CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085

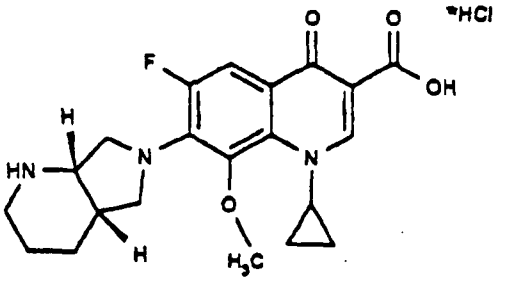
FINAL PRINTED LABELING

ASV
12-10-99

AVELOX™ (moxifloxacin hydrochloride) Tablets
Final Draft Package Insert
12/10/99 (3:00 PM)

DESCRIPTION

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



Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8-position, and an S,S – configured diazabicyclononyl ring moiety at the 7-position.

AVELOX is available in 400 mg (moxifloxacin equivalent) film-coated tablets. The inactive ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and ferric oxide.

CLINICAL PHARMACOLOGY

Absorption

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

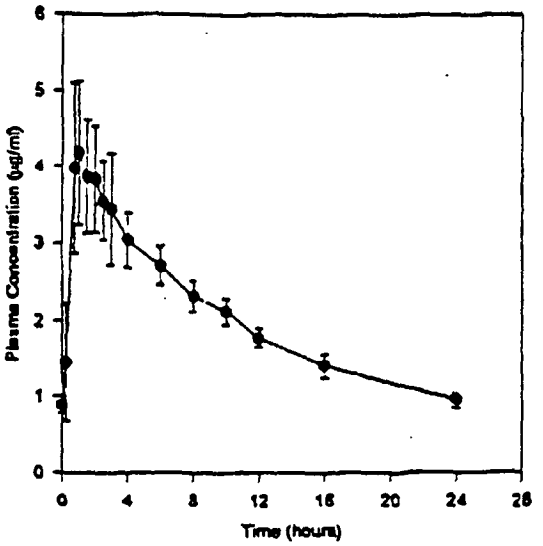
Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

The mean (± SD) C_{max} and AUC values at steady-state with a 400 mg once daily dosage regimen are 4.5 ± 0.53 µg/mL and 48 ± 2.7µg*h/mL, respectively. C_{max} is attained 1 to 3 hours after oral dosing. The mean (± SD) trough concentration is 0.95 ± 0.10 µg/mL. Plasma concentrations increase proportionately with dose

12-10-99

up to the highest dose tested (800 mg single dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen. The figure below illustrates the time course of plasma concentrations of moxifloxacin following a 400 mg dose administered at steady-state.

Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg (mean;SD) (n=10)



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, skin blister fluid, and subcutaneous tissue, and skeletal muscle following oral administration of 400 mg. Concentrations measured at 3 hours post-dose are summarized in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Dosing with 400 mg[§]

Tissue or Fluid	N	Plasma Concentration (µg/mL)	Tissue or Fluid Concentration (µg/mL or µg/g)	Tissue: Plasma Ratio
Respiratory				
Alveolar Macrophages	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial Mucosa	8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial Lining Fluid	5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus				
Maxillary Sinus Mucosa	4	3.7 ± 1.1[†]	7.6 ± 1.7	2.0 ± 0.3
Anterior Ethmoid Mucosa	3	3.7 ± 1.1[†]	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	3.7 ± 1.1[†]	9.8 ± 4.5	2.6 ± 0.6

[§] all moxifloxacin concentrations were measured after a single 400 mg dose, except the sinus concentrations which were measured after 5 days of dosing.
[†] N = 5

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

Excretion

Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2.0 L/hr and 2.6 ± 0.5 L/hr, respectively.

Special Populations

Geriatric

In 16 healthy elderly male and female volunteers (66-81 years of age) given a single 200 mg 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.

12-10-99

Whether pharmacokinetic differences exist between young and elderly females is unknown. The pharmacokinetics of moxifloxacin with repeated 400 mg administration in elderly subjects has not been studied.

Pediatric

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

Gender

Following a single 200 mg dose of moxifloxacin to 16 healthy elderly subjects, the mean AUC and C_{max} were 29% and 24% higher, respectively, in healthy elderly females compared to healthy elderly males. There are no significant differences in moxifloxacin pharmacokinetics between elderly 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 Cmax due to gender. Dosage adjustments based on gender are not necessary.

Race

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

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.

In a single-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} < 30mL/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 Cmax 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 effect of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) on the pharmacokinetics of moxifloxacin has not been studied.

12-10-99

Hepatic Insufficiency

In a single 400 mg dose study of 6 patients with mild, (Child Pugh Class A) and two patients with moderate cirrhosis (Child Pugh Class B), moxifloxacin systemic exposure (AUC and peak concentration (C_{max})) was reduced by approximately 23% and 16%, respectively. The mean AUC of the sulfate conjugate (M1) increased by 4.4-fold and ranged up to 7-fold, while the mean C_{max} increased by 3.4-fold and ranged up to 5.5-fold. The mean C_{max} of the glucuronide conjugate (M2) increased by 1.6-fold and ranged up to 3.4-fold. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for mild hepatic insufficiency (Child Pugh Class A). The pharmacokinetics of moxifloxacin with moderate and severe hepatic insufficiency (Child Pugh Classes B and C), however, have not been adequately studied. Due to the lack of clinical data, the use of moxifloxacin is not recommended with moderate and severe hepatic insufficiency. (See **DOSAGE AND ADMINISTRATION.**)

Photosensitivity Potential

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

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. There was no clinically significant effect of moxifloxacin on theophylline, warfarin, digoxin, or glyburide kinetics. Theophylline, digoxin, probenecid, and ranitidine did not affect the pharmacokinetics of moxifloxacin. However, as with all other quinolones, iron and antacids significantly reduced the bioavailability of moxifloxacin.

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

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

No significant change in prothrombin time was observed. (See **PRECAUTIONS, Drug Interactions.**)

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

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

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

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

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

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

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the

AS
12-10-99

QTc interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with high doses of intravenous (IV) moxifloxacin in dogs. Therefore, moxifloxacin should not be used with Class IA and Class III antiarrhythmics. (See **ANIMAL PHARMACOLOGY**, **WARNINGS**, and **PRECAUTIONS**.)

MICROBIOLOGY

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety.

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

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

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

Aerobic Gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

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

ASL
12-10-99

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

Aerobic Gram-positive microorganisms
Streptococcus pneumoniae (penicillin-resistant strains)
Streptococcus pyogenes

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Legionella pneumophila
Proteus mirabilis

Anaerobic microorganisms
Fusobacterium species
Peptostreptococcus species
Prevotella species

Susceptibility Tests

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

For testing Enterobacteriaceae and *Staphylococcus* species:

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

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

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)

12-10-99

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

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

For testing *Streptococcus pneumoniae* [b]:

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

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

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

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

Microorganism		MIC (µg/mL)
Enterococcus faecalis	ATCC 29212	0.06 - 0.5
Escherichia coli	ATCC 25922	0.008 - 0.06
Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Staphylococcus aureus	ATCC 29213	0.015 - 0.06
Streptococcus pneumoniae	ATCC 49619[d]	0.06 - 0.25

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

ASV
12-10-99

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

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

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

The following zone diameter interpretive criteria should be used for testing Enterobacteriaceae and *Staphylococcus* species:

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

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

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

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

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

For testing *Streptococcus pneumoniae* [f]:

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

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

ASC
12-10-99

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

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

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	28 - 35
Haemophilus influenzae	ATCC 49274[g]	31 - 39
Staphylococcus aureus	ATCC 25923	28 - 35
Streptococcus pneumoniae	ATCC 49619[h]	25 - 31

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

[h]These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

INDICATIONS AND USAGE

AVELOX Tablets are indicated for the treatment of adults (≥ 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

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

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

Community Acquired Pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Moraxella catarrhalis.*

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

ASL
12-10-99

CONTRAINDICATIONS

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

WARNINGS

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

MOXIFLOXACIN HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. THE DRUG SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA AND PATIENTS RECEIVING CLASS IA (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS, DUE TO THE LACK OF CLINICAL EXPERIENCE WITH THE DRUG IN THESE PATIENT POPULATIONS.

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

The effect of moxifloxacin on patients with congenital prolongation of the QT interval has not been studied, however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.

The magnitude of QT prolongation may increase with increasing concentrations of the drug, therefore the recommended dose should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. In 787 patients with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was 6 ± 26 msec. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 4000 patients, however certain predisposing conditions may increase the risk for ventricular arrhythmias.

AS ✓
12-10-99

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

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

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

Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe

RSV
12-10-99

cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Although not observed in moxifloxacin clinical trials, Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with quinolones. Moxifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

PRECAUTIONS

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

Information for Patients:

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

Patients should be advised:

- that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.
- to inform their physician of any other medications when taken concurrently with moxifloxacin, including over-the-counter medications.
- to contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.
- that moxifloxacin may be taken with or without meals, and to drink fluids liberally.
- that moxifloxacin should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminum), sucralfate, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See **CLINICAL**

ASV
12-10-99

PHARMACOLOGY, Drug Interactions and **PRECAUTIONS, Drug Interactions.**)

- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.

- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

- that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

- that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with moxifloxacin at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If sunburn-like reaction or skin eruptions occur, contact your physician. (See **CLINICAL PHARMACOLOGY, Photosensitivity Potential.**)

- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.

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

No clinically significant drug-drug interactions between theophylline, warfarin, digoxin, or glyburide have been observed with moxifloxacin. Theophylline, digoxin, probenecid, and ranitidine have been shown not to alter the pharmacokinetics of moxifloxacin. (See **CLINICAL PHARMACOLOGY.**)

Warfarin: No significant effect of moxifloxacin on R- and S- warfarin was detected in a clinical study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in the presence of moxifloxacin.

ASV
12-10-99

However, since some quinolones have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed.

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

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

Pregnancy: Teratogenic Effects. Pregnancy Category C:
Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose based on systemic exposure [AUC]), but decreased fetal body weights and slightly delayed fetal skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 20 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon systemic exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body weights and delayed fetal skeletal ossification.

A's C
12-10-99

When rib and vertebral malformations were combined, there was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose included mortality, abortions, marked reduction of food consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival. Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.

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

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

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

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

ADVERSE REACTIONS

Clinical efficacy trials enrolled over 4900 moxifloxacin treated patients, of whom over 4300 patients received the 400 mg dose. Most adverse events reported in moxifloxacin trials were described as mild to moderate in severity and required no treatment. Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 3.8% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of moxifloxacin treated patients were: nausea (8%), diarrhea (6%), dizziness (3%), headache (2%), abdominal pain (2%), vomiting (2%), taste perversion (1%), abnormal liver function test (1%), and dyspepsia (1%).

12-10-99

Additional events, judged by investigators to be at least possibly drug-related, that occurred in greater than 0.05% and less than 1% of moxifloxacin treated patients were:

BODY AS A WHOLE: asthenia, moniliasis, pain, malaise, lab test abnormal (not specified), allergic reaction, leg pain, pelvic pain, abdominal pain, back pain, chills, infection, pain, chest pain, hand pain
CARDIOVASCULAR: palpitation, vasodilatation, tachycardia, hypertension, peripheral edema, hypotension
CENTRAL NERVOUS SYSTEM: insomnia, nervousness, anxiety, confusion, hallucinations, depersonalization, hypertonia, incoordination, somnolence, tremor, vertigo, paresthesia
DIGESTIVE: dry mouth, constipation, oral moniliasis, anorexia, stomatitis, gastritis, glossitis, gastrointestinal disorder, cholestatic jaundice, GGTP increased
HEMIC AND LYMPHATIC: prothrombin time decrease, prothrombin time increase, thrombocythemia, thrombocytopenia, eosinophilia, leukopenia
METABOLIC AND NUTRITIONAL: amylase increased, hyperglycemia, hyperlipidemia, lactic dehydrogenase increased
MUSCULOSKELETAL: arthralgia, myalgia
RESPIRATORY: asthma, dyspnea, cough increased, pneumonia, pharyngitis, rhinitis, sinusitis
SKIN/APPENDAGES: rash, pruritus, sweating, urticaria, dry skin,
SPECIAL SENSES: tinnitus, amblyopia
UROGENITAL: vaginal moniliasis, vaginitis, cystitis, kidney function abnormal

LABORATORY CHANGES

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

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied and 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. It is not known whether moxifloxacin is dialyzable.

Single oral moxifloxacin doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was 100 mg/kg. Toxic signs after administration of a single high dose of moxifloxacin to these animals included CNS and

12-10-99

gastrointestinal effects such as decreased activity, somnolence, tremor, convulsions, vomiting and diarrhea.

DOSAGE AND ADMINISTRATION

The dose of AVELOX Tablets is one 400 mg tablet taken orally every 24 hours. The duration of therapy depends on the type of infection as described below.

Infection *	Daily Dose	Duration
Acute Bacterial Sinusitis	400 mg	10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5 days
Community Acquired Pneumonia	400 mg	10 days

* due to the designated pathogens (See **INDICATIONS AND USAGE.**)

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

Impaired Renal Function

No dosage adjustment is required in renally impaired patients. Moxifloxacin has not been studied in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired Hepatic Function

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh Class A). The pharmacokinetics of moxifloxacin in patients with moderate and severe hepatic insufficiency (Child Pugh Classes B and C) have not been adequately studied. Due to the lack of clinical data the use of moxifloxacin is not recommended in patients with moderate and severe hepatic insufficiency. (See **CLINICAL PHARMACOLOGY, Hepatic Insufficiency.**)

HOW SUPPLIED

AVELOX (moxifloxacin hydrochloride) Tablets are available as oblong, dull red film-coated tablets containing 400 mg moxifloxacin. The tablet is coded with the word "BAYER" on one side and "M400" on the reverse side.

Package	NDC Code
Bottles of 30:	0026-8581-69
ABC Pack of 5:	0026-8581-41

12-10-99

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

ANIMAL PHARMACOLOGY

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

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

Ocular toxicity was not observed in 6 month repeat dose studies in rats and monkeys. In beagle dogs, electroretinographic (ERG) changes were observed in a 2 week study at 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 quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDS). Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (e.g. seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen.

In animal 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 (30mg/kg) of moxifloxacin alone.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis

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

12-10-99

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

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

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

Community Acquired Pneumonia

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

In addition to the trial described above, a noncomparative trial of AVELOX (400 mg once daily for ten days) was also conducted in the US in patients with community acquired pneumonia. The combined moxifloxacin clinical success rates by pathogen for the two studies were as follows:

PATHOGEN	14 - 35 DAY FOLLOW-UP
Streptococcus pneumoniae	97% (30/31)
Haemophilus influenzae	92% (33/36)
Mycoplasma pneumoniae	96% (51/53)
Chlamydia pneumoniae	93% (106/114)
Moraxella catarrhalis	91% (10/11)

The microbiological eradication rates (eradication plus presumed eradication) in AVELOX treated patients were *Streptococcus pneumoniae* 97%, *Haemophilus influenzae* 92%, and *Moraxella catarrhalis* 91%.

Acute Bacterial Sinusitis

In a large, controlled double-blind study conducted in the US, AVELOX (400 mg once daily for ten days) was compared with cefuroxime axetil (250 mg twice daily for ten days) for the treatment of acute bacterial sinusitis. The trial included 457

ASV
12-10-99

patients valid for the primary efficacy determination. Clinical success (cure plus improvement) at the 7 to 21 day post-therapy test of cure visit was 90% for AVELOX and 89% for cefuroxime.

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

REFERENCES 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Made in Germany
Rx Only

Bayer Logo
Name & Address

Patient Information About:

AVELOX™

(moxifloxacin hydrochloride)
400 mg Tablets

This section contains important information about AVELOX (moxifloxacin hydrochloride), and should be read completely before you begin treatment. This section does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of AVELOX. The medicine described here can be prescribed only by a licensed health care professional. If you have any

ASV
12-10-99

questions about AVELOX talk with your health care professional. Only your health care professional can determine if AVELOX is right for you.

What is AVELOX?

AVELOX is an antibiotic used to treat lung or sinus infections caused by certain germs called bacteria. AVELOX kills many of the types of bacteria that can infect the lungs and sinuses and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). AVELOX, like all other antibiotics, does not kill viruses.

You should contact your doctor if you think your condition is not improving while taking AVELOX. AVELOX Tablets are red and contain 400 mg of active drug.

How and when should I take AVELOX?

AVELOX should be taken once a day for 5 or 10 days depending on your prescription. It should be swallowed and may be taken with or without food. Try to take the tablet at the same time each day.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of AVELOX even if you missed a dose by mistake. You should not take a double dose.

Who should not take AVELOX?

You should not take AVELOX if you have ever had a severe allergic reaction to any of the group of antibiotics known as "quinolones" such as ciprofloxacin or levofloxacin.

You should avoid AVELOX if you have a rare condition known as congenital prolongation of the QT interval. If you or any of your family members have this condition you should inform your health care professional. You should avoid AVELOX if you are being treated for heart rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone or sotalol. Inform your health care professional if you are taking a heart rhythm drug.

You should also avoid AVELOX if the amount of potassium in your blood is low. Low potassium can sometimes be caused by medicines called diuretics such as furosemide and hydrochlorothiazide. If you are taking a diuretic medicine you should speak with your health care professional.

If you are pregnant or planning to become pregnant while taking AVELOX, talk to your doctor before taking this medication. AVELOX is not recommended for

ADV 12-10-99

use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

AVELOX is not recommended for children.

What are the possible side effects of AVELOX?

AVELOX is generally well tolerated. The most common side effects caused by AVELOX, which are usually mild, include nausea, vomiting, stomach pain, diarrhea, dizziness and headache. You should be careful about driving or operating machinery until you are sure AVELOX is not causing dizziness. If you notice any side effects not mentioned in this section or you have any concerns about the side effects you are experiencing, please inform your health care professional.

In some people, AVELOX, as with some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this has not caused any serious problems in more than 4000 patients who have already taken the medication, in theory it could result in extremely rare cases of abnormal heartbeat which may be dangerous. Contact your health care professional if you develop heart palpitations (fast beating), or have fainting spells.

Which medicines should not be used with AVELOX?

You should avoid taking AVELOX with certain medicines used to treat an abnormal heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

Some medicines also produce an effect on the electrocardiogram test, including cisapride, erythromycin, some antidepressants and some antipsychotic drugs. These may increase the risk of heart beat problems when taken with AVELOX. For this reason it is important to let your health care provider know all of the medicines that you are using.

Many antacids and multivitamins may interfere with the absorption of AVELOX and may prevent it from working properly. You should take AVELOX either 4 hours before or 8 hours after taking these products.

Remember

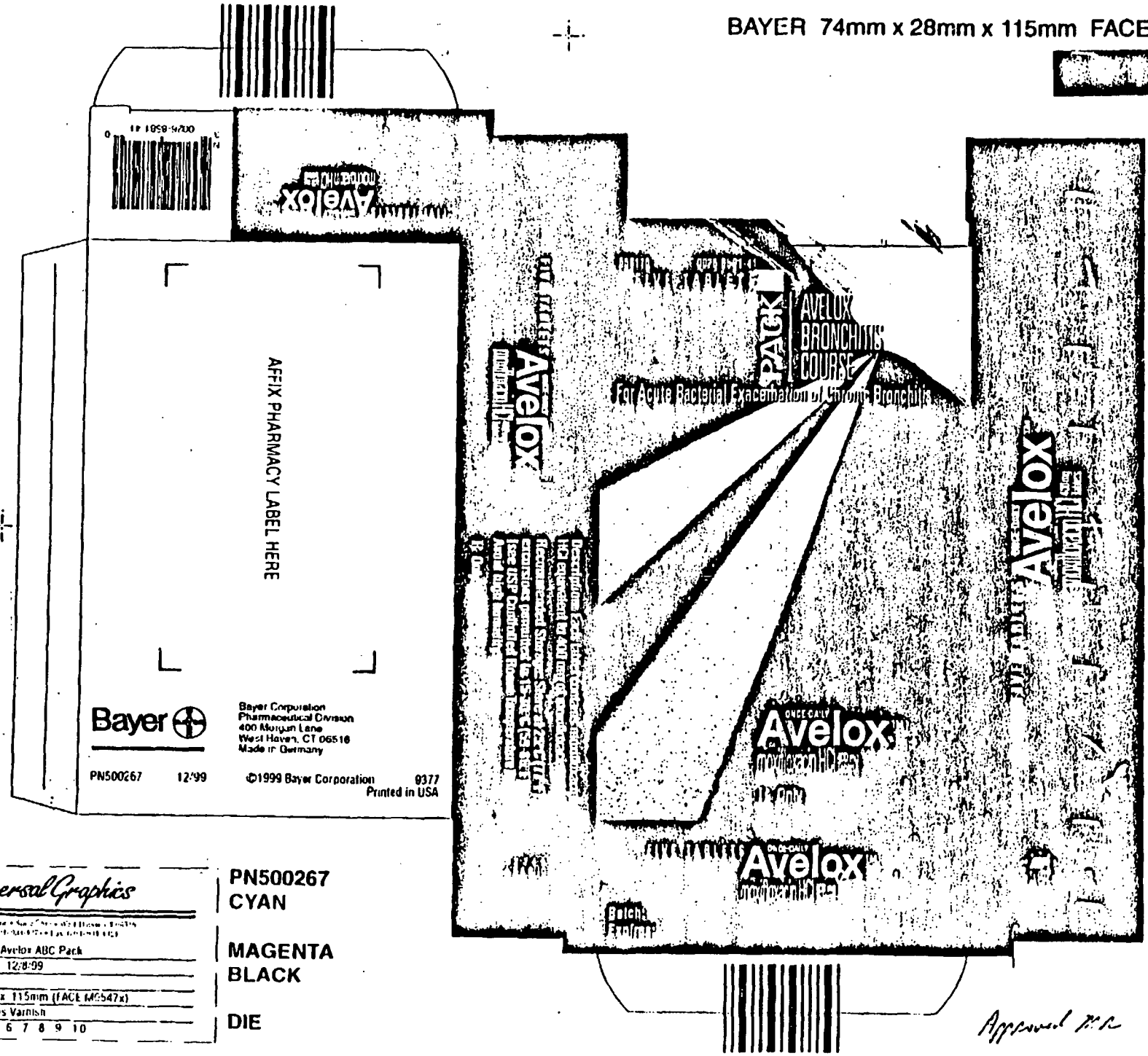
Take your dose of AVELOX once a day.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

BAYER 74mm x 28mm x 115mm FACE M0547



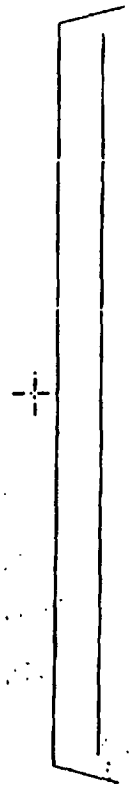
Universal Graphics

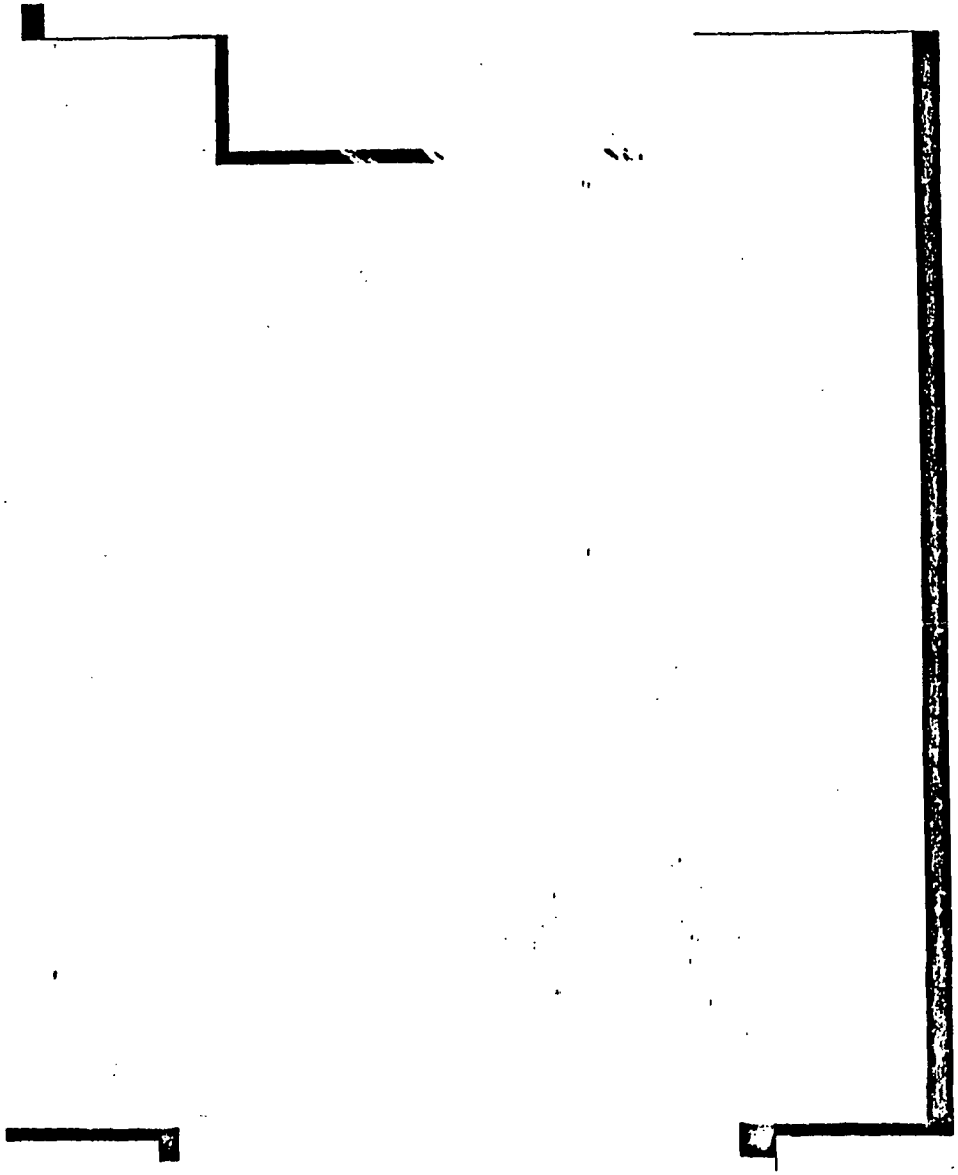
File name: PN500267/Avelox ABC Pack
Date: 12/6/99, 12/7/99, 12/8/99
Control #: 9376, 9377
Size: 74mm x 28mm x 115mm (FACE M0547x)
PMS Colors: CYMK, plus Varnish
Proof: 1 2 3 4 5 6 7 8 9 10

PN500267
CYAN
MAGENTA
BLACK
DIE

Approved [illegible] 8-99

BAYER 74mm x 28mm x 115mm FACE M0547





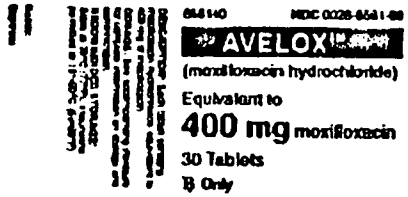
Universal Graphics

File name: PN500267/Avelox ABC Pack
Date: 12/6/99 12/7/99, 12/8/99
Control #: 9376, 9377
Size: 74mm x 28mm x 115mm (FACE M0547x)
PMS Colors: CYMK, plus Varnish
Proof 1 4 5 6 7 8 9 10

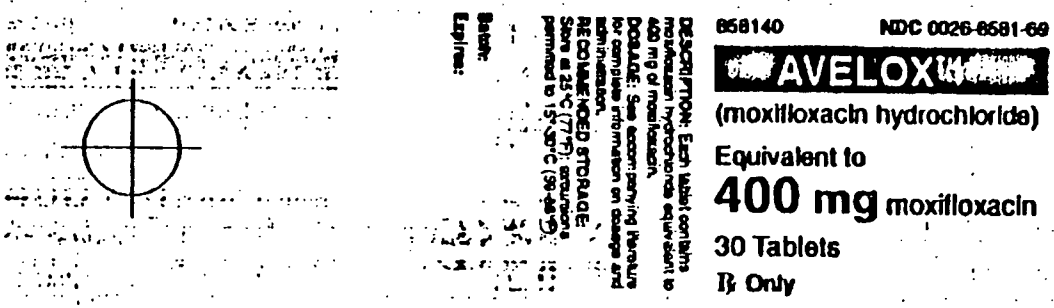
PN500267
CYAN

MAGENTA
BLACK

DIE



100%



150%
FOR READING PURPOSES ONLY

Universal Graphics

375 Morgan Lane • Suite #203 • West Haven, CT 06516
Phone: (203) 934-4275 • Fax: (203) 934-4324

File name: PL500262/400 mg, Bottles of 30
Date: 11/2/98, 11/30/98
Control #: 8794, 8852
Size: 3 1/4" x 1 1/8"
PMS Colors: PMS 032, Black, plus Varnish
Hole Location:
Pro 3 4 5 6 7 8 9 10