

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-085 / S-022

21-277 / S-017

Trade Name: **Avelox Tablets**
 Avelox I. V.

Generic Name: **moxifloxacin hydrochloride**
 moxifloxacin hydrochloride in sodium
 chloride injection

Sponsor: **Bayer Pharmaceuticals**

Approval Date: **May 18, 2004**

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-022
NDA 21-277/S-017

Bayer Pharmaceuticals Corporation
Attention: Robin Christoforides
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications dated December 23, 2003, received February 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AVELOX® (moxifloxacin hydrochloride) Tablets and AVELOX® I.V. (moxifloxacin hydrochloride in sodium chloride injection), 400 mg.

We acknowledge receipt of your submissions dated:

March 8, 2004 April 5, 2004 April 26, 2004 May 5, 2004 (2)
March 12, 2004 April 6, 2004 April 28, 2004

These supplemental new drug applications provide for the treatment of Community Acquired Pneumonia caused by multi-drug resistant *Streptococcus pneumoniae*.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted May 5, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-085/S-022 and NDA 21-277/S-017." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, significant modifications of existing indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for Community Acquired Pneumonia caused by MDRSP ages 0 months to 18 years until March 12, 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

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1. Deferred pediatric study under PREA for the treatment of Community Acquired Pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* in pediatric patients ages 0 months to 18 years.

Final Report Submission: March 12, 2009

Submit final study reports to these NDAs. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for the modification of the indication for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure (labeling)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Renata Albrecht
5/18/04 05:10:55 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

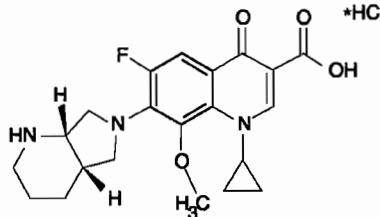
AVELOX[®]
(moxifloxacin hydrochloride) Tablets
AVELOX[®] I.V.
(moxifloxacin hydrochloride in sodium chloride injection)

MDRSP Proposed Labeling (5/5/04) rev. 2

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

DESCRIPTION

AVELOX (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as AVELOX Tablets for oral administration and as AVELOX I.V. for intravenous administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular weight of 437.9. Its empirical formula is C₂₁H₂₄FN₃O₄ *HCl and its chemical structure is as follows:



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

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

CLINICAL PHARMACOLOGY

Absorption

Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin. Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

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

	C_{max} (mg/L)	AUC (mg·h/L)	Half-life (hr)
Single Dose Oral Healthy (n = 372)	3.1 \pm 1.0	36.1 \pm 9.1	11.5 - 15.6*
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 \pm 0.5	48.0 \pm 2.7	12.7 \pm 1.9
Healthy elderly male (n = 8)	3.8 \pm 0.3	51.8 \pm 6.7	
Healthy elderly female (n = 8)	4.6 \pm 0.6	54.6 \pm 6.7	
Healthy young male (n = 8)	3.6 \pm 0.5	48.2 \pm 9.0	
Healthy young female (n = 9)	4.2 \pm 0.5	49.3 \pm 9.5	

* Range of means from different studies

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

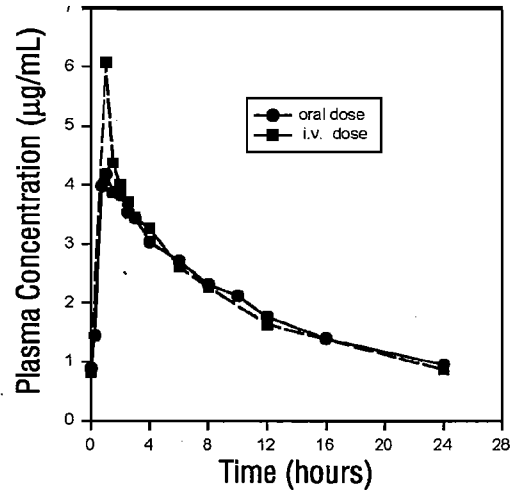
	C_{max} (mg/L)	AUC (mg·h/L)	Half-life (hr)
Single Dose I.V.			
Healthy young male/female (n = 56)	3.9 \pm 0.9	39.3 \pm 8.6	8.2 - 15.4*
Patients (n = 118)			
Male (n = 64)	4.4 \pm 3.7		
Female (n = 54)	4.5 \pm 2.0		
< 65 years (n = 58)	4.6 \pm 4.2		
\geq 65 years (n = 60)	4.3 \pm 1.3		
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 \pm 0.8	38.0 \pm 4.7	14.8 \pm 2.2
Healthy elderly (n = 12; 8 male, 4 female)	6.1 \pm 1.3	48.2 \pm 0.9	10.1 \pm 1.6
Patients** (n = 107)			
Male (n = 58)	4.2 \pm 2.6		
Female (n = 49)	4.6 \pm 1.5		
< 65 years (n = 52)	4.1 \pm 1.4		
\geq 65 years (n = 55)	4.7 \pm 2.7		

* Range of means from different studies

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

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (\pm SD) elimination half-life from plasma is 12 \pm 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

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



Distribution

Moxifloxacin is approximately 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 or intravenous 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) After Oral Dosing 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

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

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

Excretion

Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of $96\% \pm 4\%$ of an oral dose is excreted as either unchanged drug or known metabolites. The mean (\pm 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

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

Pediatric

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

Gender

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

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

Race

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

Renal Insufficiency

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

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

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

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

Hepatic Insufficiency

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

The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8.0-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). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See **DOSAGE AND ADMINISTRATION**.)

Photosensitivity Potential

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

Drug-drug Interactions

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

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

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

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

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

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

Atenolol: In a crossover study involving 24 healthy volunteers (12 male; 12 female), the mean atenolol AUC following a single oral dose of 50 mg atenolol with placebo was similar to that observed when atenolol was given concomitantly with a single 400 mg oral dose of moxifloxacin.

The mean C_{max} of single dose atenolol decreased by about 10% following co-administration with a single dose of moxifloxacin.

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

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

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

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

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

Calcium: Twelve healthy volunteers were administered concomitant moxifloxacin (single 400 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement) followed by an additional two doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no significant effect on the mean AUC of moxifloxacin. The mean C_{max} was slightly reduced and the time to maximum plasma concentration was prolonged when moxifloxacin was given with calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours). These differences are not considered to be clinically significant.

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

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

Electrocardiogram: Prolongation of the QT interval in the ECG has been observed in some

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

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

MICROBIOLOGY

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

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

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

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

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

Aerobic Gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pneumoniae (including penicillin-resistant strains*) (including multi-drug resistant strains [MDRSP]*)

Streptococcus pyogenes

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of $\geq 2 \mu\text{g/mL}$.

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

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.**

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

Aerobic Gram-positive microorganisms

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

Aerobic Gram-negative microorganisms

Citrobacter freundii
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 method¹ (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:

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

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^a:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)

^aThis interpretive standard is applicable only to broth microdilution susceptibility tests with

Haemophilus influenzae and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium¹. The current absence of data on resistant strains precludes defining any results other than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible” category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* species including *Streptococcus pneumoniae*^b:

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

^bThis 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:

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

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

^dThis 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 procedure² 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)

≥ 19

16 – 18

≤ 15

Interpretation

Susceptible (S)

Intermediate (I)

Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^e:

Zone Diameter (mm)

≥ 18

Interpretation

Susceptible (S)

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

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

For testing *Streptococcus* species including *Streptococcus pneumoniae*^f:

Zone Diameter (mm)

≥ 18

15 – 17

≤ 14

Interpretation

Susceptible (S)

Intermediate (I)

Resistant (R)

^fThese interpretive standards are applicable only to disk diffusion tests using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

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:

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	28 – 35
<i>Haemophilus influenzae</i>	ATCC 49247 ^g	31 – 39
<i>Staphylococcus aureus</i>	ATCC 25923	28 – 35
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^h	25 – 31

^gThese quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)².

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

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

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

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 $\mu\text{g/mL}$), (including multi-drug resistant strains*), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*.

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS

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 caution should be exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval. Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of

infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 7,900 patients in controlled clinical studies, including 223 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 moxifloxacin tablet treated patients in a post-marketing observational study in which ECGs were not performed. (See **CLINICAL PHARMACOLOGY, Electrocardiogram**. For I.V. use see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS, Geriatric Use**.)

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

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

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

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 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.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with quinolones, including moxifloxacin. Post-marketing surveillance reports indicate that the risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. 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**.)

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

Information for Patients:

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

Patients should be advised:

- that antibacterial drugs including AVELOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AVELOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AVELOX or other antibacterial drugs in the future.
- that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.
- to inform their physician of any other medications when taken concurrently with moxifloxacin, including over-the-counter medications.
- to contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.
- that moxifloxacin tablets may be taken with or without meals, and to drink fluids liberally.
- that moxifloxacin tablets should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate, or VIDEX[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug Interactions**.)
- that moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- 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. Oral administration of quinolones with antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as VIDEX[®] (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before or 8 hours after these agents. (See **CLINICAL PHARMACOLOGY, Drug Interactions and DOSAGE AND ADMINISTRATION**.)

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in

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

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

Pregnancy: Teratogenic Effects. Pregnancy Category C:

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

Nursing Mothers:

Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin may also be excreted in human milk. Because of the potential for serious adverse reactions in infants 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 oral moxifloxacin were greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The clinical trial data demonstrate that there is no difference in the safety and efficacy of oral moxifloxacin in patients aged 65 or older compared to younger adults.

In intravenous trials in community acquired pneumonia, 45% of moxifloxacin patients were greater than or equal to 65 years of age, and 24% were greater than or equal to 75 years of age. In the pool of 491 elderly (> 65 years) patients, the following ECG abnormalities were reported in moxifloxacin vs. comparator patients: ST-T wave changes (2 events vs. 0 events), QT prolongation (2 vs. 0), ventricular tachycardia (1 vs. 0), atrial flutter (1 vs. 0), tachycardia (2 vs. 1), atrial fibrillation (1 vs. 0), supraventricular tachycardia (1 vs. 0), ventricular extrasystoles (2 vs. 0), and arrhythmia (0 vs. 1). None of the abnormalities was associated with a fatal outcome and a majority of these patients completed a full course of therapy.

ADVERSE REACTIONS

Clinical efficacy trials enrolled over 7,900 moxifloxacin orally and intravenously treated patients, of whom over 6,700 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 3.6% of orally treated patients and 5.7 % of sequentially (intravenous followed by oral) treated patients. The latter studies were conducted in community acquired pneumonia with, in general, a sicker patient population compared to the tablet studies.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 3% of moxifloxacin treated patients were: nausea (7%), diarrhea (6%), dizziness (3%).

Additional clinically relevant uncommon events, judged by investigators to be at least possibly drug-related, that occurred in greater than or equal to 0.1% and less than 3% of moxifloxacin treated patients were:

BODY AS A WHOLE: headache, abdominal pain, injection site reaction, asthenia, moniliasis, pain, malaise, lab test abnormal (not specified), allergic reaction, leg pain, back pain, chest pain
CARDIOVASCULAR: palpitation, tachycardia, hypertension, peripheral edema, QT interval prolonged

CENTRAL NERVOUS SYSTEM: insomnia, nervousness, anxiety, confusion, somnolence, tremor, vertigo, paresthesia

DIGESTIVE: vomiting, abnormal liver function test, dyspepsia, dry mouth, constipation, oral moniliasis, anorexia, stomatitis, glossitis, flatulence, gastrointestinal disorder, GGTP increased

HEMIC AND LYMPHATIC: prothrombin decrease (prothrombin time prolonged/International Normalized Ratio (INR) increased), thrombocytopenia, thrombocytopenia, eosinophilia, leukopenia

METABOLIC AND NUTRITIONAL: amylase increased, lactic dehydrogenase increased

MUSCULOSKELETAL: arthralgia, myalgia

RESPIRATORY: dyspnea

SKIN/APPENDAGES: rash (maculopapular, purpuric, pustular), pruritus, sweating

SPECIAL SENSES: taste perversion

UROGENITAL: vaginal moniliasis, vaginitis

Additional clinically relevant rare events, judged by investigators to be at least possibly drug-related, that occurred in less than 0.1% of moxifloxacin treated patients were:

abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation, convulsions, depersonalization, depression, diarrhea (*Clostridium difficile*), dysphagia, ECG abnormal, emotional lability, face edema, gastritis, hallucinations, hyperglycemia, hyperlipidemia, hypertonia, hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic), kidney function abnormal, parosmia, pelvic pain, prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR) decreased), sleep disorders, speech disorders, supraventricular tachycardia, taste loss, tendon disorder, thinking abnormal, thromboplastin decrease, tinnitus, tongue discoloration, urticaria, vasodilatation, ventricular tachycardia

Post-Marketing Adverse Event Reports:

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

LABORATORY CHANGES

Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in $\geq 2\%$ 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, pO₂, bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities were caused by the drug or the underlying condition being treated.

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

Impaired Renal Function

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

Impaired Hepatic Function

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

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

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

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

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to AVELOX I.V. or infused simultaneously through the same intravenous line. If the same intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the "piggyback" method of administration is used, the line should be flushed before and after infusion of AVELOX I.V. with an infusion solution compatible with AVELOX I.V. as well as with other drug(s) administered via this common line.

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

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

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

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

firmly seated.

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

HOW SUPPLIED

Tablets

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

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

Package	NDC Code
Bottles of 30:	0026-8581-69
Unit Dose Pack of 50:	0026-8581-88
ABC Pack of 5:	0026-8581-41

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

Intravenous Solution – Premix Bags

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

Package	NDC Code
250 mL flexible container	0026-8582-31

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

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

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

DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION.

ANIMAL PHARMACOLOGY

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

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

No ocular toxicity was observed in a 13 week oral repeat dose study in dogs with a moxifloxacin dose of 60 mg/kg. Ocular toxicity was not observed in 6 month repeat dose studies in rats and monkeys (daily oral doses up to 500 mg/kg and 135 mg/kg, respectively). In beagle dogs, electroretinographic (ERG) changes were observed in a 2 week study at oral doses of 60 and 90 mg/kg. 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 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 sotalolol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation than that induced by the same dose (30 mg/kg) of moxifloxacin alone.

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

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis

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

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

<u>PATHOGEN</u>	<u>AVELOX</u>	<u>Clarithromycin</u>
<i>Streptococcus pneumoniae</i>	100% (16/16)	87% (20/23)
<i>Haemophilus influenzae</i>	89% (33/37)	88% (36/41)
<i>Haemophilus parainfluenzae</i>	100% (16/16)	100% (14/14)
<i>Moraxella catarrhalis</i>	85% (29/34)	100% (24/24)
<i>Staphylococcus aureus</i>	94% (15/16)	75% (6/8)
<i>Klebsiella pneumoniae</i>	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.

A large, randomized, double-blind, controlled trial was conducted in the US and Canada to compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days to an IV/PO fluoroquinolone control (trovafloxacin or levofloxacin) in the treatment of patients with clinically and radiologically documented community acquired pneumonia. This study enrolled 516 patients, 362 of which were valid for the primary efficacy analysis conducted at the 7-30 day

post-therapy visit. The clinical success rate was 86% (157/182) for AVELOX therapy and 89% (161/180) for the fluoroquinolone comparators.

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

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

Clinical Success Rates By Pathogen (Pooled CAP Studies)

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

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

The clinical and bacteriological efficacy of AVELOX in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC $\geq 2 \mu\text{g}/\text{mL}$) was evaluated in 9 clinical studies: 4 comparative, double-blind tablet studies; 2 noncomparative, open-label tablet studies; 1 comparative, double-blind sequential intravenous to oral study; and 2 comparative, open-label, sequential intravenous to oral studies. All studies required strict assessment criteria with investigator assessment of treatment outcome as success or failure only. The primary efficacy parameter in these studies was clinical cure at the test-of-cure visit, which ranged from Day 6 to 44 post-treatment. Of the 21 AVELOX treated broth microdilution confirmed valid for efficacy PRSP patients, 7 had PRSP bacteremia, 12 had severe pneumonia (by the Original American Thoracic Society criteria). The clinical success rates of *S. pneumoniae* and PRSP valid for efficacy patients are summarized in the following table.

Pathogen	AVELOX		Comparators	
	n/N	%	n/N	%
All <i>S. pneumoniae</i>	230/244	94	138/162	85
<i>S. pneumoniae</i> bacteremia	53/58	91	35/41	85
<i>S. pneumoniae</i> with Penicillin MIC $\geq 2 \mu\text{g}/\text{mL}$	21/21*	100	5/5	100
<i>S. pneumoniae</i> bacteremia with Penicillin MIC $\geq 2 \mu\text{g}/\text{mL}$	7/7	100	2/2	100

*All of these patients were bacteriologic successes at the test-of-cure visit, and 7 of the 21

patients had MIC = 4 µg/mL

Avelox was effective in the treatment of community acquired pneumonia (CAP) caused by multi-drug resistant *Streptococcus pneumoniae* MDRSP* isolates. Of 37 microbiologically evaluable patients with MDRSP isolates, 35 patients (95.0%) achieved clinical and bacteriological success post-therapy. The clinical and bacteriological success rates based on the number of patients treated are shown in the table below.

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

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

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

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

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

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

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

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

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

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

Acute Bacterial Sinusitis

In a large, controlled double-blind study conducted in the US, AVELOX Tablets (400 mg once

daily for ten days) were compared with cefuroxime axetil (250 mg twice daily for ten days) for the treatment of acute bacterial sinusitis. The trial included 457 patients valid for the primary efficacy determination. Clinical success (cure plus improvement) at the 7 to 21 day post-therapy test of cure visit was 90% for AVELOX and 89% for cefuroxime.

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

Uncomplicated Skin and Skin Structure Infections

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

REFERENCES: 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests Eighth Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

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 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, sinus, or skin 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 5-14 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. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking AVELOX and call your health care professional.

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 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 dizziness, nausea, and diarrhea. If diarrhea persists call your health care provider. 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 7,900 patients who have already taken the medication in clinical studies, 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.

Convulsions have been reported in patients receiving quinolone antibiotics. Be sure to let your physician know if you have a history of convulsions. Quinolones, including AVELOX, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

Quinolones, including AVELOX, have been rarely associated with inflammation of tendons. If

you experience pain, swelling or rupture of a tendon, you should stop taking AVELOX and call your health care professional.

What about other medicines I am taking?

Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. 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.

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.

For more complete information about AVELOX request full prescribing information from your health care professional, pharmacist, or visit our website at www.aveloxusa.com.



Bayer HealthCare

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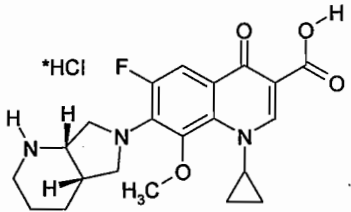
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085 / S-022

21-277 / S-017

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW		DUE DATE 18-Aug-2004	1. ORGANIZATION HFD-590	2. NDA NUMBER 21-085 and 21-277
3. NAME AND ADDRESS OF APPLICANT Bayer Corporation Pharmaceutical Division ATTN: Andrew S. Verderame 400 Morgan Lane West Haven, CT 06516			4. TYPE OF SUPPLEMENT PAS	
			5. DOCUMENT(S)	
			NUMBERS 21-085/SE1-022 21-277/SE1-017	DATED 23-Dec-2003
			RECEIVED 24-Dec-2003	
6. NAME OF DRUG Avelox Tablets (NDA 21-085) Avelox I.V. (NDA 21-277)			7. NONPROPRIETARY NAME moxifloxacin hydrochloride tablets (NDA 21-085) and moxifloxacin hydrochloride in NaCl injection (NDA 21-277)	
8. SUPPLEMENT PROVIDES FOR: Addition of "(including multi-drug resistant strains [MDRSP])" to INDICATIONS AND USAGE: "Community Acquired Pneumonia caused by <i>Streptococcus pneumoniae</i> ".				9. AMENDMENTS/DATES N/A
10. PHARMACOLOGICAL CATEGORY Antibacterial		11. HOW DISPENSED <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		12. RELATED IND/NDA/DMF(s) N/A
13. DOSAGE FORM(S) tablets (NDA 21-085) and intravenous solution (NDA 21-277)			14. POTENCY (CIES) 400 mg (both NDAs)	
15. CHEMICAL NAME AND STRUCTURE				16. MEMORANDA N/A
				
<p>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</p>				
17. COMMENTS These efficacy supplements provide for the following change in the Community Acquired Pneumonia (CAP) indication caused by <i>Streptococcus pneumoniae</i> : addition of a multi-drug resistant strains (MDRSP). The applicant has stated that that the action on this application would not result in increased use of an active moiety and, therefore, this supplement qualifies for the environmental assessment (EA) categorical exclusion based on 21 CFR 25.31(a) requirement. Since these supplements provide for a modification of a list of microorganisms in the existing indication, this is a reasonable assertion.				
18. CONCLUSIONS AND RECOMMENDATIONS Recommend approval.				
19. REVIEWER				
NAME Dorota Matecka		SIGNATURE [signed electronically in DFS]		DATE OF DRAFT REVIEW 11-May-2004
20. CONCURRENCE: HFD-590/NSchmuff [signed electronically in DFS]				
DFS CC LIST	<input type="checkbox"/> L	Dorota Matecka	<input type="checkbox"/> L	Med:
	<input type="checkbox"/> R	MSeggel	<input type="checkbox"/> R	PM
				PharmTox
				Micro

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dorota Matecka
5/12/04 10:46:11 AM
CHEMIST

Mark Seggel
5/13/04 09:01:47 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085 / S-022

21-277 / S-017

STATISTICAL REVIEW(S)

Statistical Team Leader's Memorandum

TO: NDAs 21-085/S-022 and 21-277/S-017 (12/24/03)

FROM: Karen Higgins, Sc.D.
Statistical Team Leader
FDA/CDER/OPaSS/DB3

RE: Avelox (moxifloxacin) tablets and I.V., Community-acquired pneumonia caused by multidrug-resistant *Streptococcus pneumoniae* (MDRSP)

1. Introduction	1
2. Multi-Drug Resistance Data	1
3. Previous Approval for MDRSP	4
4. Conclusions	4

1. Introduction

These supplemental NDAs dated 12/24/03 submitted by Bayer Pharmaceuticals Corporation contain data to support the claim of efficacy of moxifloxacin in the treatment of community-acquired pneumonia (CAP) due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP). MDRSP is defined as *Streptococcus pneumoniae* resistant to at least two of the following antimicrobial agents: penicillin; second-generation cephalosporins; macrolides (clarithromycin, erythromycin or azithromycin); tetracycline; and trimethoprim-sulfamethoxazole (TMP-SMX). Moxifloxacin tablets and I.V. have been previously reviewed and approved for the indication of CAP (Original NDA 21-085 12/9/98 and NDA 21-277 11/02/00) and for the indication of CAP due to penicillin-resistant *Streptococcus pneumoniae* (PRSP) (supplemental NDA 21-085/S-015 and NDA 21-277/S007 dated 12/18/02).

This NDA does not contain study results from any additional controlled clinical trials. Since the controlled studies have been previously reviewed, a full statistical review will not be conducted for this NDA. Instead, this memo will briefly summarize the efficacy information on multi-drug-resistant *Streptococcus pneumoniae* (MDRSP). Please see the medical and microbiology reviews for a more detailed review of these submissions.

2. Multi-Drug Resistance Data

Data from seven clinical studies, 4 comparative controlled and 3 non-comparative studies, in community-acquired pneumonia (CAP) were reviewed by the sponsor for cases of MDRSP. Thirty-seven evaluable (41 intent-to-treat) subjects with MDRSP were identified. Only 6 evaluable (8 intent-to-treat) subjects were found in the control arms. Given that there were so few comparator subjects, they will not be discussed

further in this review. The following table contains the information on how many MDRSP cases came from each study.

Table 1: CAP studies containing MDRSP isolates

Study	ITT	Evaluable
100039 (controlled)	11	10
100353 (controlled)	4	2
100222 (controlled)	1	1
D96-026 (controlled)	4	4
D96-025 (uncontrolled)	2	2
10872 (ongoing uncontrolled)	0	0
100224 (ongoing uncontrolled)	19	18
Total	41	37

Full study reports from studies 100039, 100353, 100222, D96-026, and D96-025 were previously submitted and reviewed. Study 10872 did not contribute any cases of MDRSP. Study 100224, which contains many of the MDRSP isolates, is currently ongoing and no study report was included with this submission. However, the case report forms for all MDRSP subjects were submitted as part of either this submission (NDA 21-085/022 or the previous PRSP submission NDA 21-085/015). The title of this study is “Prospective, non-comparative, open-label, multicenter, multinational trial to evaluate the safety and effectiveness of moxifloxacin oral tablets, 400 mg once daily for 10 days in the treatment of patients with drug resistant *Streptococcus pneumoniae* community acquired pneumonia.”

The approved regimen for moxifloxacin for the treatment of CAP is 400 mg once daily for 7-14 days. This was the dose and duration used in study 100039. Studies D96-025, D96-026, 100222, and 100224 studied moxifloxacin 400mg once daily for 10 days. Study 100353 studied moxifloxacin 400mg once daily for 7 – 10 days

Clinical cure rate was 95% (35/37) in the clinical evaluable population (95% exact confidence interval¹ [81.8%, 99.3%]). Of the 4 patients who were only included in the intent-to-treat population 3 were indeterminate and 1 was a cure. Assuming that the indeterminates are failures, the clinical efficacy would be 87.8% (36/41) for the intent-to-treat population.

The following table lists the drug class resistance pattern of the 37 evaluable cases of MDRSP. In summary, 7 patients were resistant to all 5, 6 patients were resistant to 4, 11 were resistant to 3 and 13 were resistant to 2.

¹ Calculated using the Clopper-Pearson Method in StatXact Version 5

Table 2: Number of evaluable subjects by resistance pattern

Resistance	Number of Subjects
Penicillin, Cefuroxime, Macrolide, TMP/SMX, Tetracycline	7
Penicillin, Cefuroxime, Macrolide, TMP/SMX ¹	4
Penicillin, Cefuroxime, Macrolide, Tetracycline	1
Penicillin, Cefuroxime, TMP/SMX, Tetracycline	1
Penicillin, Cefuroxime, Macrolide	1
Penicillin, Macrolide, TMP/SMX ²	1
Penicillin, Cefuroxime, TMP/SMX	6
Cefuroxime, Macrolide, Tetracycline	1
Macrolide, TMP/SMX, Tetracycline ³	2
Cefuroxime, Tetracycline	1
Cefuroxime, TMP/SMX	4
Macrolide, TMP/SMX	3
Macrolide, Tetracycline	3
TMP/SMX, Tetracycline	2

1 Subject 100224/1037 had both a respiratory and blood isolate resistant for Penicillin, Cefuroxime, Macrolide, and TMP/SMX. This patient was only counted once.

2 Subject 10039/48013 had both a respiratory and blood isolate resistant for Penicillin, Macrolide, and TMP/SMX. This patient was only counted once.

3 Subject 10024/1032 had a blood isolate resistant to Macrolide, Tetracycline, and TMP/SMX and a respiratory isolate resistant to all 5 agents. Only the respiratory isolate was counted.

The following table contains the number of resistant cases individually for each of the 5 antibiotics screened along with the clinical efficacy of each.

Table 3: Clinical efficacy by antimicrobial agent, evaluable population

Screening Susceptibility	n/N (%)	95% C.I.*
Penicillin-resistant	21/21 (100)	(83.9, 100.0)
Cephalosporine-resistant	25/26 (96)	(80.4, 99.9)
Macrolide-resistant	22/23 (96)	(78.1, 99.9)
Tetracycline-resistant	17/18 (94)	(72.7, 99.9)
TMP/SMX-resistant	28/30 (93)	(77.9, 99.2)
Resistant to more than one of the above antibiotics	35/37 (95)	(81.8, 99.3)

* 95% Clopper-Pearson exact confidence interval

Note that the rates and confidence intervals are based on data pooled from the different studies. There were no adjustments conducted to account for the different studies.

Table 2 above lists the patterns of resistance across antimicrobial agents. We can use these patterns to investigate which agent's resistance tend to appear more or less likely in the presence of another agent's resistance in this limited population of subjects with isolates resistant to 2 or more agents. Penicillin and cefuroxime resistance appear positively correlated, as does penicillin and TMP/SMX resistance and macrolide and tetracycline resistance. Tetracycline and TMP/SMX resistance do not often appear

within the same sample. This is also found, though to less an extent, with macrolide and TMP/SMX resistance and cefuroxime and macrolide resistance

3. Previous Approval for MDRSP

Only one drug, gemifloxacin, currently has an indication of MDRSP for CAP. The following table contains the data that was used to help support the gemifloxacin approval along with similar data for moxifloxacin. The amount of information used for the approval of gemifloxacin can be used as a threshold for other drugs that are studied for this indication. The comparison of the data from the gemifloxacin NDA and this NDA are given in the following table.

Table 4: Clinical efficacy versus gemifloxacin in the evaluable population

Screening Susceptibility	Gemifloxacin n/N (%)	Moxifloxacin n/N (%)
Penicillin-resistant	11/11 (100)	21/21 (100)
Cefuroxime-resistant	15/15 (100)	25/26 (96)
Macrolide-resistant	19/22 (86.4) ¹ 14/16 (87.6) ²	22/23 (96)
Tetracycline-resistant	13/16 (81.3)	17/18 (94)
TMP/SMX-resistant	16/16 (100)	28/30 (93)
Resistant to more than one of the above antibiotics [95% confidence interval] ³	21/24 (87.5) [67.6%, 97.3%]	35/37 (95) [81.8%, 99.3%]

1 Clarithromycin resistant

2 Erythromycin resistant

3 95% exact confidence interval calculated using the Clopper-Pearson method in StatXact Version 5.

Note that if we use the lower bound of the 95% confidence interval for the gemifloxacin MDRSP cure rate as the threshold for MDRSP (67.6%), we can see that the moxifloxacin confidence interval falls completely above this point. Note that the overall rates and confidence intervals are based on data simply pooled from studies with available data. There were no adjustments conducted to account for the different studies.

4. Conclusions

In general there is minimal information regarding the efficacy of moxifloxacin in the treatment of patients with CAP due to MDRSP. There were only 37 evaluable subjects with MDRSP, with the majority of these subjects coming from uncontrolled studies. However, the amount of information is similar to that used for the approval of CAP due to MDRSP for gemifloxacin. Furthermore, the results obtained are similar to those seen for gemifloxacin.

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/s/

Karen Higgins
5/10/04 02:24:09 PM
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Mohammad Huque
5/14/04 03:59:44 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085 / S-022

21-277 / S-017

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

NDA 21-085/S-022
NDA 21-277/S-017

Regulatory Project Manager Review of Final Printed Labeling (FPL)

Materials Reviewed:

Product	NDA #	Supplement #	Letter Date	Receipt Date
AVELOX® (moxifloxacin hydrochloride) Tablets	21-085	SE1-022	June 8, 2004	June 10, 2004
AVELOX® I.V. (moxifloxacin hydrochloride in sodium chloride injection)	21-277	SE1-017	June 8, 2004	June 10, 2004

Compared to:

- Draft labeling for NDA 21-085/S-022 and NDA 21-277/S-017 approved May 18, 2004.

Applicant: Bayer Pharmaceuticals Corporation

Background:

Supplements NDA 21-085/S-022 and NDA 21-277/S-017 provided for the addition of “(including multi-drug resistant strains [MDRSP])*” to **INDICATIONS AND USAGE: Community Acquired Pneumonia** caused by *Streptococcus pneumoniae* section of the label. These supplements were approved on draft labeling on May 18, 2004 and final printed labeling (FPL) was requested.

Review and Comments:

The FPL for the Avelox® package insert submitted on June 8, 2004 was compared electronically to the draft labeling for the Avelox® package insert approved May 18, 2004. The sponsor included language for the Changes Being Effected labeling supplements regarding fluoroquinolone class labeling (NDA 21-277/S-019 and NDA 21-085/S-024 submitted on April 7, 2004) in the FPL. There were no differences found between the FPL submitted on June 8, 2004 and the draft labeling approved May 18, 2004 other than the CBE fluoroquinolone class labeling language which contained revisions to the **WARNINGS** section of the label to include additional peripheral neuropathy and tendon effects language.

Recommendations:

An Acknowledge and Retain letter should be issued informing the applicant that the FPL for NDA 21-085/S-022 and NDA 21-277/S-017 is acceptable.

Susan Peacock, M.S.
Regulatory Project Manager
HFD-590

Ellen F. Molinaro, R.Ph.
Chief, Project Management Staff
HFD-590

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/s/

Susan Peacock
8/2/04 04:24:34 PM
CSO

Ellen Molinaro
8/2/04 04:28:48 PM
CSO



NDA 21-085/S-022
NDA 21-277/S-017

PRIOR APPROVAL SUPPLEMENT

Bayer Pharmaceuticals Corporation
Attention: Robin Christoforides
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Christoforides:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number
AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg	NDA 21-085	S-022
AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V.	NDA 21-277	S-017

Review Priority Classification: Standard (S)

Date of supplements: December 23, 2003

Date of receipt: December 24, 2003

These supplemental applications propose the following change:

- Addition of multi-drug resistant *Streptococcus pneumoniae* (MDRSP) microorganism to the current approved labeling.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on February 22, 2004 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be October 22, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until February 28, 2008. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of

NDA 21-085/S-022

NDA 21-277/S-017

Page 2

section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,
{See appended electronic signature page}
Ellen F. Molinaro, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Molinaro
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NDA 21-085/S-022 and NDA 21-277/S-017