxicity

Phototoxicity has been reported in patients receiving certain fluoroquinolones. In keeping with good medical practice, the patient should be advised to avoid excessive sunlight or artificial ultraviolet light (e.g., sunlamps) during treatment with AVELOX and for one day following completion of treatment. If a sunburn-like reaction or skin eruptions occur, the physician should be contacted. A study in human volunteers concluded that AVELOX has no measurable phototoxic potential.

Photocarcinogenicity

Some members of the fluoroquinolone class of drugs (of which AVELOX is a member) have been shown to produce skin tumours in the Hairless (Skh-1) mouse when concomitantly exposed to daily irradiations of UV-A light for 16 weeks. In this model, in the absence of exposure to UV-A light, mice treated with the fluoroquinolone did not develop skin tumours. The clinical significance of these findings, particularly for short term use, is not known. Photocarcinogenicity studies with AVELOX have not yet been carried out. During treatment with AVELOX and for one day following completion of treatment, exposure to excessive sunlight or artificial ultraviolet light (e.g., sunlamps) should be avoided.

Vision Disorders

If vision disorder occurs in association with the use of AVELOX, consult an eye specialist immediately.

Special Populations

The safety and efficacy of AVELOX (moxifloxacin hydrochloride) in pregnant women and nursing women have not been established. AVELOX is not recommended for children under the age of 18 years.

Pregnant Women

Adequate and well-controlled studies have not been performed in pregnant women. The extent of exposure in pregnancy is very limited. AVELOX should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus (see **TOXICOLOGY**).

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 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 resulted in maternal toxicity, decreased fetal body weights and delayed fetal skeletal ossification. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (12.5 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.

Nursing Women

The safety and efficacy of AVELOX (moxifloxacin hydrochloride) in nursing women have not been established.

AVELOX is excreted in the breast milk of rats and may also be excreted in human milk. Because of the potential for unknown effects from moxifloxacin in infants being nursed by mothers taking moxifloxacin, a decision should be made to either discontinue nursing or discontinue the administration of moxifloxacin, taking into account the importance of moxifloxacin therapy to the mother and the possible risk to the infant (see **TOXICOLOGY**).

Pediatrics (<18 years of age)

AVELOX is not recommended for children under the age of 18 years. Fluoroquinolones, including AVELOX, cause arthropathy and osteochondrosis in juvenile animals of several species. The significance of these findings to humans is unknown (see **TOXICOLOGY**).

Geriatrics (≥65 years of age)

In controlled multiple-dose clinical trials with oral moxifloxacin, 23% of patients who received moxifloxacin were ≥65 years of age and 9% were ≥75 years of age. In intravenous multiple-dose trials, 45% of the patients who received intravenous moxifloxacin were ≥65 years of age, and 24% were ≥75 years of age. The clinical trial data demonstrate that there is no significant difference in the safety of moxifloxacin in patients aged 65 or older compared to younger adults (see **ACTION AND CLINICAL PHARMACOLOGY**, **DOSAGE AND ADMINISTRATION**).

In the pool of 248 moxifloxacin-treated and 243 comparator-treated elderly (≥65 years) patients enrolled in the two pivotal intravenous trials of community acquired pneumonia, the following ECG abnormalities were reported in moxifloxacin vs. comparator patients: QT prolongation (4 vs. 1), ventricular tachycardia (3 vs. 0), tachycardia (2 vs. 1), atrial fibrillation (1 vs. 0), supraventricular tachycardia (1 vs. 0), ventricular extrasystoles (1 vs. 0), and arrhythmia (0 vs. 1). A majority of these patients completed a full-course of therapy.

Monitoring and Laboratory Tests

When intravenous therapy is initiated, patients should be appropriately monitored. If signs of cardiac arrhythmia occur during treatment with AVELOX, treatment should be stopped and an ECG should be performed (see **WARNINGS AND PRECAUTIONS**: **Cardiovascular**: **QT Interval Prolongation**).

Moxifloxacin in vitro activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking AVELOX.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Over 8600 courses of AVELOX (moxifloxacin hydrochloride tablets) and AVELOX I.V. (moxifloxacin hydrochloride injection) treatment have been evaluated for drug safety during clinical development. Of these, 8050 patients received the 400 mg dose. Most adverse events reported in trials were described as transient in nature, mild to moderate intensity, and required no additional treatment. AVELOX was discontinued due to adverse drug reactions (those judged by the investigators to be possibly or probably related to AVELOX) in 3.1% of patients (206 out

of 6734) treated with moxifloxacin hydrochloride tablets and 7.0% of patients (131 out of 1872) treated with intravenous moxifloxacin hydrochloride.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The overall rate of adverse drug reactions during clinical trials was 26% (1734/6734) with AVELOX and 26% (483/1872) with AVELOX I.V. The major difference between the oral and intravenous treatment groups relates to local injection site reactions known to be associated with intravenous administration. The common adverse drug reactions seen in clinical trials (those judged by the investigators to be possibly or probably related to moxifloxacin) are summarized in Table 2.

Table 2 – Common Clinical Trial Adverse Drug Reactions (≥1% to <10%)

	moxifloxacin hydrochloride n=8606
Body as a Whole	
abdominal pain	2%
headache	2%
injection site reaction	1%
Cardiovascular	
in patients with concomitant hypokalemia: QT interval prolongation	1%
Digestive	
nausea	7%
diarrhea	5%
dyspepsia	1%
vomiting	2%
Metabolic	
liver function test abnormal	1%
Nervous	
dizziness	3%

Uncommon Clinical Trial Adverse Drug Reactions

Uncommon adverse drug reactions seen in clinical trials (those judged by the investigators to be possibly or probably related to moxifloxacin) are listed in Table 3 and Table 4.

Table 3 – Uncommon Clinical Trial Adverse Drug Reactions (≥0.1% to <1%)

	moxifloxacin hydrochloride n=8606
Body as a Whole	asthenia, chest pain, fever, infection, malaise, moniliasis, pain
Cardiovascular	hypertension, palpitation, phlebitis, QT interval prolongation, tachycardia, vasodilatation

Table 3 – Uncommon Clinical Trial Adverse Drug Reactions (≥0.1% to <1%)

	moxifloxacin hydrochloride n=8606
Digestive	decreased appetite and food intake, constipation, dry mouth, flatulence, gastrointestinal disorder, GGTP increased, glossitis, nausea and vomiting, oral moniliasis, stomatitis
Hemic and Lymphatic	anemia**,** eosinophilia, leukopenia, prothrombin/INR decreased, thrombocythemia
Metabolic and Nutritional	amylase increased, lactic dehydrogenase increased (in connection with abnormal liver function tests)
Musculo-Skeletal	arthralgia, myalgia
Nervous	anxiety, insomnia, nervousness, paresthesia, somnolence, tremor, vertigo
Respiratory	dyspnea, pharyngitis, pneumonia, rhinitis
Skin and Appendages	pruritus, rash, sweating, urticaria
Special Senses	taste perversion
Urogenital	kidney function abnormal, vaginal moniliasis, vaginitis

Table 4 – Rare Clinical Trial Adverse Drug Reactions (<0.1%)

	moxifloxacin hydrochloride n=8606
Body as a Whole	abdomen enlarged, accidental overdose, aggravation reaction, allergic reaction, back pain, cachexia, cellulitis, chest pain substernal, chills, drug level increased, edema, face edema, hand pain, hernia, infection fungal, inflammation, injection site edema, injection site hypersensitivity, injection site inflammation, injection site pain, lab test abnormal, lack of drug effect, leg pain, multisystem organ failure, neoplasm, overdose, pelvic pain, peritonitis, photosensitivity reaction, reaction unevaluable, sepsis
Cardiovascular	AV block first degree, angina pectoris, atrial fibrillation, cardiovascular disorder, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, electrocardiogram abnormal, heart failure, hemorrhage, hypotension, migraine, myocardial infarct, peripheral edema, peripheral vascular disorder, postural hypotension, shock, supraventricular tachycardia, syncope, thrombophlebitis, vascular headache, ventricular tachycardia, ventricular extrasystoles
Digestive	aphthous stomatitis, cheilitis, cholestatic jaundice, colitis, cholangitis, diarrhea (Clostridium difficile), dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, hepatic failure, hyperchlorhydria, increased appetite, jaundice (predominantly cholestatic), liver damage, melena, mouth ulceration, pancreatitis, pseudomembraneous colitis, salivary gland enlargement, thirst, tongue discoloration, tongue disorder, tongue edema
Endocrine	diabetes mellitus, female lactation

Table 4 – Rare Clinical Trial Adverse Drug Reactions (<0.1%)

	moxifloxacin hydrochloride n=8606
Hemic and Lymphatic	abnormal platelets, coagulation disorder, hypochromic anemia, lymphocytosis, lymphangitis, monocytosis, pancytopenia, prothrombin/INR increased, sedimentation rate increased, thrombocytopenia, thromboplastin decreased
Hypersensitivity	allergic reaction, face edema, urticaria
Metabolic and Nutritional	bilirubinemia, dehydration, enzymatic abnormality, gamma globulins increased, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoproteinemia, hypophosphatemia, lipase increased, NPN increased, weight gain
Musculo-Skeletal	arthritis, arthrosis, leg cramps, myasthenia, tendon disorder
Nervous	abnormal dreams, agitation, amnesia, aphasia, cerebral infarct, circumoral paresthesia, coma, confusion, convulsion, depersonalization, depression (in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideation/thoughts or suicide attempts), emotional lability, euphoria, grand mal convulsion, hallucinations, hyperkinesia, hypertonia, hypesthesia, hypotonia, incoordination, paresthesia, personality disorder, sleep disorder, speech disorder, thinking abnormal, twitching, vestibular disorder
Respiratory	apnea, asthma, atrophic rhinitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, hyperventilation, lung disorder, pleural effusion, respiratory disorder, sinusitis, surgery
Skin and Appendages	acne, dry skin, eczema, fungal dermatitis, herpes simplex, maculopapular rash, psoriasis, purpuric rash, pustular rash, skin disorder, skin ulcer, vesiculobullous rash, Stevens-Johnson syndrome
Special Senses	abnormal vision, amblyopia, blindness, deafness, diplopia, ear pain, eye disorder, hyperacusis, parosmia (including smell perversion, decreased smell and loss of smell), hearing impairment including partial permanent deafness, photophobia, taste loss, tinnitus
Urogenital	acute kidney failure, albuminuria, balanitis, cystitis, dysuria, hematuria, hypomenorrhea, kidney function abnormal, kidney pain, leukorrhea, menstrual disorder, polyuria, pyuria, salpingitis, urinary frequency, urinary retention, urinary tract infection, urine abnormality, vulvovaginitis

Abnormal Hematologic and Clinical Chemistry Findings

Changes in laboratory parameters without regard to drug relationship that are not listed above as adverse drug reactions and which occurred in ≥2% of oral moxifloxacin-treated patients in controlled clinical trials (n=4301) are summarized in Table 5.

Table 5 – Changes in Laboratory Parameters seen in Clinical Trials

	moxifloxacin hydrochloride n=4301
increases in:	albumin, alkaline phosphatase, amylase, basophils, bicarbonate, calcium, chloride, cholesterol, creatinine, eosinophils, globulin, glucose, hematocrit, hemoglobin, LDH, lymphocytes, monocytes, neutrophils, PCO_2, phosphorus,

Table 5 – Changes in Laboratory Parameters seen in Clinical Trials

	moxifloxacin hydrochloride n=4301
	platelets, potassium, prothrombin time/INR , RBCs, serum transaminases, sodium, theophylline, total bilirubin, triglycerides, urea, uric acid, WBCs
decreases in:	albumin, amylase, basophils, bicarbonate, calcium, chloride, creatinine, eosinophils, globulin, glucose, hematocrit, hemoglobin, LDH, lymphocytes, monocytes, neutrophils, phosphorus, platelets, PO_2, potassium, prothrombin time/INR, RBCs, serum transaminases, sodium, theophylline, total bilirubin, urea, uric acid, WBCs

Post-Market Adverse Drug Reactions

The safety of moxifloxacin has been studied in two prospective post-marketing surveillance studies involving nearly 33,000 patients.

Adverse reactions with moxifloxacin based on post-marketing reports (from more than eight million patient treatments) are summarized in Table 6.

Table 6 – Adverse Reactions Identified in Post-Marketing Surveillance

Cardiovascular	ventricular tachyarrythmias including Torsades de Pointes and cardiac arrest have been reported especially in patients with severe underlying proarrhythmic conditions in very rare cases (see **WARNINGS AND PRECAUTIONS**)
Endocrine and Metabolism	hypoglycemia
Hepatic	hepatitis, fulminant hepatitis
Hypersensitivity	anaphylactic reaction, shock (anaphylactic), angioedema (including laryngeal edema; potentially life-threatening)
Musculo-Skeletal	Exacerbation of symptoms of myasthenia gravis, tendon rupture
Nervous	psychotic reaction (potentially culminating in self-injurious behavior, such as suicidal ideation/thoughts or suicide attempts), peripheral neuropathy and polyneuropathy
Special Senses	transient loss of vision

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

Additional serious adverse events reported with moxifloxacin regardless of drug relationship are listed in Table 7.

Table 7 – Serious Adverse Events Reported Regardless of Drug Relationship

Cardiac	atrial arrhythmia, atrial flutter, bradycardia, myocardial infarct (death), tachyarrhythmia, ventricular fibrillation, ventricular tachycardia
Hepatic	cholestatic hepatitis, fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases), hepatic failure, hepatitis
Hypersensitivity	allergic vasculitis, anaphylactoid reaction, anaphylaxis, tongue edema
Renal	acute kidney failure
Skin and Appendages	Toxic Epidermal Necrolysis (potentially life threatening)

DRUG INTERACTIONS

Overview

AVELOX (moxifloxacin hydrochloride) is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. Moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes. As with all other fluoroquinolones, iron and antacids significantly reduced bioavailability of moxifloxacin.

Drug-Drug Interactions

Table 8 – Established or Potential Drug-drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Antacids, Sucralfate, Metal Cations, Multivitamins	CT/T	Fluoroquinolones form chelates with alkaline earth and transition metal cations. Administration of fluoroquinolones with antacids containing aluminum or magnesium, as well as sucralfate, metal cations such as iron, and multivitamins containing iron or zinc, and formulations containing divalent and trivalent cations such as didanosine chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of fluoroquinolones, resulting in systemic concentrations considerably lower than desired.	AVELOX should be taken at least 4 hours before or 8 hours after these agents (see **DOSAGE AND ADMINISTRATION**).
Ranitidine	CT	Concomitant administration with ranitidine does not change the absorption characteristics of moxifloxacin. Absorption parameters (C_{max}, t_{max}, AUC) are comparable indicating absence of an influence of gastric pH on moxifloxacin uptake from the GI-tract.	No clinically relevant interactions.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	T	Although not observed with moxifloxacin in preclinical and clinical trials, some fluoroquinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).	Concomitant administration of a nonsteroidal anti-inflammatory drug with a fluoroquinolone may increase the risks of CNS stimulation and convulsions.

Table 8 – Established or Potential Drug-drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Calcium supplements	CT	When moxifloxacin is given with high dose calcium supplements, only a slightly reduced rate of absorption is observed while the extent of absorption remains unaffected.	No clinically relevant interactions.
Warfarin	CT	**Changes in INR:** Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors.	Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.
Drugs metabolized by Cytochrome P450 enzymes (e.g., midazolam, cyclosporine, warfarin, theophylline)	CT/T	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.	No clinically relevant interactions.
Antidiabetic agents	CT/T	Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with fluoroquinolones, including moxifloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide, etc) or with insulin.	In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient receiving moxifloxacin, discontinue the drug immediately and an appropriate therapy should be instituted (see **ADVERSE REACTIONS**).
Oral contraceptives	CT	No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.	No clinically relevant interactions.
Itraconazole	CT	Exposure (AUC) to itraconazole is only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin are not significantly altered by itraconazole.	No clinically relevant interactions.
Digoxin	CT	The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin and vice versa. After repeated dosing in healthy volunteers, moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.	No clinically relevant interactions.
Morphine	CT	Parenteral administration of morphine does not reduce the oral availability of moxifloxacin and only slightly decreases C_{max} (17%).	No clinically relevant interactions.
Atenolol	CT	The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects, AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.	No clinically relevant interactions.

Table 8 – Established or Potential Drug-drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Probenecid	CT	No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion.	No clinically relevant interactions.

Legend: C=Case Study; CT=Clinical Trial; T=Theoretical

Drug-Food Interactions

AVELOX may be taken with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

There are no reported laboratory test interactions.

Drug-Lifestyle Interactions

Fluoroquinolones including AVELOX may result in an impairment of the patient's ability to drive or operate machinery due to central nervous system (CNS) reactions and vision disorders (see **ADVERSE REACTIONS**).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose for AVELOX (moxifloxacin hydrochloride tablets) and AVELOX I.V. (moxifloxacin hydrochloride injection) is 400 mg once daily for all indications. The duration of therapy and route of administration is dependent upon the type and severity of infection as described in Table 9.

Table 9 – Dosage and Administration Information for Approved Indications

Infection[a]	Daily Dose	Route of Administration	Usual Duration
Acute Bacterial Sinusitis	400 mg	PO	7-10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	PO	5 days
Community Acquired Pneumonia (Mild/Moderate)	400 mg	PO	10 days
Community Acquired Pneumonia in Hospitalized Patients (Mild/Moderate/Severe)	400 mg	I.V./PO	7-14 days
Complicated Intra-abdominal Infections	400 mg	I.V./PO	5-14 days
Complicated Skin and Skin Structure Infections in Hospitalized Patients	400 mg	I.V./PO	7 –21 days

a due to the designated pathogens (see **INDICATIONS AND CLINICAL USE**).

Special Populations

Gender

Clinical trial data indicate that there are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration. Dosage adjustments based on gender are not necessary (see **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (<18 years of age)

AVELOX is not recommended for children under the age of 18 years (see **WARNINGS AND PRECAUTIONS, TOXICOLOGY**).

Geriatrics (≥65 years of age)

Clinical trial data demonstrate that there is no significant difference in the safety of moxifloxacin in patients aged 65 or older. Dosage adjustments based on age are not necessary (see **ACTION AND CLINICAL PHARMACOLOGY**, **WARNINGS AND PRECAUTIONS**).

Hepatic Impairment

Based on the pharmacokinetic data, no dosage adjustment is required for patients with mild or moderate hepatic insufficiency (Child Pugh Classes A and B). Due to limited clinical data, the use of moxifloxacin is not recommended in patients with severe hepatic insufficiency (Child Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY**, **WARNINGS AND PRECAUTIONS**).

Renal Impairment

Based on pharmacokinetic data, no dosage adjustment is necessary in renally impaired patients, including patients on chronic dialysis (i.e., hemodialysis or continuous ambulatory peritoneal dialysis). A study in 24 patients with renal impairment found no significant changes in the pharmacokinetic properties of oral moxifloxacin As renal function decreases, concentrations of the glucuronide conjugate (M2) increased by a factor of 2.8 (Cl_{cr}<30 mL/min), 7.5

(hemodialysis) and 13.3 (continuous ambulatory peritoneal dialysis) (see **ACTION AND CLINICAL PHARMACOLOGY**, **WARNINGS AND PRECAUTIONS**).

The clinical implication of increased exposure to the sulfate (M1) and the glucuronide (M2) conjugates of moxifloxacin in renally impaired patients, including those undergoing hemodialysis and continuous ambulatory peritoneal dialysis (HD and CAPD), has not been studied. Clinical efficacy of moxifloxacin treatment in dialysis patients (HD and CAPD) has not been studied.

Administration

Oral Administration

AVELOX (moxifloxacin hydrochloride) is administered orally, independent of meals. The tablets are swallowed whole. Patients should be advised to drink fluids liberally and take moxifloxacin at least 4 hours before or 8 hours after antacids containing magnesium or aluminium, or multivitamins containing iron or zinc. Do not crush or chew the tablets. Swallow each tablet whole with a drink of water.

Intravenous Administration

AVELOX I.V. (moxifloxacin hydrochloride injection) should be administered over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. Rapid or bolus intravenous infusion must be avoided. It is not intended for intramuscular, intrathecal, intraperitoneal or subcutaneous administration. The recommended dose is 400 mg once daily for Community Acquired Pneumonia and Complicated Intra-abdominal Infections. The recommended duration of infusion should not be shortened and the recommended dose should not be exceeded (see **WARNINGS AND PRECAUTIONS**).

Sequential I.V./PO Therapy

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

As with all parenteral products, the intravenous mixture should be inspected visually for clarity, discolouration, particulate matter, precipitate and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Since the premixed minibags are for single-use only, any unused portion should be discarded.

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 is used for sequential infusion of other drugs, 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
- 1M Sodium Chloride Injection
- 5% Dextrose Injection, USP
- Sterile Water for Injection, USP
- 10% Dextrose for Injection, USP
- Lactated Ringer's for Injection

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of AVELOX I.V.

Missed Dose

If a dose is missed, it should be taken as soon as the patient remembers on the same day. Double doses should not be taken to compensate for a missed dose.

Reconstitution

Not applicable.

OVERDOSAGE

In the event of acute overdosage of AVELOX (moxifloxacin hydrochloride), the stomach should be emptied. ECG monitoring is recommended due to the possible prolongation of the QT interval. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Moxifloxacin and the glucuronide conjugate (M2) are removed from the body by hemodialysis (approximately 9% and 4%, respectively, 5 hour dialysis sessions) and by continuous ambulatory peritoneal dialysis (approximately 3% and 2%, respectively).

The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure.

Toxic signs after administration of a single high dose of moxifloxacin in animals included CNS and gastrointestinal effects (see **WARNINGS AND PRECAUTIONS**, **TOXICOLOGY**).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AVELOX (moxifloxacin hydrochloride) is a synthetic fluoroquinolone with a broad spectrum of activity and a bactericidal mode of action. The bactericidal action results from the interference of moxifloxacin with bacterial topoisomerases II (DNA gyrase) and IV. Topoisomerases are

essential enzymes which control DNA topology and assist in DNA replication, repair and transcription.

Killing curves demonstrated that moxifloxacin exhibits a concentration dependent bactericidal effect. Minimum bactericidal concentrations are in the range of minimum inhibitory concentrations.

Fluoroquinolones, including moxifloxacin, differ in chemical structure and mechanism of action from macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to other classes of antimicrobial agents. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram negative bacteria, Gram positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin. Conversely, Gram positive bacteria that are resistant to moxifloxacin may be susceptible to other fluoroquinolones (see **MICROBIOLOGY**).

Pharmacodynamics

Resistance

Resistance mechanisms which inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. There is no cross-resistance between moxifloxacin and these agents. Plasmid-mediated resistance has not been observed to date.

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, a proposed mechanism of fluoroquinolone resistance.

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 $<1 \times 10^{-11}$ in one strain of *Staphylococcus aureus* and one strain of *Streptococcus pneumoniae*.

Effect on the Intestinal Flora

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia.

Pharmacokinetics

Pharmacokinetics are linear in the range of 50 to 800 mg (single dose) and up to 600 mg (once daily oral dosing over 10 days).

The mean (±SD) C_{max} and AUC values at steady-state with a 400 mg oral once daily dosage regimen are 4.5±0.53 g/L and 48±2.7 mg*h/L, respectively. C_{max} is attained 1 to 3 hours after oral dosing. The mean (±SD) trough concentration is 0.95±0.10 mg/L. The mean (±SD) C_{max} and AUC values at steady-state with a once daily dosage regimen of 400 mg intravenous moxifloxacin hydrochloride infused over 60 minutes in healthy young males are 4.2±0.8 g/L and

38±4.7 mg*h/L, respectively. C_{max} is achieved at the end of a 60 minute infusion (see **DOSAGE AND ADMINISTRATION**).

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). Moxifloxacin hydrochloride is eliminated from plasma by first-order process. 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. The time course of plasma concentrations of moxifloxacin hydrochloride following steady-state oral and intravenous administration is illustrated in Figure 1, and pharmacokinetic parameters of moxifloxacin hydrochloride are presented in Table 10.

Figure 1 – Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained with Once Daily Dosing of 400 mg Either Orally (n=10 males) or by I.V. Infusion (n=12 elderly males and females)

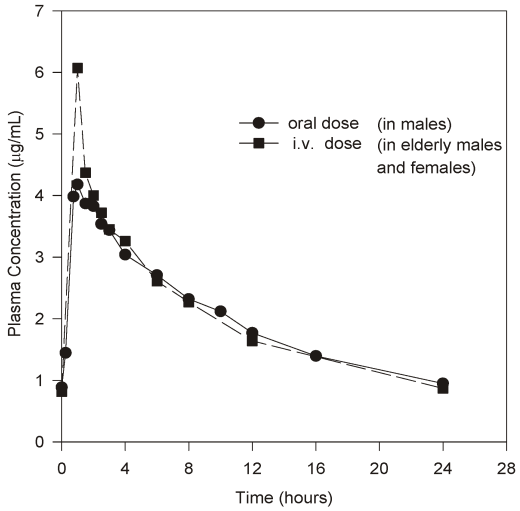


Table 10 – Pharmacokinetic Parameters of Moxifloxacin After Oral and Intravenous Administration of 400 mg Single or Multiple Doses

Population years (range)	Dose	C_{max} (CV)[a] mg/L	AUC (CV)[a] mg*h/L	t_{max}[b] (range) hr	$t_{1/2}$ (CV)[a] hr	Comment
Single Dose Studies – Oral Administration						
38 males (23-45)	400 mg	2.50 (27%)	26.9 (17%)	1.5 (0.5-2.6)	13.1 (6%)	
18 males (20-25)	400 mg	4.13 (27%)	51.5 (10%)	1.75 (0.5-2.5)	13.9 (10%)	
Single Dose Studies – Intravenous Administration						
6 males (19-43)	400 mg	4.6 (33%)	36.9 (19%)	N/A	13.4 (17%)	30 min. infusion
6 males (24-44)	400 mg	4.5 (25%)	34.0 (22%)	0.5	11.9 (10%)	30 min. infusion
12 males (20-44)	400 mg	4.3 (21%)	42.9 (11%)	0.5	13.5 (20%)	33 min. infusion
12 males (23-41)	400 mg	3.6 (28%)	34.6 (19%)	1.0 (1.0-1.25)	15.4 (16%)	60 min. infusion

Table 10 – Pharmacokinetic Parameters of Moxifloxacin After Oral and Intravenous Administration of 400 mg Single or Multiple Doses

Population years (range)	Dose	C_{max} (CV)[a] mg/L	AUC (CV)[a] mg*h/L	t_{max}[b] (range) hr	$t_{1/2}$ (CV)[a] hr	Comment
9 males, 11 females (19-32)	400 mg	4.6 (18%)	46.3 (18%)	1.0 (0.5-1.3)	12.4 (10%)	60 min. infusion
13 males (24-36)	400 mg	3.6 (20%)	39.8 (14%)	1.0 (0.55-1.5)	14.1 (17%)	60 min. infusion
7 males (25-41)	400 mg	5.0 (22%)	44.7 (19%)	1.0 (0.5-1.0)	8.0 (18%)	60 min. infusion
Multiple Dose Studies						
8 males (22-43)	400 mg OD/PO x 5 days	3.10 (29%)	30.9 (11%)	0.5 (0.5-4.0)	9.6 (11%)	Day 1
		3.24 (17%)	33.9 (20%)	1.5 (0.5-3.0)	15.1 (5%)	Day 5
10 males, 5 females (19-41)	400 mg OD/PO x 10 days	3.4 (22%)	36.7 (13%)	1.8 (0.75-3.0)	9.3 (12%)	Day 1
		4.5 (12%)	48.0 (6%)	1.0 (0.75-2.5)	12.7 (15%)	Day 10
9 males (20-40)	400 mg OD	4.1 (39%)	40.9 (10%)	1.0 (0.5-2.5)	10.7 (16%)	Day 1
		4.1 (28%)	46.7 (15%)	1.8 (0.5-3.0)	14.0 (15%)	Day 7
9 males (23-38)	400 mg I.V.	6.6 (30%)	36.3 (11%)	0.25	9.3 (17%)	Day 1; 15 min. infusion
11 males, 7 females (65-75)	400 mg I.V.	6.6 (27%)	38.6 (21%)	0.26	8.6 (15%)	Day 1; 15 min. infusion
		5.9 (21%)	47.4 (20%)	1.0	10.1 (16%)	Day 5; 60 min. infusion
12 males (25-42); 8 active, 4 placebo	400 mg I.V.	3.6 (20%)	34.8 (11%)	1.0	9.9 (15%)	Day 1; 60 min. infusion
		4.1 (20%)	37.8 (11%)	1.0	14.7 (16%)	Day 10; 60 min. infusion
20 males, 12 females (23-74); varying degrees of renal function	400 mg, PO	4.4 (34%)	43.4 (31%)	0.8 (0.5-1.5)	14.9 (38%)	$C1_{cr}$>90 mL/min
		4.9 (30%)	40.1 (22%)	0.3 (0.3-2.5)	15.2 (15%)	$C1_{cr}$>60-90 mL/min
		3.5 (41%)	35.8 (30%)	0.8 (0.5-2.5)	16.2 (15%)	$C1_{cr}$>30-60 mL/min
		3.2 (14%)	43.9 (29%)	1.5 (0.5-2.5)	14.5 (19%)	$C1_{cr}$<30 mL/min
12 males, 4 females (22-62) 8 HD; 8 CAPD	400 mg PO	3.2 (23%)[c]	40.4 (29%)[c, d]	3.0 (1.0-4.0)[c]	18.7 (25%)[c]	$C1_{cr}$<20 mL/min and on HD
		4.0 (18%)[c]	49.6 (25%)[c, d]	2.5 (0.9-4.2)[c]	11.4 (23%)[c]	$C1_{cr}$<20 mL/min and on CAPD

Table 10 – Pharmacokinetic Parameters of Moxifloxacin After Oral and Intravenous Administration of 400 mg Single or Multiple Doses

Population years (range)	Dose	C_{max} (CV)[a] mg/L	AUC (CV)[a] mg*h/L	t_{max}[b] (range) hr	$t_{1/2}$ (CV)[a] hr	Comment
18 males (30-64); 10 healthy; 8 with hepatic disease	400 mg PO	3.0 (26%)	32.8 (26%)	0.8 (0.5-3.0)	13.4 (18%)	healthy volunteers
		2.5 (34%)	25.1 (26%)	0.5 (0.5-2.5)	11.7 (26%)	patients with hepatic disease, Child Pugh Class A and B
16 males (42-64); 8 healthy; 8 with hepatic disease	400 mg PO	3.3 (1.4)[e]	30.8 (1.3)[e]	1.5 (0.5-3.0)	11.6 (1.1)[e]	healthy volunteers
		2.6 (1.2)[e]	34.6 (1.2)[e]	1.25 (0.5-2.5)	13.6 (1.2)[e]	patients with hepatic disease, Child Pugh Class B
9 healthy males (23-45)	400 mg I.V./PO	3.4 (20%)	35.5 (14%)	1.0 (0.75-1.5)	11.6 (10%)	I.V. alone; 60 min. infusion
		3.0 (12%)	28.5 (12%)	1.0 (0.5-1.5)	11.8 (6%)	I.V. plus 5 g charcoal 5 minutes prior to infusion; immediately after infusion and 2, 4, 8 hours post-infusion; 60 min. infusion
		0.6 (73%)	5.4 (65%)	0.75 (0.5-1.25)	10.8 (11%)	PO plus 10 g charcoal 15 minutes before, 2, 4, 8 hours after dosing

a values are geometric means (Coefficient of Variation)
b median (range)
c pharmacokinetic values are after 7-day once-daily dosing regimen
d values are $AUC_{(0-24)ss}$
e values are geometric means (SD)
Legend: OD=once daily; C_{max}= maximum serum concentration; t_{max}=time to C_{max}; AUC=area under concentration vs. time curve; $t_{1/2}$=serum half-life, Cl_{cr}=creatinine clearance, HD=hemodialysis, CAPD=continuous ambulatory peritoneal dialysis

Absorption

Moxifloxacin hydrochloride, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin hydrochloride is approximately 90 percent. Co-administration with a high fat meal (i.e., 500 calories from fat) does not affect absorption of moxifloxacin hydrochloride.

Consumption of one cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

Distribution

Moxifloxacin hydrochloride is approximately 50% bound to serum proteins, independent of drug concentration. As shown in Table 11, the volume of distribution of moxifloxacin hydrochloride ranges from 1.7 to 2.7 L/kg. Moxifloxacin hydrochloride 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, 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.

In animal experiments, radiolabelled moxifloxacin hydrochloride was shown to cross the blood-brain barrier only to a small extent.

Table 11 – Moxifloxacin Concentrations (mean±SD) in Plasma and Tissues After Oral or Intravenous Dosing with 400 mg[a]

Tissue or Fluid	N	Tissue or Fluid Concentration (mg/L or µg/g)	Tissue or Fluid: Plasma Ratio[b]
Respiratory			
Alveolar Macrophages	5	61.8±27.3	21.2±10.0
Bronchial Mucosa	8	5.5±1.3	1.7±0.3
Epithelial Lining Fluid	5	24.4±14.7	8.7±6.1
Sinus[c]			
Maxillary Sinus Mucosa	4	7.6±1.7	2.0±0.3
Anterior Ethmoid Mucosa	3	8.8±4.3	2.2±0.6
Nasal Polyps	4	9.8±4.5	2.6±0.6
Intra-Abdominal			
Abdominal tissue[d]	8	7.6±2.0	2.7±0.8
Abdominal exudate[d]	10	3.5±1.25	1.6±0.7
Abscess fluid	6	2.3±1.5	0.8±0.4
Skin, Musculoskeletal			
Blister Fluid	5	2.6±0.9	0.9±0.2
Subcutaneous Tissue	6	0.9±0.3[e]	0.4±0.6
Skeletal Muscle	6	0.9±0.3[e]	0.4±0.1

a moxifloxacin concentrations were measured 3 hours after a single oral or intravenous 400 mg dose, except as noted.
b tissue or fluid: plasma ratio was determined on an individual patient basis and then averaged for each site of infection
c sinus concentrations were measured after 5 days of dosing
d measured 2 hours after dosing
e reflects only non-protein bound concentrations of drug

Metabolism

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 dose is converted to a glucuronide conjugate (M2), which is found exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% of the parent drug, while plasma concentrations of M1 are generally less than 10% those of

moxifloxacin. The sulfate (M1) and glucuronide (M2) conjugates are not microbiologically active.

Excretion

Approximately 45% of an oral 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±2.0 L/hr and 2.6±0.5 L/hr, respectively.

Special Populations and Conditions

Pediatrics (<18 years of age)

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

Geriatrics (≥65 years of age)

Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and 16 young (8 male; 8 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 oral dose of 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 Phase I studies, the pharmacokinetics in elderly patients following infusion of 400 mg were similar to those observed in young patients (see **DETAILED PHARMACOLOGY**).

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 mg/L, an AUC_{24} of 47 mg*h/mL, and an elimination half-life of 14 hours following 400 mg daily PO.

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 that in 18 healthy controls. The mean peak concentration (C_{max}) was 79% and 84%, respectively, of control values.

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 8.0-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), respectively. 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). Due to limited clinical data, the use of moxifloxacin is not recommended with severe hepatic insufficiency (Child Pugh Class C) (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

The pharmacokinetic parameters of moxifloxacin are not significantly altered by mild, moderate, or severe renal impairment. No dosage adjustment is necessary in patients with renal impairment, including those patients on 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 22% and 21% in the patients with moderate (Cl_{cr}≥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 sulfate and glucuronide conjugates are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal impairment has not been studied.

The pharmacokinetics of single- 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). Pharmacokinetic comparisons are to historical pharmacokinetic values from healthy volunteers (Cl_{cr}>90 mL/min; administered a single 400 mg oral dose of moxifloxacin). 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 subjects. 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 7.3 to 13.2, 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 moxifloxacin once daily 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 28% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Moxifloxacin and the glucuronide conjugate (M2) were removed from the body by HD (approximately 9% and 4%, respectively) and by CAPD (approximately 3% and 2%, respectively). Systemic exposure (AUC) to M2 was equal to or greater than moxifloxacin exposure in HD and CAPD subjects following single dosing and at steady state (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**).

QT Prolongation

One pharmacokinetic study in 9 male and 9 female healthy volunteers showed that at the expected time of peak plasma concentrations and at a heart rate of 75 beats/minute, a 400 mg oral dose of moxifloxacin was associated with a mean QT prolongation (uncorrected for heart-rate) of 14±13 msec (3.8%±3.5%) compared to baseline. Exercise data indicated the absence of a reverse-rate dependence.

In clinical pharmacology studies (n=112 subjects), the aggregate mean prolongation of the QTc interval at the expected time of peak plasma concentrations after a single oral dose of 400 mg moxifloxacin was 7±23 msec (1.8%±5.6%). One patient had an increase in QTc greater than 60 msec.

In clinical pharmacology studies (n=29) with 400 mg intravenous moxifloxacin, the aggregate mean prolongation of the QTc interval at the end of a one hour infusion was 20.6±23 msec (5.5%±5.9%). Two patients had an increase in QTc greater than 60 msec (see **WARNINGS AND PRECAUTIONS**).

STORAGE AND STABILITY

AVELOX tablets:
Store at room temperature (15°C -30°C). Avoid freezing.

AVELOX I.V. minibags:
Store at room temperature (15°C -30°C). DO NOT REFRIGERATE. Protect from light.

AVELOX I.V. glass bottles:
Store at room temperature (15°C -30°C). DO NOT REFRIGERATE.

At cool storage temperatures, precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator.

Since the premixed minibags and glass bottles are for single-use only, any unused portion should be discarded.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AVELOX (moxifloxacin hydrochloride) 400 mg Tablets

Each oblong, convex-shaped, dull red film-coated AVELOX tablet is engraved “BAYER” on one side and “M400”on the other. Each tablet contains 400 mg moxifloxacin (as hydrochloride). The tablets are packaged in bottles of 30.

AVELOX tablets are also composed of the following non-medicinal ingredients: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, magnesium stearate, red ferric oxide, hydroxypropyl methyl cellulose, polyethylene glycol 4000, and titanium dioxide.

AVELOX I.V. (moxifloxacin hydrochloride injection) 400 mg Minibags and Glass Bottles

Each AVELOX I.V. 250 mL ready-to-use minibag or glass bottle contains 400 mg moxifloxacin (as hydrochloride) in 0.8% saline with a pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow and is not affected by, or indicative of, product stability. **NO FURTHER DILUTION OF THIS PRODUCT IS NECESSARY.**

The non-medicinal ingredients are sodium chloride, USP, and Water for Injection, USP. It may also contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

As with all parenteral products, the intravenous mixture should be inspected visually for clarity, discoloration, particulate matter, precipitate and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

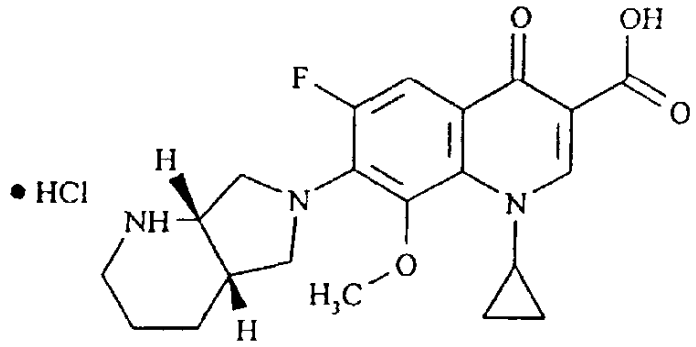
Proper name: moxifloxacin hydrochloride

Chemical name: 1-cyclopropyl-7-[(S,S)-2,8-diaza-bicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride

Molecular formula: $C_{21}H_{24}FN_3O_4 \bullet HCl$

Molecular weight: 437.9 g/mol

Structural formula:



Physicochemical properties: Moxifloxacin hydrochloride is a pale yellow solid substance. It shows no melting point and decomposes above 250°C. It has a pH in the range of 3.9-4.6. Moxifloxacin is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and virtually insoluble in acetone and toluene. Moxifloxacin differs from other fluoroquinolones in that it has a methoxy function at the 8-position, and an S,S configurated diazabicyclononyl ring moiety at the 7-position.

CLINICAL TRIALS

Acute Bacterial Sinusitis

Trial Design

Table 12 – Design of Acute Bacterial Sinusitis Pivotal Trials

Study No. / Country	Study Design	Primary Efficacy Parameter	Treatment Regimen	# of Pts.	Gender[a]	Mean Age ± SD (Years)[a]
0116 Europe and Israel	Randomized, Double-blind, Active Controlled	Clinical Response at Day 3 post-treatment	Moxifloxacin 400 mg OD x 7 days	211	F: 114 (54%) M: 97 (46%)	39.6±14.5
			Cefuroxime Axetil 250 mg BID x 10 days	225	F: 126 (56%) M: 99 (44%)	39.9±13.9
0125[b] USA	Open-label, Uncontrolled	Overall Clinical Response at Day 27-31 post-treatment[c]	Moxifloxacin 400 mg OD x 7 days	336	F: 208 (62%) M: 128 (38%)	41.0±13.4
0126 Canada, USA	Randomized, Double-blind, Active Controlled	Overall Clinical Response at Day 27-31 post-treatment[c]	Moxifloxacin 400 mg OD x 7 days	191	F: 126 (66%) M: 65 (34%)	42.5±13.8
			Cefuroxime Axetil 250 mg BID x 10 days	193	F: 134 (69%) M: 59 (31%)	42.4±14.8
0161 Europe and Israel (1)	Randomized, Double-blind, Active Controlled	Clinical Response at Day 4-7 post-treatment	Moxifloxacin 400 mg OD x 10 days	217	F: 110 (51%) M: 107 (49%)	38.6±14.7
			Cefuroxime Axetil 250 mg BID x 10 days	222	F: 124 (56%) M: 98 (44%)	39.3±14.5
100107 USA (2)	Randomized, Double-blind, Active Controlled	Clinical Response at Day 7-14 post-treatment	Moxifloxacin 400 mg OD x 10 days	223	F: 139 (62%) M: 84 (38%)	40.1±13.9
			Cefuroxime Axetil 250 mg BID x 10 days	234	F: 140 (60%) M: 94 (40%)	39.0±12.7

a demographic data refers to patients valid for efficacy
b all patients underwent antral puncture in this study
c Overall Clinical Response for Studies 0125 and 0126 includes failures occurring at end of therapy which are carried forward and included in the clinical evaluations at the follow-up (Day 27-31 post-treatment) timepoint
Legend: OD=once daily; BID=twice daily

Efficacy – Clinical Response

Table 13 – Clinical Response Rates – Clinically Evaluable Patients in Pivotal Acute Bacterial Sinusitis Trials

Study Number	Moxifloxacin 400 mg OD x 7 days n/N (%)	Moxifloxacin 400 mg OD x 10 days n/N (%)	Comparator n/N (%)	95% Confidence Intervals
0116	204/211 (97%)	N/A	204/225 (91%)	1.5%, 10.6%
0125	270/336 (80%)	N/A	N/A	76%, 84%[a]
0126	154/191 (81%)	N/A	176/193 (91%)	-17.1%, -3.8%
0161	N/A	203/217 (94%)	210/222 (95%)	-5.5%, 3.4%
100107	N/A	200/223 (90%)	209/234 (89%)	-5.1%, 6.2%

a the 95% confidence interval for Study 0125 was constructed using a normal approximation to the binomial distribution, with a continuity correction, in contrast to the confidence intervals for the other studies which were constructed using Mantel-Haenszel weights

Efficacy – Microbiological Outcome

Table 14 – Bacteriological Response Rates – Clinically and Microbiologically Evaluable Patients in Pivotal Acute Bacterial Sinusitis Trials

Study Number	Moxifloxacin 400 mg OD x 7 days n/N (%)[a]	Moxifloxacin 400 mg OD x 10 days n/N (%)[a]	Comparator n/N (%)[a]	95% Confidence Intervals
0116	103/109 (95%)	N/A	96/115 (84%)	3.6%, 19.7%
0125	72/74 (97%)[b]	N/A	N/A	N/A[c]
0161	N/A	84/86 (98%)	68/72 (94%)	-3.2%, 8.7%

a culture specimens obtained by needle aspirate, endoscopic cannulation and swab
b Bacteriological Response for Study 0125 was determined at end of therapy
c statistical analysis was not performed for the Bacteriological Response for Study 0125

Table 15 – Pathogen Eradication Rates – Clinically and Microbiologically Evaluable Patients in Acute Bacterial Sinusitis Trials

Study Number	Moxifloxacin 400 mg OD x 7 days n/N (%)	Moxifloxacin 400 mg OD x 10 days n/N (%)	Comparator n/n (%)
Streptococcus pneumoniae			
0116	38/39 (97%)	N/A	45/48 (94%)
0125	29/30 (97%)	N/A	N/A
0161	N/A	36/38 (95%)	32/32 (100%)
Combined	67/69 (97%)	36/38 (95%)	77/80 (96%)
Haemophilus influenzae			
0116	28/29 (97%)	N/A	30/35 (86%)
0125	24/30 (80%)	N/A	N/A
0161	N/A	17/17 (100%)	15/16 (94%)
Combined	52/59 (88%)	17/17 (100%)	45/51 (88%)
Moraxella catarrhalis			
0116	14/14 (100%)	N/A	8/9 (89%)
0125	15/18 (83%)	N/A	N/A
0161	N/A	10/10 (100%)	5/5(100%)
Combined	29/32 (91%)	10/10 (100%)	13/14 (93%)

Acute Bacterial Exacerbations of Chronic Bronchitis

Trial Design

Table 16 – Design of Acute Exacerbations of Chronic Bronchitis Pivotal Trials

Study No. / Country	Study Design	Primary Efficacy Parameter	Treatment Regimen	# of Pts.	Gender[a]	Mean Age ± SD (Years)[a]
0124 Europe[b] (3)	Randomized, Double-blind, Active Controlled	Clinical Response at Day 7 post-treatment	Moxifloxacin 400 mg OD x 5 days	322	F: 131 (41%) M: 191 (59%)	60.0±14.0
			Clarithromycin 500 mg BID x 7 days	327	F: 136 (42%) M: 191 (58%)	60.2±13.5
0127 Canada, USA (4)	Randomized, Double-blind, Active Controlled	Overall Clinical Response at Day 7-17 post-treatment[c]	Moxifloxacin 400 mg OD x 5 days	250	F: 115 (46%) M: 135 (56%)	56.8±15.2
			Moxifloxacin 400 mg OD x 10 days	256	F: 116 (45%) M: 140 (55%)	56.1±15.6
			Clarithromycin 500 mg BID x 10 days	251	F: 124 (49%) M: 127 (51%)	55.4±15.9

a demographic data refers to patients valid for efficacy
b Europe: Austria, France, Germany, Greece, Spain, Switzerland, United Kingdom
c Overall Clinical Response for Study 0127 includes failures occurring at end of therapy which are carried forward and included in the clinical evaluations at the follow-up (Day 7-17 post-treatment) timepoint
Legend: OD=once daily; BID=twice daily

Efficacy – Clinical Response

Table 17 –Clinical Response Rates – Clinically Evaluable Patients in Pivotal AECB Trials

Study Number	Moxifloxacin 400 mg OD x 5 days n/N (%)	Comparator[a] n/N (%)	95% Confidence Intervals
0124	287/322 (89%)	289/327 (88%)	-3.9%, 5.8%
0127	222/250 (89%)	224/251 (89%)	-6.1%, 4.2%

a 10-day regimen for 0127, 7-day regimen for 0124

Efficacy – Microbiological Outcome

Table 18 – Bacteriological Response Rates – Clinically and Microbiologically Evaluable Patients in Pivotal AECB Trials

Study Number	Moxifloxacin 400 mg OD x 5 days n/N (%)	Comparator[a] n/N (%)	95% Confidence Intervals
0124	89/115 (77%)	71/114 (62%)	3.6%, 26.9%
0127	127/143 (89%)	110/129 (85%)	-3.7%, 10.5%

a 10-day regimen for 0127, 7-day regimen for 0124

Table 19 – Pathogen Eradication Rates – Clinically and Microbiologically Evaluable Patients in Pivotal AECB Trials

Study Number	Moxifloxacin 400 mg OD x 5 days n/N (%)	Comparator[a] n/N (%)
Haemophilus influenzae		
0124	40/44 (91%)	23/43 (53%)
0127	33/37 (89%)	31/41 (76%)
Combined	73/81 (90%)	54/84 (64%)
Haemophilus parainfluenzae		
0124	5/9 (56%)	4/4 (100%)
0127	16/16 (100%)	14/14 (100%)
Combined	21/25 (84%)	18/18 (100%)
Streptococcus pneumoniae		
0124	32/38 (84%)	35/36 (97%)
0127	16/16 (100%)	21/23 (91%)
Combined	48/54 (89%)	56/59 (95%)
Staphylococcus aureus		
0124	1/1 (100%)	9/11 (82%)
0127	15/16 (94%)	7/8 (88%)
Combined	16/17 (94%)	16/19 (84%)
Moraxella catarrhalis		
0124	14/16 (87%)	23/24 (96%)
0127	29/34 (85%)	24/24 (100%)
Combined	43/50 (86%)	47/48 (98%)
Klebsiella pneumoniae		
0124	N/A	N/A
0127	17/20 (85%)	10/11 (91%)
Combined	17/20 (85%)	10/11 (91%)

a 10-day regimen for Study 0127, 7-day regimen for Study 0124

Community Acquired Pneumonia – Oral Administration

Trial Design

Table 20 – Design of Community Acquired Pneumonia Pivotal Trials for Oral Administration

Study No. / Country	Study Design	Primary Efficacy Parameter	Treatment Regimen	# of Pts.	Gender[a]	Mean Age ± SD (Years)[a]
0119 Europe[b], ROW[c] (5)	Randomized, Double-blind, Active Controlled	Clinical Response at Day 3-5 post-treatment	Moxifloxacin 200 mg OD x 10 days	180	F: 65 (36%) M: 115 (64%)	47.8±20.5
			Moxifloxacin 400 mg OD x 10 days	177	F: 71 (40%) M: 106 (60%)	48.1±20.8
			Clarithromycin 500 mg BID x 10 days	174	F: 63 (36%) M: 111 (64%)	46.3±18.7
0129 USA (6)	Open-label, Uncontrolled	Overall Clinical Response at Day 14-35 post-treatment[d]	Moxifloxacin 400 mg OD x 10 days	196	F: 83 (42%) M: 113 (58%)	48.9±18.5
0130 USA (7)	Randomized, Double-blind, Active Controlled	Overall Clinical Response at Day 14-35 post-treatment[d]	Moxifloxacin 400 mg OD x 10 days	194	F: 104 (54%) M: 90 (46%)	48.4±17.3
			Clarithromycin 500 mg BID x 10 days	188	F: 95 (51%) M: 93 (49%)	48.5±17.5

a demographic data refers to patients valid for efficacy
b Europe: Austria, Germany, Greece, Italy, Norway, Sweden, Switzerland, United Kingdom
c ROW (Rest of the World): Australia, Hong-Kong, Indonesia, Israel, New Zealand, Philippines, South Africa, Taiwan
d Overall Clinical Response for Studies 0129 and 0130 includes failures occurring at end of therapy which are carried forward and included in the clinical evaluations at the follow-up (Day 14-35 post-treatment) timepoint
Legend: OD=once daily; BID=twice daily

Efficacy – Clinical Response

Table 21 – Clinical Response Rates – Clinically Evaluable Patients in Pivotal CAP Trials

Study Number	Moxifloxacin 400 mg OD x 10 days n/N (%)	Comparator n/N (%)	95% Confidence Intervals
0119	167/177 (94%)	164/174 (94%)	-6.7%, 4.1%
0129	182/196 (93%)	N/A	88.1%, 95.9%[a]
0130	184/194 (95%)	178/188 (95%)	-3.7%, 5.3%

a the 95% confidence interval for Study 0129 was constructed using a normal approximation to the binomial distribution, with a continuity correction, in contrast to the confidence intervals for the other studies which were constructed using Mantel-Haenszel weights

Efficacy – Microbiological Outcome

Table 22 – Bacteriological Response Rates – Clinically and Microbiologically Evaluable Patients in Pivotal CAP Trials

Study Number	Moxifloxacin 400 mg OD x 10 days n/N (%)	Comparator n/N (%)	95% Confidence Intervals
0119	37/47 (79%)	29/41 (71%)	-10.2%, 26.2%
0129	106/116 (91%)	N/A	84.3%, 95.6%[a]
0130[b]	107/110 (97%)	105/109 (96%)	-4.6%, 6.5%

a the 95% confidence interval for Study 0129 was constructed using a normal approximation to the binomial distribution, with a continuity correction, in contrast to the confidence intervals for the other studies which were constructed using Mantel-Haenszel weights

b Bacteriological Response rates for Study 0130 were determined at end of therapy, in contrast to Clinical Response (end of therapy plus follow-up)

Table 23 – Pathogen Eradication Rates – Clinically and Microbiologically Evaluable Patients in Pivotal CAP Trials

Study Number	Moxifloxacin 400 mg OD x 10 days n/N (%)	Comparator n/N (%)
Streptococcus pneumoniae		
0119[a]	14/16 (88%)	12/13 (92%)
0129	13/14 (93%)	N/A
0130	17/17 (100%)	18/19 (95%)
Combined	44/47 (74%)	30/32 (94%)
Haemophilus influenzae		
0119[a]	6/8 (75%)	5/10 (50%)
0129	11/13 (85%)	N/A
0130	22/23 (96%)	14/16 (88%)
Combined	39/44 (87%)	19/26 (73%)
Mycoplasma pneumoniae		
0119[a]	22/24 (92%)	30/32 (94%)
0129	27/29 (93%)	N/A
0130	23/24 (96%)	20/20 (100%)
Combined	72/77 (94%)	50/52 (96%)
Chlamydia pneumoniae		
0119[a]	19/19 (100%)	21/23 (91%)
0129	56/63 (89%)	N/A
0130	42/45 (93%)	43/44 (98%)
Combined	117/127 (92%)	64/67 (96%)
Moraxella catarrhalis		
0119[a]	1/2 (50%)	3/3 (100%)
0129	4/4 (100%)	N/A
0130	6/7 (86%)	2/2 (100%)
Combined	11/13 (85%)	5/5 (100%)

a patients who only had positive serology for a CAP pathogen in Study 0119 were not included in the clinically and microbiologically evaluable population

Community Acquired Pneumonia – Intravenous Administration

Trial Design

Table 24 – Design of Community Acquired Pneumonia Pivotal Trials for Sequential I.V./Oral Administration

Study No. / Country	Study Design	Primary Efficacy Parameter	Treatment Regimen	# of Pts.	Gender[a]	Mean Age ± SD (Years)[a]
100039 Canada, USA (8, 9)	Randomized, Double-blind, Active Controlled	Clinical Response at Day 7-30 post-treatment	Sequential (OD x 7-14 days) I.V. Moxifloxacin 400 mg followed by PO Moxifloxacin 400 mg	182	F: 82 (45%) M: 100 (55%)	62.9±16.1
			Sequential (OD x 7-14 days) I.V. Alatrofloxacin 200 mg followed by PO Trovafloxacin 200 mg	53	F: 84 (47%) M: 96 (53%)	60.7±16.8
			Sequential (OD x 7-14 days) I.V. Levofloxacin 500 mg followed by PO Levofloxacin 500 mg	127		
200036 Europe[b], Israel, South Africa (9, 10)	Randomized, Open-label, Active Controlled	Clinical Response at Day 5-7 post-treatment	Sequential (OD x 7-14 days) I.V. Moxifloxacin 400 mg followed by PO Moxifloxacin 400 mg	258	F: 92 (36%) M: 166 (64%)	54.8±20.6
			Sequential (7-14 days) I.V. Amoxicillin 1000 mg / Clavulanate 200 mg TID followed by PO Amoxicillin 500 mg / Clavulanate 125 mg TID ± PO Clarithromycin 500 mg BID	280	F: 100 (36%) M: 180 (64%)	55.4±19.6

a demographic data refers to patients valid for efficacy

b Europe: Austria, Germany, Greece, Italy, Norway, Sweden, Switzerland, United Kingdom

Legend: OD=once daily; BID=twice daily; TID=three times daily; I.V. =intravenous; PO=oral

Efficacy – Clinical Response

Table 25 – Clinical Response Rates – Clinically Evaluable Patients in Pivotal I.V./PO CAP Trials

Study Number	Moxifloxacin 400/400 mg IV/PO OD for 7-14 days n/N (%)	Comparator n/N (%)	95% Confidence Intervals
100039	157/182 (86%)[a]	161/180 (89%)	-8.9%, 4.2%
200036	241/258 (93%)[b]	239/280 (85%)	2.9%, 13.2%

a In Study 100039, the moxifloxacin treatment group contained more patients with severe pneumonia, *Pseudomonas* pneumonia, shock at study entry, a smoking history and poor general health status than the control regimen. Of these, the presence of severe disease, declining general health status and a positive smoking history were significant predictors of clinical failure.

b The difference in response rates seen between the moxifloxacin arms in the two studies was due to the assessment of clinical response conducted early (Day 5-7 post-therapy) in Study 200036 compared to Day 7-30 post-therapy for Study 100039. The response rate of 83.7% at the late follow-up visit 21-28 days post-therapy in Study 200036 was similar to the 86% response rate in Study 100039 at its later clinical response assessment visit.

Efficacy – Microbiological Outcome

Table 26 – Bacteriological Response Rates – Clinically and Microbiologically Evaluable Patients in Pivotal I.V./PO CAP Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD for 7-14 days n/N (%)	Comparator n/N (%)	95% Confidence Intervals
100039[a]	59/75 (79%)	61/69 (88%)	-21.4%, 3.0%
200036	60/64 (94%)	58/71 (82%)	1.21%, 22.91%

a The bacteriological response rates listed for Study 100039 correspond to respiratory sites only. Including both respiratory and blood sites, the response rates were 64/80 (80%) for moxifloxacin vs. 70/78 (90%) for active control.

Table 27 – Pathogen Eradication Rates – Clinically and Microbiologically Evaluable Patients in Pivotal I.V./PO CAP Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD for 7-14 days n/N (%)	Comparator n/N (%)
Streptococcus pneumoniae		
100039	34/39 (87%)	36/40 (90%)
200036	29/29 (100%)	26/32 (82%)
Combined	63/68 (93%)	62/72 (86%)
Haemophilus influenzae		
100039	11/13 (85%)	15/17 (88%)
200036	12/12 (100%)	9/10 (90%)
Combined	23/25 (92%)	24/27 (89%)
Mycoplasma pneumoniae		
100039	9/10 (90%)	13/13 (100%)
200036	13/13 (100%)	16/17 (94%)
Combined	22/23 (96%)	29/30 (97%)
Chlamydia pneumoniae		
100039	10/11 (91%)	8/8 (100%)
200036	3/3 (100%)	4/5 (80%)

Table 27 – Pathogen Eradication Rates – Clinically and Microbiologically Evaluable Patients in Pivotal I.V./PO CAP Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD for 7-14 days n/N (%)	Comparator n/N (%)
Combined	13/14 (93%)	12/13 (92%)
Staphylococcus aureus		
100039	3/4 (75%)	5/7 (71%)
200036	2/3 (67%)	2/5 (40%)
Combined	5/7 (71%)	7/12 (58%)

Community Acquired Pneumonia Caused by Multi-drug Resistant *Streptococcus pneumoniae* (MDRSP)

Multi-Drug Resistant Streptococcus pneumoniae (MDRSP) are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 µg/mL), 2nd generation cephalosporins (eg, cefuroxime axetil), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Table 28 – Clinical Cure and Bacteriological Eradication Rates for All Moxifloxacin-treated MDRSP CAP Patients According to the Number of Antimicrobials the Isolate was Resistant to – Valid-per-protocol Population (n=37)

S. pneumoniae with MDRSP	Clinical Cure Rate	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%)

Table 29 – Clinical Cure and Bacteriological Eradication Rates for All Moxifloxacin-treated MDRSP CAP Patients According to Multi-drug Resistant Phenotype – Valid-per-protocol Population (n=37)

Screening Susceptibility	Clinical Cure Rate	Bacteriological Eradication Rate
Penicillin-resistant	21/21 (100%)	21/21 (100%)
Second Generation Cephalosporin-resistant	25/26 (96%)	25/26 (96%)
Macrolide-resistant[a]	22/23 (96%)	22/23 (96%)
Trimethoprim/sulfamethoxazole-resistant	28/30 (93%)	28/30 (93%)
Tetracycline-resistant	17/18 (94%)	17/18 (94%)

a Macrolide antimicrobials tested included azithromycin, clarithromycin, and erythromycin

Complicated Intra-abdominal Infection – Intravenous Administration

Trial Design

Sequential intravenous/oral administration of moxifloxacin hydrochloride has been studied in two pivotal Phase III trials for the indication of complicated intra-abdominal infections (cIAI). The primary diagnosis of each patient was an intra-abdominal infection in which an operative procedure or percutaneous drainage was required for diagnosis and management. An overview of the design of the trials is provided in Table 30.

Table 30 – Design of Complicated Intra-abdominal Infections Pivotal Trials for Sequential I.V./Oral Administration

Study No. / Country	Study Design	Primary Efficacy Parameter	Treatment Regimen	# of Pts.	Gender[a]	Mean Age ± SD (Years)[a]	APACHE II Score[a]
100272 Canada, USA, Israel	Randomized, Double-blind, Active Controlled	Clinical Response at Day 25-50 after start of treatment	Sequential (OD x 5-14 days) I.V. Moxifloxacin 400 mg followed by PO Moxifloxacin 400 mg	183	F: 69 (38%) M: 114 (62%)	47.4± 16.7	6.9±4.2
			Sequential (OD x 5-14 days) I.V. Piperacillin/Tazobactam 3.375 g QID followed by Amoxicillin/Clavulanate 800 mg BID	196	F: 65 (33%) M: 131 (67%)	45.1±16.5	5.9±4.2
10209 Europe[b], Argentina, Brazil, Israel, Mexico, South Africa	Randomized, Open-label, Active Controlled	Clinical Response at Day 28-42 after start of treatment	Sequential (OD x 5-14 days) I.V. Moxifloxacin 400 mg followed by PO Moxifloxacin 400 mg	246	F: 98 (40%) M: 148 (60%)	48.7±20.4	6.8±6.0
			Sequential (5-14 days) I.V. Ceftriaxone 2 g OD + Metronidazole 500 mg TID followed by PO Amoxicillin 500 mg / Clavulanate 125 mg TID	265	F: 108 (41%) M: 157 (59%)	47.8± 20.5	6.6±6.4

a demographic data refers to patients valid for clinical efficacy [183/339 (54%), 196/342 (57%) in Study 100272; 246/293 (84%), 265/302 (88%) in Study 10209]

b Europe: Austria, Belgium, Finland, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, Switzerland
Legend: OD=once daily; BID=twice daily; TID=three times daily; QID=four times daily; I.V.=intravenous; PO=oral

Efficacy – Clinical Response

Table 31 – Clinical Response Rates – Clinically Evaluable Patients in Pivotal I.V./PO cIAI Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD for 5-14 days n/N (%)	Active Control Regimen n/N (%)	95% Confidence Intervals for Difference (Mantel-Haenszel)[a]
100272	146/183 (80%)	153/196 (78%)	-7.4, 9.3
10209	199/246 (81%)	218/265 (82%)	-8.9, 4.2

a protocol defined delta of 10%

Efficacy – Microbiological Outcome

Table 32 – Bacteriological Response Rates – Clinically and Microbiologically Evaluable Patients in Pivotal I.V./PO cIAI Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD for 5-14 days n/N (%)	Active Control Regimen n/N (%)	95% Confidence Intervals for Difference (Mantel-Haenszel)[a]
100272	117/150 (78%)	126/163 (77%)	-9.9, 8.7
10209	131/166 (79%)	144/177 (81%)	-10.6, 6.3

a protocol defined delta of 10%

Table 33 – Pathogen Eradication Rates[a] – Clinically and Microbiologically Evaluable Patients in Pivotal I.V./PO cIAI Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD for 5-14 days n/N (%)	Active Control Regimen n/N (%)
Gram-Positive Aerobes		
Enterococcus faecalis		
100272	8/11 (72.7%)	8/15 (53.3%)
10209	8/9 (88.9%)	9/14 (64.3 %)
Combined	16/20 (80.0%)	17/29 (58.69%)
Streptococcus anginosus		
100272	25/34 (73.5%)	39/48 (81.3%)
10209	5/7 (71.4%)	8/8 (100.0%)
Combined	30/41 (73.2%)	47/56 (83.9%)
Gram-Negative Aerobes		
Escherichia coli		
100272	67/87 (77.0%)	69/90 (76.7%)
10209	92/117 (78.6%)	102/120 (85.0%)
Combined	159/204 (77.9%)	171/210 (81.4%)
Proteus mirabilis		
100272	3/4 (75.0%)	5/5 (100.0%)
10209	6/7 (85.7%)	6/9 (66.7%)
Combined	9/11 (81.8%)	11/14 (78.6%)
Anaerobes		
Bacteroides fragilis		
100272	35/41 (85.4%)	36/50 (72.0%)
10209	30/36 (83.3%)	28/31 (90.3%)
Combined	65/77 (84.4%)	64/81 (79.0%)
Bacteroides thetaiotaomicron		
100272	29/36 (80.6%)	27/38 (71.1%)
10209	1/2 (50.0%)	3/3 (100.0%)
Combined	30/38 (78.9%)	30/41 (73.2%)
Clostridium perfringens		
100272	6/7 (85.7%)	3/5 (60.0%)
10209	2/3 (66.7%)	6/8 (75.0%)
Combined	8/10 (80.0%)	9/13 (69.2%)

a includes eradication and presumed eradication

Complicated Skin and Skin Structure Infections – Intravenous Administration

Trial Design

Table 34 – Design of Complicated Skin and Skin Structure Infection Pivotal Trials for Sequential I.V./Oral Administration

Study No. / Country	Study Design	Primary Efficacy Parameter	Treatment Regimen	# of Pts.	Gender[c]	Mean Age ± SD (Years)[c]
100273 NA[a]/SA/ Israel (11)	Randomized, Double-blind, Active Controlled	Clinical Response at Day 10-42 post-treatment (for assessment of cure)	Sequential (OD x 7-14 days) I.V. Moxifloxacin 400 mg followed by PO Moxifloxacin 400 mg	306	F: 62 (34%) M: 118 (66%)	52.4±15.9
			Sequential (7-14 days) I.V. Pipercillin/tazobactam 3.0/0.375 g q6h followed by PO Amoxicillin/clavulanic acid suspension 800/114 mg BID	311	F: 65 (35%) M: 122 (65%)	52.8±15.4
10279 Europe[b], ROW	Randomized, Open-label, Active Controlled	Clinical Response at Day 14-28 post-treatment	Sequential (OD x 7-21 days) I.V. Moxifloxacin 400 mg followed by PO Moxifloxacin 400 mg	406	F: 142 (45%) M: 173 (55%)	51.8±1.08
			Sequential (7-21 days) I.V. Amoxicillin 1000 mg / Clavulanate 200 mg TID followed by PO Amoxicillin 500 mg / Clavulanate 125 mg TID	398	F: 119 (38%) M: 198 (62%)	51.1±18.3

a NA (North America): Canada, United States, Mexico; SA (South America): Argentina, Chile, Peru
b Europe: Germany, Hungary, Spain; ROW (Rest of World): Colombia, Mexico, Republic of South Africa, Philippines, Taiwan, Israel
c Demographic data refers to patients valid for efficacy
Legend: OD=once daily; BID=twice daily; TID=three times daily; I.V.=intravenous; PO=oral

Efficacy – Clinical Response

Table 35 – Clinical Response Rates - Clinically Evaluable Patients in Pivotal IV/PO cSSSI Studies[a]

Study Number	Moxifloxacin 400/400 mg I.V./PO OD n/N[b] (%)	Comparator n/N (%)	95% Confidence Intervals
100273	143/180 (79.4)	153/187 (81.8)	-12.04, 3.29[c]
10279	254/315 (80.6)	268/317 (84.5)	-9.41, 2.18[d]

a 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.
b n=number of patients with a clinical cure; N=total number of patients
c Protocol defined delta of 15% - using the Mantel-Haenszel formula
d Protocol defined delta of 10% - using the Mantel-Haenszel formula

Efficacy – Microbiological Outcome

Table 36 – Bacteriological Response Rates – Clinically and Microbiologically Evaluable Patients in Pivotal IV/PO cSSSI Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD n/N[a] (%)	Comparator n/N (%)	95% Confidence Intervals
100273	92/119 (77.3)	96/118 (81.4)	-14.8, 5.2
10279	127/167 (76.0)	140/172 (81.4)	-13.0, 4.4

a n=number of patients with a bacteriological response, N=total number of patients

Table 37 – Pathogen Eradication Rates – Clinically and Microbiologically Evaluable Patients in Pivotal I.V./PO cSSSI Trials

Study Number	Moxifloxacin 400/400 mg I.V./PO OD n/N (%)	Comparator n/N (%)
Enterobacter cloacae		
100273	4/5 (80.0)	1/2 (50.0)
10279	5/6 (83.3)	2/4 (50.0)
Combined	9/11 (81.8)	3/6 (50.0)
Escherichia coli		
100273	7/8 (87.5)	11/12 (91.7)
10279	24/30 (80.0)	16/20 (80.0)
Combined	31/38 (81.6)	27/32 (84.4)
Klebsiella pneumoniae		
100273	5/6 (83.3)	4/7 (57.1)
10279	5/5 (100.0)	2/2 (100.0)
Combined	10/11 (90.9)	6/9 (66.7)
Staphylococcus aureus (methicillin-susceptible strains)[a]		
100273	50/64 (78.1)	47/59 (79.7)
10279	48/59 (81.4)	71/78 (91.0)
Combined	98/123 (79.7)	118/137 (86.1)

a Methicillin susceptibility was only determined in the North American study

DETAILED PHARMACOLOGY

Animal Pharmacology

Fluoroquinolones have been shown to cause arthropathy in immature animals. In studies in juvenile dogs oral doses of moxifloxacin, the active ingredient in AVELOX, >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, respectively.

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

Ocular toxicity was not observed in 6-month oral repeat dose studies in rats and monkeys. In Beagle dogs, electroretinographic (ERG) changes were observed in a 2-week study at oral doses of 60 and 90 mg/kg. Histopathological changes were observed in the retina from one of four dogs at 90 mg/kg, a dose associated with mortality in this study.

Some fluoroquinolones 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.

Elevated liver transaminase levels occurred in rats, monkeys and dogs. Single cell necrosis in the liver was observed in rats at 500 mg/kg/day and in monkeys at 250 mg/kg/day.

Human Pharmacology

Pharmacokinetics

Pharmacokinetics are linear in the range of 50-800 mg (single dose) and up to 600 mg (once daily oral dosing over 10 days).

The mean (±SD) C_{max} and AUC values at steady-state with a 400 mg oral once daily dosage regimen are 4.5±0.53 g/L and 48±2.7 mg*h/L, respectively. C_{max} is attained 1 to 3 hours after oral dosing. The mean (±SD) trough concentration is 0.95±0.10 mg/L. The mean (±SD) C_{max} and AUC values at steady-state with a once daily dosage regimen of 400 mg intravenous moxifloxacin infused over 60 minutes in healthy young males are 4.2±0.8 g/L and 38±4.7 mg*h/L, respectively. C_{max} is achieved at the end of a 60 minute infusion (see **DOSAGE AND ADMINISTRATION**).

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). Moxifloxacin is eliminated from plasma by first-order process. 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. The time course of plasma concentrations of moxifloxacin following steady-state oral and intravenous administration is illustrated in Figure 1, and pharmacokinetic parameters of moxifloxacin are presented in Table 10 (see **ACTION AND CLINICAL PHARMACOLOGY**).

Absorption and Bioavailability

Moxifloxacin hydrochloride, 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 absorption of moxifloxacin.

Consumption of one cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

Distribution

Moxifloxacin is approximately 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, 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 Table 11 (see **ACTION AND CLINICAL PHARMACOLOGY**). The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Metabolism

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 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. The sulfate (M1) and glucuronide (M2) conjugates are not microbiologically active.

Excretion

Approximately 45% of an oral 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±2.0 L/hr and 2.6±0.5 L/hr, respectively.

Special Populations

Pediatrics (<18 years of age)

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

Geriatrics (≥65 years of age)

Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and 16 young (8 male; 8 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 oral dose of 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 Phase I studies, the pharmacokinetics in elderly patients following infusion of 400 mg were similar to those observed in young patients.

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 g/L, an AUC_{24} of 47 g*h/mL, and an elimination half-life of 14 hours following 400 mg daily PO.

Renal Insufficiency

The pharmacokinetic parameters of moxifloxacin are not significantly altered by mild, moderate, or severe renal impairment. Based on pharmacokinetic data, no dosage adjustment is necessary in patients with renal impairment, including those patients on 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 22% and 21% in the patients with moderate (Cl_{cr}≥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 sulfate and glucuronide conjugates are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal impairment has not been studied.

The pharmacokinetics of single 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). Pharmacokinetic comparisons are to historical pharmacokinetic values from health volunteers (Cl_{cr}>90 mL/min; administered a single 400 mg oral dose of moxifloxacin). 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 subjects. 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 7.3 to 13.2, 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 moxifloxacin once daily 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 28% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Moxifloxacin and the glucuronide conjugate (M2) were removed from the body by HD (approximately 9% and 4%, respectively) and by CAPD (approximately 3% and 2%, respectively). Systemic exposure (AUC) to M2 was equal to or greater than moxifloxacin exposure in HD and CAPD subjects following single dosing and at steady state. (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**).

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 that in 18 healthy controls. The mean peak concentration (C_{max}) was 79% and 84%, respectively, of control values.

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 8.0-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), respectively. 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). Due to limited clinical data, the use of moxifloxacin is not recommended with severe hepatic insufficiency (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**).

QT Prolongation

The effect of moxifloxacin on the QT interval has been extensively studied in pre-clinical models, healthy volunteers and patients. These data are briefly described below. The clinical pharmacology program included single-dose, multiple-dose and cross-over studies of healthy male and female volunteers aged 18 to 75 years treated with oral and intravenous moxifloxacin 400 mg. The patient data are derived from the Phase III clinical studies with oral and intravenous moxifloxacin 400 mg. In all cases, the QT data presented are corrected for heart rate (QTc) using Bazett's correction. The baseline pre-treatment QTc interval measured on Day 1 of treatment prior to drug administration was used in all cases for calculations of the relative QTc interval change. QTc at C_{max} was defined to be end of infusion for the intravenous data, and 2 hours after drug administration for the oral data.

In clinical pharmacology single-dose studies (n=112 subjects) with 400 mg oral moxifloxacin, the aggregate mean prolongation of the QTc interval at the expected time of peak plasma concentration after a single oral dose of 400 mg moxifloxacin was 7±23 msec (1.8%±5.6%). In a multi-dose clinical pharmacology study (n=47) with 400 mg oral moxifloxacin, the mean

prolongation at steady-state of the QTc interval (measured on Day 10) was 12.3 msec. There were four male patients with a QTc greater than 450 msec and one male patient with a QTc increase of greater than 60 msec.

In clinical pharmacology single-dose studies (n=29) with 400 mg intravenous moxifloxacin, the aggregate mean prolongation of the QTc interval at the end of a one hour infusion was 20.6±23 msec (5.5%±5.9%). In a multi-dose clinical pharmacology study (n=7) with 400 mg intravenous moxifloxacin, the mean prolongation of the QTc interval at steady-state (Day 10) was 12.6 msec. There were four male patients with a QTc interval greater than 450 msec. Two patients had a QTc increase of greater than 60 msec.

In 787 patients with paired valid ECGs in Phase III clinical trials, the mean±SD prolongation of the QTc interval was 6±26 msec at the estimated time of C_{max} after oral dosing with moxifloxacin 400 mg. In 176 patients with paired valid ECGs in Phase III clinical trials, the mean±SD prolongation of the QTc interval after a one hour infusion of intravenous moxifloxacin 400 mg was 9±24 msec (Day 1; n=176) and 3±29 msec (Day 3; n=290). An analysis of data from the two Phase III studies at various time intervals after moxifloxacin infusion revealed the following increases in QTc. Within 0-3 hours after a 60 minute 400 mg moxifloxacin infusion (n=86) on the first day of exposure, the mean±SD increase in QTc was 14±26 msec. However, on the first day of exposure, if a time window of 0-4 hours after a 60 minute 400 mg moxifloxacin infusion (n=176) is utilized, the mean±SD increase in QTc was 9±24 msec. If the time window of 1-3 hours after a 60 minute 400 mg moxifloxacin infusion (n=90) is examined, the mean±SD increase in QTc was 5±20 msec. The corresponding values on Day 3 of a daily 60 minute infusion of 400 mg moxifloxacin were 7±30 msec (0-3 hours; n=71), 3±29 msec (0-4 hours; n=290) and 0±26 msec (1-4 hours; n=83) (see **WARNINGS AND PRECAUTIONS**).

MICROBIOLOGY

AVELOX (moxifloxacin hydrochloride) has in vitro activity against a wide range of Gram-positive and Gram-negative aerobic, anaerobic, as well as intracellular organisms. The bactericidal action of moxifloxacin results from inhibition of both topoisomerase II (DNA gyrase) and topoisomerase IV. Both are required for bacterial DNA replication, transcription, repair, and recombination. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, a proposed mechanism of fluoroquinolone resistance.

The mechanism of action for fluoroquinolones, 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. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to other classes of antimicrobial agents.

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 $<1 \times 10^{-11}$ in one strain of *Staphylococcus aureus* and one strain of *Streptococcus pneumoniae*.

Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria, Gram-positive bacteria resistant to other fluoroquinolones may

be susceptible to moxifloxacin. Conversely, Gram-positive bacteria that are resistant to moxifloxacin may be susceptible to other fluoroquinolones.

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 CLINICAL USE** section. In vitro activity of moxifloxacin against clinical isolates is presented in Table 38.

Table 38 – Moxifloxacin In Vitro Activity Against Clinical Isolates

Species	No. of Isolates	MIC (mg/L)		
		MIC_{50}	MIC_{90}	Range
GRAM-POSITIVE				
Enterococcus faecalis[a,b]	16	0.25	2	0.25-16
Streptococcus anginosus[a]	40	0.125	0.25	0.06-0.25
Staphylococcus aureus	115	0.06	0.125	0.03-4
Streptococcus pneumoniae Penicillin-susceptible Penicillin-intermediate Penicillin-resistant (penicillin MIC≥2 μg/mL)	77 5324 964 348	0.125	0.25 0.25 0.25 0.25	0.06-0.5 0.06-1 0.06-1 0.06-0.25
GRAM-NEGATIVE				
Bacteroides fragilis[a]	71	0.5	1	0.03-8
Bacteroides thetaiotaomicron[a]	52	1	2	0.125-16
Clostridium perfringens[a]	10	0.5	0.5	0.25-0.5
Escherichia coli[a]	182	0.125	0.25	0.008-16
Haemophilus influenzae	120	0.03	0.06	0.008-0.25
Haemophilus parainfluenzae	39	0.06	0.5	0.015-8
Klebsiella pneumoniae	48	0.125	0.5	0.06-4
Moraxella catarrhalis	86	0.06	0.125	0.03-0.25
Proteus mirabilis[a]	10	0.25	0.5	0.25-0.5
OTHER MICROORGANISMS				
Chlamydia pneumoniae	19		1	0.06-1
Mycoplasma pneumoniae	131		0.06	0.06-0.12

a from clinical trials only

b *(Vancomycin sensitive strains only; many strains are only moderately susceptible)*

Moxifloxacin exhibits in vitro minimum inhibitory concentrations (MICs) of 2 mg/L or less against most (≥90%) strains of the microorganisms listed in Table 39; 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.

The following in vitro data are available and presented in Table 39, **but their clinical significance is unknown.**

Table 39 – Moxifloxacin In Vitro Activity with Unknown Clinical Significance

Species	No. of Isolates	MIC (mg/L)		
		MIC_{50}	MIC_{90}	Range
Bacteroides fragilis[a]	310		2	0.25-4
Clostridium perfringens[a]	88		0.5	0.5
Enterobacter cloacae	92		0.5	0.06-0.5
Enterococcus faecalis[a]	1019		16	0.5-16
Enterococcus faecium	925		16	0.12- >32
Enterococcus species	2562		16	0.25- >32
Escherichia coli[a]	276		0.06	0.008-4
Fusobacterium species	160		1	0.25-8
Haemophilus influenzae				
Beta-lactamase positive	477		0.06	0.016-0.06
Beta-lactamase negative	999		0.06	0.016-0.06
Legionella pneumophila	67	0.015-0.03	0.015-0.125	0.03-0.125
Legionella species	149		0.125	0.015-0.25
Listeria monocytogenes	80	0.25	0.5	0.06-0.5
Morganella morganii	92	0.06-0.25	0.13-16	0.03-8
Moraxella catarrhalis	1203		0.06	0.03-0.125
Beta-lactamase positive	712		0.06	0.03-0.125
Beta-lactamase negative	83		0.06	0.03-0.12
Mycobacterium tuberculosis	276		0.5	0.25-0.5
Neisseria gonorrhoeae	68	0.008-0.016	0.015-0.03	0.004-0.12
Peptostreptococcus species	125		0.25	0.25-1
Prevotella species	176		0.5	0.125-4
Proteus mirabilis[a]	236		0.25	0.25-4
Pseudomonas aeruginosa	371		8	8- >32
Staphylococcus aureus				
Methicillin-susceptible	526		0.12	0.06-2
Methicillin-resistant	309		4	2-8
Staphylococcus epidermidis	233		0.12	0.1-2
Streptococcus viridans group	334		0.25	0.25-0.5
Streptococcus agalactiae	191		0.5	0.25-0.5
Streptococcus pyogenes	1607		0.25	0.1-0.25

a not from clinical trials

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 broth or agar dilution method such as CLSI Performance Standards for Antimicrobial Susceptibility Testing or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according criteria listed in Table 40.

Table 40 – Interpretation of MIC Values

MIC (mg/L)	Interpretation
For testing *Enterobacteriaceae* and *Staphylococcus* spp.	
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)
For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]	
≤1.0	Susceptible (S)
For testing *Streptococcus* species (including *Streptococcus pneumoniae*)[b] and *Enterococcus* species	
≤1.0	Susceptible (S)
2.0	Intermediate (I)
≥4.0	Resistant (R)

a This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM) broth incubated in ambient air at 35°C ± 2 degrees for 20-24 hours (12)

b This interpretive standard is applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth (CAMHB) with 2-5% (v/v) lysed horse blood broth incubated in ambient air at 35°C ± 2 degrees for 20-24 hours (12)

The current absence of data on resistant strains of *Enterobacteriaceae*, *Staphylococcus* spp, *Haemophilus influenzae* and *Haemophilus parainfluenzae* 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 *Streptococcus* species (including *Streptococcus pneumoniae*) and *Enterococcus* species, 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 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 MIC values listed in Table 41.

Table 41 – Acceptable Limits for Quality Control Strains to Monitor the Accuracy of MICs (mg/L) for Moxifloxacin Susceptibility Testing

Organism	MIC (mg/L)
Escherichia coli ATCC[a] 25922	0.008-0.06
Enterococcus faecalis ATCC 29212	0.06-0.5
Staphylococcus aureus ATCC 29213	0.015-0.06
Haemophilus influenzae ATCC 49247[b]	0.008-0.03
Streptococcus pneunoniae ATCC 49619[c]	0.06-0.5

a ATCC is a registered trademark of the American Type Culture Collection

b This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM) broth (12)

c 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% (v/v) lysed horse blood (12)

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 (CLSI Performance Standards for Antimicrobial Susceptibility Testing) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg of 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 criteria listed in Table 42.

Table 42 – Interpretation of Zone Diameters

Zone Diameter (mm)	Interpretation
For testing *Enterobacteriaceae* and *Staphylococcus* spp.	
≥19	Susceptible (S)
16-18	Intermediate (I)
≤15	Resistant (R)
For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]	
≥18	Susceptible (S)
For testing *Streptococcus* species (including *Streptococcus pneumoniae)*[b] and *Enterococcus* species	
≥18	Susceptible (S)
15-17	Intermediate (I)
≤14	Resistant (R)

a interpretive standard is applicable only to disk diffusion tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM) incubated in 5% CO_2 at 35 ^{O}C ± 2 degrees for 16-18 hours (12)

b This interpretive standard is applicable only to disk diffusion tests using Mueller-Hinton agar supplemented with 5% (v/v) sheep blood incubated in 5% CO_2 at 35 ^{O}C ± 2 degrees for 20-24 hours (12)

The current absence of data on resistant strains of *Enterobacteriaceae*, *Staphylococcus* spp, *Haemophilus influenzae* and *Haemophilus parainfluenzae* 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 *Streptococcus pneumoniae*, 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 zone diameters listed in Table 43.

Table 43 – Acceptable Limits for Quality Control Strains used to Monitor Accuracy of Disk Diffusion Tests with 5 µg Moxifloxacin Disk

Organism	Zone Diameter (mm)
Escherichia coli ATCC[a] 25922	28-35
Staphylococcus aureus ATCC 25923	28-35
Haemophilus influenzae ATCC 49247[b]	31-39
Streptococcus pneumoniae ATCC 49619[c]	25-31

a ATCC is a registered trademark of the American type Culture Collection

b These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM) incubated in 5% CO_2 at 35°C ± 2 degrees for 16-18 hours (12)

c These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% (v/v) defibrinated sheep blood incubated in 5% CO_2 at 35°C ± 2 degrees for 20-24 hours

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to moxifloxacin as MICs can be determined by standardized procedures (13) such as reference agar dilution methods[a]. The MICs obtained should be interpreted according to the criteria listed in Table 44.

Table 44 – Interpretation of MIC Values for Anaerobic Bacteria[a]

MIC (mg/L)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

a This interpretive standard is applicable to reference agar dilution susceptibility tests using Brucella agar supplemented with 5 µg hemin, 1 µg vitamin K1 per mL and 5% (v/v) laked sheep blood (13)

Acceptable ranges of MICs (mg/L) for control strains for reference broth microdilution testing and reference agar dilution testing are listed in Table 45.

Table 45 – Acceptable Limits for Quality Control Strains to Monitor the Accuracy of MICs (mg/L) for Moxifloxacin Susceptibility Testing for Anaerobic Bacteria

Organism	MIC (mg/L)
Reference Agar Dilution Susceptibility Testing[a]	
Bacteroides fragilis ATCC[b] 25285	0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741	1.0-4.0
Eubacterium lentum ATCC 43055	0.125-0.5

a These quality control ranges are applicable to reference agar dilution tests using Brucella agar supplemented with 5 µg hemin, 1 µg vitamin K_1 per mL and 5% (v/v) laked sheep blood (13)

b ATCC is a registered trademark of the American Type Culture Collection

TOXICOLOGY

The major toxicological target organs for moxifloxacin, the active ingredient in AVELOX, are the same as have been seen with other fluoroquinolones. These include the hemopoietic system (hypocellularity of the bone marrow in dogs and monkeys), the central nervous system (convulsions in monkeys) and the liver (raised liver enzymes, single cell necrosis in rats, dogs and monkeys). These changes were commonly seen only after prolonged treatment or treatment with high doses of moxifloxacin.

Acute Toxicity

The acute toxicity was investigated in mice and rats following oral and intravenous administration and in monkeys following oral administration (see Table 46).

Table 46 – Results of Acute Toxicity Animal Studies

Species	Strain (Sex)	#/Group	Route of Administration	LD_{50} mg/kg B.W. (Confidence Interval for 95%)
Mouse	NMRI (♂)	5	PO	approx. 435
	NMRI (♀)		PO	approx. 758 (440-1305)
	NMRI (♂)		I.V.	approx. 105 (84-132)
	NMRI (♀)		I.V.	approx. 130 (116-145)
	WU (♂)		PO	approx. 1320
	WU (♀)		PO	approx. 1320
	WU (♂)		I.V.	approx. 112
	WU (♀)		I.V.	approx. 146
Monkey	Cynomolgus (♂)	2	single dose/PO	approx. 1500 mg/kg

Repeated Dose Toxicity

As shown in Table 47, moxifloxacin was examined in repeated dose toxicity studies in rats (oral and intravenous), Beagle dogs (oral) and Rhesus monkeys (oral and intravenous).

Table 47 – Results of Repeated Dose Toxicity Animal Studies

Species (# per Group)	Dose / Route	Treatment Duration	Findings
Wistar rats (10 ♂, 10 ♀)	0, 20, 100 mg/kg orally (young animals), 100 mg/kg orally (old animals)	4 weeks	Treatment was tolerated without symptoms. The clear NOAEL is 100 mg/kg for both old and young rats.
Wistar rats (10 ♂, 10 ♀)	0, 20, 100, 500 mg/kg orally by gavage	4 weeks	↓ body weight gain at 100 and 500 mg/kg in males. NOAEL for males=20 mg/kg (C_{max}=0.712 mg/L). NOAEL for females=500 mg/kg (C_{max}=5.22 mg/L).
Wistar rats (10 ♂, 10 ♀)	0, 5, 15, 45 mg/kg I.V.	4 weeks	With the exception of local effects at the injection site, no other effects were observed. The NOAEL for local irritation=5 mg/kg. The systemic NOAEL is 45 mg/kg (C_{max}=8.57 mg/L).

Table 47 – Results of Repeated Dose Toxicity Animal Studies

Species (# per Group)	Dose / Route	Treatment Duration	Findings
Wistar rats (15 ♂, 15 ♀)	0, 20, 100, 500, 750 mg/kg orally by gavage (2 groups per dose)	13 weeks for all groups 1 group was examined after a 4 week recovery period	↓ body weight gain at 100, 500 and 750 mg/kg males. ↑ ASAT, ALAT, LDH in 500 and 750 mg/kg males; 750 mg/kg females. No histopathology results. NOAEL for females=100 mg/kg (C_{max}=0.756 mg/L) NOAEL for males=20 mg/kg (C_{max}=1.22 mg/L).
Wistar rats (20 ♂, 20 ♀)	0, 20, 100, 500 mg/kg orally by gavage	28 weeks	↑ water consumption in 100 mg/kg males; 500 mg/kg males and females. ↓ body weight gain at 500 mg/kg in both sexes. ↑ ASAT, ALAT in all 500 mg/kg males; ↑ LDH and bilirubin in 500 mg/kg males; ↑ APH at 500 mg/kg in both sexes. ↓ N-DEM, O-DEM in 100 and 500 mg/kg males. ↓ P450 in 500 mg/kg males; ↑ P450 in 20, 100, 500 mg/kg females. Histopath: liver 500 mg/kg in both sexes; thyroid 500 mg/kg in males. NOAEL for females=100 mg/kg (C_{max}=0.822 mg/L) NOAEL for males=20 mg/kg (C_{max}=1.48 mg/L).
Beagle dogs (4 ♂, 4 ♀)	0, 10, 30, 90 mg/kg PO (capsule)	4 weeks	Female terminated (2 weeks) in poor condition. Forepaws flexed at 10, 30, 90 mg/kg. ↑ vacuolization subcapsular cortex of the lens at 90 mg/kg. Prolongation of QT interval at 90 mg/kg. Histopath: chondropathy at 90 and 30 mg/kg. NOAEL= >10 mg/kg (C_{max}=2.19 mg/L)
Beagle pups (2 ♂, 2 ♀)	0, 10, 30, 90 mg/kg PO (capsule)	4 weeks	90 mg/kg female terminated in poor condition. Vomiting, salivation and ↓ body weight gain at 90 mg/kg. Histopath: blistering of articular cartilage at 30 and 90 mg/kg NOAEL=10 mg/kg (C_{max}=2.97 mg/L)
Rhesus monkeys (3 ♂, 3 ♀)	0, 10, 50, 250* mg/kg orally by gavage *reduced to 150 mg/kg from Day 23	4 weeks	↓ body weight gain, ↑ ASAT, ALAT, GLDH. Convulsions at 250 mg/kg. Histopath: liver, bone marrow, testes and prostate at 250 mg/kg NOAEL=50 mg/kg (C_{max}=5.32 mg/L)
Rhesus monkeys (3 ♂, 3 ♀)	0, 100, 150 mg/kg orally by gavage	4 weeks	↓ body weight gain at 150 mg/kg; histopath: liver and bone marrow at 100 and 150 mg/kg NOAEL= <100 mg/kg (C_{max}=9.63 mg/L)
Rhesus monkeys (4 ♂, 4 ♀)	0, 15, 45, 135 mg/kg orally by gavage	13 weeks	Salivation at 45 mg/kg. Salivation, vomiting, reduced activity and ↓ body weight gain in males at 135 mg/kg. NOAEL=15 mg/kg (C_{max}=2.35 mg/L for males, 1.95 mg/L for females)
Rhesus monkeys (4 ♂, 4 ♀)	0, 15, 45, 135 mg/kg orally by gavage	26 weeks	Mortality at 135 mg/kg. ↑ ALAT and GLDH at 45 mg/kg. Histopath: liver and bone marrow at 135 mg/kg. NOAEL=15 mg/kg (C_{max}=2.42 mg/L)
Rhesus monkeys (3 ♂, 3 ♀)	0, 5, 15, 45 mg/kg I.V.	4 weeks	Vomiting, salivation, drooping eyelid at 45 mg/kg NOAEL for local irritation=15 mg/kg NOAEL for systemic toxicity=15 mg/kg (C_{max}=5.07 mg/L)

Table 47 – Results of Repeated Dose Toxicity Animal Studies

Species (# per Group)	Dose / Route	Treatment Duration	Findings
Rhesus monkeys (3 ♂, 3 ♀)	0, 200, 400 mg/animal I.V. infusion	4 weeks	Hypoactivity, vomiting, salivation and spastic movements at 400 mg/animal; vascular and perivascular inflammation at 200 and 400 mg/animal NOAEL for local irritation= >200 mg/kg NOAEL for systemic toxicity=200 mg/kg (C_{max}=9.90 mg/L)

Legend: ALAT=Serum alanine aminotransferase; ASAT=Aspartate aminotransferase; N-DEM=aminopyrin-N-demethylase; O-DEM=p-nitroanisol-N-demethylase; GLDH=glutamate dehydrogenase; LDH=Lactate dehydrogenase; NOAEL=No Observable Adverse Effect Level

Carcinogenicity

Conventional long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, a 38-week rat initiation-promotion bioassay showed moxifloxacin to have no carcinogenic potential.

Reproductive Toxicology

Moxifloxacin was not teratogenic in rats at oral doses as high as 500 mg/kg/day (63 times the recommended human dose on a mg/kg basis or 13 times on a mg/m^2 basis). Decreased fetal body weights and slightly delayed fetal skeletal development occurred in rats at a maternally toxic dose of 500 mg/kg. Maternal toxicity was observed at 100 and 500 mg/kg/day. There was no evidence of teratogenicity when Cynomolgus monkeys were dosed as high as 100 mg/kg/day (12.5 times the recommended human dose on a mg/kg basis or 4.5 times on a mg/m^2 basis). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. There was an increase in abortions observed in Cynomolgus monkeys at doses of 30 mg/kg and higher. In an oral pre-postnatal development study conducted in rats, marginal effects observed at 500 mg/kg/day included extended duration of pregnancy, increased prenatal loss, reduced birth weight and decreased survival index. Treatment-related maternal mortality occurred at 500 mg/kg/day.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day (3500 mg/m^2) which corresponds to 63 times the recommended human dose on a mg/kg basis or 13 times on a mg/m^2 basis. At the systemically toxic dose of 500 mg/kg there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

In an intravenous rabbit study, moxifloxacin at 20 mg/kg was found to decrease the gestation rate, decrease fetal weights and delay ossification.

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

Mutagenesis

Moxifloxacin was not mutagenic in 4 strains (TA 98, TA 100, TA 1535, TA 1537) of the Ames Salmonella reversion assay. As with other fluoroquinolones, the Ames test with strain TA102

was positive and may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the HGPRT mutation assay in Chinese Hamster Ovary cells. An equivocal result was obtained in the HGPRT mutation assay with v79 cells. Under in vitro conditions, moxifloxacin was clastogenic in the v79 chromosome aberration assay at a concentration of 300 μg/mL. No evidence of genotoxicity was observed in the Unscheduled DNA Synthesis assay in rat primary hepatocytes. There was no evidence of genotoxicity in vivo in a mouse micronucleus test and in a mouse dominant lethal test.

Cardiac Effects

As has been observed with other fluoroquinolones, a prolongation of the QT-interval was observed in dogs treated with an oral dose of 90 mg/kg or with an intravenous bolus dose of 30 mg/kg. The effect was only slight when the drug was given as a slow infusion or orally. No arrhythmias were observed in dogs following treatment with oral doses of moxifloxacin. At intravenous doses of more than 300 mg/kg resulting in a plasma concentration greater than 200 mg/L, moxifloxacin caused reversible ventricular arrythmias in dogs.

In beagle dogs, moxifloxacin at a dose of 30 mg/kg I.V. in combination with sotalol lowered mainly the systolic blood pressure and increased the heart rate back to starting values (before sotalol). In combination with sotalol, the QTc was markedly elevated by moxifloxacin (+113 msec); this effect seems to be additive to the sotalol-effect.

Arthrotoxicity

Fluoroquinolones are known to cause lesions in the cartilage of the major diarthodial joints in immature animals. The lowest oral dose of moxifloxacin causing joint toxicity in juvenile dogs was four times the maximum recommended therapeutic dose (400 mg/50 kg person) on a mg/kg basis, with plasma concentrations two to three times higher than those at the recommended therapeutic dose.

Phototoxicity

Double-blind placebo controlled clinical studies with moxifloxacin have shown it to be without measurable phototoxicity (see **WARNINGS AND PRECAUTIONS**).

Moxifloxacin has been evaluated in several in vitro and in vivo photostability and phototoxicity studies under conditions of UV-A/B light to simulate natural sunlight exposure. Moxifloxacin has been shown to be photostable, and to lack photogenotoxicity or photomutagenicity in mouse 3T3 fibroblasts. It was also negative in phototoxicity studies in guinea pigs, pigmented and non-pigmented rats and hairless mice.

REFERENCES

1. Siegert R, Gehanno P, Nikolaidis P, Bagger-Sjoback D, Ibanez JM, Hampel B, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. The Sinusitis Study Group. Respir Med. 2000 Apr;94:337-44.
2. Burke T, Villanueva C, Mariano H, Jr., Huck W, Orchard D, Haverstock D, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. Sinusitis Infection Study Group. Clin Ther. 1999 Oct;21(10):1664-77.
3. Wilson R, Kubin R, Ballin I, Deppermann KM, Bassaris HP, Leophonte P, et al. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. J Antimicrob Chemother. 1999 Oct;44(4):501-13.
4. Chodosh S, DeAbate CA, Haverstock D, Aneiro L, Church D. Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis. The Bronchitis Study Group. Respir Med. 2000 Jan;94(1):18-27.
5. Hoeffken G, Meyer HP, Winter J, Verhoef L. The efficacy and safety of two oral moxifloxacin regimens compared to oral clarithromycin in the treatment of community-acquired pneumonia. Respir Med. 2001 Jul;95(7):553-64.
6. Patel T, Pearl J, Williams J, Haverstock D, Church D. Efficacy and safety of ten day moxifloxacin 400 mg once daily in the treatment of patients with community-acquired pneumonia. Community Acquired Pneumonia Study Group. Respir Med. 2000 Feb;94(2):97-105.
7. Fogarty C, Grossman C, Williams J, Haverstock D, Church D. Efficacy and safety of moxifloxacin vs. clarithromycin for community-acquired pneumonia. Infect Med. 1999 November 1999;16:748-63.
8. File TM, Larsen SL, Fogarty CM, Schechter RB, Peloquin S, Choudhri SH, et al. Safety and efficacy of sequential (IV to PO) moxifloxacin for the treatment of community-acquired pneumonia in hospitalized patients. Today's Therapeutic Trends. 2001;19:251-70.
9. Lode H, Grossman C, Choudhri S, Haverstock D, McGivern J, Herman-Gnjidic Z, et al. Sequential IV/PO moxifloxacin treatment of patients with severe community-acquired pneumonia. Respir Med. 2003 Oct;97(10):1134-42.
10. Finch R, Schurmann D, Collins O, Kubin R, McGivern J, Bobbaers H, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. Antimicrob Agents Chemother. 2002 Jun;46:1746-54.
11. Giordano P, Song J, Pertal P, Herrington J, Kowalsky S. Sequential intravenous/oral moxifloxacin versus intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate for the treatment of complicated skin and skin structure infection. Int J Antimicrob Agents. 2005 November;26(5):357-64.

12. CLSI. Performance standards for antimicrobial susceptibility testing. CLSI Document M100-S15. 15th Informational Supplement ed. Wayne, PA2005.

13. NCCLS. Methods for antimicrobial susceptibility testing of anaerobic bacteria. Approved Standard NCCLS Document M11-A6. 6th ed ed. Wayne, PA2004.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICATION

PATIENT MEDICATION INFORMATION

PrAVELOX®

Moxifloxacin tablets (as moxifloxacin hydrochloride)

PrAVELOX® I.V.

Moxifloxacin injection (as moxifloxacin hydrochloride)

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

Serious Warnings and Precautions

- Fluoroquinolone antibiotics, like AVELOX, are related to disabling and possibly long lasting effects such as:
  - inflamed tendon (tendonitis), tendon rupture.
  - nerve damage (peripheral neuropathy).
  - problems in the brain such as:
    - convulsions
    - nervous breakdown
    - confusion
    - and other symptoms
- Fluoroquinolone antibiotics, like Avelox:
  - have lengthened the heartbeat (QT prolongation)
  - have led to serious allergic reactions, including death
  - may be related to increased tendonitis (inflamed tendon)
  - may worsen myasthenia gravis (a muscle disease)
  - may lead to seizures and nervous breakdowns. Tell your doctor if you have brain or spinal cord problems (such as epilepsy)
  - may cause liver injury which may lead to death
- For further information and symptoms see:
  - the "**To help avoid side effects and ensure proper use**,…" section
  - the "**What are possible side effects from using AVELOX?**" section

Talk to your doctor to see if AVELOX is right for you.

What is AVELOX used for?

Your doctor has prescribed AVELOX because you have a certain type of bacterial infection.

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

How does AVELOX work?

AVELOX is an antibiotic. It kills many of the types of bacteria that can infect the lungs, sinuses, abdomen, and skin.

What are the ingredients in AVELOX Tablets?

Medicinal ingredients: 400 mg of moxifloxacin as moxifloxacin hydrochloride

Non-medicinal ingredients: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, magnesium stearate, red ferric oxide, hydroxypropyl methyl cellulose, polyethylene glycol 4000, and titanium dioxide.

What are the ingredients in AVELOX I.V.?

Medicinal ingredients: 250 mL minibags contain 400 mg of moxifloxacin as moxifloxacin hydrochloride

Non-medicinal ingredients: sodium chloride, USP, and Water for Injection, USP. It may also contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

AVELOX Tablets come in the following dosage forms:

Tablets: oblong, convex-shaped, dull red film-coated tablets containing 400 mg moxifloxacin (as hydrochloride). They are engraved with "BAYER" on one side and "M400" on the other.

AVELOX I.V. comes in the following dosage forms:

Intravenous infusion: ready-to-use 250 mL latex-free flexible bags containing 400 mg of moxifloxacin (as hydrochloride) in 0.8% saline.

Do not use AVELOX if:

- you are allergic to AVELOX (moxifloxacin hydrochloride) or other fluoroquinolone antibiotics.
- you are allergic to any other ingredient in the formulation (see "**What are the ingredients in AVELOX** Tablets?").

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AVELOX. Talk about any health conditions or problems you may have, including if you:

- have or have a family history of irregular heart rhythm (such as QT prolongation).
- have or have had heart problems such as heart failure, an irregular heartbeat, or a slow heartbeat.
- have low potassium blood levels (see "**The following may interact with AVELOX**:").
- have a history of seizures.
- are pregnant, planning to become pregnant, or if you are breast feeding.
- are less than 18 years of age.
- have a history of tendon problems (such as pain, swelling or rupture of a tendon) related to the use of fluoroquinolone antibiotics.
- have myasthenia gravis (a muscle disease).
- have diabetes as AVELOX may affect blood sugar levels. AVELOX may also affect blood sugar levels in those without diabetes.
- have an aortic aneurysm which is an abnormal bulge in a large blood vessel called the aorta.
- have or if anyone in your family has a condition called aneurysm disease which is an abnormal bulge in any large blood vessel in the body.
- have an aortic dissection which is a tear in the wall of the aorta.
- have any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis or Behcet's disease.
- have high blood pressure.
- have atherosclerosis, which is a hardening of your blood vessels.

Other warnings you should know about:

Blood Sugar Changes

Medicines like AVELOX can cause blood sugar levels to rise and drop in patients with diabetes. Serious cases of hypoglycemia (low blood sugar levels) that caused coma or death have been seen with medicines like AVELOX. If you have diabetes, check your blood sugar levels often while taking AVELOX.

While taking Avelox:

- Avoid too much sunlight or artificial ultraviolet light (such as sunlamps).
    - Contact your doctor if a sunburn or rash occurs.
- Do not drive or use machinery if you feel dizzy or lightheaded.

Quinolones, including AVELOX and AVELOX I.V. have been associated with an enlargement or "bulge" of a large blood vessel called the aorta (aortic aneurysm) and a tear in the aorta wall (aortic dissection).

- The risk of these problems is higher if you:
    - are elderly
    - have or anyone in your family has had aneurysm disease
    - have an aortic aneurysm or an aortic dissection
    - have any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis or giant cell arteritis or Behcet's disease
    - have high blood pressure or atherosclerosis
- If you experience sudden, severe pain in your abdomen, chest or back, a pulsating sensation in your abdomen, dizziness or loss of consciousness, get immediate medical help.

Tendon problems can happen within the first 48 hours of treatment.

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

The following may interact with AVELOX:

- Antacids or vitamin/mineral supplements
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Antidiabetic medicines (such as, insulin, glyburide, glibenclamide)
- Quinidine, procainamide, amiodarone, sotalol, cisapride[b], erythromycin, antipsychotics, tricyclic antidepressants, diuretics (furosemide, hydrochlorothiazide).

[b] no longer marketed in Canada

How to take AVELOX:

- You must take AVELOX exactly as prescribed by your doctor. YOU SHOULD NOT INCREASE THE PRESCRIBED DOSE.
- You can take AVELOX with or without food.
- You should drink lots of fluids while taking AVELOX.
- If your doctor decides to stop the treatment, dispose of all unused AVELOX tablets.

Usual dose:

- Take one 400 mg AVELOX tablet once a day.
- Swallow each AVELOX tablet whole with a drink of water. Do not crush or chew AVELOX tablets.

- If you are taking antacids or vitamin/mineral supplements which contain magnesium or aluminium, take AVELOX at least 4 hours before or 8 hours after taking the supplement or antacid.
- Your doctor has decided on the best dose for you and for how long based on your needs. The usual adult dose of AVELOX I.V. (injectable medicine) is one 250 mL minibag once a day.
- The usual length of treatment with AVELOX is 5-10 days. IT IS IMPORTANT TO COMPLETE THE FULL LENGTH OF TREATMENT, EVEN IF YOU BEGIN TO FEEL BETTER.

Overdose:

If you think you have taken too much AVELOX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your tablet you should take it as soon as you remember on the same day. If you do not take your tablet on one day, take your normal dose (one tablet) on the next day. Do not take a double dose to make up for a forgotten dose. If you are unsure about what to do, consult your healthcare professional.

What are possible side effects from using AVELOX?

All medicines, including AVELOX, can cause side effects, although not everyone gets them.

These are not all the possible side effects you may feel when taking AVELOX. If you have any side effects not listed here or if conditions worsen or do not improve then:

- contact your healthcare professional.
- see the "**To help avoid side effects and ensure proper use**, …" section.

Stop taking AVELOX and contact your doctor if:

a) you have symptoms of an allergic reaction such as:
   - rash, hives, blistering or other skin reaction
   - swelling of the mouth, throat, limbs
   - difficulty breathing
   - irregular or rapid heartbeat, or fainting spells

b) you have pain, swelling or rupture of a tendon. These side effects may last more than 30 days. You should:
   - rest
   - avoid physical exercise

c) you have neuropathy (damage to the nerves) with symptoms such as:

- pain, burning, tingling, numbness or weakness

d) you have severe diarrhea (bloody or watery) with or without:

- fever
- stomach pain or tenderness

You may have Clostridium difficile colitis (bowel inflammation). See your doctor right away.

Other side effects include:

- your eyesight worsens or changes. These side effects may last more than 30 days. See your doctor or eye specialist right away.
- nausea, dizziness
- worsening of myasthenia gravis (a muscle disease) with symptoms such as:
  - weakness
  - difficulty walking, swallowing, drooping eyelids

  Do not use AVELOX if you have this condition.
- mental problems such as:
  - confusion, headache, shaking
  - hallucinations, depression, agitation
  - difficulty sleeping, anxiety, nervousness, suicidal thoughts

  These side effects may last more than 30 days.

  Contact your doctor if you have suicidal thoughts.

Self-Limiting Side Effects:

- feeling lightheaded
- insomnia (difficulty sleeping)
- nightmares

If any of these affect you severely, tell your doctor or pharmacist.

Serious Side Effects and What to do About Them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			

Serious Side Effects and What to do About Them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Irregular heartbeat or fainting spells			✓
Mental health problems: • anxiety • confusion • depression • feeling agitated • restless or nervous • suicidal thoughts or actions • hallucinations • inability to think clearly or pay attention • memory loss • paranoia or loss of touch with reality (These side effects may last more than 30 days)			✓
Neurological problems: • seizures/convulsions • tremors		✓	
Nervous system side effects: • symptoms of neuropathy (damage to the nerves): numbness**,** tingling, pain, burning or weakness			✓
Rise in the pressure within your skull: • blurred or double vision • headaches • nausea		✓	
Tendon pain, inflammation, or rupture (these side effects may last more than 30 days)			✓
Symptoms of an allergic reaction (which may lead to death): • rash			✓

Serious Side Effects and What to do About Them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
• hives • rapid heartbeat • difficulty breathing • difficulty swallowing • swelling of face, lips, or tongue			
Liver problems with symptoms such as yellowing of the skin and/or eyes, nausea, abdominal pain, dark urine, and pale stools			✓
Symptoms of a severe bowel condition (Clostridium difficile colitis): • persistent diarrhea • bloody or watery diarrhea • abdominal or stomach pain/cramping • blood/mucus in stool			✓
VERY RARE			
Hypoglycemia (low blood sugar) such as: • change in mood • change in vision • confusion • dizziness • fast heartbeat • feeling faint • headache • hunger • shaking • sweating • weakness		✓	
UNKNOWN			
Aortic aneurysm (abnormal bulge in a large blood vessel called the aorta) /Aortic dissection (tear in the wall of the aorta):			✓

Serious Side Effects and What to do About Them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
• dizziness • loss of consciousness • pulsating sensation in the abdomen • sudden, severe pain in abdomen, chest or back			

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

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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

Storage:

AVELOX tablets should be stored:

- at room temperature (15°C –30°C)

- in a tightly closed container away from heat and direct light.

Do not freeze the tablets.

AVELOX I.V. should be stored:

- at room temperature (15°C –30°C)
- away from heat and direct light.

Do not refrigerate.

Keep out of reach and sight of children.

If you want more information about AVELOX:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website http://www.bayer.ca or by contacting Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This leaflet was prepared by:

Bayer Inc.
2920 Matheson Blvd East,
Mississauga, Ontario
L4W 5R6
Canada

Last Revised: February 18, 2020

Bayer