CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 21-085/S-015 + 21-277/S-007

Trade Name Avelox

Generic Name moxifloxacin

Sponsor Bayer

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 21-085/S-015
21-277/S-007

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Pharmacology Review(s)	✓
Statistical Review(s)	✓
Microbiology Review(s)	✓
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Bioequivalence Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085/S-015
21-277/S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-014, S-015, S-017
NDA 21-277/S-006, S-007, S-009

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides, Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications submitted December 17, 2002, received on December 18, 2002, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg (NDA 21-085/S-015) and AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V. (NDA 21-277/S-007).

We acknowledge receipt of your submissions dated:

January 31, 2003	February 12, 2003 (2)	February 26, 2003
February 3, 2003	February 19, 2003 (2)	
February 5, 2003 (2)	February 24, 2003	

These supplemental applications provide for the modification of the indication for Community Acquired Pneumonia to add "(including penicillin-resistant strains, MIC penicillin ≥ 2µg/mL)" to *Streptococcus pneumoniae*. Specifically, the following changes to the package insert were made:
Double underline=added text
~~Strikethrough~~=deleted text

- **MICROBIOLOGY** Section:

  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 ~~susceptible~~ strains* ~~only~~)
  Streptococcus pyogenes
  *Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of ≥ 2 µg/mL

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 pneumoniae* (penicillin-resistant strains)~~
Streptococcus viridans group

- **INDICATIONS AND USAGE** Section:

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 µg/mL), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*.

- **CLINICAL STUDIES** Section:

Community Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)

The clinical and bacteriological efficacy of AVELOX in the treatment of Community Acquired Pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC ≥ 2 µg /mL) was evaluated in 9 clinical studies: 4 comparative, double-blind tablet studies; 2 non-comparative, 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 *S. pneumoniae*	230/244	94	138/162	85
S. pneumoniae bacteremia	53/58	91	35/41	85
S. pneumoniae with Penicillin MIC ≥ 2 µg /mL	21/21*	100	5/5	100

S. pneumoniae bacteremia with Penicillin MIC ≥ 2 µg /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

- **REFERENCES**: 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically ~~Fifth~~ Sixth Edition. Approved Standard NCCLS Document M7-A6~~5~~, Vol. 23~~0~~, No. 2, NCCLS, Wayne, PA, January, 2003~~0~~.
  2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests ~~Seventh~~ Eighth Edition. Approved Standard NCCLS Document M2-A8~~7~~, Vol. 23~~0~~, No. 1, NCCLS, Wayne, PA, January, 2003~~0~~.

- **Patient Information About: AVELOX®** Section:

  AVELOX Tablets are red and contain 400 mg of active drug.

- Minor editorial changes to the package insert were also made.

Please refer to your supplemental new 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	Date Submitted	Date Received
AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg	NDA 21-085	S-014	September 30, 2002	October 1, 2002
		S-017	January 28, 2003	January 30, 2003
AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V.	NDA 21-277	S-006	September 30, 2002	October 1, 2002
		S-009	January 28, 2003	January 30, 2003

These supplemental applications, submitted as "Supplement- Changes Being Effected," provide for the following changes to the labeling:
Double underline=added text
~~Strikethrough~~=deleted text

Package Insert:

- **WARNINGS** Section:

"~~Although not observed in clinical trials~~, Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with quinolones, including moxifloxacin."

- **PRECAUTIONS, Drug Interactions**, Warfarin sub-section:

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. ~~However, since some~~ Qquinolones, 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 ~~antimicrobial~~ is administered concomitantly with warfarin or its derivatives.

- **ADVERSE REACTIONS,** Additional clinically relevant uncommon events:

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

- **ADVERSE REACTIONS,** Additional clinically relevant rare events:

"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, sleep disorders, speech disorders, supraventricular tachycardia, taste loss, tendon disorder, thinking abnormal, thromboplastin decrease, tinnitus, tongue discoloration, urticaria, vasodilatation, ventricular tachycardia"

- **ADVERSE REACTIONS, Post-Marketing Adverse Event Reports** sub-section:

Additional adverse events reported from worldwide post-marketing experience with moxifloxacin include anaphylactic reaction, anaphylactic shock, hepatitis (predominantly cholestatic), pseudomembranous colitis, psychotic reaction, Stevens-Johnson syndrome, syncope, and tendon rupture.

- **DOSAGE AND ADMINISTRATION**

  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.

- **Patient Information About: AVELOX®** Section:

  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 healthcare professional.

  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 ~~and dizziness.~~ If diarrhea persists call your healthcare 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 healthcare professional.

Remember

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

- Minor editorial changes to the package insert were also made.

Flexibag and Overwrap:

- The following statement was added to the flexibag and overwrap. :

  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.

We have 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 February 26, 2003).

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 ten 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-014, S-015, S-017 and NDA 21-277/S-006, S-007, S-009." Approval of these submissions by the FDA is not required before the labeling is used.

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third

party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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. 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". FDA generally does not consider studies submitted to a NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to a NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for the addition of penicillin-resistant *Streptococcus pneumoniae* to the Community Acquired Pneumonia 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 insert(s) 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, HF-2
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)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085/S-015
21-277/S-007

FINAL PRINTED LABELING

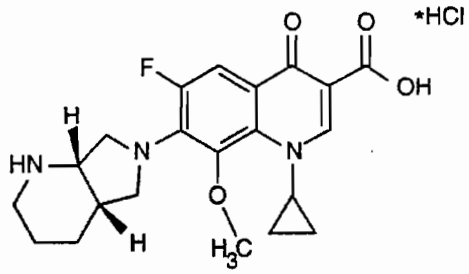
AVELOX®
(moxifloxacin hydrochloride) Tablets

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

2/25/03

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

Absorption

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

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

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

	C_{max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose Oral Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Multiple Dose Oral Healthy young male/female (n = 15) Healthy elderly male (n = 8)	 4.5 ± 0.5 3.8 ± 0.3	 48.0 ± 2.7 51.8 ± 6.7	 12.7 ± 1.9

Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	

* Range of means from different studies

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

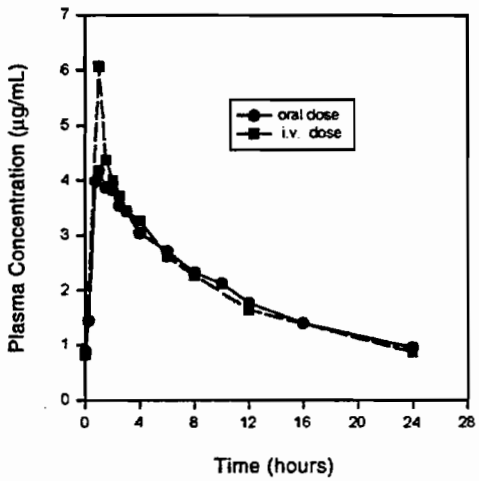
	C_{max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose I.V.			
Healthy young male/female (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)			
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
≥ 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose I.V.			
Healthy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

* Range of means from different studies

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

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

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



Distribution

Moxifloxacin is approximately 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

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

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

Excretion

Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2.0 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 16 young (8 male; 8 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics. In 16 healthy elderly male and female volunteers (66-81 years of age) given a single 200 mg dose of oral moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was not statistically different between young and elderly males and elimination half-life was unchanged. No dosage adjustment is necessary based on age. In large phase III studies, the concentrations around the time of the end of the infusion in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients.

Pediatric

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

Gender

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher,

respectively, in females compared to males. There are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration.

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

Race

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

Renal Insufficiency

The pharmacokinetic parameters of moxifloxacin are not significantly altered by mild, moderate, or severe renal impairment. No dosage adjustment is necessary in patients with renal impairment.

In a single oral dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin were reduced by 22% and 21% in the patients with moderate ($CL_{CR} \geq 30$ 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 sulfate and glucuronide conjugates are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal impairment has not been studied.

The effect of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) on the pharmacokinetics of moxifloxacin has not been studied.

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, 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, 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.

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

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

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

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

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

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

Antacids: When moxifloxacin (single 400 mg tablet dose) was administered two hours before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum

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

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

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

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

MICROBIOLOGY

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

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

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

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

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

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

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of ≥ 2 µg/mL

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 method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* species:

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

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

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

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

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

For testing *Streptococcus* species including *Streptococcus pneumoniae* [b]:

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

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate"

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

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

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

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

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

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

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

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

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

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

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

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

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

For testing *Streptococcus* species including *Streptococcus pneumoniae*[f]:

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

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

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

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For

the diffusion technique, the 5-μg moxifloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	28 – 35
Haemophilus influenzae	ATCC 49247[g]	31 – 39
Staphylococcus aureus	ATCC 25923	28 – 35
Streptococcus pneumoniae	ATCC 49619[h]	25 – 31

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

[h] These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 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 μg/mL), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*.

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.

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.

Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug 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.**)

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

Patients should be advised:

- that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.
- to inform their physician of any other medications when taken concurrently with moxifloxacin, including over-the-counter medications.
- to contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.
- that moxifloxacin 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, 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, thrombocythemia, 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, 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 reported from worldwide post-marketing experience with moxifloxacin include anaphylactic reaction, anaphylactic shock, hepatitis (predominantly cholestatic), pseudomembranous colitis, psychotic reaction, Stevens-Johnson syndrome, syncope, and tendon rupture.

LABORATORY CHANGES

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

OVERDOSAGE

Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient should be carefully observed and given supportive treatment. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure. It is not known whether moxifloxacin is removed by peritoneal or hemodialysis.

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

DOSAGE AND ADMINISTRATION

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

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

* 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. Moxifloxacin has not been studied in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired Hepatic Function
No dosage adjustment is required in patients with mild 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 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 500mg/kg and 135mg/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 sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation than that induced by the same dose (30mg/kg) of moxifloxacin alone.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis

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

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

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

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

Community Acquired Pneumonia

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

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)

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

Community-Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)

The clinical and bacteriological efficacy of AVELOX in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC ≥ 2 μg /mL) was evaluated in 9 clinical studies: 4 comparative, double-blind tablet studies; 2 non-comparative, 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 *S. pneumoniae*	230/244	94	138/162	85
S. pneumoniae bacteremia	53/58	91	35/41	85
S. pneumoniae with Penicillin MIC ≥ 2 μg /mL	21/21*	100	5/5	100
S. pneumoniae bacteremia with Penicillin MIC ≥ 2 μg /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

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 healthcare 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 healthcare 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 7900 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 have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

Quinolones 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 healthcare 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 healthcare professional, pharmacist, or visit our website at www.aveloxusa.com.

New Logo

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516
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2/03

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/s/

Renata Albrecht
2/28/03 04:07:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085 / S-015
21-277 / S-007

MEDICAL REVIEW(S)

Medical Officer's Review of Efficacy Supplements NDA 21-085/S-015 and NDA 21-277/S-007

AVELOX® (moxifloxacin hydrochloride) Tablets and AVELOX® (moxifloxacin hydrochloride in sodium chloride) Injection, for Community Acquired Pneumonia due to Penicillin-resistant *Streptococcus pneumoniae*

Submission/Review Dates

Date of Submission:	December 17, 2002
Date of Receipt	December 18, 2002
Date Assigned:	December 19, 2002
Date Review Completed:	February 15, 2003

Applicant

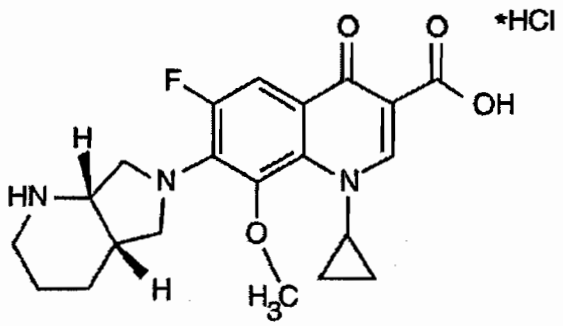
Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, Connecticut 06516

Contact Person

Robin M. Christoforides, Associate Director, Regulatory Affairs
Phone: 203-812-2112
Facsimile: 203-812-5029

Drug Identification

Generic name:	moxifloxacin hydrochloride
Trade Name:	Avelox®
Chemical Structure:	



Chemical Name:	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
Empirical Formula:	$C_{21}H_{24}FN_3O_4$ *HCl
Pharmacologic category:	antimicrobial-fluoroquinolone
Dosage Forms:	-AVELOX® Tablets containing moxifloxacin HCl (equivalent to 400 mg moxifloxacin) -AVELOX® I.V. is 0.8% sodium chloride aqueous solution of moxifloxacin HCl (containing 400 mg moxifloxacin)
Routes of administration:	oral, intravenous
Related IND:	IND 49, 489 and IND 52,786
Related NDAs:	NDA 21-085 and NDA 21-277

Abbreviations used in this Review:

AE = Adverse Event
BITT = Bacteriologic Intent to Treat
BPP = Bacteriologic Per Protocol Population
CAP = Community Acquired Pneumonia
CPP = Clinical Per Protocol Population
EOT = End of Therapy
ITT = Intent to Treat
IV = Intravenous
MIC = Minimum Inhibitory Concentrations
MO = Medical Officer
PSSP = Penicillin Sensitive *Streptococcus Pneumoniae*
PRSP = Penicillin Resistant *Streptococcus Pneumoniae*
SAE = Serious Adverse Event
TOC = Test of Cure
PO = Oral

NOTE:
Text and/or Tables in **Arial Font** are from the applicant's submissions, taken verbatim for inclusion in this document. Text taken verbatim from other reviews of this application will be clearly identified as such. This review is written in **Times New Roman Font** with the **MO Comments** in ***italics***.

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EXECUTIVE SUMMARY

Recommendations on Approvability

Based on the review performed on the original NDA submissions (NDA 21-085 and NDA 21-277) and the review performed for the current efficacy supplements (NDA 21-085/S-015 and NDA 21-277/S-007), the applicant has provided substantial evidence to support efficacy for the claim: Community Acquired Pneumonia due to *S. pneumoniae* with penicillin MIC $\geq$ 2 ug/mL. These efficacy supplements are thus recommended for APPPROVAL.

Summary of Clinical Findings

The overall Avelox CAP program consisted of 9 clinical studies: 4 comparative, double-blind tablet studies; 2 non-comparative, open-label tablet studies; 1 comparative, double-blind sequential intravenous to oral study; and 2 comparative, open-label, sequential intravenous to oral studies. 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. Five of these 9 studies contributed PRSP isolates to the application (3 oral and 2 IV; 3 controlled, and 2 un-controlled trials). One study (study 100224 which is an on-going open-labeled study specifically designed to enrich for *S. pneumoniae* cases) contributed 62% (13/21) of the moxifloxacin PRSP cases.

These supplemental applications have shown substantial evidence (from *in vitro* studies as well as the clinical CAP program) of moxifloxacin efficacy for the important etiological bacterial agent for CAP, *S. pneumoniae* (both for PSSP as well as PRSP). The "threshold" of the numbers of cases for each of the categories (*S. pneumoniae* cases overall, *S. pneumoniae* bacteremic cases, PRSP cases, PRSP bacteremic cases) that had been set by levofloxacin application for PRSP claim has now been achieved by this moxifloxacin application. Both clinical and bacteriological success rates for the PP population in each of these categories show similar results when compared to the control data composed of both PO and IV comparators (please also see Summary Table 14 under Conclusions section).

PRSP database for Levofloxacin and Moxifloxacin (#cured/total)

	Levofloxacin	**Moxifloxacin (data at the time of IV approval)**	**Moxifloxacin (data from current application)**
All CAP studies: # with *S. pneumoniae*	245/250 (98%)	149/164 (91%)	230/244 (94%)
# with *S. pneumoniae* bacteremia	55/55 (100%)	30/34 (88%)	53/58 (91%)
All CAP studies: # with PRSP	15/15 (100%)	12/13 (92.3%)*	21/21 (100%)**
# with PRSP bacteremia	6	2	8^
# with Severe Dz	5	6	12^^
# Hospitalized	9	7	15

*includes all broth microdilution confirmed PRSP isolates + one patient with only E-test done (PCN MIC at 6 ug/mL). This patients (from study 0140) was the single failure.

** includes all broth microdilution confirmed PRSP isolates ONLY

^ one of the patients had PCN MIC of 2 ug/ml in the respiratory culture but 1 ug/ml in the blood isolate

^^ this "severe disease" number was determined by the original ATS (American Thoracic Society) criteria (see Appendix 1)

Summary of the issue linking "severity" of CAP disease to PRSP claim for CAP

An issue that has been brought to focus during the review of this application is whether a drug must show efficacy in the more severe forms of CAP disease prior to being able to be considered for a claim of efficacy against PRSP. It has been discussed in both the original levofloxacin and moxifloxacin applications/reviews that some level of comfort with successful treatment of "severe" CAP disease with PRSP need to be part of the "weight of the evidence" to garner the PRSP claim. This concept originated primarily because it was unclear when PRSP initially emerged whether there would be different patient characteristics associated with having disease with PRSP as compared to disease with PSSP, and it was important to gain experience with the most serious spectrum of the disease. As time has passed however, and our understanding and experience with PRSP disease have increased, no different patient characteristics associated with having PRSP have been found.

Specifically for the use of quinolone class to treat CAP, the severity of disease with PRSP are no different than with PSSP. Moreover, close scrutiny of what is defined as "severe" is quite variable across all the different CAP programs by different Applications, or even within the same program but in different studies. Different sets of criteria or scores are used resulting in the same patients could be categorized as having "severe" disease by one set of criteria and having "moderate" disease by another set of criteria. In addition, although the "need for hospitalization" characteristic may sound helpful in further identifying the patient with "severe" disease; in actuality, there appears to be little correlation between the severity scores and hospitalization rates. Hospitalization is probably more a result of the design of the study at hand (IV study versus PO study), or the standard of practice at the site where the patient is enrolled.

Thus, having adequate evidence in numbers of *S. pneumoniae* bacteremic patients (both PSSP and PRSP) within the population with *S. pneumoniae* CAP continues to be an important factor in considering PRSP efficacy claims, because these bacteremic cases establish the specificity of diagnosis (with *S. pneumoniae* as the etiological bacterial agent causing disease). At this time however, given the body of evidence presented, requiring demonstration of efficacy of a quinolone class drug in "severe" CAP disease in order to garner the PRSP claim **does not appear to be essential** given the lack of data linking PRSP to severe disease, and given the lack of consistency in the criteria used to assess severity of CAP disease.

What **is essential** is the need for using the same instrument (validated scoring system such as the Fine-PORT criteria) when evaluating "severe" disease for CAP across different CAP programs and/or within the studies of the same CAP program. This consistency could provide better understanding of the level of disease and the ability to compare results. This is critical for all CAP patients undergoing clinical trials regardless of specific organisms, resistant or sensitive.

Labeling

The Applicant's proposed changes (specific to the claim of PRSP for CAP) to the current label is acceptable with minor changes to the Clinical Studies section as follows (see Labeling section: pages 50-1 for the exact recommended wording)

- Would recommend identifying the severity scale used to categorize "severe" patients
- Would remove words about [redacted] (this characteristic was not helpful in identifying "severe" patients; see explanation above)
- Would not list [redacted] as a separate row in the Clinical Studies Table. There were no [redacted] in this application. Would add a footnote to the Table instead and state "7 of the 21 patients had MIC = 4 ug/mL".

APPEARS THIS WAY
ON ORIGINAL

CLINICAL REVIEW

CLAIM SOUGHT / INDICATION AND DOSAGE

Claimed indication: Community acquired pneumonia caused by penicillin-resistant strains of *S. pneumoniae*

Dosage regimen: 400 mg orally once daily for 7 to 14 days

APPLICANT'S PROPOSED CHANGES IN LABELING

Proposed Changes to MICROBIOLOGY section

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

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of ≥ 2 µg/mL

Proposed Changes to INDICATIONS AND USAGE section

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 µg/mL), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*.

No Proposed Changes to the DOSAGE AND ADMINISTRATION section

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.
For Community Acquired Pneumonia: Daily Dose = 400 mg for Duration of 7-14 days

Proposed Addition to the CLINICAL STUDIES Section

Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)
Community-Acquired Pneumonia

The clinical and bacteriological efficacy of AVELOX in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC ≥ 2 µg /mL) was evaluated in 9 clinical studies: 4 comparative, double-blind tablet studies; 2 non-comparative, 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 PRSP patients, 7 had PRSP bacteremia, 12 had severe pneumonia and 15 [redacted] Of the 5 comparator-treated patients, 2 had bacteremia, 2 had severe pneumonia and 3 required hospitalization. The bacteriological eradication rates of *S. pneumoniae* and PRSP patients are summarized in the following table.

Pathogen	AVELOX		Comparators	
	n/N	%	n/N	%
All *S. pneumoniae*	227/244	93	139/162	86
S. pneumoniae bacteremia	51/56	91	35/39	90
S. pneumoniae with Penicillin MIC ≥2 ug/mL	21/21	100	5/5	100
S. pneumoniae with Penicillin MIC ≥4 ug/mL	7/7	100	1/1	100
S. pneumoniae bacteremia with Penicillin MIC ≥2 ug/mL	7/7	100	2/2	100

LABELING FOR OTHER RELEVANT APPROVED DRUGS

Labeling for Other fluoroquinolone: Levaquin®

Approved for the Indication of Community-Acquired Pneumonia with PRSP
PCN MIC > 2 ug/ml

> ***MO Comment**: The only other fluroquinolone currently approved for this claim is Levaquin®. The following are the relevant excerpts from the most current Levaquin Label (amended 10-30-02 via NDA 020634/SE1-025). It shows that what the Applicant (Bayer) is proposing to change in their label with the garnering of the PRSP claim is similar to what is written in the Levaquin® label.*

MICROBIOLOGY section

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including penicillin-resistant strains*)
Streptococcus pyogenes

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of 2 g/mL

INDICATIONS AND USAGE section

Community-acquired pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 g/mL), *Haemophilus influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES.**)

CLINICAL STUDIES section

Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin-resistant strains (MIC value for penicillin ≥2 g/mL). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double-blind study, two open label randomized studies, and three open label non-comparative studies. The total number of clinically evaluable patients with *S.pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with *S. pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator-treated patients with *S. pneumoniae* was 39/41 (95%).

Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* (MIC value for penicillin 2 g/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having severe disease. Of the 4 comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator-treated patients achieved clinical success. All three of the comparator-treated patients were bacteremic and had disease classified as severe.

Labeling for Out of Class Comparator: Augmentin XR®

Approved for the Indication of Community-Acquired Pneumonia with Penicillin Reduced Susceptibility SP (PCN MIC up to 2 ug/ml)

> ***MO Comment**: This drug was approved 9/25/02. The following are the relevant excerpts from the Augmentin XR® label (9/25/02) resulting from the approval of NDA 50-785 resubmission for the indications of community-acquired pneumonia and acute bacterial sinusitis. In that approval, the claim for S. pneumoniae with reduced suspectibility to penicillin (i.e. penicillin MICs ≤ 2 ug/mL) was granted for both indications.*

MICROBIOLOGY section

Aerobic Gram-positive Microorganisms
Streptococcus pneumoniae (including isolates with penicillin MICs ≤ 2 µg/mL)
Staphylococcus aureus (including β-lactamase producing strains)

INDICATIONS AND USAGE section

Augmentin XR Extended Release Tablets are indicated for the treatment of patients with community-acquired pneumonia or acute bacterial sinusitis due to confirmed, or suspected β-lactamase-producing pathogens (i.e., *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*, *K. pneumoniae*, or methicillin-susceptible *S. aureus*) and *S. pneumoniae* with reduced susceptibility to penicillin (i.e., penicillin MICs = 2 µg/mL). *Augmentin XR* is not indicated for the treatment of infections due to *S. pneumoniae* with penicillin MIC ≥4 µg/mL. Data are limited with regard to infections due to *S. pneumoniae* with penicillin MICs ≥4 µg/ml (See CLINICAL STUDIES Section).

Of the common epidemiological risk factors for patients with resistant pneumococcal infections, only age >65 years was studied. Patients with other common risk factors for resistant pneumococcal infections (e.g., alcoholism, immune-suppressive illness, and presence of multiple co-morbid conditions) were not studied.

In patients with community-acquired pneumonia in whom penicillin-resistant *S. pneumoniae* is suspected, bacteriological studies should be performed to determine the causative organisms and their susceptibility when *Augmentin XR* is prescribed. Once the results are known, therapy should be adjusted appropriately.

Acute bacterial sinusitis or community-acquired pneumonia due to a penicillin-susceptible strain of *S. pneumoniae* plus a beta-lactamase-producing pathogen can be treated with another *Augmentin* product containing lower daily doses of amoxicillin (i.e., 500 mg q8h or 875 mg q12h). Acute bacterial sinusitis or community-acquired pneumonia due to *S. pneumoniae* alone can be treated with amoxicillin.

CLINICAL STUDIES section

Data on the efficacy of *Augmentin XR* in the treatment of community acquired pneumonia due to *Streptococcus pneumoniae* with reduced susceptibility to penicillin was accrued from the three controlled clinical studies and the one non-comparative study. The majority of these cases were accrued from the non-comparative study.

Clinical Outcome for CAP due to *S. pneumoniae*						
Penicillin MIC of *S. pneumoniae* Isolates	**Intent To Treat**			**Clinically Evaluable**		
	n*/N	**%**	**95% CI ‡**	***n*/N***	**%**	**95% CI ‡**
All *S. pneumoniae*	184/214	86.0	–	157/172	91.3	–
MIC ≥2.0 µg/ml**	17/20	85.0	62.1, 96.8	14/15	93.3	68.1, 99.8
MIC = 2.0 µg/ml	13/14	92.9	66.1, 99.8	10/10	100	69.2, 100
MIC = 4.0 µg/ml	4/6	66.7	22.3, 95.7	4/5	80.0	28.4, 99.5

* *n*/N= patients with pathogen eradicated or presumed eradicated/ total number of patients

‡ Confidence limits calculated using exact probabilities

** *S. pneumoniae* strains with penicillin MICs of ≥2 µg/mL are considered resistant to penicillin.

REGULATORY MATERIALS REVIEWED

- NDA 21-085 (Avelox PO) Medical Officer, Statistical, and Microbiological Reviews for CAP and AECB
- NDA 21-277 (Avelox IV) Associated electronic files, Medical Officer, Statistical, and Microbiological Reviews
- NDA 20-634 /SE1-008 and NDA 20-635 /SE1-007 (Levaquin®), Medical Officer and Statistical Reviews
- FDA Anti-infectives Advisory Committee Meeting slides (December 1, 1999) Moxifloxacin Clinical Efficacy
- FDA Anti-infectives advisory committee meeting slides (May 16, 2001) Telithromycin Drug-Resistant *S. Pneumoniae*
- NDA 21-277 Medical Officer Addendum Review
- NDA 50-785 (Augmentin XR®) Resubmission Medical Officer Review
- NDA 21-158 (Factive) Resubmission Medical Officer Review of Community Acquired Pneumonia indication
- NDA21-085/S-015 and NDA 21-277/S-007 (Avelox for PRSP CAP) Associated electronic files and Responses to MO queries (January and February 2003)

REGULATORY HISTORY

- December 9, 1998: Avelox Tablet NDA 21-085 submitted. Included in the claims were for *Streptococcus pneumoniae* (including penicillin resistant strains, MIC > 2 ug/ml) for CAP.
- December 10, 1999: NDA 21-085 approved but PRSP claims not included. CAP indication only receives approval for "mild to moderate disease"

Main reason for not granting PRSP claim was that the available data on Avelox® was not substantial in showing efficacy in patients with proven pneumococcal disease of serious nature (i.e. in patients with CAP with pneumococcal bacteremia). The following table is taken from the initial NDA 21-085 MO (Andrea Meyerhoff) Review.

Clinical efficacy in CAP patients with S. pneumoniae bacteremia from all controlled, double-blinded studies of oral moxifloxacin

STUDY	Moxifloxacin 400 mg	Control
ORAL MOXIFLOXACIN		
Study 0119	1/1 (100%)	1/1 (100%)*
Study 0140	6/9 (67%)	10/10 (100%)**

*Clarithromycin
**High dose amoxicillin

- October 6, 2000: Efficacy supplements to NDA 21-085 for claims of PRSP for CAP and ABS submitted. Teleconference between the Division and Bayer: The Division relayed to Bayer that thus far only one product was approved for PRSP for CAP. The approvability of PRSP in Sinusitis was only possible in conjunction with the approval for a more serious indication such as CAP. Moreover, IV dosage form of Avelox was not yet available nor "severe" CAP yet approved.

- November 2, 2000: Avelox IV NDA 21-277 submitted. Included once again were claims for PRSP.

- March 6, 2001: 4-month Safety Update with six additional isolates from ongoing studies (for a total of 19 PRSP CAP cases; 13 evaluable only because E-test values between 1.5 to 2.0 ug/ml were excluded.)

- October 30, 2001: Withdrew the claim for PRSP in CAP and ABS as proposed in the draft labeling provided in the efficacy supplements to the PO Avelox NDA 21-085.

- November 30, 2001: Avelox IV NDA 21-277 Approved but PRSP claims still not granted.

The main reason for not granting PRSP claim was that the available data on Avelox® was not substantial in meeting the "threshold" set by Levaquin® application. The total number of *S. pneumoniae* cases, the number of *S. pneumoniae* bacteremic cases, the number of PRSP cases, as well as the number of PRSP bacteremic cases all were less than the threshold set by the Levaquin application. Please see further discussion below under efficacy review section. The following numbers are taken from the MO (R. Johann-Liang) Addendum Review to NDA 21-277.

PRSP database for Levofloxacin and Moxifloxacin (#cured/total)

	Levofloxacin	Moxifloxacin 400 mg
All CAP studies: # with *S. pneumoniae*	245/250 (98%)	149/164 (91%)
# with *S. pneumoniae* bacteremia	55/55 (100%)	30/34 (88%)
All CAP studies: # with PRSP	15/15 (100%)	12/13 (92.3%)*
# with PRSP bacteremia	6	2
# with Severe Disease	5	6
# Hospitalized	9	7

*includes all broth microdilution confirmed PRSP isolates + one patient with only E-test done (PCN MIC at 6 ug/mL). This patients (from study 0140) was the single failure.

- December 17, 2002: Resubmission for PRSP CAP and ABS

CHEMISTRY/MANUFACTURING AND CONTROLS

Please see Chemist's review of NDA 21-085 (PO Avelox) and NDA 21-277 (IV Avelox) original submissions.

ANIMAL PHARMACOLOGY/TOXICOLOGY

Please see the Pharmacology/toxicology review of NDA 21-085 (PO Avelox) and NDA 21-277 (IV Avelox) original submissions.

MICROBIOLOGY

Please see Dr. Peter Dionne's Microbiologist's Review.

In Vitro Activity

Briefly, as part of the evidence of moxifloxacin's *in vitro* activity, the Applicant has submitted the surveillance summary [redacted] There were two multicenter surveillance studies of respiratory pathogens, including *S. pneumoniae* conducted in the years 1997-1998 and in 1999. The MIC_{90}s of moxifloxacin for *S. pneumoniae* during the two time periods were 0.25 ug/mL for 5,640 isolates and 0.125 ug/mL for 4,940 isolate, respectively. The MIC_{90}s for moxifloxacin for *S. pneumoniae* were independent of susceptibility or resistance to penicillin.

In Vivo Activity during Clinical CAP Trials

In the second submission to NDA 21-085 (subsequently withdrawn), the applicant presented 19 total isolates of PRSP through their 4 month Safety Update (3/6/2001). However, of that 19, only 13 were evaluable only because E-test values between 1.5 to 2.0 ug/mL were excluded.).

For this current supplement application, the Applicant is treating only PRSP cases confirmed with broth microdilution technique as bacteriologically evaluable. Thus, when the new PRSP cases from the on-going study 100224 are included, there is a total of 21 cases of PRSP, all confirmed by broth microdilution and all deemed "eradicated."

> ***MO COMMENT:*** *This new PRSP isolate evaluability criteria by the Applicant is acceptable for this review since 1) the broth microdilution technique is the reference method for determining minimum inhibitory concentrations 2) the*

majority of PRSP isolates only with E-test values (6 out of 7) cannot be used anyway because the values were all between 1.5 – 2.0 ug/ml; there was only one isolate that had an E-test MIC value out of the breakpoint range at 6 ug/ml.

Hence, it is agreed that the review of the current supplemental application will focus on the 21 PRSP isolates which all had MIC determinations by the reference method of broth microdilution technique.

BIOSTATISTICS

Please see Dr. Karen Higgins' Statistical Review.

CLINICAL REVIEW OF EFFICACY

Previously Submitted PRSP Data

CAP - PRSP Review Section from NDA 21-277 Addendum MO Review

> **MO Comment**: *Since the current supplemental application under review is a continuation of the Applicant's quest for the PRSP claim for Avelox' CAP indication, this section is taken directly from the CAP – PRSP Section from NDA 21-277 MO's Addendum Review. This will provide a background for the reader as to the rationale behind the unsuccessful previous attempt by the Applicant to garner the PRSP claim.*

The following highlighted text, which is taken verbatim from Dr. Meyerhoff's original review, discusses the clinical efficacy in CAP for oral moxifloxacin compared with oral high-dose amoxicillin or clarithromycin:

Table 21: Clinical efficacy CAP due to *S. pneumoniae*: oral formulations

	Moxifloxacin 400 mg po q D	Control*
All CAP studies	80/89 (90%)	67/75 (89%)

*Control = amoxicillin 1000 mg po tid or clarithromycin 500mg po bid

Inspection of the above Table 21 shows that for the treatment of CAP, the results for oral moxifloxacin and comparator are similar to what was observed in intravenous study #100039. Efficacy rates are similar for the two treatment groups across most populations. The open-label design of study #200036 and the different pattern of efficacy data when compared with study #100039 or with results from the CAP studies in the NDA for the oral formulation makes the results of #200036 less central to the review of drug efficacy.

Results from study #100039 support the demonstration of efficacy of intravenous moxifloxacin in a manner consistent with what was observed for the oral formulation of the drug, except that there appears to be slightly lower efficacy for moxifloxacin among microbiologically evaluable patients with severe CAP. The results from study #200036 do not refute this overall finding of clinical efficacy for intravenous moxifloxacin in CAP.

Efficacy in patients with *S. pneumoniae* bacteremia

Dr. Meyerhoff expressed a need to evaluate the efficacy of intravenous moxifloxacin in patients with more severe disease, as there was a high likelihood that these patients would be treated with the intravenous formulation rather than the oral. Initial data appeared to suggest somewhat lower efficacy rates for moxifloxacin than comparator in the

subpopulation of microbiologically evaluable patients with severe disease. Therefore, she analyzed data from patients with pneumococcal bacteremia as a means of better understanding the efficacy of intravenous moxifloxacin in this subpopulation.

She went on to state:
Patients with CAP and pneumococcal bacteremia are important to the understanding of drug efficacy for two reasons: 1) they represent the 'gold standard' of diagnostic criteria for pneumococcal pneumonia, and 2) they represent a category of severe disease for which the demonstration of drug efficacy is critical. Patients with pneumococcal pneumonia and bacteremia have a substantially higher mortality than those with pneumococcal infection confined to the lung.

Table 22 presents a summary of clinical efficacy rates in patients with pneumococcal bacteremia across all controlled, double-blinded studies of oral or intravenous moxifloxacin.

Table 22. Clinical efficacy in CAP patients with *S. pneumoniae* bacteremia from all controlled, double-blinded studies of oral or intravenous moxifloxacin

STUDY	Moxifloxacin 400 mg	Control
ORAL MOXIFLOXACIN		
Study 0119	1/1 (100%)	1/1 (100%)*
Study 0140	6/9 (67%)	10/10 (100%)**
INTRAVENOUS MOXIFLOXACIN		
Study 100039	9/10 (90%)	11/11 (100%)***
TOTAL	**16/20 (80%)**	**22/22 (100%)**

*Clarithromycin
**High dose amoxicillin
***Trovafloxacin or levofloxacin

Review of Table 22 shows that efficacy of moxifloxacin demonstrated in controlled, double-blinded trials of patients with CAP and pneumococcal bacteremia is markedly lower than efficacy observed with control agents. Penicillin or amoxicillin have long been drugs of choice for the treatment of pneumococcal infections. The increasing importance of penicillin resistance among clinical isolates of *S. pneumoniae* suggests that the effectiveness of these drugs may be waning. A drug that can be considered an adequate replacement for these agents should demonstrate comparable efficacy.

Efficacy in CAP due to penicillin-resistant *S. pneumoniae* (PRSP)
The data presented in Table 22 are important to the consideration of both moxifloxacin efficacy in the treatment of severe pneumococcal infections and efficacy in resistant pneumococcal infections. Consideration of a claim for efficacy in the treatment of infections due to PRSP warrants that efficacy in the treatment of pneumococcal infections due to susceptible strains be well characterized. As noted above, Table 22 raises issues

regarding moxifloxacin success rates in patients with bacteremia, one of the most serious complications of pneumococcal pneumonia.

At the time of the submission of the NDA for oral moxifloxacin, the sponsor requested a claim for efficacy in the treatment of CAP due to PRSP. This was not approved for two reasons. One reason was that the small body of data regarding efficacy in bacteremic patients suggested low rates for moxifloxacin (Table 4, study 0140). The other was that there was a very small number of resistant pneumococcal isolates, and moxifloxacin efficacy observed in these infections was lower than was seen in pneumococcal infections in general. Table 5 below revisits these data, and demonstrates that, while sample sizes were extremely small, some question was raised regarding moxifloxacin efficacy in infections due to PRSP.

Table 23. Clinical efficacy of oral moxifloxacin in CAP: *S. pneumoniae* and PRSP

	Moxifloxacin 400 mg po q D	Control
CAP due to *S. pneumoniae* (all isolates)	80/89 (90%)	67/75 (89%)
CAP due to PRSP	6/8 (75%)	3/3 (100%)

For the purpose of reconsidering the claim for efficacy of moxifloxacin in CAP due to PRSP, the sponsor combined all PRSP isolates from studies of both the oral and intravenous formulations in US and ex-US studies. Those isolates identified in the US studies were tested for penicillin susceptibility using both e-test and broth dilution. All of these isolates met the criterion for penicillin resistance (MIC$\geq$ 2.0 mcg/ml) when tested using broth dilution, the standard criterion that defines penicillin resistance. Clinical efficacy for patients from whom this small number of organisms was isolated was observed to be 100%.

There were also PRSP isolates identified in ex-US studies. In these studies, only the e-test was used to assess penicillin resistance. Because 6 of the 7 isolates identified in these studies had MIC values by e-test $\leq$ 2.0 mcg/ml and were not tested by the reference method (broth dilution), they are not regarded as meeting the criteria of penicillin resistant. As has been noted in the Microbiology review, values obtained by the e-test method can differ from those obtained with the reference method by one dilution, and are therefore not reliable indicators of penicillin resistance for review purposes. There was one patient in the ex-US population with a PRSP isolate with a PCN MIC 6.0 mcg/ml by e-test(patient 10674/study 140) who may be regarded as having been infected with PRSP. This patient was a clinical failure.

Additional data from a study of oral moxifloxacin (#100224) were submitted in the four-month safety update. This study provided an additional six patients from whom a PRSP isolate was cultured and tested by both e-test and broth dilution. All six of these patients were clinical cures. Thus the total database from patients with CAP provides 13 PRSP isolates with a clinical cure rate of 12/13 (92.3%). These results are summarized below in Table 24.

Table 24. Clinical efficacy in patients with CAP due to PRSP

Study/Patient No.	Isolate	PCN MIC Etest	PCN MIC broth	Clinical response
100039(iv)/13007	*S. pneumoniae*	3.0	2.0	Resolution
100039(iv)/13025	*S. pneumoniae*	4.0	4.0	Resolution
100039(iv)/48013	*S. pneumoniae*	1.5	2.0	Resolution
100039(iv)/71001	*S. pneumoniae*	3.0	4.0	Resolution
D96-025(po)/4006	*S. pneumoniae*	2.0	2.0	Resolution
D96-026 (po)/248	*S. pneumoniae*	4.0	4.0	Resolution
140 (po)/10674	*S. pneumoniae*	6.0	-	Failure
100224 (po)/1012	*S. pneumoniae*	3.0	2.0	Resolution
100224 (po)/1019	*S. pneumoniae*	8.0	4.0	Resolution
100224 (po)/1028	*S. pneumoniae*	3.0	4.0	Resolution
100224 (po)/1032	*S. pneumoniae*	1.5	2.0	Resolution
100224 (po)/604001	*S. pneumoniae*	2.0	2.0	Resolution
100224 (po)/614002	*S. pneumoniae*	1.0	2.0	Resolution

The data presented regarding clinical efficacy of moxifloxacin in patients with CAP and pneumococcal bacteremia suggest that moxifloxacin is less effective than comparator agents. These data raise questions regarding the appropriateness of this drug for the treatment of severe pneumococcal pneumonia. With such questions outstanding, it would be premature to recommend approval of claims for efficacy in the treatment of pneumonia due to PRSP.

Efficacy in sinusitis due to penicillin-resistant *S. pneumoniae* (PRSP)

The sponsor has also submitted data to support a claim for efficacy of moxifloxacin in the treatment of patients with sinusitis due to PRSP. These data were submitted following discussions with the sponsor in whom it was established that if a claim for PRSP in sinusitis were sought, it would be necessary to show efficacy for PRSP in CAP as well. Data supporting drug efficacy in more serious resistant pneumococcal infections is warranted prior to the consideration of a resistance claim for a less serious infections. By pooling data from 3 oral and 2 intravenous studies of moxifloxacin in sinusitis, the sponsors provided data on 13 patients infected with PRSP. Overall efficacy observed for this population was 11/13 (85%). The sponsor has begun to accrue a database

characterizing moxifloxacin efficacy in resistant pneumococcal infections, however questions raised about drug efficacy in patients with pneumococcal bacteremia suggest that this issue be addressed prior to approving any resistance claims.

***MO Comment**: The above highlighted text in Dr. Meyerhoff's review questions moxifloxacin's efficacy in patients with pneumococcal bacteremia. It states clearly that in order to establish a claim for PRSP, drug efficacy in more serious resistant pneumococcal infections (i.e. CAP) is warranted prior to the consideration of a resistance claim for a less serious infections (i.e. sinusitis). For my addendum review (Nov. 30, 2001), I requested the following two tables be populated with PRSP data for moxifloxacin and the control drugs across all CAP studies (previous as well as on-going). The data from the following Tables 25 and 26 were than compared to the Levofloxacin PRSP data (Table 27).*

The Levaquin application for PRSP has set a "threshold" for approval of other antibiotics seeking the PRSP claim. Thus, the PRSP data for Avelox through all CAP studies (using the data from applicant's submission of Tables 25 and 26) are summarized in the table 27 side-by-side with the Levaquin data that was used to grant approval for that drug.

Applicant's Submission (Previously submitted PRSP Data)

Table 25: Characteristics of Moxifloxacin-Treated Patients with Community Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae*

Study No.	Patient Number	Penicillin MIC (μg/mL)	Clinical Outcome	Bacteriological outcome[a]	Bacteremic?	Severe?[b]	Hospitalized?	Post Therapy Day at which Clinical Response Assessed
D96-026	248	4	Resolved	PE	No	No	No	20
D96-025	4006	2	Resolved	PE	No	Yes	No	21
140	10011	2	Failed	PP	No	No	Yes	8
	10099	2	Resolved	E	No	No	Yes	25
	10370	2	Resolved	PE	No	No	Yes	28
	10674	8	Failed	PP	No	No	Yes	0[c]
	10304	2	Resolved	PE	No	No	Yes	22
	10434	2	Resolved	PE	No	No	No	23
100224	1012	2	Resolved	PE	No	Yes	No	12
	1019	4	Resolved	PE	No	No	Yes	11
	1028	4	Resolved	PE	No	Yes	Yes	10
	1032	2	Resolved	PE	Yes	No	No	11
	604001	2	Resolved	PE	No	No	No	11
	614002	2	Resolved	PE	No	Yes	Yes	36
Study 10039	13007	2	Resolved	PE	No	No	Yes	12
	13025	4	Resolved	PE	No	Yes	Yes	13
	48013	2	Resolved	PE	Yes	No	Yes	12
	71001	4	Resolved	PE	No	Yes	Yes	18
Study 20036	38101	2	Resolved	PE	No	Yes	Yes	29

a: PE = presumed eradication, E = eradication, PP = presumed persistence, P = persistence

b: Severity was defined using the ATS criteria: Patient was considered to have severe pneumonia if the patient had any of the following: Respiratory rate > 30 breaths /minute; PaO_2/FiO_2 ratio < 250 mmHg; required mechanical ventilation; bilateral or multilobar involvement on chest x-ray; increase in the size of opacity by ≥ 50% within 48 hours of admission; Shock: systolic blood pressure < 90 mmHg or diastolic blood

pressure < 60 mmHG; requirement for vasopressor therapy for > 4 hours, urine output < 20 ml/hour or a total urine output < 80 ml in 4 hours unless another explanation available.

c: Patient failed therapy on treatment Day 6

Table 26: Characteristics of Comparator-Treated Patients with Community Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae*

Study No. Comparator	Patient Number	Penicillin MIC (μg/mL)	Clinical Outcome	Bacteriological outcome[a]	Bacteremic?	Severe?[b]	Hospitalized?	Post Therapy Day at which Clinical Response Assessed
140								
Amoxicillin	10003	2	Resolved	PE	Yes	No	Yes	27
Amoxicillin	10109	2	Resolved	PE	Yes	No	Yes	25
Amoxicillin	10343	2	Resolved	PE	No	No	No	21
Study 10039								
Levofloxacin	4006	2	Resolved	PE	No	Yes	Yes	12
Study 20036								
Amoxicillin/Clavulanate	8902	2	Failed	PP/E[c]	Yes	Yes	Yes	0[d]
Amoxicillin/Clavulanate	12902	2	Failed	PP	Yes	Yes	Yes	7

a: PE = presumed eradication, E = eradication, PP = presumed persistence, P = persistence

b: Severity was defined using the ATS criteria: Patient was considered to have severe pneumonia if the patient had any of the following: Respiratory rate > 30 breaths /minute; PaO_2/FiO_2 ratio < 250 mmHg; required mechanical ventilation; bilateral or multilobar involvement on chest x-ray; increase in the size of opacity by ≥ 50% within 48 hours of admission; Shock: systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHG; requirement for vasopressor therapy for > 4 hours, urine output < 20 ml/hour or a total urine output < 80 ml in 4 hours unless another explanation available.

c: Organism was eradicated from the blood site and classified as presumed persistence for the respiratory site because patient was a clinical failure.

d: Patient failed therapy on treatment Day 3

Table 27: IV Avelox and PRSP: Comparison to Levofloxacin and Moxifloxacin Databases

	Levofloxacin Application		**Moxifloxacin Application**	
All CAP studies	8 studies total, 7 studies contributing PRSP organisms 4 randomized, 1 double-blind, only 1 PRSP isolate came from the double-blind study		7 studies total; 4 studies contributing PRSP organisms 5 randomized, 4 double-blind, 6 PRSP isolates coming from double-blind studies ** on-going Nosocomial Pneumonia study (a double-blind study) is contributing 6 PRSP isolates to this application (added later to the IV-avelox NDA as part of 4 month safety update)**	
# Patients with *S. pneumoniae* CAP across all studies #cured/total (%response)	Levofloxacin **245/250 (98%)**	Control **39/41 (95%)**	Moxifloxacin Uncontrolled Studies 36/37 (97%) Controlled Studies 113/127 (89%) All Studies Total **149/164 (91%)**	Control 111/129 (86%) **111/129 (86%)**
# Patients with *S. pneumoniae* **bacteremia**	Levofloxacin **55/55 (100%)**		Moxifloxacin **30/34 (88%)**	Control **31/32 (97%)**
# Patients with PRSP across all CAP studies	Levofloxacin **15/15 (100%)** 15 evaluable of 18 total 11/15 "pivotal" meaning response evaluation during 5-21 day period post-Tx	Control 3/3 (100%) 3 evaluable of 4 total	Moxifloxacin **12/13 (92.3 %)** 13 evaluable of 19 total because E-test values between 1.5 to 2.0 µg/mL were excluded. Studies 140 and 20036 used E-test only. Clinical response date for all "resolved" cases were assessed between Post-Tx days 10-36	Control 1/1 (100%) 1 evaluable of 6 total because E- test values were all 2 µg/mL and thus excluded
PRSP Patient Characteristics	Levofloxacin %total		Moxifloxcin %total	
# Bacteremic	**6 6/15 (40%)**		**2 2/13 (15%)**	
# with Severe Dz	5 5/15 (33%)		6 6/13 (46%)	
# Hospitalized	9 9/15 (60%)		7 7/13 (54%)	

New PRSP Data in the Current Submission

In this current submission, the Applicant has included new data (PSSP as well as PRSP) in support of the PRSP claim for the CAP indication. The following table lists clinical efficacy in patients with CAP due to PRSP from all Avelox® CAP studies. The new cases added to the original list of patients from NDA 21-277 are shown in shaded rows of the Table 1. The new isolates are from two studies (100224 and 100353).
The PSSP cases as well as the number of *S. pneumoniae* bacteremic cases from these studies were also submitted as additional/new data to this current efficacy supplement application.

Table 1: Clinical efficacy in patients with CAP due to PRSP (new data added)

Study/Patient No.	Isolate	PCN MIC broth	Clinical response
100039(iv)/13007	*S. pneumoniae*	2.0	Resolution
100039(iv)/13025	*S. pneumoniae*	4.0	Resolution
100039(iv)/48013	*S. pneumoniae*	2.0	Resolution
100039(iv)/71001	*S. pneumoniae*	4.0	Resolution
D96-025(po)/4006	*S. pneumoniae*	2.0	Resolution
D96-026 (po)/248	*S. pneumoniae*	4.0	Resolution
100224 (po)/1012	*S. pneumoniae*	2.0	Resolution
100224 (po)/1019	*S. pneumoniae*	4.0	Resolution
100224 (po)/1028	*S. pneumoniae*	4.0	Resolution
100224 (po)/1032	*S. pneumoniae*	2.0	Resolution
100224 (po)/604001	*S. pneumoniae*	2.0	Resolution
100224 (po)/614002	*S. pneumoniae*	2.0	Resolution
100224 (po)/1037	*S. pneumoniae*	2.0	Resolution
100224 (po)/606005	*S. pneumoniae*	2.0	Resolution
100224 (po)/609004	*S. pneumoniae*	2.0	Resolution
100224 (po)/613006	*S. pneumoniae*	2.0	Resolution
100224 (po)/617006	*S. pneumoniae*	2.0	Resolution
100224 (po)/617008	*S. pneumoniae*	2.0	Resolution
100224 (po)/618008	*S. pneumoniae*	4.0	Resolution
100353 (iv)/23028	*S. pneumoniae*	4.0	Resolution
100353 (iv)/30077	*S. pneumoniae*	2.0	Resolution
21 patients total	*PRSP*	7 with MIC=4	All "cure"

Summary of All CAP studies in the Avelox® Clinical Program

The following table briefly summarizes each of the 9 CAP Avelox® studies.
For the purposes of formatting in the table, the following abbreviations were used.

bacT = bacteriological	DB = double-blind	min = minimum	quinol = quinolone
clarithro = clarithromycin	dx = diagnosis	mod = moderate	trovo = trovofloxacin
Comp = comparative	imp = impairment	moxi = moxifloxacin	tx = treatment
cr cl = creatinince clearance	levo = levofloxacin	preg = pregnant	vent = ventilator
pp = per protocol			

Table 2: Summary of the 9 CAP studies

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
100224 on-going study prospective non-comp open-label multicenter ORAL tablets 400 mg tabs QD x 10 days	Evaluate the safety and efficacy of oral moxi for CAP associated with drug-resistant *S. pneumoniae* Only pts suspected having PRSP enrolled. Presumption: Gram stain ≥ 25 PMN/lpf and ≤10 squamous cells G+cocci or chains OR positive urinary antigen	Clinical response at the TOC visit Moxi given for min of 48 hours for tx to be deemed failure; min of 5 doses to be deemed a success	-Fever -WBC ≥10K -Bands ≥15% -Wbc <4.5k -At least 2 of prod cough, purulent sputum, dyspnea, or tachypnea, rigors, chills, pleuritic chest pain, rales ; +Xray	-quinol allergy -preg -nursing -nursing home residents -hosp>48 hrs prior to dx of pneumonia -mod to severe hepatic imp -cr cl < 50 -other abx -drugs with QT issues study entry -APACHE II score >30	US, Spain, France, South Africa 2/3/2000 start as of 10/1/02, Enrolled: n=222 Doc Spn: n=72 TOCpp 71/72 (99%) TOCbacteremia 20/20 (100%) TOC-PRSP 13/13 (100%) by broth dilution Test of Cure Visit (day 7 to 22 post-treatment)	Serious AE: N=11 US N=13 nonUS No death PremD/C: N=10
D96-025 Completed prospective Uncontroll non-blind, multicenter	Evaluate the safety and clinical/bacteriological efficacy of moxi in CAP	Clinical response at the TOC Moxi given for min of 48 hours for tx to be deemed failure; min of 5 doses to be deemed a success	2 or more of Fever, WBC ≥10K, Bands ≥15%, prod cough, purulent sputum, dyspnea, or tachypnea, rigors, chills, pleuritic chest pain, rales; AND +Xray	quinol allergy -preg -nursing -NYHA Class IV -severe LRTI requiring IV or vent -hosp>48 hrs prior to dx of pneumonia -mod to severe hepatic imp -cr cl <30 -other abx -drugs with QT issues	Clin Eval: n=196 182/196 (93%) (88%, 96%) Clin & Micro eval: N=116 110/116 (95%) (89%, 98%) TOCpp 13/14 (93%) TOCbacteremia ----------	Serious AE: N=14 (6%) Death: 2(1%) PremD/C: N=18 (7%)

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
				study entry	TOC-PRSP 1/1 (100%) by broth dilution --- Test of Cure Visit (day 14 to 35 post-treatment)	
D96-026 Prospective Randomized Doubleblind Multicenter 400mg QD PO moxi vs. 500 mg PO Clarithro BID x 10d	Compare the two regimens in regards to clinical and bacT responses Null hypothesis of inequivalence was to be rejected if the lower limit of the confidence interval was greater than –10%	Clinical response at the TOC Moxi given for min of 48 hours for tx to be deemed failure; min of 5 doses to be deemed a success	2 or more of Fever, WBC ≥10K, Bands ≥15%, prod cough, purulent sputum, dyspnea, or tachypnea, rigors, chills, pleuritic chest pain, rales; AND +Xray	quinol allergy -preg -nursing -NYHA Class IV -severe LRTI requiring IV or vent -hosp>48 hrs prior to dx of pneumonia -mod to severe hepatic imp -cr cl <30 -other abx -drugs with QT issues study entry	Clin Eval: n=194 Clinical Response Moxi: 184/194 (94.8 %) Clarithro: 178/188 (94.7%) (-3.7%, 5.3%) Micro Response Moxi: 106/110 (96%) Clarithro: 100/104 (96%) TOCpp 17/17 (100%) TOCbacteremia --- TOC-PRSP 1/1 (100%) by broth dilution --- Test of Cure Visit (day 14 to 35 post-treatment)	Serious AE: Moxi: N=9 (4%) Clarithro: N=14 (6%) Death: 1 in each group (<1%) PremD/C: Moxi: N=6 (3%) Claritho: N=12 (5%)
Study 0119 Prospective Randomized DB Moxi 200mg PO Moxi 400 mg PO	Compare the three regimens in regards to clinical and bacT responses	Compare clinical response at EOT(for Europe)	All 3 1)Fever and/or WBC ≥10K, Bands ≥15%,	quinol allergy -preg -nursing -NYHA Class IV	Clinical Response Moxi 200: 146/161 (90.7%) (-7.5, 5.2)	Serious AE: Moxi 200: 15 Moxi 400: 17 Clarithro: 16

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
vs. Clarithro 500 mg BID X 10 days Non-US study	Null hypothesis of inequivalence was to be rejected if the lower limit of the confidence interval was greater than −10%	At TOC (for FDA) Moxi given for min of 48 hours for tx to be deemed failure; min of 5 doses to be deemed a success	2)1 or more prod cough, purulent sputum, dyspnea, or tachypnea, rigors, chills, pleuritic chest pain, rales 3) +Xray	-severe LRTI requiring IV or vent -hosp>48 hrs prior to dx of pneumonia -mod to severe hepatic imp -cr cl <30 -other abx -drugs with QT issues study entry	Moxi 400: 141/152 (92.8%) (-8.6, 4.5) Clarithro: 141/153 (92.2%) Moxi200 to Moxi400 (-8.2, 4.1) Micro Response Moxi 200: 29/33 (88%) Moxi 400: 29/34 (85%) Clarithro: 31/38 (82%) TOCpp 13/15 (87%) TOCbacteremia 1/1 (100%) Test of Cure Visit (day 21 to 44 post-treatment)	Death: Moxi 200:5 Moxi 400:2 Claritho: 5 PremD/C: Moxi 200:7 Moxi 400: 11 Claritho: 11 Penicillin susceptibilites of the *S. pneumoniae* isolates were determined by E-TEST

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
Study 0140 Prospective Randomized DB PO Moxi 400 mg QD to PO Amoxil 1 gm TID x10days Non-US study	Compare safety and efficacy Patients suspected of having pneumococcalCAP Null hypothesis of inequivalence was to be rejected if the lower limit of the confidence interval was greater than –10%	Compare clinical response at EOT (for Europe) At TOC (for FDA) Moxi given for min of 48 hours for tx to be deemed failure; min of 5 doses to be deemed a success	All 4 1)Fever 2) +Xray 3)1 or more prod cough, purulent sputum, dyspnea, or tachypnea, rales 4) 2 or more of rapid onset of symptoms, temp >39, rigors, chills, pleuritic chest pain, xray c/w lobar infiltrate, or gram+ cocci on sputum gram stain	quinol allergy -preg -nursing -NYHA Class IV -severe LRTI requiring IV or vent -hosp>48 hrs prior to dx of pneumonia -mod to severe hepatic imp -cr cl <30 -other abx -drugs with QT issues study entry	Clinical Response Clin Evaluable Moxi 400: 143/160 (89%) (-6.6, 6.7%) Amoxil: 159/178 (89%) Micro Response Moxi 400: 49/58 (84%) Amoxil: 53/65 (82%) TOCpp Moxi 35/42 (83%) Amoxil 36/43 (84%) TOCbacteremia 6/9 (67%) Cure rate was 67% (4/6) in the PRSP cases that were identified by E-test only Study 0140 was unique in having abnormally low bacteriological eradication rates in both cases of S. pneumoniae bacteremia and PRSP cases that were identified by E-testing. Reasons for this suboptimal response rate unclear but note that the comparator	Serious AE: Moxi 400: 23 (11.5%) Amoxil: 19 (9.1%) Death: Moxi 400:3 Amoxil: 4 Not-related to drug therapy PremD/C: Moxi 400: 8 Amoxil: 8 Penicillin susceptibilites of the *S. pneumoniae* isolates were determined by E-TEST Test of Cure Visit (day 15 to 40 post-treatment)

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
					arm is also low. Possibly related to seriously ill patients requiring hospitalization.	
100222 prospective randomized DB Moxi 400 mg PO Clarithro 500 mg PO BID x 10 days	Compare efficacy and safety in the treatment of non-hospitalized patients with CAP	Primary efficacy variable was clinical improvemt as measured by a change in the sum of 5 pneumonia symptom scores Fatigue Cough Dyspnea Sputum Pleuritic chest pain	Scores measured at baseline and Day 14. Severity scale for each of the 5 symptoms was a 6 point scale from 0 (no symptom) to 5 (very severe symptoms) Two-sample t-test	quinol allergy -preg -nursing -NYHA Class IV -severe LRTI requiring IV or vent -hosp>48 hrs prior to dx of pneumonia -mod to severe hepatic imp -cr cl <30 -other abx -drugs with QT issues study entry	Clinical Response Clin Evaluable Moxi 400: 94% Clarithro: 94% Micro Response ------ TOCpp Moxi 8/8 (100%) TOCbacteremia 1/1 (100%) No PRSP	Serious AE: Moxi 400: 19 (8%) Clarithro: 11 (4%) Death: Moxi 400:1 Not-related to drug therapy PremD/C: Moxi 400: 16 (6%) Clarithro: 16 (6%) Test of Cure Visit (4 days post therapy)
100039 prospective rand third-party Blinded IV/PO moxi 400/400 mg QD 7-14d compare to IV/PO trovo 200/200 (initial phase) IV/PO levo 500/500 (contin phase) IV for at least 3 days	Compare safety and efficacy in the treatment of CAP Agreed to pool the two comparators Stratification by severity Stratum 1: mild to moderate Stratum 2: Severe APACHE scores used	Clinical response at the TOC visit Test of Cure Visit (7-30 days post therapy) Primary population for analysis was the population of patients valid for efficacy Null hypothesis: control group had a success rate higher than the moxi group	All 3 1)Fever and/or WBC ≥10K, Bands ≥15%, 2)1 or more prod cough, purulent sputum, dyspnea, or tachypnea, rigors, chills, pleuritic chest pain, rales 3) +Xray both vent and non-vent allowed	quinol allergy -preg -nursing -nursing-home residents -hosp >48hrs prior to dx -mod to severe hepatic imp -cr cl <50 -hx of tendonopathy -other abx -drugs with QT issues study entry -APACHE II score of >30	Clinical Response Clin Evaluable Moxi 400: 157/182 (86%) (-8.9%, 4.2%) Comparator: 161/180 (89%) Stratum 1 Moxi 109/121 (90%) Comp: 122/131 (93%) Stratum 2 Moxi 48/61 (79%) Comp 39/49 (80%) Micro Response	Serious AE: Moxi 400: 57 (23%) Comp: 50 (19%) Death: Moxi 400:13 (5%) Comp: 12 (5%) Not-related to drug therapy PremD/C: Moxi 400: 23 (9%) Comp: 24 (9%) **Moxi had lower

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
		by at least 15%			Moxi 400: 66/80 (83%) Comp: 70/78 (90%) (-22%, 3%) TOCpp Moxi 34/39 (87%) Amoxil 36/43 (84%) TOCbacteremia 9/10 (90%) PRSP broth microdilution 4/4 (100%)	clinical success rates in clinically and microbiologically valid patients compared to control patients but this lower microbiologic response rate in the moxi group was due predominantly to an imbalance with respect to cases of Pseudomonas pneumonia. There were 5 cases of Pseudomonas pneumonia in the moxifloxacin group compared to one in the control group. The micro response rates for moxi against all common CAP pathogens were similar to those for the FQ controls**

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
200036 prospective rand OPEN study IV/PO moxi 400/400 mg QD 7-14d compare to IV/PO Augmentin ± clarithro PO IV for at least 3 days Europe study	Compare safety and efficacy in the treatment of CAP Stratification by severity Stratum 1: mild to moderate Stratum 2: Severe APACHE scores used ** stratified as severe if RR>30, hypoxemia PO2 < 60mmHg; vent required; Xray with multiple lobar infiltrates; diastolic blood pressure <60mmHg; require vasopressors for >4 hours**	Clinical response at the TOC visit Null hypothesis: control group had a success rate higher than the moxi group by at least 10 Test of Cure Visit (5-7days post therapy) Also provided the f/u visit (day 21-28 post therapy)	All 3 1)Fever and/or WBC ≥10K, Bands ≥15%, 2)1 or more prod cough, purulent sputum, dyspnea, or tachypnea, rigors, chills, pleuritic chest pain, rales 3) +Xray	quinol allergy -preg -nursing -nursing-home residents -hosp >48hrs prior to dx -mod to severe hepatic imp -cr cl <50 -hx of tendonopathy -other abx -drugs with QT issues study entry -coexistent disease considered likely to affect the outcome of the study	Clinical Response Clin Evaluable Moxi 400: 241/258 (93%) (2.9%, 13.2%) Comparator: 239/280 (85%) F/u visit Moxi 216/258 (84%) Comp 208/280 (74%) Stratum1 Moxi 122/129 (95%) Comp: 123/143 (86%) Stratum 2 Moxi 119/129 (92%) Comp 116/137 (85%) Micro Response Moxi 400: 60/64 (94%) Comp: 58/71 (82%) TOCpp Moxi 27/27 (100%) TOCbacteremia 11/11 (100%) no PRSP broth microdilution cases one PRSP 1/1 (100%) by E-test	Serious AE: Moxi 400: 38 (12.6%) Comp: 53 (16.5%) Death: Moxi 400:9 (3%) Comp: 17 (5%) Not-related to drug therapy PremD/C: Moxi 400: 25 (8%) Comp: 25 (8%)

Study # and Title	Objective	Main Efficacy Parameter	Inclusion	Exclusion	Results	Safety
100353 prospective randomized OPEN study IV/PO moxi 400/400 mg QD 7-10d compare to IV Ceftriaxone 2 gm ± IV/PO azithromycin ± IV/PO metronidazole followed by cefuroxime axetil PO± PO azithromycin ± PO metronidazole	Compare safety and efficacy in the treatment of CAP or nursing home pneumonia Stratification by nursing home residence (1) or not (2)	Clinical response at the TOC visit IV/PO moxi was said to be non-inferior to the control treatment if the lower limit of a two-sided 95% confidence interval for the weighted difference in clinical response rates was greater than –15%.	1) +Xray 2) and at least 2 of -Fever -WBC ≥10K, Bands ≥15%, -prod cough, -purulent sputum, -dyspnea, or tachypnea, -rigors, chills, -pleuritic chest pain, -rales	quinol allergy -preg -nursing -hosp >48hrs prior to dx -mod to severe hepatic imp -serum cl >3mg/100ml -hx of tendonopathy -other abx -drugs with QT issues study entry -coexistent disease considered likely to affect the outcome of the study	Clinical Response Clin Evaluable Moxi 400: 90/108 (83%) (-11.1%, 9.4%) Comparator: 90/113 (80%) Micro Response Moxi 400: 18/22 (81%) Comp: 17/28 (61%) TOCpp Moxi 9/10 (90%) TOCbacteremia 3 / 4 (75%) PRSP – CAP broth microdilution 2/2 (100%)	Serious AE: Moxi 400: 34 (20%) Comp: 24 (14%) Death: Moxi 400:10 (6%) Comp: 7 (4%) Not-related to drug therapy PremD/C: Moxi 400: 19 (11%) Comp: 6 (4%)

MO COMMENT: *So when all the CAP studies in the Avelox ® clinical program are pulled together, there are 9 studies in total. Eight of these studies have been completed. One-study (study 100224, a prospective, non-comparative, open-label study using oral moxifloxacin 400 mg tablets in CAP associated with drug-resistant S. pneumoniae) is still on-going. Six of the nine studies were ORAL treatment studies (all QD therapy for 10 days) and the remaining three sequential IV (for at least 3 days) then PO therapy studies.*

Two of the 9 studies were un-controlled studies with the remaining 7 studies being controlled studies (active controlled). The comparator drugs used for oral studies were clarithromycin and high-dose Amoxil, whereas the comparator drugs used for IV studies were other flouroquinolones (trovofloxacin and levofloxacin), Augmentin (IV form not approved in US), and Ceftriaxone/metronidazole. For these active-controlled trials, the delta ranged from 10 to 15%. Six of the nine studies were US studies and three non-US. The main efficacy parameter was clinical response at the TOC visit, which across the 9 studies ranged from 4 days post therapy to 35 days post therapy. Out of the 9 CAP trials, the PRSP cases came from 5 studies (see later section). For these 5 studies, the TOC visit outcome assessment occurred between days 7 to 35 post-therapy.

Definitions of Outcome

The Applicant's definitions for Clinical "cure" and Clinical "success" for each of the above 9 CAP studies are shown below in Table 3.

MO COMMENT: *According to the FDA guidance for antimicrobial drugs development for the treatment of CAP, a "clinical cure" should be defined as "complete resolution of all signs and symptoms or pneumonia and improvement or lack of progression of all abnormalities on chest radiograph as assessed by the 7-21 day test-of-cure visit". The sponsor's definition is slightly different in that it allows for the persistence of symptoms as long as such symptoms do not require re-treatment with additional antibiotics. This is acceptable assuming that the sponsor's TOC visit date occurs sufficiently after the last dose of antibiotic such that recurrences or relapses could be detected.*

Table 3: Definitions of Outcome across CAP Studies

CAP Study	Exact Definition of Clinical Success **(Cure)**	Exact Definition of Clinical Failure **(Failure)**	Exact Definition of Unable to Determine **(Indeterminate)***
D96-025	Disappearance of acute signs and symptoms related to the infection or continued improvement where additional or alternative antimicrobial therapy is not required.	Insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy is required.	Clinical assessment is not possible to determine. (e.g., early withdrawal with <5 days of study drug therapy, due to adverse event). Reasons for an indeterminate response must be recorded.
D96-026	Disappearance of acute signs and symptoms related to the infection or continued improvement where additional or alternative antimicrobial therapy is not required.	Insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy is required.	Clinical assessment is not possible to determine. (e.g., early withdrawal with <5 days of study drug therapy, due to adverse event). Reasons for an indeterminate response must be recorded.
0119	Resolution of clinical signs and symptoms related to infection not requiring further antibiotic therapy.	Failure to respond, or insufficient response to study antibiotics requiring modification in antibiotic therapy, or resulting in death from the primary diagnosis.	Patients in whom clinical assessment was not possible to determine (early withdrawals due to adverse events, protocol violation, etc.).
0140	Any patient with disappearance of acute signs and symptoms related to infection or sufficient improvement, such that additional or alternative antimicrobial therapy was not required.	Any patient with insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy was required, or death from the primary diagnosis.	any patient in whom a clinical assessment could not be determined (e.g. early withdrawal < 2 days of study drug therapy; patient not available for assessment; etc...). Reasons for an assessment as "indeterminate" had to be fully documented in the case report form.
100222	The disappearance of acute signs	The insufficient lessening of the signs	Clinical assessment is not possible to

	and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy is not required.	and symptoms of infection such that additional or alternative antimicrobial therapy is required.	determine. Reasons for an indeterminate response must be recorded.
100224	The disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy is not required.	The insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy is required.	A clinical assessment is not possible to determine. Reasons for an indeterminate response were to be recorded in the CRF.
100039	The disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy is not required.	The insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy is required.	A clinical assessment is not possible to determine. Reasons for an indeterminate response were to be recorded in the CRF.
200036	Disappearance of acute signs and symptoms related to the infection; further antibacterial therapy not required.	Failure to respond or insufficient response to the study drug treatment, requiring a modification in antibacterial therapy or resulting in death from the primary diagnosis.	Patients in whom a clinical assessment is not possible to determine (e.g. due to early withdrawal from the study because of adverse events, protocol violation, withdrawn consent etc.).
100353	Disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy is not required.	Insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy is required.	Not possible to determine response to treatment. Reasons for an indeterminate response were to be recorded in the CRF.

* The following are the common reasons why patients were classified as indeterminate:

1. Patient lost to follow-up
2. Patient withdrew from study due to an adverse event or withdrew consent
3. Patient treated with an alternate antibiotic for an infection other than community acquired pneumonia
4. Inadequate duration of study drug therapy (< 48 hours in cases classified as "failure" and < 5 days in cases classified as "cures")
5. Protocol violation that may have influenced the possible efficacy of the study drug (for example, inadvertent administration of an open label antibiotic for the pneumonia)

Patient Accounting Across CAP studies

The following table accounts for patients throughout the Avelox® CAP program starting with the numbers of patients enrolled into each of the 9 studies, categorized by treatment arm.

Table 4: Patient Accounting Across CAP Studies for the populations with *S. pneumoniae* isolates

CAP study	#Total enrolled		# in ITT Analysis		# in ITT with Micro Analysis		# with *S. pneumo* (total) in ITT		# with *S. pneumo* (total) in PP		# with *S. pneumo* bacteremia in ITT		# with *S. pneumo* bacteremia in PP	
	M	C	M	C	M	C	M	C	M	C	M	C	M	C
D96-025	254	0	254	0	147	0	16	0	14	0	0	0	0	0
D96-026	237	237	237	236	133	133	18	22	17	19	0	0	0	0
0119	224	222	224	222	63	61	30	28	15	13	10	7	3	3
0140	203	208	200	208	76	83	53	53	42	43	10	11	9	10
100222	253	265	253	265	31	35	10	10	8	8	1	2	1	1
100224	222	0	222	0	117	0	90	0	72	0	26	0	20	0
100039	253	263	249	258	103	107	49	53	39	40	12	16	10	11
200036	306	322	301	321	82	94	38	36	27	27	15	17	11	10
100353	167	168	167	168	41	40	20	16	10	12	6	8	4	6
9 studies	2119	1685	2107	1678	793	553	324	218	244	162	79	61	58	41

M: Moxifloxacin; C: Comparators; Micro: microbiological

MO COMMENT: *Since two of the oral studies (D96-025 and 100224) were uncontrolled studies, the total number of patients in each of the categories were less for the comparators group. However, the proportion of patient number reductions as the categories become more stringent (column headings going from left to right) are similar for the moxifloxacin treated group and the comparators group. Patients with culture-proven S. pneumoniae CAP (ITT) were 15% (324/2107) of the total ITT population for moxifloxacin group and 13% (218/1678) in the comparators group. Similarly, patients with S. pneumoniae blood culture positive CAP (ITT) were 10% (79/793) of the total microbiological ITT population for moxifloxacin group and 11% (41/553) in the comparators group.*

It is interesting to note that the open-labeled uncontrolled study 100224 (on-going) which was designed to enrich for S. pneumoniae (only patients with positive Gram stain for Gram+ cocci in pairs or chains were enrolled) did show a much higher ratio of the rate of evaluable S. pneumoniae recovery (PP) over the number of total enrolled patients (32%: 72/222) as compared to the overall ratio of 12% (244/2119).

Efficacy Pooled for *S. pneumoniae* Across All CAP studies

The following two tables show the moxifloxacin efficacy for all PP patients with *S. pneumoniae* CAP. Table 5 shows all *S. pneumoniae* isolates from the PP population and Table 6 shows all *S. pneumoniae* blood isolates accounting for the PP *S. pneumoniae*

bacteremic patients. The results are depicted with the studies separated out by uncontrolled and controlled data, and strictly PO and IV/PO sequential studies.

Table 5: Bacteriological Success Rates Against *S. pneumoniae* (Respiratory and /or Blood Isolates) Across All Moxifloxacin Tablet and Sequential IV/PO Studies in CAP

Study	Regimen	Design	Moxifloxacin 400 mg	Comparators
D96-025	PO	Open, UC	13/14 (93%)	
100224	PO	Open, UC	71/72 (99%)	
Uncontrolled total			**84/86 (98%)**	
D96-026	PO	DB, C	17/17 (100%)	18/19 (95%)
0119	PO	DB, C	13/15 (87%)	12/13 (92%)
0140	PO	DB, C	35/42 (83%)	36/43 (84%)
100222	PO	DB, C	8/8 (100%)	6/8 (75%)
Controlled PO total			**73/82 (89%)**	**72/83 (87%)**
	PO total		**183/199 (92%)**	
100039	IV/PO	DB, C	34/39 (87%)	36/40 (90%)
200036	IV/PO	Open, C	27/27 (100%)	22/27 (81%)
100353	IV/PO	Open, C	9/10 (90%)	9/12 (75%)
Controlled IV total			**70/76 (92%)**	**67/79 (85%)**
	IV total		**70/76 (92%)**	
Controlled CAP Studies Total			**143/158 (91%)**	**139/162 (86%)**
ALL STUDIES			**227/244 (93%)**	**139/162 (86%)**

MO COMMENT: *The bacteriological response rate for S. pneumoniae CAP patients treated with moxifloxacin overall was 93% with a range of 89 – 98% depending on the type of study. Uncontrolled (in this case only PO) studies had the best success rate (98%) followed by Open, controlled studies (in this case only IV studies) at 97% (studies 200036 and 100353 combined), followed by double-blinded controlled PO studies (89%) and lastly the double-blinded controlled IV study at 87%. For the controlled trials, the overall response rate for the moxifloxacin group (93%) is slightly better than the response rates of the comparators group (86%). However, the Table above shows that Moxifloxacin's overall response rate is increased by the results from the uncontrolled PO trials and the controlled, but open-labeled IV trials. When only the response rates from double-blinded controlled trials are compared, the rates are exactly the same in both groups (moxifloxacin-treated group: 107/121 or 88% versus comparator-treated group: 108/123 or 88%). Similar numbers are shown when looking at the clinical success rates in patients with S. pneumoniae CAP across all studies (Table 6 below).*

Table 6: Clinical Success Rates in patients with *S. pneumoniae* CAP Across All Moxifloxacin Tablet and Sequential IV/PO Studies

Study	Regimen	Design	Moxifloxacin 400 mg	Control
D96-025	PO	Open, UC	13/14 (93%)	
100224	PO	Open, UC	72/72 (100%)	
Uncontrolled total			**85/86 (99%)**	
D96-026	PO	DB, C	17/17 (100%)	18/19 (95%)
0119	PO	DB, C	14/15 (93%)	12/13 (92%)
0140	PO	DB, C	35/42 (83%)	37/43 (86%)
100222	PO	DB, C	8/8 (100%)	6/8 (75%)
Controlled PO total			**74/82 (90%)**	**73/83 (88%)**
	PO total		**159/168 (95%)**	73/83 (88%)
100039	IV/PO	DB, C	35/39 (90%)	36/40 (90%)
200036	IV/PO	Open, C	27/27 (100%)	20/27 (74%)
100353	IV/PO	Open, C	9/10 (90%)	9/12 (75%)
Controlled IV total			**71/76 (93%)**	**65/79 (82%)**
	IV total		**71/76 (93%)**	65/79 (82%)
Controlled CAP Studies Total			**145/158 (92%)**	**138/162 (85%)**
ALL STUDIES			**230/244 (94%)**	**138/162 (85%)**

***S. pneumoniae* Bacteremia**

Table 7: Clinical Success Rates in CAP patients with *S. pneumoniae* Bacteremia from All PO and IV Moxifloxacin CAP Trials

Study	Regimen	Design	Moxifloxacin 400 mg	Comparators
100224	PO	Open, UC	20/20 (100%)	
Uncontrolled total			**20/20 (100%)**	
0119	PO	DB, C	3/3 (100%)	3/3 (100%)
0140	PO	DB, C	6/9 (67%)	10/10 (100%)
100222	PO	DB, C	1/1 (100%)	0/1 (0%)
Controlled PO total			**10/13 (77%)**	**13/14 (93%)**
	PO total		**30/33 (91%)**	
100039	IV/PO	DB, C	9/10 (90%)	11/11 (100%)
200036	IV/PO	Open, C	11/11 (100%)	7/10 (70%)
100353	IV/PO	Open, C	3 / 4 (75%)	4/6 (75%)
Controlled IV total			**23/25 (92%)**	**22/27 (81%)**
	IV total		**23/25 (92%)**	
Controlled CAP Studies Total			**33/38 (87%)**	**35/41 (85%)**
ALL STUDIES			**53/58 (91%)**	**35/41 (85%)**

MO COMMENT: *With the additional bacteremic cases, the overall clinical response rate for the moxifloxacin group (91%) is similar to the overall rate in*

the comparator group (90%). There was concern expressed in the original PO Avelox MO Review (NDA 21-085) regarding the comparative lower response rate for the bacteremic patients in the moxifloxacin group (77%) in contrast to the comparators group (93%). This difference is a result of one study only (study 0140). The Applicant's statement regarding this phenomenon in the current application was as follows.

"Study 0140 was unique in having abnormally low bacteriological eradication rates in both cases of *S. pneumoniae* bacteremia and PRSP cases that were identified by E-testing. Reasons for this suboptimal response rate is unclear."

Given that one oral study did have a discrepancy in response rates between the two groups, this phenomenon was not seen again in any other study, including the IV studies that followed the NDA 21-085 Review and was part of the NDA 21-277 Review. Thus, except for the one study (0140), the bacteremic patients response rates are similar across the CAP studies and between the moxifloxacin-treated groups and the comparators-treated groups.

Evaluation of Data on Penicillin-resistant *S. pneumoniae*

Avelox CAP studies contributing PRSP cases

We next turn to a close-up look at the PRSP database, accounting for the numbers of patients across all the CAP studies, comparing the response rates to PSSP cases, and finally examining the individual characteristics of each of the 21 PRSP by-patient listings.

Table 8: Patient Accounting Across CAP Studies with PRSP numbers

CAP study	#Total enrolled		# with *S. pneumo* (total) in PP		# with PRSP in PP analysis	
	Moxi	Comp	Moxi	Comp	Moxi	Comp
D96-025	254	0	14	0	1	0
D96-026	237	237	17	19	1	1
0119	224	222	15	13	0	0
0140	203	208	42	43	0	0
100222	253	265	8	8	0	0
100224	222	0	72	0	13	0
100039	253	263	39	40	4	3
200036	306	322	27	27	0	0
100353	167	168	10	12	2	1
Totals	**2119**	**1685**	**244**	**162**	**21**	**5**

MO COMMENT: *Since two of the oral studies (D96-025 and 100224) were uncontrolled studies, the total number of patients in each of the categories were less for the comparators group. However, the proportion of patient number*

reductions as the categories become more stringent (column headings going from left to right) are similar for the moxifloxacin treated group and the comparators group. Patients with culture-proven S. pneumoniae CAP (PP) were 12% (244/2119) of the total enrolled population for moxifloxacin group and 10% (162/1685) in the comparators group. Similarly, patients PRSP CAP (PP) were 8.6 % (21/244) of the total S. pneumoniae positive PP population for moxifloxacin group and 3.1 % (5/162) in the comparators group.

It should be noted that because the Applicant defined the PP PRSP cases as only those with confirmed MICs by broth dilution technique, all the non-US studies with only E-test MICs are no longer contributors of PRSP isolates to the analysis. Thus, out of the 9 CAP studies all together, only 5 studies contribute cases to the PRSP PP population. A summary of those 5 studies are as follows.

- D96-025: Oral, Un-Controlled, TOC (14-35d post), US study
- D96-026: Oral, Controlled, Clarithromycin (delta 10%), TOC (14-35d post), US
- 100224: Oral, Un-Controlled, enriched for *S. pneumoniae* (+ Gram Stain) TOC (7-22d post), US
- 100039: IV/Oral, Controlled, Trovofloxacin/Levofloxacin (delta 15%), TOC (7-30d post), US
- 100353: IV/Oral, Controlled, Ceftriaxone/Metronidazole (delta 15%), TOC (10-14d post), US

MO COMMENT: *So out of 9 CAP trials, PRSP cases are coming from 5 studies (3 oral and 2 IV; 3 controlled, and 2 un-controlled trials). Study 100224 which contributes 62% of the PRSP cases (13/21) in the moxifloxacin arm is an on-going study. It is important to note that this study was designed to enrich for S. pneumoniae cases, enrolling only patients with gram-positive cocci in the screening Gram stain.*

Efficacy in PRSP Cases with Comparison to PSSP Cases

The following Tables depict the pathogen eradication rates by PSSP (*S. pneumoniae* MIC < 2 ug/ml) in Table 9 and by PRSP (*S. pneumoniae* MIC ≥ 2 ug/ml) in Table 10. The Tables are again delineated by the types of CAP trials (un-controlled vs. controlled, oral vs. IV). It should be noted that the numbers from these two Tables are not equal to the patient accounting tables above (Tables 4 and 8) because for these following two Tables 9 and 10, only the patients with confirmed MICs by the broth dilution technique are listed.

Pooled Pathogen Eradication Rates by Penicillin Sensitivity of S. pneumoniae causative pathogens at the TOC visit: Clinical and Microbiologically Evaluable Patients in the Moxifloxacin CAP Studies (BROTH Dilution technique ONLY patients)

Table 9: Response Rates for PSSP Cases (*S. pneumoniae* MIC < 2 μ/ml)

Study	Regimen	Design	Moxifloxacin 400 mg	Control
D96-025	PO	Open, UC	7/8 (88%)	
100224	PO	Open, UC	58/59 (98%)	
Uncontrolled total			**65/67 (97%)**	
D96-026	PO	DB, C	13/13 (100%)	14/15 (93%)
100222	PO	DB, C	5/5 (100%)	3/3 (100%)
Controlled PO total			**18/18 (100%)**	**17/18 (94%)**
	PO total		**83/85 (98%)**	
100039	IV/PO	DB, C	30/35 (86%)	33/37 (89%)
100353	IV/PO	Open, C	7/8 (88%)	8/11 (73%)
Controlled IV total			**37/43 (86%)**	**41/48 (85%)**
	IV total		**37/43 (86%)**	
Controlled CAP Studies Total			**55/61 (90%)**	**58/66 (88%)**
ALL STUDIES			**120/128 (94%)**	**58/66 (88%)**

Table 10: Response Rates for PRSP Cases (*S. pneumoniae* MIC ≥ 2 μ/ml)

Study	Regimen	Design	Moxifloxacin 400 mg	Control
D96-025	PO	Open, UC	1/1 (100%)	
100224	PO	Open, UC	13/13 (100%)	
Uncontrolled total			**14/14 (100%)**	
D96-026	PO	DB, C	1/1 (100%)	1/1 (100%)
Controlled PO total			**1/1 (100%)**	**1/1 (100%)**
	PO total		**15/15 (100%)**	
100039	IV/PO	DB, C	4/4 (100%)	3/3 (100%)
100353	IV/PO	Open, C	2/2 (100%)	1/1 (100%)
Controlled IV total			**6/6 (100%)**	**4/4 (100%)**
	IV total		**6/6 (100%)**	
Controlled CAP Studies Total			**7/7 (100%)**	**5/5 (100%)**
ALL STUDIES			**21/21 (100%)**	**5/5 (100%)**

MO COMMENT: *These two Tables show that the clinical and microbiologic PP patients with PSSP and PRSP had good response rates overall, and that the response rates for patients with penicillin-resistant organisms treated with moxifloxacin or the comparators were not worse than patients with penicillin-sensitive strains treated with moxifloxacin or the comparators. Actually, every PP PRSP case (both in the moxifloxacin group and the comparators group) was*

deemed to be a success where as the overall response rate for PP PSSP cases was 94% for moxifloxacin group and 88% for the comparators group.

Moxifloxacin PRSP numbers in Comparison to Levaquin PRSP numbers

The following Table 11 includes a new moxifloxacin column to show the latest data in comparison to the data from the original levofloxacin numbers and the moxifloxacin numbers at the time of NDA 21-277 (Avelox ® IV) approval.

Table 11: PRSP database for Levofloxacin and Moxifloxacin (#cured/total)

	Levofloxacin	Moxifloxacin #1 (Nov. 2000)	Moxifloxacin #2 (Dec. 2002)
All CAP studies: # with *S. pneumoniae*	245/250 (98%)	149/164 (91%)	230/244 (94%)
# with *S. pneumoniae* bacteremia	55/55 (100%)	30/34 (88%)	53/58 (91%)
All CAP studies: # with PRSP	15/15 (100%)	12/13 (92.3%)*	21/21 (100%)**
# with PRSP bacteremia	6	2	8^
# with Severe Disease	5	6	12^^
# Hospitalized	9	7	15

*includes all broth microdilution confirmed PRSP isolates + one patient with only E-test done (PCN MIC at 6 ug/mL). This patients (from study 0140) was the single failure.
** includes all broth microdilution confirmed PRSP isolates ONLY
^ one of the patients had PCN MIC of 2 ug/ml in the respiratory culture but 1 ug/ml in the blood isolate
^^ this "severe disease" number was determined by the original ATS (American Thoracic Society) criteria (see Appendix 1)

MO COMMENT: *In not granting the PRSP claim at the time of the IV Avelox approval, the rationale given was that "the total number of S. pneumoniae cases, the number of S. pneumoniae bacteremic cases, the number of PRSP cases, as well as the number of PRSP bacteremic cases all were less than the threshold set by the levofloxacin application....In particular, the number of patients who had a successful outcome form PRSP bacteremia were too small (n=2)...". At this time, with the current set of data, moxifloxacin numbers have exceeded the levofloxacin threshold, including the number of PRSP bacteremic cases. It is also important to point out that there was more controlled data for moxifloxacin (5 double-blind studies in the moxifloxacin application versus 1 double-blind study in the levofloxacin application).*

Also included in the rationale of granting or not granting the PRSP claim was the characteristics of the PRSP cases that constituted the "weight of the evidence". These characteristics were bacteremia (denoting the specificity of the diagnosis of true illness with the organism in the blood), severity of CAP disease, and the need for hospitalization. These characteristics of the PRSP cases are further discussed below.

Patient Characteristics of PRSP Cases

The following Table details the pertinent characteristics of each of the 21 patients with PRSP treated with moxifloxacin. It shows the age, gender, culture site of the organism, penicillin MIC values by broth dilution method, clinical severity of disease as checked in the case report forms (CRF) by the investigator (mild, moderate, or severe disease) at enrollment, severity score by the American Thoracic Society (ATS) original criteria (see Appendix 1 for the criteria listing provided by the Applicant), severity score by the ATS modified criteria (again, see Appendix 1), this reviewer's assessment of why the patient was given the ATS severity rating (extracted from the electronic CRF of each patient), hospitalization status, post-treatment day when the patient was assessed for response (TOC), and the outcome.

Table 12: PRSP Patient Listing (only studies with MIC testing by broth dilution)

Study#	Type Of study*	Pt#	Demo	Cult. Site **	PCN MIC ug/ml	Sv Inv ***	Sv Ori ^	Sv Rev ^^	Why Severity score ^^^	Hosp	Post Tx Assess Day	Clin/ Micro outcome
D96-025	PO, UC	4006	M, 70y	R	2	Mo	Y	N	Bilateral inf	No	21	Cure/PE
D96-026	PO, C	248	M, 62y	R	4	Mo	N	N	-	No	20	Cure/PE
100224	PO, UC	1012	M, 86y	R	2	Mo	Y	Y	2m: BI, ↓DBP	No	12	Cure/PE
		1019	F, 75y	R	4	Mo	N	N	-	Yes	11	Cure/PE
		1028	F, 81y	R	4	Mo	Y	Y	2m: BI, ↓DBP	Yes	10	Cure/PE
		1032	M, 80y	R, B	2	Sv	Y	N	Multilobar inf	No	11	Cure/PE
		1037	M, 61y	R, B	2	Sv	Y	Y	2m: BI, ↑↑RR	Yes	10	Cure/PE
		604001	M, 81y	R	2	Mi	Y	N	↓Diastolic BP	No	11	Cure/PE
		606005	M, 72y	R	2	Sv	N	N	-	Yes	11	Cure/PE
		609004	M, 66y	R	2	Mo	N	N	-	Yes	10	Cure/PE
		613006	M, 48y	R	2	Mo	N	N	-	No	12	Cure/E
		614002	M, 72y	R, B	2	Mo	Y	Y	2m: BI, ↓DBP	Yes	36	Cure/PE
		617006	M, 44y	R, B	2	Mo	N	N	-	Yes	9	Cure/PE
		617008	F, 56y	R, B	2	Mo	Y	N	BI	Yes	13	Cure/PE
		618008	F, 58y	R	4	Mi	N	N	-	Yes	11	Cure/PE
100039	IV, B,C	13007	F, 58y	R	2	15;2	N	N	-	Yes	12	Cure/PE
		13025	M, 70y	R	4	9 ; 1	Y	N	BI	Yes	13	Cure/PE
		48013	F, 50y	R, B	2	20;2	Y	N	↓DBP	Yes	12	Cure/PE
		71001	M, 49y	R	4	7;1	Y	N	BI	Yes	18	Cure/PE
100353	IV,O,C	23028	M, 83y	R,B	4	4	N	N	-	Yes	10	Cure/PE
		30077	F, 48y	R,B	2	3	Y	N	BI	Yes	10	Cure/E
5 studies	3 PO 2 IV 2 UC 3C		14M 7F Mean age: 65 (44-86)	**8 pts with + bld cx.**	14 pts MIC =2; 7 pts =4	Mi= 3 Mo =12 S=6	12 Sev	4 Sev	Mainly bilateral infiltrate on Xray or ↓DBP	15 Hosp	Mean 13.5d (9-36)	

*PO (oral); UC (Uncontrolled); C (Controlled); IV (intravenous); B (Blinded); O (Open-labeled)

** R (respiratory); B (Blood)

***Explanation of this Sv Inv (Severity Investigator) Column

-PO Studies had a checkbox for the investigator to put impression of severity on entry: so column Sv Inv is either of the following three: Mi: Mild; Mo: Moderate; Sv: Severe;

-100039 used APACHE II Scores: so column Sv Inv is APACHE II score followed by stratum classification (1 is mild or moderate; 2 is severe)

-100353 used Fine classification: so column Sv Inv is Fine Risk Classification

^ Sv Ori: Designation of severe disease as per the original ATS severity criteria (See Appendix I)

^^Sv Rev: Designation of severe disease as per the revised ATS severity criteria (See Appendix I)

^^^Reasons found from CRF review as to why the severity designation: BI (bilateral infiltrate); 2m (2 Minor Criteria); DBP (diastolic blood pressure); RR (respiratory rate)

MO COMMENT: *There are several points to discuss here regarding the above Table that lists each PRSP patient with pertinent characteristics.*

1) *Again, although the Avelox CAP program overall was well-controlled, the majority of the PRSP cases are coming from the 100224 study which was an open-labeled uncontrolled study.*
2) *The majority of PRSP patients were male and almost ½ were less than 65 years of age.*
3) *There were 8 patients out of the 21 who had both respiratory and blood cultures positive for S. pneumoniae, thus satisfying the criteria that the specificity of the diagnosis of the true illness with the organism be shown (with bacteremic cases).*
4) *The penicillin MICs by broth dilution technique showed that the majority of the isolates were right at 2 ug/ ml. However, 7 isolates were listed as 4 ug/ml and all deemed to have successful outcome. Note that there were no isolates here beyond the 4 ug/ml penicillin MIC.*
5) *As discussed under the section in definitions of outcome, it was pointed out that the Applicant's definition was slightly different from the FDA guidance in that it allows for the persistence of symptoms as long as such symptoms do not require re-treatment with additional antibiotics. This is acceptable since we see here that the TOC visit date is far enough away from the last dose of antibiotic (mean of 13.5 days) that recurrences or relapses could be detected.*
6) *The columns that show the severity and hospitalization assessments need some further discussion (see next section).*

Severity of Disease and Relationship to Resistance Claim

It has been discussed in both the original levofloxacin and moxifloxacin applications/reviews that some level of comfort with successful treatment of "severe" CAP disease with PRSP need to be part of the "weight of the evidence" to garner the PRSP claim. This concept originated primarily because it was unclear when PRSP initially emerged whether there would be different characteristics associated with having disease with PRSP as compared to disease with PSSP, and it was important to gain experience with the most serious spectrum of the disease. As time has passed however, and our understanding and experience with PRSP disease have increased, no different patient characteristics associated with having PRSP have been found. Specifically for the use of a drug in the quinolone class to treat CAP, the severity of disease with PRSP are no different than with PSSP.

This was illustrated with the Tables 9 and 10 above where the outcomes of treatment for PRSP were no worse than the outcomes with PSSP. Moreover, close scrutiny of what is defined as "severe" is quite variable across all the different CAP programs by different Applications, or even within the same program but in different studies. Different sets of criteria or scores are used resulting in the same patients being categorized as having "severe" disease by one set of criteria and having "moderate" disease by another set of criteria. For example, the above Table illustrates that in the same patient group,

depending on the severity criteria used, the patients' severity classification changes from "6/21" to "12/21" to "4/21".

In addition, although the "need for hospitalization" characteristic may sound helpful in further identifying the patient with "severe" disease, in actuality, there appears to be little correlation between the severity scores and hospitalization. Hospitalization is probably more a result of the design of the study at hand (IV study versus PO study), or the standard of care at the site where the patient is enrolled.

To further examine this issue, the Applicant was asked to re-score the same 21 patients with a validated severity scoring system (PORT score: Fine et al, A Prediction Rule to Identify Low-Risk Patients with Community-acquired Pneumonia. N Engl J Med 1997; 336:243-50; see also Appendix II). The following Table 13 shows the discrepancy in results depending on the different methods used.

Table 13: Severity of Disease: Comparison of ATS Criteria and PORT Score

Study#	Type Of study	Pt#	Severity Original ATS criteria	Severity Revised ATS Criteria	PORT Score (Fine Criteria)	Hospitali -zation
D96-025	PO, UC	4006	Y	N	1	No
D96-026	PO, C	248	N	N	3	No
100224	PO, UC	1012	Y	Y	3	No
		1019	N	N	4	Yes
		1028	Y	Y	4	Yes
		1032	Y	N	3	No
		1037	Y	Y	5	Yes
		604001	Y	N	3	No
		606005	N	N	3	Yes
		609004	N	N	1	Yes
		613006	N	N	1	No
		614002	Y	Y	3	Yes
		617006	N	N	1	Yes
		617008	Y	N	1	Yes
		618008	N	N	1	Yes
100039	IV, B,C	13007	N	N	2	Yes
		13025	Y	N	3	Yes
		48013	Y	N	1	Yes
		71001	Y	N	1	Yes
100353	IV,O,C	23028	N	N	3	Yes
		30077	Y	N	2	Yes
5 studies	**3 PO 2 IV 2 UC 3C**		**12 patients with severe disease by this criteria**	**4 patients with severe disease by this criteria**	**I = 8 II = 2 III = 8 IV = 2 V = 1 ONLY 3 with severe dz**	**15 Hosp**

MO Comment: *Continuing on with the discussion above, it can be concluded that examining the level of severity in the overall CAP program is crucial (but with usage of consistent severity criteria or scoring systems), but at this point in time, there is no evidence to necessarily link provision of "severe" cases to garnering PRSP claim. This point is further illustrated by the two graph figures below. The "severe" disease categories (IV and V) by the PORT scoring system is rare for both PRSP (14%: 3/21) and PSSP (14%: 30/211 in the moxifloxacin-treated group and 16%: 24/154) in the comparator-treated group) cases.*

FIGURE 1: PRSP cases (n=21) by PORT severity score. Class IV and V denotes "severe" CAP disease and is 14% (3/21) for PRSP cases.

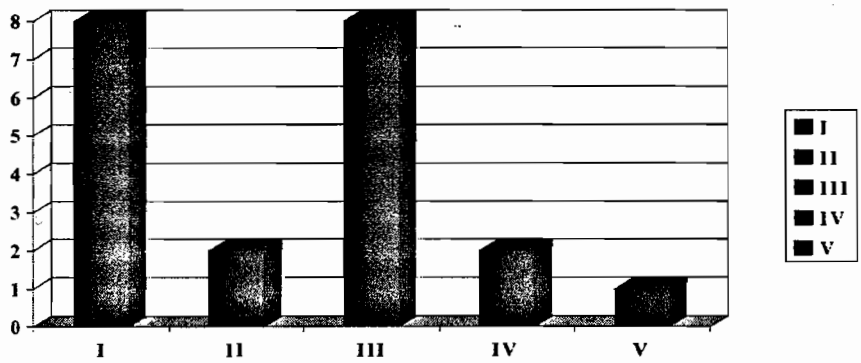
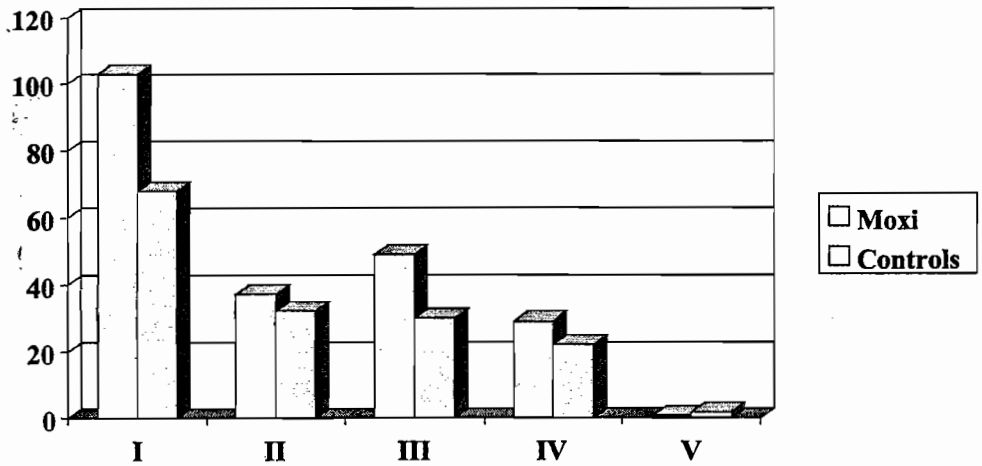


FIGURE 2: PSSP cases (moxifloxacin-treated n=211 and comparator-treated n=154) by PORT severity score. Class IV and V denotes "severe" CAP disease and is 14% (30/211) in the moxifloxacin-treated group and 16% (24/154) in the comparator-treated group) for PSSP cases.



Thus, having adequate evidence in numbers of *S. pneumoniae* bacteremic patients (both PSSP and PRSP) within the population with *S. pneumoniae* CAP continues to be important in considering PRSP resistance claim because these bacteremic cases establish the specificity of diagnosis (with *S. pneumoniae* as the etiological bacterial agent causing disease). At this time however, given the body of evidence presented, requiring demonstration of efficacy of a quinolone class drug in "severe" CAP disease in order to garner the PRSP claim **does not appear to be essential** given the lack of data linking PRSP to severe disease, and given the lack of consistency in the criteria used to assess severity of CAP disease.

> **MO COMMENT**: *It should be pointed out that if the tools to assess severity were used inappropriately or if the tools were actually the wrong tools, then one cannot state with a substantial degree of confidence that severity of illness is not reflected by PRSP versus PSSP. However, it may be fair to say that if severity of illness is reflective of the PRSP versus PSSP, then it's effect is either very subtle, and subsequently clinically unimportant, or it's effect is important in a patient subpopulation which has not been clearly identified as of yet.*

What **is essential** is the need for using the same instrument (validated scoring system such as the Fine-PORT criteria) when evaluating "severe" disease for CAP across different CAP programs and/or within the studies of the same CAP program. This consistency could provide better understanding of the level of disease and the ability to compare results. This is critical for all CAP patients undergoing clinical trials regardless of specific organisms, resistant or sensitive.

CLINICAL REVIEW OF SAFETY

There are no new safety issues to review/discuss with this efficacy supplement. A detailed assessment of moxifloxacin tablet and intavenous moxifloxacin safety in the treatment of CAP has been reviewed via the moxifloxacin tablet (NDA 21-085) and moxifloxacin IV (NDA 21-277) NDAs respectively. Based on this information, both moxifloxacin tablets and intravenous moxifloxacin were shown to be safe for the treatment of CAP.

CONCLUSIONS and RECOMMENDATIONS

For moxifloxacin treatment of CAP due to PRSP, the applicant has stated the following in their concluding remarks.

"Analysis of pooled data from moxifloxacin CAP studies suggests that moxifloxacin is an effective treatment for CAP due to S. pneumoniae including cases of CAP due to PRSP. The success rate for patients with CAP due to S. pneumoniae was 93% across all IV/PO and PO moxifloxacin CAP studies. In the subset of CAP patients with S. pneumoniae bacteremia, the clinical success rate for moxifloxacin was 91%. In cases of CAP due to PRSP, moxifloxacin treated patients had a clinical success rate of 100% including a 100% success rate in 7 patients with PRSP (MIC $\geq$ 2) bacteremia. Thus, moxifloxacin achieved an overall cure rate against PRSP that was similar or better than that against penicillin-susceptible S. pneumoniae....demonstrates that moxifloxacin is an effective treatment for CAP due to penicillin-sensitive and penicillin-resistant S. pneumoniae..."

It is agreed that this supplemental application has shown substantial evidence (from in vitro studies as well as the clinical CAP studies) of moxifloxacin efficacy for the important etiological bacterial agent for CAP, *S. pneumoniae* (both for PSSP as well as PRSP). The "threshold" of the numbers of cases for each of the categories (*S. pneumoniae* cases overall, *S. pneumoniae* bacteremic cases, PRSP cases, PRSP bacteremic cases) that had been set by levofloxacin application for PRSP claim has now been achieved by this application (See next Summary Table 14). Both clinical and bacteriological success rates for the PP population in each of these categories show similar results when compared to the control data composed of both PO and IV comparators.

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Table 14: PRSP Database for Levofloxacin and Moxifloxacin

	Levofloxacin Application		**Moxifloxacin Application #2**		**Moxifloxacin Application #3 CURRENT SUBMISSION**	
All CAP studies	8 studies total, 7 studies contributing PRSP organisms 4 randomized, 1 double-blind, only 1 PRSP isolate came from the double-blind study		7 studies total; 4 studies contributing PRSP organisms 5 randomized, 4 double-blind, 6 PRSP isolates coming from double-blind studies		9 studies total; 5 studies contributing PRSP organisms by broth dilution; 7 randomized; 5 double-blind Still only 6 PRSP isolates coming from double-blind studies	
# Patients with *S. pneumoniae* CAP across all studies #cured/total (%response)	Levofloxacin **245/250 (98%)**	Control **39/41 (95%)**	Moxifloxacin Uncontrolled Studies 36/37 (97%) Controlled Studies 113/127 (89%) All Studies Total **149/164 (91%)**	Control 111/129 (86%) **111/129 (86%)**	Moxifloxacin Uncontrolled Studies 85/86 (99%) Controlled Studies 145/158 (92%) All Studies Total **230/244 (94%)**	Control 138/162 (85%) **138/162 (85%)**
# Patients with *S. pneumoniae* **bacteremia**	Levofloxacin **55/55 (100%)**		Moxifloxacin **30/34 (88%)**	Control **31/32 (97%)**	Moxifloxacin **53/58 (91%)**	Control 35/41 (85%)
# Patients with PRSP across all CAP studies	Levofloxacin **15/15 (100%)** 15 evaluable of 18 total 11/15 "pivotal" meaning response evaluation during 5-21 day period post-Tx	Control 3/3 (100%) 3 evaluable of 4 total	Moxifloxacin **12/13 (92.3 %)** 13 evaluable of 19 total because E-test values between 1.5 to 2.0 µg/mL were excluded. Studies 140 and 20036 used E-test only. Includes one patient from study 140 with E-test (PCN MIC at 6 ug/ml) Clinical response date for all "resolved" cases were assessed between post-Tx days 10-36	Control 1/1 (100%) 1 evaluable of 6 total because E- test values were all 2 µg/mL and thus excluded	Moxifloxacin **21/22 (95%)** 22 evaluable of 28 total because E-test values between 1.5 to 2.0 µg/mL were excluded. Studies 140 and 20036 used E-test only. Includes one patient from study 140 with E-test (PCN MIC at 6 ug/ml) Clinical response date for all "resolved" cases were assessed between post-Tx days 9-36	Control 5/5 (100%) 5 evaluable of 10 total because E- test values were all 2 µg/mL and thus excluded
PRSP Patient Characteristics	Levofloxacin %total		Moxifloxcin %total		Moxifloxcin %total	
# Bacteremic	**6 6/15 (40%)**		**2 2/13 (15%)**		**8 8/22 (36%)**	
# with Severe Dz	5 5/15 (33%)		6 6/13 (46%)		12 12/22 (55%)	
# Hospitalized	9 9/15 (60%)		7 7/13 (54%)		15 15/22 (68%)	

An issue that has been brought to focus during the review of this application is whether a drug must show efficacy in the more severe forms of CAP disease prior to being able to be considered for a claim of efficacy against PRSP. It has been discussed in both the original levofloxacin and moxifloxacin applications/reviews that some level of comfort with successful treatment of "severe" CAP disease with PRSP need to be part of the "weight of the evidence" to garner the PRSP claim. This concept originated primarily because it was unclear when PRSP initially emerged whether there would be different patient characteristics associated with having disease with PRSP as compared to disease with PSSP, and it was important to gain experience with the most serious spectrum of the disease. As time has passed however, and our understanding and experience with PRSP disease have increased, no different patient characteristics associated with having PRSP have been found.

Specifically for the use of quinolone class to treat CAP, the severity of disease with PRSP are no different than with PSSP. Moreover, close scrutiny of what is defined as "severe" is quite variable across all the different CAP programs by different Applications, or even within the same program but in different studies. Different sets of criteria or scores are used resulting in the same patients could be categorized as having "severe" disease by one set of criteria and having "moderate" disease by another set of criteria. In addition, although the "need for hospitalization" characteristic may sound helpful in further identifying the patient with "severe" disease; in actuality, there appears to be little correlation between the severity scores and hospitalization rates. Hospitalization is probably more a result of the design of the study at hand (IV study versus PO study), or the standard of practice at the site where the patient is enrolled.

Thus, having adequate evidence in numbers of *S. pneumoniae* bacteremic patients (both PSSP and PRSP) within the population with *S. pneumoniae* CAP continues to be an important factor in considering PRSP efficacy claims, because these bacteremic cases establish the specificity of diagnosis (with *S. pneumoniae* as the etiological bacterial agent causing disease). At this time however, given the body of evidence presented, requiring demonstration of efficacy of a quinolone class drug in "severe" CAP disease in order to garner the PRSP claim **does not appear to be essential** given the lack of data linking PRSP to severe disease, and given the lack of consistency in the criteria used to assess severity of CAP disease.

What **is essential** is the need for using the same instrument (validated scoring system such as the Fine-PORT criteria) when evaluating "severe" disease for CAP across different CAP programs and/or within the studies of the same CAP program. This consistency could provide better understanding of the level of disease and the ability to compare results. This is critical for all CAP patients undergoing clinical trials regardless of specific organisms, resistant or sensitive.

This moxifloxacin supplemental application for PRSP claim in the indication of CAP has shown sufficient evidence of efficacy based on the current rationale for granting this claim. The safety of moxifloxacin in the treatment of CAP disease overall has already been shown with the approval of previous PO Avelox® NDA 21-085 and IV Avelox®

NDA 21-277. Thus, approval of NDA 21-085/S-015 and 21-277/S-007 is recommended at this time with the following changes to the relevant sections in the package insert.

LABELING

MICROBIOLOGY Section

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

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of $\geq$ 2 µg/mL

INDICATIONS AND USAGE Section

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin $\geq$ 2 µg/mL), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*. (See CLINICAL STUDIES)

CLINICAL STUDIES Section

Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)
Community-Acquired Pneumonia

(add this section beneath the section on CAP)

The clinical and bacteriological efficacy of AVELOX in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (penicillin MIC $\geq$ 2 µg /mL) was evaluated in 9 clinical studies: 4 comparative, double-blind tablet studies; 2 non-comparative, 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 and 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 *S. pneumoniae*	230/244	94	138/162	85
S. pneumoniae bacteremia	53/58	91	35/41	85
S. pneumoniae with Penicillin MIC ≥2 ug/mL	21/21*	100	5/5	100
S. pneumoniae bacteremia with Penicillin MIC ≥2 ug/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 ug/mL

Rosemary Johann-Liang, MD
Medical Officer
DSPIDP, HFD-590

Rigoberto Roca, MD
Medical Team Leader
DSPIDP, HFD-590

Cc:
Original NDA 21-085 and 21-277 file
HFD-590
HFD-590/DivDir/RAlbrecht
HFD-590/PM/SPeacock
HFD-590/CPM/EFrank
HFD-590/PharmTox/SHundley
HFD-590/Chem/DMatecka
HFD-590/Micro/PDionne
HFD-590/MicroTL/SBala
HFD-725/Biostat/KHiggins

APPENDIX I

American Thoracic Society Criteria

Original and Revised ATS Criteria for Severe Community-Acquired Pneumonia

ATS Original Criteria

Patient considered to have severe pneumonia if one or more of the following criteria
present.
Respiratory rate >30
Pao_2/Fio_2 < 250 mmHG
Bilateral or multilobar involvement on chest X-ray
Shock: Systolic BP < 90 mm Hg or Diastolic BP < 60 mm Hg
Need for mechanical ventilation
Increase in size of infiltrate by > 50% within 48 hours of admission
Requirement for vasopressor therapy for > 4 hours
urine output < 20 ml/hour or a total urine output < 80 ml in 4 hours unless another explanation available

ATS Revised Criteria

Minor Criteria
Respiratory rate >30
Pao_2/Fio_2 < 250 mmHG
Bilateral pneumonia or multilobar pneumonia
Systolic BP < 90 mm Hg
Diastolic BP < 60 mm Hg
Major Criteria
Need for mechanical ventilation
Increase in size of infiltrate by > 50% within 48 hours of admission
Septic shock or need for vasopressor therapy for > 4 hours
Acute renal failure (urine output < 80 ml in 4 hours or serum creatinine > 2 mg/dL in the absence of chronic renal failure)
Diagnosis of severe pneumonia requires the presence of:
Presence of two or more Minor Criteria at the time of assessment, or
Presence of one or more Major Criteria at the time of assessment or later in the hospital stay

---

(reference: American Thoracic Society Guidelines for the Initial Management of Adults with Community-acquired Pneumonia: Diagnosis, Assessment of Severity, and Initial Antimicrobial Therapy. Am Rev Respir Dis 1993 Vol 148: 1418-1426)

APPENDIX II

PORT (Pneumonia Patient Outcomes Research Team Score) Calculation

The PORT score was collected prospectively in only one of the CAP studies included in this submission (study 100353). We therefore applied a retrospective calculation to the data from the other studies to estimate the PORT score.

We used the definition shown below.

PORT Risk Score – Step 1
Assign patient to Risk Class I if all of the following are met:
Patient is ≤ 50 years of age
Patient does **NOT** have a history of any of the following coexisting conditions:
- Neoplastic disease
- Congestive Heart Failure
- Cerebrovascular Disease
- Renal Disease
- Liver Disease

Patient does **NOT** have any of the following abnormalities on physical examination:
- Altered Mental Status
- Pulse ≥ 125 beats/minute
- Respiratory rate ≥ 30 breaths/minute
- Systolic blood pressure < 90 mm Hg
- Temperature < 35°C or ≥ 40°C

PORT Risk Score – Step 2

If patient is not assigned to Risk Class I, assign patient to Risk Classes II to V based on total score:

Patient Characteristic	Points Assigned[a]
Demographic Factor	
Age	
Male	No of years of age
Female	No of years of age - 10
Nursing Home Resident	+10
Comorbid Illnesses	
Neoplastic disease[b]	+30
Liver Disease[c]	+20
Congestive Heart Failure[d]	+10
Cerebrovascular Disease[e]	+10
Renal Disease[f]	+10
Physical Examination Finding	
Altered mental status[g]	+20
Respiratory rate > 30 breaths/min	+20
Systolic Blood Pressure < 90 mm Hg	+20
Temperature < 35°C or > 40°C	+15
Pulse > 125 beats/min	+10
Laboratory or radiographic Finding	
Arterial pH < 7.35	+30
Blood urea nitrogen > 30 mg/dL	+20
Sodium < 130 mEq/L	+20
Glucose > 250 mg/dL	+10
Hematocrit < 30%	+10
Arterial partial pressure of O_2 < 60 mm Hg[h]	+10
Pleural Effusion	+10

a) A total point score for a given patient is obtained by adding the patient's age in years (age –10 for females) and the points for each applicable patient characteristic.
b) Any cancer except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within 1 year of presentation.
c) A clinical or histological diagnosis of cirrhosis or other form of chronic liver disease such as chronic active hepatitis.
d) Systolic or diastolic ventricular dysfunction documented by history and physical examination, as well as chest radiography, echocardiography, MUGA scanning, or left ventriculography.
e) A clinical diagnosis of stroke, transient ischemic attack, or stroke documented by MRI or CT scan.
f) A history of chronic renal disease or abnormal blood urea nitrogen and creatinine values documented in the medical record.
g) Disorientation (to person, place, or time, not known to be chronic), stupor, or coma.
h) O_2 saturation < 90% on pulse oximetry, or intubation before admission also considered abnormal.

Risk Class	No. of Points
II	≤ 70
III	71 - 90
IV	91 - 130
V	> 130

The variables for this scoring system were generated as described below:

Demographic Factors: age and sex were obtained from the demographic section of the case report form. Nursing home information was only collected in one study (study 100353). However, very few patients from nursing homes would have qualified for the studies in the submission, so it is felt that very little was missed by not having this information in all studies.

Comorbid illnesses: These conditions were obtained from the medical history section of the case report forms. The ICD9 coding system was used to select the appropriate conditions. The ICD9 codes used for each condition are shown below; existence of any of the conditions in the categories was cause to assign the points for that condition.

Neoplastic disease:

malignant neoplasm pharynx
malignant neoplasm esophagus
malignant neoplasm stomach
malignant neoplasm colon
malignant neoplasm larynx
malignant neoplasm upper lobe lung
malignant neoplasm bronch/lung
malignant melanoma face/neck
malignant melanoma trunk
malignant neoplasm breast
Kaposi sarcoma
malignant neoplasm uterus
malignant neoplasm cervix
malignant neoplasm corpus uterine
malignant neoplasm prostate
malignant neoplasm bladder
malignant neoplasm kidney
multiple myeloma
chronic lymphoid leukemia
chronic myeloid leukemia
digestive neoplasm
brain neoplasm

Liver disease:

cirrhosis of liver
chronic liver disease
hepatitis
liver disorder

Congestive heart failure:

congestive heart failure
left heart failure
heart failure

Congestive heart failure points were also assigned if a pre-therapy X-ray finding of pulmonary congestion was evident.

Cerebrovascular disease:

ASCVD (Atherosclerotic cerebrovascular disease)
carotid artery occlusion no infarction
vertebral artery syndrome
trans cerebral ischemia
cerebrovascular accident
AC cerebrovascular insufficiency

Renal disease:

acute nephritis
acute renal failure
chronic renal failure
renal failure
renal sclerosis
hydronephrosis
renal and ureteral disorder

Renal disease points were also assigned if pre-therapy creatinine was > 2 mg/dL

Physical Examination Findings

Altered mental status – not available as this variable was not routinely collected in any of the studies.

Respiratory rate, Systolic blood pressure (SBP), temperature, and pulse were all taken from the vital signs section of the case report form (pre-therapy visit)

Laboratory or radiographic finding:

BUN, sodium, glucose, and hematocrit were obtained from the pre-therapy laboratory values

Existence of pleural effusion was detected from the X-ray findings from the pre-therapy visit

CO2 concentration < 19 (at pre-therapy) was substituted for Arterial pH < 7.35 as arterial blood gasses were not routinely obtained in any of the pneumonia studies.

Arterial partial pressure was only available from study 100353

Note that due to the unavailability of data for altered mental status and arterial partial pressure, these estimates of PORT score may in some cases underestimate the actual PORT score. Therefore the PORT scores shown here should be considered a lower bound for the actual PORT scores.

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

/s/

Rosemary Johann-Liang
3/3/03 01:42:44 PM
MEDICAL OFFICER

Rigoberto Roca
3/6/03 11:47:11 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER'S REVIEW OF NDA

NDA 21-277
AVELOX

Applicant
Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, Connecticut 06516
Contact: Mr Andrew Verderame, Associate Director, Regulatory Affairs
Phone: 203-812-5172

Submission/Review Dates
Date of submission: November 4, 2000
Date review completed: September 24, 2001

Drug Identification

Generic name:	moxifloxacin (BAY 12-8039)
Proposed trade name:	Avelox
Pharmacologic category:	antimicrobial-fluoroquinolone
Route of administration:	intravenous

Regulatory materials reviewed
NDA 21-085, volumes 1.1-1.2, 1.269-1.298 and associated electronic files, submitted 12/9/98

[redacted]

NDA 20-596 (Raxar), MO review
NDA 20-677 (Zagam), MO review
Meeting minutes and handouts for meeting between Bayer and Division of Special Pathogens, May 1997
Correspondence between Bayer and Division of Special Pathogens from spring 1997 to autumn 2000

INTEGRATED REVIEW OF EFFICACY

Background
The oral formulation of Avelox (NDA 21-085) was approved December 10, 1999 for the indications community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), and acute sinusitis. A fourth indication, uncomplicated skin and skin structure infections, was approved April 27, 2001. The CAP indication is the only one for which there were studies performed with the intravenous formulation, and these studies provided the efficacy data for the application under review here (NDA 21-277). The plan of the sponsor was to demonstrate the efficacy of intravenous moxifloxacin for the treatment of CAP with a single North American study and demonstrate comparable bioavailability between the oral and iv formulations. These data would then support approval of the intravenous formulation for any indications already approved for the oral

formulation. In a May 1997 meeting, this strategy was discussed with the review division and found mutually agreeable. The sponsor was advised that failure to demonstrate efficacy of the intravenous formulation for the treatment of CAP and/or comparable bioavailability of the two formulations would put approval of the other indications at risk. At that meeting, the division also asked if other clinical trials were being conducted with the iv formulation, and Bayer acknowledged that there was a European CAP study with the same design as the North American one, but with amoxi-clavulanate as the comparator. Bayer added that they intended to use the data from the European study as supportive for organisms and safety.

In August 1997 and October 1998, the MO received and reviewed 2 different phase III protocols for intravenous moxifloxacin for CAP. The study described in the August '97 protocol used ceftriaxone/cefuroxime as comparator, the study described in the October '98 protocol used trovafloxacin as comparator. The trial that used ceftriaxone/cefuroxime (August '97 submission) [redacted] In July 1999, Bayer changed the comparator in the October '98 protocol to levofloxacin because of safety concerns with trovafloxacin.

In August 1999, the MO requested clarification from Bayer regarding the number of trials being planned for iv moxifloxacin for CAP. In an email dated Aug 16, 1999, Bayer informed the division that the 'Trovan study' (#100039, for which levofloxacin had been substituted as the comparator) 'is still the only one trial for a moxifloxacin NDA.'

During summer and fall of 2000, there were a series of pre-NDA discussions with Bayer regarding several issues in the planned iv NDA. Records of the Oct 4, 2000 pre-NDA meeting mention study #200036, an open label, ex-US study using amoxicillin-clavulanate as comparator with clarithromycin added at investigator's discretion. It appeared that this study was a source of resistant pneumococcal isolates.

NDA 21-277 was submitted in November 2000. Early review of the submission to determine fileability identified CAP studies #100039 and #200036 showed that the sponsor identified these studies as pivotal. The study report for #200036 documented the start of that study in February 1999, 6 months before Bayer's August 1999 statement that #100039 was the only trial in the moxifloxacin iv NDA.

Clinical efficacy of moxifloxacin iv in CAP

Review of the documents and correspondence described above suggests that the sponsor elected to include this second CAP study in NDA 21-277 some time after August 1999. The use of data from additional studies to provide information on resistant isolates can be a means of supplementing the database for drug efficacy against resistant pneumococcal isolates, which are notoriously difficult to identify in clinical specimens. The review division has recognized this difficulty, and the MO has viewed the results of study #200036 as a potential source of additional information about moxifloxacin efficacy in the treatment of penicillin-resistant *S. pneumoniae* (PRSP) infections. It should be pointed out, however, that as an open label study, #200036 does not provide the same

level of evidence for efficacy as would a prospective double-blinded, randomized, controlled study such as #100039. For these reasons, #200036 was regarded by the reviewing MO as a possible source of PRSP isolates. Because of the difference in design, possibility of bias, and lower level of evidence provided by the data from #200036, efficacy data from this study were analyzed separately. Tables 1 and 2 below summarize efficacy results across various populations for each study.

Table 1. Clinical response at TOC for Study 100039

Valid for Efficacy	All stratum	Moxifloxacin	157/182 (86%)
		Control	161/180 (89%)
		95% CI (Mantel-Haenszel)	(-8.9%, 4.2%)
		95% CI (Normal approx.)	(-10.5%, 4.1%)
	Severe stratum	Moxifloxacin	48/61 (78.7%)
		Control	39/49 (79.6%)
		95% CI (Normal approx.)	(-16.2%, 14.4%)*
Valid for Safety	All stratum	Moxifloxacin	168/249 (67%)
		Control	173/258 (67%)
		95% CI (Mantel-Haenszel)	(-7.5%, 8.7%)
		95% CI (Normal approx.)	(-8.1%, 9.0%)
	Severe stratum	Moxifloxacin	48/83 (57.8%)*
		Control	41/75 (54.7%)*
		95% CI (Normal approx.)	(-12.3%,18.7%)*
Microbiologically Valid for efficacy valid patients	All stratum	Moxifloxacin	66/80 (83%)
		Control	70/78 (90%)
		95% CI (Mantel-Haenszel)	(-17.2%, 4.1%)*
		95% CI (Normal approx.)	(-18.0%, 3.5%)*
	Severe stratum	Moxifloxacin	24/31 (77.4%)*
		Control	20/24 (83.3%)*
		95% CI (Normal approx.)	(-26.9%, 15.0%)*

* Calculated by the biostatistics reviewer.

Table 2: Clinical response for Study 200036.

Per protocol at TOC visit	All stratum	Moxifloxacin Control 95% CI	241/258 (93.4%) 239/280 (85.4%) (2.91 %, 13.19%)
	Severe stratum	Moxifloxacin Control 95% CI	119/129 (92.2%) 116/137 (84.7%) (0.0%, 15.2%)*
Per protocol at visit 21-28 days post therapy	All stratum	Moxifloxacin Control 95% CI	216/258 (83.7%) 208/280 (74.3%) (2.60%, 16.27%)
	Severe stratum	Moxifloxacin Control 95% CI	105/129 (81.4%) 97/137 (70.8%) (0.4%, 20.7%)*
Valid for Safety ITT at visit 21-28 days post therapy	All stratum	Moxifloxacin Control 95% CI	220/301 (73.1%) 209/321 (65.1%) (1.63%, 15.96%)
	Severe stratum	Moxifloxacin Control 95% CI	108/158 (68.4%) 98/163 (60.1%) (-2.2%, 18,7%)*
Microbiologically Valid at follow-up	All stratum	Moxifloxacin Control 95% CI	56/64 (87.5%) 53/71 (74.6%) (-0.21%, 25.91%)
	Severe stratum	Moxifloxacin Control 95% CI	32/37 (86.5%) 31/40 (77.5%) (-8.0%, 26.0%)*

* Calculated by the reviewer.

Inspection of Tables 1 and 2 shows consistently different results between the double-blinded study (#100039) and the open label study (#200036). Efficacy rates are generally similar across treatment groups in study #100039, with the exception of certain subpopulations (eg. microbiologically valid) where moxifloxacin efficacy is slightly lower than control. In study #200036, point estimates of efficacy rates for moxifloxacin are consistently about 10 points higher than those reported for control.

Revisiting the data in NDA 21-085 describing the efficacy of oral moxifloxacin for the treatment of CAP provides another means of assessing the data from study #200036. Table 3 below presents clinical efficacy in CAP for oral moxifloxacin compared with oral high-dose amoxicillin or clarithromycin, similar comparators to those used in study #200036.

Table 3. Clinical efficacy CAP due to *S. pneumoniae*: oral formulations

	Moxifloxacin 400 mg po q D	Control*
All CAP studies	80/89 (90%)	67/75 (89%)

*Control = amoxicillin 1000 mg po tid or clarithromycin 500mg po bid

Inspection of Table 3 shows that for the treatment of CAP, the results for oral moxifloxacin and comparator are similar to what was observed in intravenous study #100039. Efficacy rates are similar for the two treatment groups across most populations. The open-label design of study #200036 and the different pattern of efficacy data when compared with study #100039 or with results from the CAP studies in the NDA for the oral formulation makes the results of #200036 less central to the review of drug efficacy.

Results from study #100039 support the demonstration of efficacy of intravenous moxifloxacin in a manner consistent with what was observed for the oral formulation of the drug, except that there appears to be slightly lower efficacy for moxifloxacin among microbiologically evaluable patients with severe CAP. The results from study #200036 do not refute this overall finding of clinical efficacy for intravenous moxifloxacin in CAP.

Efficacy in patients with *S. pneumoniae* bacteremia

The evaluation of efficacy for intravenous moxifloxacin warrants consideration of those patients with more severe disease than would be treated with an oral formulation. As noted in table 1 above, there is a suggestion of somewhat lower efficacy rates for moxifloxacin than comparator in the subpopulation of microbiologically evaluable patients with severe disease. The MO analyzed data from patients with pneumococcal bacteremia as a means of better understanding the efficacy of intravenous moxifloxacin in this subpopulation. Patients with CAP and pneumococcal bacteremia are important to the understanding of drug efficacy for two reasons: 1) they represent the 'gold standard' of diagnostic criteria for pneumococcal pneumonia, and 2) they represent a category of severe disease for which the demonstration of drug efficacy is critical. Patients with pneumococcal pneumonia and bacteremia have a substantially higher mortality than those with pneumococcal infection confined to the lung.

Table 4 presents a summary of clinical efficacy rates in patients with pneumococcal bacteremia across all controlled, double-blinded studies of oral or intravenous moxifloxacin.

Table 4. Clinical efficacy in CAP patients with *S. pneumoniae* bacteremia from all controlled, double-blinded studies of oral or intravenous moxifloxacin

Study	Moxifloxacin 400 mg	Control
ORAL MOXIFLOXACIN		
Study 0119	1/1 (100%)	1/1 (100%)*
Study 0140	6/9 (67%)	10/10 (100%)**
INTRAVENOUS MOXIFLOXACIN		
Study 100039	9/10 (90%)	11/11 (100%)***
TOTAL	**16/20 (80%)**	**22/22 (100%)**

*Clarithromycin
**High dose amoxicillin
***Trovafloxacin or levofloxacin

Review of Table 4 shows that efficacy of moxifloxacin demonstrated in controlled, double-blinded trials of patients with CAP and pneumococcal bacteremia is markedly lower than efficacy observed with control agents. Penicillin or amoxicillin have long been drugs of choice for the treatment of pneumococcal infections. The increasing importance of penicillin resistance among clinical isolates of *S. pneumoniae* suggests that the effectiveness of these drugs may be waning. A drug that can be considered an adequate replacement for these agents should demonstrate comparable efficacy.

Efficacy in CAP due to penicillin-resistant *S. pneumoniae* (PRSP)
The data presented in Table 4 are important to the consideration of both moxifloxacin efficacy in the treatment of severe pneumococcal infections and efficacy in resistant pneumococcal infections. Consideration of a claim for efficacy in the treatment of infections due to PRSP warrants that efficacy in the treatment of pneumococcal infections due to susceptible strains be well characterized. As noted above, Table 4 raises issues regarding moxifloxacin success rates in patients with bacteremia, one of the most serious complications of pneumococcal pneumonia.

At the time of the submission of the NDA for oral moxifloxacin, the sponsor requested a claim for efficacy in the treatment of CAP due to PRSP. This was not approved for two reasons. One reason was that the small body of data regarding efficacy in bacteremic patients suggested low rates for moxifloxacin (Table 4, study 0140). The other was that there was a very small number of resistant pneumococcal isolates, and moxifloxacin efficacy observed in these infections was lower than was seen in pneumococcal infections in general. Table 5 below revisits these data, and demonstrates that, while sample sizes were extremely small, some question was raised regarding moxifloxacin efficacy in infections due to PRSP.

Table 5. Clinical efficacy of oral moxifloxacin in CAP: *S. pneumoniae* and PRSP

	Moxifloxacin 400 mg po q D	Control
CAP due to *S. pneumoniae* (all isolates)	80/89 (90%)	67/75 (89%)
CAP due to PRSP	6/8 (75%)	3/3 (100%)

For the purpose of reconsidering the claim for efficacy of moxifloxacin in CAP due to PRSP, the sponsor combined all PRSP isolates from studies of both the oral and intravenous formulations in US and ex-US studies. Those isolates identified in the US studies were tested for penicillin susceptibility using both e-test and broth dilution. All of these isolates met the criterion for penicillin resistance (MIC$\geq$ 2.0 mcg/ml) when tested using broth dilution, the standard criterion that defines penicillin resistance. Clinical efficacy for patients from whom this small number of organisms was isolated was observed to be 100%.

There were also PRSP isolates identified in ex-US studies. In these studies, only the e-test was used to assess penicillin resistance. Because 6 of the 7 isolates identified in these studies had MIC values by e-test $\leq$ 2.0 mcg/ml and were not tested by the reference method (broth dilution), they are not regarded as meeting the criteria of penicillin resistant. As has been noted in the Microbiology review, values obtained by the e-test method can differ from those obtained with the reference method by one dilution, and are therefore not reliable indicators of penicillin resistance for review purposes. There was one patient in the ex-US population with a PRSP isolate with a PCN MIC 6.0 mcg/ml by e-test(patient 10674/study 140) who may be regarded as having been infected with PRSP. This patient was a clinical failure.

Additional data from a study of oral moxifloxacin (#100224) were submitted in the four-month safety update. This study provided an additional six patients from whom a PRSP isolate was cultured and tested by both e-test and broth dilution. All six of these patients were clinical cures. Thus the total database from patients with CAP provides 13 PRSP isolates with a clinical cure rate of 12/13 (92.3%). These results are summarized below in Table 6.

Table 6. Clinical efficacy in patients with CAP due to PRSP

Study/Patient No.	Isolate	PCN MIC Etest	PCN MIC broth	Clinical response
100039(iv)/13007	*S. pneumoniae*	3.0	2.0	Resolution
100039(iv)/13025	*S. pneumoniae*	4.0	4.0	Resolution
100039(iv)/48013	*S. pneumoniae*	1.5	2.0	Resolution
100039(iv)/71001	*S. pneumoniae*	3.0	4.0	Resolution
D96-025(po)/4006	*S. pneumoniae*	2.0	2.0	Resolution
D96-026 (po)/248	*S. pneumoniae*	4.0	4.0	Resolution
140 (po)/10674	*S. pneumoniae*	6.0	-	Failure
100224 (po)/1012	*S. pneumoniae*	3.0	2.0	Resolution
100224 (po)/1019	*S. pneumoniae*	8.0	4.0	Resolution
100224 (po)/1028	*S. pneumoniae*	3.0	4.0	Resolution
100224 (po)/1032	*S. pneumoniae*	1.5	2.0	Resolution
100224 (po)/604001	*S. pneumoniae*	2.0	2.0	Resolution
100224 (po)/614002	*S. pneumoniae*	1.0	2.0	Resolution

The data presented regarding clinical efficacy of moxifloxacin in patients with CAP and pneumococcal bacteremia suggest that moxifloxacin is less effective than comparator agents. These data raise questions regarding the appropriateness of this drug for the treatment of severe pneumococcal pneumonia. With such questions outstanding, it would be premature to recommend approval of claims for efficacy in the treatment of pneumonia due to PRSP.

Efficacy in sinusitis due to penicillin-resistant *S. pneumoniae* (PRSP)

The sponsor has also submitted data to support a claim for efficacy of moxifloxacin in the treatment of patients with sinusitis due to PRSP. These data were submitted following discussions with the sponsor in which it was established that if a claim for PRSP in sinusitis were sought, it would be necessary to show efficacy for PRSP in CAP as well.. Data supporting drug efficacy in more serious resistant pneumococcal infections is warranted prior to the consideration of a resistance claim for a less serious infections. By pooling data from 3 oral and 2 intravenous studies of moxifloxacin in sinusitis, the sponsors provided data on 13 patients infected with PRSP. Overall efficacy observed for this population was 11/13 (85%). The sponsor has begun to accrue a database characterizing moxifloxacin efficacy in resistant pneumococcal infections, however questions raised about drug efficacy in patients with pneumococcal bacteremia suggest that this issue be addressed prior to approving any resistance claims.

Conclusion

Questions raised about drug efficacy in patients with pneumococcal bacteremia who received oral moxifloxacin arise again in patients who received the intravenous formulation. This is an important component of the evaluation of drug efficacy for any intravenous formulation, and the results presented here do not adequately establish efficacy in this subpopulation of seriously ill patients with pneumococcal pneumonia. Similar questions are raised by the observation of lower efficacy rates for moxifloxacin in the subpopulation of patients with severe CAP who were microbiologically evaluable. These findings call into question the approvability of intravenous moxifloxacin for CAP, and suggest that consideration of resistance claims can only occur after moxifloxacin efficacy in serious pneumococcal infection has been established.

Andrea Meyerhoff MD MSc DTMH
Medical Officer

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085/S-015
21-277/S-007

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	DUE DATE 10/18/03	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	DATED	RECEIVED
21-085/SE1-015 21-277/SE1-007 21-085/SE1-016 21-277/SE1-008	12/17/02	12/19/02

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:
New microorganism under the Community-Acquired Pneumonia and Acute Bacterial Sinusitis indications.

9. AMENDMENTS/DATES
BC 2/5/03

10. PHARMACOLOGICAL CATEGORY
Antibacterial

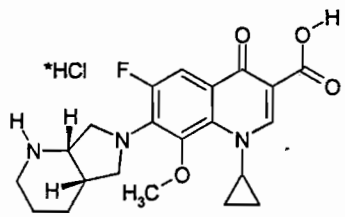
11. HOW DISPENSED
|X| Rx | | OTC

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



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

16. MEMORANDA
N/A

17. COMMENTS
These are efficacy supplements that do not provide for any chemistry changes. The environmental assessment for these applications is addressed in the amendment dated February 5, 2003. See page 2 for further details.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval.

19. REVIEWER

NAME	SIGNATURE	DATE OF DRAFT REVIEW
Dorota Matecka	*[signed electronically in DFS]*	2/24/03

20. CONCURRENCE: HFD-590/NSchmuff *[signed electronically in DFS]*

DFS CC LIST		L			L			
L = Action Letter	R	L	Dorota Matecka		L	Med:		PharmTox
R = Review	R	L	NSchmuff	R	L	PM		Micro
						Biopharm		

Review # 1
NDA 21-085/SE1-015 and SE1-016 (Avelox Tablets)
NDA 21-277/SE1-007 and SE1-008 (Avelox I.V.)

REVIEW NOTES

These prior approval efficacy supplements provide for the following changes in the indications of Avelox:

a) NDA 21-085/SE1-015 and NDA 21-277/SE1-007 propose to add Streptococcus pneumoniae (including penicillin-resistant strains, MIC penicillin > 2 μg/mL) to the list of microorganisms under the community acquired pneumonia indication (CAP); and

b) NDA 21-085/SE1-016 and NDA 21-277/SE1-008 propose to add Streptococcus pneumoniae (including penicillin-resistant strains, MIC penicillin > 2 μg/mL) to the list of microorganisms under the acute bacterial sinusitis (ABS).

The efficacy supplements do not require a chemistry manufacturing and controls (CMC) review because no CMC changes are made within these submissions. The only pertinent item to the CMC review of these supplements is the update on the environmental assessment (EA) status. The applicant has submitted an amendment dated February 2, 2003 requesting an exemption of an EA for these submissions. The applicant stated that the action on these applications would not result in increased use of an active moiety. Since these supplements provide for a modification of existing indications by including an additional organism to the list of microorganisms under these indications, this is a reasonable assertion. The applicant is requesting exemption of an environmental assessment for these submissions as per 21 CFR 25.31(a). The request is acceptable.

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/s/

Dorota Matecka
3/2/03 05:26:09 PM
CHEMIST

Norman Schmuff
3/3/03 07:09:10 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085 /S-015
21-277/S007

ENVIRONMENTAL ASSESSMENT and/or FONSI

ENVIRONMENTAL

Date: September 19, 2001

Name of Applicant/Petitioner: Bayer Corporation
Pharmaceutical Division

Address: 400 Morgan Lane
West Haven, CT 06516

The submission of an environmental assessment for the proposed action to distribute Avelox Tablets is not required.

As a result of our expected combined marketing and sales volumes from both Avelox Tablets and Avelox IV, the concentration of Avelox to enter the environment in the 5th year of marketing and sales of both products, will be below 1 part per billion. Thus, as per 21 CFR section 25.31(b), the submission of an environmental assessment is not required for this Avelox Tablet submission, NDA# 21-085/S-009.

As calculated by the formula in CDER's document, "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Application and Supplements," the concentration of Avelox entering the aquatic environment from the sale of all Avelox products, in the fifth year of marketing and sales, will be less than 1.0 part per billion.

Since the manufacture and distribution of Avelox tablets fits the requirements of 21 CFR 25.31(b) categorical exclusion, an environmental assessment is not being submitted.

Signature of Responsible Official
Gary Toczylowski
Director of Health, Environment
And Safety

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085/S-015
21-277/S-007

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

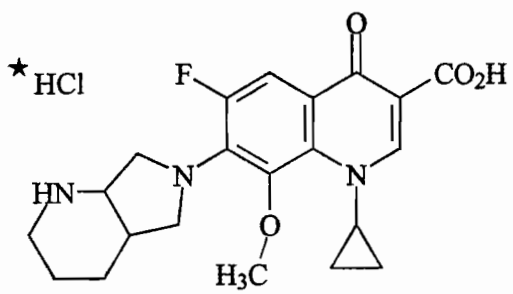
NDAs: 21-085/277 (SE1 015 & 007, respectively)
Type of Submission: Supplemental Submissions
Review Number: 1
Date of Submission: 12/18/02
Information to Sponsor: Yes ( ) No (X)

Sponsor: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Manufacturer of Drug Substance:
Bayer AG
D-51368 Leverkusen
Germany

Reviewer: Stephen G. Hundley, Ph.D, DABT
Pharmacology/Toxicology Reviewer
Division: Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 2/11/03

Drug Product: Avelox® Tablets, 400 mg and Avelox® I.V.
Generic Name: Avelox® (moxifloxacin hydrochloride)
Drug Substance: Moxifloxacin hydrochloride
Chemical Name: 1-Cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro -8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride
CAS#: 186826-86-8
Molecular Formula: $C_{21}H_{24}N_3FO_4 \bullet HCl$
Molecular Weight: 437.9
Molecular Structure:



PHARMACOLOGY/TOXICOLOGY COVER SHEET

Relevant INDs: 49,489 & 52,786

Drug Class: Antimicrobial Fluoroquinolone

Indication: Community Acquired Pneumonia (including penicillin-resistant *Streptococcus pneumoniae*)

Clinical Formulation: Tablets (400 mg) and Moxifloxacin HCl in NaCl for injection

Route of Administration: Oral and I.V. infusion

Proposed Use: 400 mg daily by tablets or I.V. infusion (60 minutes) for 7 to 14 consecutive days.

EXECUTIVE SUMMARY

Recommendations:

Approvability – The NDA submission is approvable from the perspective of nonclinical pharmacology and toxicology.

Nonclinical Studies – Additional nonclinical studies are not required.

Labeling – The sponsor's proposed label is acceptable with regard to the nonclinical pharmacology and toxicology portions of the label. No labeling changes to the nonclinical sections were proposed by the sponsor.

Summary of Nonclinical Findings:

Previously reviewed nonclinical toxicology studies with moxifloxacin submitted under NDAs 21-085 and 21-277 (Pharmacology/Toxicology Reviews issued 12/8/99 and 7/24/01) were considered sufficient to support the currently approved indications for Avelox®. Included in the list of approved indications is community acquired pneumonia (400 mg daily dosage for a period of 7 to 14 days). The current supplemental indication is for community acquired pneumonia to include penicillin-resistant *Streptococcus pneumoniae* and utilizes the currently approved dosing regimen. Therefore, no additional nonclinical toxicology studies and information were submitted or required for this supplemental indication.

EXECUTIVE SUMMARY

No additional Pharmacology/Toxicology NDA Review is provided beyond the Cover Sheet and Executive Summary.

Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Concurrence:

Kenneth Hastings, Dr. P.H., DABT
Pharmacology/Toxicology Supervisor & Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

cc:

HFD-590/CSO/S. Peacock
HFD-590/MO/R. Johann-Liang
HFD-590/MO/R. Roca
HFD-590/Biopharm/D. Chilukuri
HFD-590/Micro/P. Dionne
HFD-590/Chem/D. Matecka
HFD-590/Stat/K. Higgins

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/s/

Steve Hundley
2/13/03 02:44:47 PM
PHARMACOLOGIST

Kenneth Hastings
2/14/03 08:11:30 AM
PHARMACOLOGIST

Renata Albrecht
2/14/03 04:54:56 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085/S-015
21-277/S-007

STATISTICAL REVIEW(S)

Statistical Team Leader's Memorandum

TO: NDAs 21-085/S-015 and 21-277/S007 (12/18/02)

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

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

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1 Introduction

These supplemental NDAs dated 12/18/02 contain information from 9 community-acquired pneumonia studies, 7 of which are controlled studies. All of the controlled studies have been previously submitted and reviewed by a statistics reviewer (reviews dated 11/9/1999 for NDA 21-085 by Liji Shen, 10/16/2001 for NDA 21-277 by Qian Li, and 11/19/2002 by Karen Higgins for submission dated 9/11/02). The one previously submitted uncontrolled study (study D96-025) was reviewed by the medical and microbiology reviewers for NDA 21-085. Additional information for this NDA is the uncontrolled study 100224, which is briefly described below. 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 penicillin-resistant *Streptococcus pneumoniae* (PRSP) from these studies. Please see the medical and microbiology reviews for a more detailed review of this submission.

2 Background

These submissions contain additional information on the efficacy of moxifloxacin in the treatment of community-acquired pneumonia (CAP) caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP). Bayer submitted an NDA for this indication in December of 1998 with the Avelox Tablet, NDA 21-085. The NDA was approved in December of 1999. However, the PRSP claim was not included in the indication. In November 2000, Bayer submitted the I.V. NDA 21-277 containing the claim of PRSP. In January 2001, supplements to the tablet NDA were submitted for PRSP (S-009 and 011 for CAP and Sinusitis, respectively). However, these claims were withdrawn by Bayer in October 2001. In November 2001, the Avelox IV NDA was approved without the PRSP claim.

The current submissions contain information from 9 studies in CAP. Five of these studies contain patients with PRSP. The following table contains the study number, design of the study, number of patients with PRSP CAP, and information on when the completed study report was submitted to the Division. Note that the majority of the information given in the review is based on two submissions received from the sponsor based on queries from the division (E-mails dated 1/31/03 at 12:41 PM and 2/19/03 at 11:34 AM from Robin Christofordies).

Table 1: Summary of CAP studies

Study Number	Study Design*** (N on Avelox arm)	Number of PRSP Isolates on Avelox arm	When submitted
D96-025	Uncontrolled (N=254)	1	Submitted with NDA 21-085 (12/1998)
D96-026	Controlled (N=237)	1	Submitted with NDA 21-085 (12/1998)
0119	Controlled (N=224*)	0	Submitted with NDA 21-085 (12/1998)
0140	Controlled (N=203)	1**	Submitted with NDA 21-085 (12/1998)
100222	Controlled (N=253)	0	Submitted to IND 49489 (9/11/02)
100224	Uncontrolled, Ongoing (N=72)	13	Full study report not yet submitted
100039	Controlled (N=249)	4	Submitted with NDA 21-277 (11/2000)
100353	Controlled (N=167)	2	Submitted to NDA 21-277 (9/11/02)
200036	Controlled (N=301)	0	Submitted with NDA 21-277 (11/2000)

* An additional Avelox arm (N=229) was dosed at 200 mg QD for 10 days
**PRSP diagnosed based on E-test only
*** The controls were clarithromycin for studies D96-026, 0119, and 100222, amoxicillin for 0140, trovafloxacin or levofloxacin for 100039, ceftriaxone/cefuroxime axetil for 100353, and amoxicillin/clavulanate for 200036.

Studies D96-025, D96-026, 0119, 0140, 10022, and 100224 dosed at 400 mg QD orally for 10 days. Studies 100039 and 200036 dosed IV to oral at 400 mg QD for 7 – 14 days. Study 100353 dosed IV to oral at 400 mg QD for 7 – 10 days. Study 100224 focused enrollment on patients suspected of having *Streptococcus pneumoniae*.

Statistics reviews were completed on NDA 21-085 and NDA 21-277 and include reviews of studies D96-026, 0119, 0140, 100039, and 200036. A brief statistical review was completed on study 100353 and study 100222. A statistical review was not done on uncontrolled study D96-025. The new uncontrolled study 100224 is briefly described here.

Study 100224

Study 100224 is the only study not previously submitted to the Division. The title of 1000224 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." Note that 13 of the 21 CAP PRSP cases came from this one study. This study was enriched to find PRSP cases since only patients suspected of having CAP due to *Streptococcus pneumoniae* were to be enrolled.

The sponsor has provided only minimal information regarding the results as of the 10/01/02 cutoff date. As of this cutoff date, there were a total of 222 patients enrolled. Of these patients, 90 had documented *S. pneumoniae*. There were 72 valid for efficacy patients with documented *S. pneumoniae*, 20 of which had *S. pneumoniae* bacteremia and 13 of which had PRSP.

3 Efficacy for PRSP

There were a total of 21 valid for efficacy patients in 5 of the 9 studies with PRSP isolated from a blood culture, good quality sputum, or from a specimen obtained by bronchoscopy or open lung biopsy and confirmed using broth microdilution. Patients diagnosed with PRSP based on E-test only were excluded from the analysis.

All 21 patients were considered clinical and bacteriologic cures at the test of cure visit, as defined in the 5 protocols ranged from 7 to 30 days post-treatment. The following table contains the number of PRSP isolates for both the moxifloxacin and the control arms. Of the 21 moxifloxacin patients, only 2 had a bacteriologic outcome of eradicated, the remaining 19 had an outcome of presumed eradication based on clinical response. All 5 of the control PRSP patients had a bacteriologic outcome of presumed eradicated. Of the 21 moxifloxacin patients, 8 had PRSP bacteremia and 12 were considered as having severe disease.

Table 2: Number of patients in the valid for efficacy population with PRSP isolates

Study	Moxifloxacin	Control
D96-025	1	None
D96-026	1	1
100224	13	None
100039	4	3
100353	2	1
Total	**21**	**5**

Note that the controls had a cure rate of 100% though only levofloxacin, the treatment of 2 of the control subjects in study 100039, currently has an indication for PRSP. Also note that the vast majority of the data comes from study 100244 which had an enriched patient population.

Results are similar for the modified intent to treat (MITT) population which includes all patients with PRSP isolated at baseline regardless of their follow-up or compliance with the protocol. There are two additional patients with PRSP isolates in the moxifloxacin arms from studies 100039 and 100353 and 1 additional patient in the control arm from study 100039. These additional 3 patients were considered non-successes for both clinical and microbiologic outcome. Note that the sponsor considered missing or indeterminate outcomes as non-successes. However, the information on why a patient was considered a non-success was not provided. The clinical success rates for moxifloxacin and control are 91.3% (21/23) and 83.3% (5/6).

Table 3: Number of patients in the MITT population with PRSP isolates

Study	Moxifloxacin	Control
D96-025	1	None
D96-026	1	1
100224	13	None
100039	5	4
100353	3	1
Total	**23**	**6**

As stated earlier, only one drug, levofloxacin, currently has an indication for PRSP for CAP. The following table contains the data that was used to help support the levofloxacin approval along with similar data for moxifloxacin. The amount of information used for the approval of levofloxacin can be used as a threshold for other drugs that are studied for this indication. The comparison of the data from the levofloxacin NDA and this NDA are given in the following table. Note that the levofloxacin data also does not include any isolates confirmed only by E-test.

Table 4: Clinical efficacy versus Levofloxacin in valid for efficacy population

	Levofloxacin*** n/N (%) [95% CI]*	Moxifloxacin** n/N (%) [95% CI]*
All CAP studies: # with *S. pneumoniae*	245/250 (98%) [95.4, 99.4]	230/244 (94%) [90.6, 96.8]
All CAP studies: # with PRSP	15/15 (100%) [78.2, 1.00]	21/21 (100%) [83.9, 1.00]

* All confidence intervals were calculated using an exact method.
** Clinical success rates for Moxifloxacin MITT population are 252/324 (78%) and 21/23 (91%).
*** Levofloxacin rates are those reported in the levofloxacin label.

Note that if we use the lower bound of the 95% confidence interval for the levofloxacin PRSP cure rate as the threshold for PRSP (78.2%), we can see that the moxifloxacin confidence interval falls completely above this point. However, moxifloxacin would not make a similar threshold for the supportive information on *S. pneumoniae* (95.4%).

As stated above, of the 21 moxifloxacin subjects with PRSP, 8 (38%) had PRSP bacteremia and 12 (57%) had severe disease. These percentages are similar to what was seen with levofloxacin with 6 (40%) having PRSP bacteremia and 5 (33%) with severe disease.

4 Efficacy for *S. pneumoniae* and *S. pneumoniae* bacteremia

Clinical and bacteriological efficacy in the subset of patients with *Streptococcus pneumoniae* and with *Streptococcus pneumoniae* bacteremia are supportive information for the efficacy of patients with PRSP.

4.1 Streptococcus pneumoniae

The clinical results for the valid for efficacy patients with *Streptococcus pneumoniae* were similar across the studies and treatment arms with most studies having very high success rates. These results are given in the following table.

Results for the modified intent to treat population, which includes all patients with S. pneumoniae isolated at baseline regardless of their follow-up or compliance with the protocol, are lower, but again, similar across treatment arms. These results for clinical success are given in the following table.

Table 5: Clinical success rates at the test of cure for valid for efficacy and MITT patients with *Streptococcus pneumoniae*

	Valid for Efficacy			MITT		
Study	**Moxifloxacin n/N (%) [95% CI]****	**Control* n/N (%)**	**Difference (95% C.I.)****	**Moxifloxacin n/N (%) [95% CI]****	**Control* n/N (%)**	**Difference (95% C.I.)****
D96-025	13/14 (93%) [66.1, 99.8]	None	N/A	13/16 (81%) [54.4, 96.0]	None	N/A
D96-026	17/17 (100%)	18/19 (95%)	5.3 (-14.6, 25.5)	17/18 (94%)	18/22 (82%)	12.6 (-11.0, 34.6)
0119	14/15 (93%)	12/13 (92%)	1.0 (-25.7, 30.0)	18/30 (60%)	18/28 (64%)	-4.3 (-29.3, 21.4)
0140	35/42 (83%)	37/43 (86%)	-2.7 (-19.9, 13.6)	39/53 (74%)	40/53 (75%)	-1.9 (-19.2, 15.0)
100222	8/8 (100%)	6/8 (75%)	25.0 (-14.4, 60.0)	10/10 (100%)	8/10 (80%)	20.0 (-13.2, 52.5)
100224	72/72 (100%) [95.0, 100.0]	None	N/A	79/90 (88%) [79.2, 93.7]	None	N/A
100039	35/39 (90%)	36/40 (90%)	0.0 (-16.1, 15.5)	36/49 (73%)	37/53 (70%)	3.4 (-14.4, 21.4)
100353	9/10 (90%)	9/12 (75%)	15.0 (-21.5, 47.1)	9/20 (45%)	9/16 (56%)	-11.3 (-41.8, 22.3)
200036	27/27 (100%)	20/27 (74%)	25.9 (11.0, 46.3)	31/38 (82%)	23/36 (64%)	17.7 (-2.9, 37.7)

* The controls were clarithromycin for studies D96-026, 0119, and 100222, amoxicillin for 0140, trovafloxacin or levofloxacin for 100039, ceftriaxone/cefuroxime axetil for 100353, and amoxicillin/clavulanate for 200036.

** All confidence intervals were calculated using an exact method. Difference and 95% CIs were calculated as Moxifloxacin – Control.

The results for bacterial response were very similar to the clinical results reported above. Note that for patients without a bacterial response at the test of cure visit, their response is inferred based on the clinical response. Therefore these two outcomes, clinical and bacterial response, are quite often based on the same information which accounts for the similar results.

4.2 Streptococcus pneumoniae *bacteremia*

The results for the patients with *Streptococcus pneumoniae* bacteremia were varied across the studies, though the numbers of patients are small in this subset. The clinical results for both the valid for efficacy and modified intent to treat are given in the following table. The bacterial results are similar to the clinical results.

Table 6: Clinical success rates at the test of cure on subset of valid for efficacy and MITT patients with *Streptococcus pneumoniae* bacteremia

	Valid for Efficacy			MITT		
Study	**Moxifloxacin n/N (%) [95% CI]****	**Control* n/N (%)**	**Difference (95% C.I.)****	**Moxifloxacin n/N (%) [95% CI]****	**Control* n/N (%)**	**Difference (95% C.I.)****
D96-025	0	None	N/A	0	None	N/A
D96-026	0	0	N/A	0	0	N/A
0119	3/3 (100%)	3/3 (100%)	0.0 (-63.2, 63.2)	5/10 (50%)	5/7 (71%)	-21.4 (-60.1, 27.3)
0140	6/9 (67%)	10/10 (100%)	-33.3 (-65.5, 1.9)	6/10 (60%)	10/11 (91%)	-30.9 (-63.4, 7.8)
100222	1/1 (100%)	0/1 (0%)	1.0 (-55.3, 100.0)	1/1 (100%)	1/2 (50%)	50.0 (-67.0, 97.5)
100224	20/20 (100%) [83.2, 100.0]	None	N/A	20/26 (77%) [56.4, 91.0]	None	N/A
100039	9/10 (90%)	11/11 (100%)	-10.0 (-42.9, 18.9)	9/12 (75%)	11/16 (69%)	6.3 (-30.5, 38.3)
100353	3/4 (75%)	4/6 (67%)	8.3 (-46.4, 56.8)	3/6 (50%)	4/8 (50%)	0.0 (-49.2, 49.2)
200036	11/11 (100%)	7/10 (70%)	30.0 (-2.3, 61.9)	14/15 (93%)	10/17 (59%)	34.5 (3.5, 60.5)

* The controls were clarithromycin for studies D96-026, 0119, and 100222, amoxicillin for 0140, trovafloxacin or levofloxacin for 100039, ceftriaxone/cefuroxime axetil for 100353, and amoxicillin/clavulanate for 200036.

** All confidence intervals were calculated using an exact method. Difference and 95% CIs were calculated as Moxifloxacin – Control.

5 Overall Efficacy

The following table gives the overall clinical success rates for both the valid for efficacy and the MITT populations. The valid for efficacy results are not reported for study 100224 since it is currently ongoing. The results are fairly consistent across study and treatment arms. The current MITT results for study 100224 are similar to results seen in the other studies.

Table 7: Clinical success rates at the test of cure for the valid for efficacy and MITT patients

	Valid for Efficacy			MITT		
Study	**Moxifloxacin n/N (%)**	**Control* n/N (%)**	**Difference (95% C.I.)****	**Moxifloxacin n/N (%)**	**Control* n/N (%)**	**Difference (95% C.I.)****
D96-025	182/196 (93%)	None	N/A	190/254 (75%)	None	N/A
D96-026	184/194 (95%)	178/188 (95%)	0.2 (-4.3, 4.6)	190/237 (80%)	188/236 (80%)	0.5 (-6.7, 7.7)
0119	141/152 (93%)	141/153 (92%)	0.6 (-5.3, 6.5)	152/224 (68%)	157/222 (71%)	-2.9 (-11.4, 5.7)
0140	143/177 (81%)	159/185 (86%)	-5.2 (-12.8, 2.5)	154/200 (77%)	164/208 (79%)	-1.8 (-9.9, 6.2)
100222	195/204 (96%)	187/195 (96%)	-0.3 (-4.3, 3.7)	218/253 (86%)	233/265 (88%)	-1.8 (-7.6, 4.0)
100224	N/A***	None	N/A	191/222 (86%)	None	N/A
100039	157/182 (86%)	161/180 (89%)	-3.2 (-9.9, 3.5)	168/249 (67%)	173/258 (67%)	0.4 (-7.8, 8.6)
100353	90/108 (83%)	90/113 (80%)	3.4 (-6.5, 13.9)	93/167 (56%)	93/168 (55%)	0.3 (-10.3, 11.0)
200036	241/258 (93%)	239/280 (85%)	8.1 (2.9, 13.2)	243/301 (81%)	242/321 (75%)	5.3 (-1.1, 11.8)

* The controls were clarithromycin for studies D96-025, 0119, and 100222, amoxicillin for 0140, trovafloxacin or levofloxacin for 100039, ceftriaxone/cefuroxime axetil for 100353, and amoxicillin/clavulanate for 200036.

** Confidence intervals were calculated using a normal approximation to the binomial. Difference and 95% CIs were calculated as Moxifloxacin – Control.

*** Not available, study currently ongoing.

6 Conclusions

In general there is very little information regarding the efficacy of moxifloxacin in the treatment of patients with CAP due to PRSP. There were only 23 subjects with PRSP, with 13 of these subjects coming from an ongoing uncontrolled study.

However, the amount of information is similar to that used for the approval of CAP due to PRSP for levofloxacin. Furthermore, the results obtained are similar to those seen for levofloxacin.

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/s/

Karen Higgins
3/7/03 04:54:05 PM
BIOMETRICS

Aloka Chakravarty
3/10/03 10:58:27 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 21-085/S-015
21-277/S-007

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Section 16: Debarment Certification

Bayer hereby certifies under FD&C Act, Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Mary E. Taylor, MPH
Vice President, North America Regulatory Affairs
Bayer Corporation, Pharmaceutical Division

APPEARS THIS WAY
ON ORIGINAL

Section 16 **Debarment Certification**

Bayer hereby certifies under FD&C Act, Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Section 13: The following information is hereby provided pursuant to 21 CFR § 314.53(c):

Patent Number:	4,990,517
Expiration Date:	30 June 2009 (An application for extension of the patent term to 6 December 2011 was filed with the U.S. Patent and Trademark Office on 28 January 2000.)
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

Patent Number:	5,607,942
Expiration Date:	4 March 2014
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

Patent Number:	5,849,752
Expiration Date:	5 December 2016
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

The undersigned declares that Patent Numbers 4,990,517; 5,607,942; and 5,849,752 cover the formulations, compositions and/or methods of use of moxifloxacin. This product is the subject of this application for which approval is being sought.

Mary E. Taylor, MPH
Vice President, North America Regulatory Affairs
Bayer Corporation, Pharmaceutical Division

Section 14: Patent Certification

All investigations relied upon by Bayer in this NDA were conducted by or for Bayer using drug substance and drug product in accordance with the patents listed in the Patent Information section.

Please reference Section 13, Patent Information.

Section 13: The following information is hereby provided pursuant to 21 C.F.R. § 314.53(c):

Patent Number:	4,670,444
Expiration Date:	30 June 2009 (An application for extension of the patent term to 6 December 2011 was filed with the U.S. Patent and Trademark Office on 28 January 2000.)
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

Patent Number:	5,607,942
Expiration Date:	4 March 2014
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

Patent Number:	5,849,752
Expiration Date:	5 December 2016
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

The undersigned declares that Patent Numbers 4,990,517; 5,607,942; and 5,849,752 cover the formulations, compositions and/or methods of use of moxifloxacin. This product is the subject of this application for which approval is being sought.

Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs
Bayer Corporation

EXCLUSIVITY SUMMARY for NDA # 21-085/S-015 and NDA 21-277/S-007

Trade/Generic Name AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg and AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V, 400 MG/250ML

Applicant Name Bayer Corporation Pharmaceutical Division HFD-590

Approval Date February 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_ X__/ NO /___/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination

bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-085 moxifloxacin hydrochloride

NDA # 21-277 moxifloxacin hydrochloride in NaCl injection

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_ X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # D96-025
Investigation #2, Study # D96-026
Investigation #3, Study # 100224

Investigation #4, Study # 100039
Investigation #5, Study # 100353

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	D96-025	YES /_X__/	NO /___/
Investigation #2	D96-026	YES /_X__/	NO /___/
Investigation #3	100224	YES /_ __/	NO /_X__/
Investigation #4	100039	YES /_X__/	NO /___/
Investigation #5	100353	YES /_X__/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 21-085 Study # 100224, D96-025, D96-026

NDA # 21-277 Study # 100039, 100353

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	D96-025	YES /___/	NO /_X__/
Investigation #2	D96-026	YES /___/	NO /_X__/
Investigation #3	100224	YES /___/	NO /_X__/
Investigation #4	100039	YES /___/	NO /_X__/
Investigation #5	100353	YES /___/	NO /_X__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 3 , Study # 100224

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #3 100224

IND # 49,489 YES /_X__/ ! NO /___/ Explain:
52, 786

Investigation !

IND YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or

for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

SUSAN PEACOCK _____

Signature of Preparer Date
Title: REGULATORY PROJECT MANAGER

RENATA ALBRECHT, M.D.
Signature of Office or Division Director Date

cc:
Archival NDA
HFD-590/Division File
HFD-590/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Renata Albrecht
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING ISSUES IDENTIFIED

NDA 21-085/S-015/S-016
NDA 21-277/S-007/S-008

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides, Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Christoforides:

Please refer to your December 17, 2002, supplemental new drug applications submitted on 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-015
		S-016
AVELOX® I.V.(moxifloxacin hydrochloride in sodium chloride injection) 400 mg/250 ml	NDA 21-277	S-007
		S-008

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on February 16, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

- Environmental Assessment: Please submit an environmental assessment for your applications or a claim of categorical exclusion, as applicable.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

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/s/

Renata Albrecht
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-277

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Christoforides:

Please refer to your New Drug Application (NDA) 21-277 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avelox® (moxifloxacin hydrochloride in NaCl Injection) I.V.

We also refer to your April 1, 2002 and December 17, 2002 submissions, requesting a waiver of pediatric studies. The Pediatric Final Rule (21 CFR Parts 201, 312, 314 and 601; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule) is no longer in effect and therefore the provision in the regulation allowing the FDA to grant or deny waivers/deferrals no longer exists. However, the FDA still encourages sponsors to conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

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

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/s/

Renata Albrecht
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-015
NDA 21-085/S-016
NDA 21-277/S-007
NDA 21-277/S-008

Bayer Pharmaceutical Division
Attention: Robin Christoforides, Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mrs. 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-015
		S-016
AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V.	NDA 21-277	S-007
		S-008

Review Priority Classification: Standard (S)

Date of supplements: December 17, 2002

Date of receipt: December 18, 2002

These supplemental applications propose the following changes:

NDA number	**Supplement Number**	**Change**
NDA 21-085	S-015	Add " (including penicillin-resistant strains, MIC penicillin ≥ 2µg/mL)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Community Acquired Pneumonia.**
NDA 21-277	S-007	
NDA 21-085	S-016	Add " (including penicillin-resistant strains, MIC penicillin ≥ 2µg/mL)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Acute Bacterial Sinusitis.**
NDA 21-277	S-008	

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file these applications on February 16, 2003, in accordance with 21 CFR 314.101(a). If these applications are filed, the user fee goal date will be October 17, 2003.

All communications concerning these supplements 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 question, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, 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

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

/s/

Ellen Frank
1/13/03 02:52:48 PM
NDA 21-085/S-015, NDA 21-085/S-016, NDA 21-277/S-007, & NDA 21-277/S-008

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA# : 21-085/S-015 and NDA 21-277/S-007 Supplement Type (e.g. SE5): SE1

Stamp Date: December 18, 2002 Action Date: February 28, 2003

HFD-590 Trade and generic names/dosage form: AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg and AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V., 400 mg/250 mL.
Applicant: Bayer Corporation Pharmaceutical Division Therapeutic Class: 4030100

Indication(s) previously approved: Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Uncomplicated skin and Skin Structure Infections.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: Modification of the indication for Community Acquired Pneumonia to add " (including penicillin-resistant strains, MIC penicillin > 2µg/mL)" to *Streptococcus pneumoniae*

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- **X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min____	**kg____**	**mo.____**	**yr._0__**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr._16__**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- **X There are safety concerns**
- **X Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 02/28/2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Susan Peacock
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Susan Peacock
3/12/03 01:58:36 PM

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-085/S-015 NDA 21-277/S-007	Efficacy Supplement Type SE1	Supplement Number	
Drug: AVELOX® (moxifloxacin hydrochloride)		Applicant: Bayer Corporation Pharmaceutical Division	
RPM: Susan Peacock		HFD-590	Phone # 301-827-2173
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	10-23-03
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review N/A
❖ User Fee Information	
• User Fee	(X) Paid Paid previously to NDA 21-277
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	2/13/03 Filing Review
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NDA 21-085/S-009 September 28, 2001 WD NDA 21-277/S-011 September 28, 2001 WD
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None by FDA (X) Press Release by Applicant ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	See MO Review
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	7-17-02, 10-3-2000
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A

• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9-24-01, 3-6-03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	4-17-01, 3-3-03
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	SEE MO REVIEW
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	3-10-03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	10-01-01, 3-03-03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	SEE CMC REVIEW
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation **N/A**
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested **N/A**
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2-14-03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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

/s/

Susan Peacock
3/14/03 10:00:06 AM

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-085 /SE 1 - 009
- 011

Drug Avelox Tablets (moxifloxacin HCl tablets), 400mg Applicant Bayer

RPM Yoon Kong/ Valerie Jensen Phone (301) 827-2127

■ 505(b)(1)
☐ 505(b)(2) Reference listed drug

☐ Fast Track ☐ Rolling Review Review priority: ■ S ☐ P

Pivotal IND(s)

Application classifications:
Chem Class

Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary S-009/ 10-01-01
S-011/ 10-18-01
Secondary S-009/ 12-01-01
S-011/ 12-18-01

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■ User Fee Paid (data contained in NDA 21-277)
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☐ AP ☐ AE ■ NA
- Labeling & Labels
  FDA revised labeling and reviews..... N/A
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... Levaquin
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No
  Immediate container and carton labels ..... N/A
  Nomenclature review ..... N/A
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo)..... N/A

OC Clearance for approval..... N/A

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) – N/A ☐ Materials requested in AP letter

- Post-marketing Commitments N/A
  - Agency request for Phase 4 Commitments..... N/A
  - Copy of Applicant's commitments ..... N/A

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ■ No
  - Copy of Press Release or Talk Paper..... N/A

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)]..... N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... N/A

- Exclusivity Summary ..... N/A

- Debarment Statement X

- Financial Disclosure
  - No disclosable information ..... See MO Review
  - Disclosable information – indicate where review is located ..... See MO Review

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings ..... N/A
  - Date of EOP2 Meeting N/A
  - Date of pre NDA Meeting N/A
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting ..... N/A
  - Date of Meeting ..... N/A
  - Questions considered by the committee ..... N/A
  - Minutes or 48-hour alert or pertinent section of transcript ..... N/A

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....

- Clinical review(s) and memoranda ..... draft including X
- Safety Update review(s) ..... N/A
- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ■ Deferred
  Pediatric Page..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable
- Statistical review(s) and memoranda ..... N/A
- Biopharmaceutical review(s) and memoranda..... N/A
- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A
- Microbiology (efficacy) review(s) and memoranda X
- DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies ..... N/A

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda ..... N/A
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- DMF review(s) ..... N/A
- Environmental Assessment review/FONSI/Categorical exemption ..... See CMC Review
- Micro (validation of sterilization) review(s) and memoranda ..... N/A
- Facilities Inspection (include EES report)
  Date completed N/A ..... ☐ Acceptable ☐ Not Acceptable
- Methods Validation ..... N/A ☐ Completed ☐ Not Completed
  .....

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... N/A

- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(203) 812-2112

3. PRODUCT NAME
AVELOX® TABLETS

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
YES
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.*
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

*USER FEE PREVIOUSLY PAID TO NDA 21-277.

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
NDA 21-085

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, on reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robin M Christoforides	Robin M. Christoforides Associate Director, Regulatory Affairs	12/17/02

FORM FDA 3397 (5/98)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(203) 812-5172

3. PRODUCT NAME
AVELOX® Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. YES

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO NDA 21-277 (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
NDA 21-085

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, on reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew S. Verderame	Andrew S. Verderame Associate Director, Regulatory Affairs	December 14, 2000

FORM FDA 3397 (5/98)

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

Name of Drug Product	NDA Number	Supplement Number
AVELOX® (moxifloxacin hydrochloride) Tablets, 400 mg	NDA 21-085	S-015
		S-016
AVELOX® (moxifloxacin hydrochloride in NaCl injection) I.V.	NDA 21-277	S-007
		S-008

Applicant: Bayer Corporation Pharmaceutical Division

Date of Application: December 17, 2002
Date of Receipt: December 18, 2002
Date of Filing Meeting: January 31, 2003
Filing Date: February 16, 2003

Indication(s) requested: PRSP in CAP and ABS

NDA number	Supplement Number	Change
NDA 21-085	S-015	Add " (including penicillin-resistant strains, MIC penicillin ≥ 2μg/mL)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Community Acquired Pneumonia.**
NDA 21-277	S-007	
NDA 21-085	S-016	Add " (including penicillin-resistant strains, MIC penicillin ≥ 2μg/mL)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Acute Bacterial Sinusitis.**
NDA 21-277	S-008	

Type of Application: Full NDA _____ Supplement ____X__SE1____
(b)(1) ____X_____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S__X_____ P_____
Resubmission after a withdrawal or refuse to file ___X____
Chemical Classification: (1,2,3 etc.)_N/A_____
Other (orphan, OTC, etc.)_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: _____ Waived (e.g., small business, public health) ___ _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES___X____ NO_____
User Fee ID#____N/A_____
Clinical data? YES ____X___ NO _____ Referenced to NDA# _21-085/S-009 & 21-085/S-011_____
Date clock started after UN _____

User Fee Goal date: _18 October 2003_____

Action Goal Date (optional) _____

NDA 21-085/S-015 and NDA 21-277/S-007	CAP	End of February
NDA 21-085/S-016 and NDA 21-277/S-008	ABS	June

- Does the submission contain an accurate comprehensive index? (YES) NO
- Form 356h included with authorized signature? (YES) NO
  If foreign applicant, the U.S. Agent must countersign.
- Submission complete as required under 21 CFR 314.50? (YES) NO
  If no, explain:
  Claim for categorical exclusion as required under 21 CFR 314.50(d)(1)(iii) not submitted 17-Dec-2002; was submitted 5-Feb-2003
- If electronic NDA, does it follow the Guidance? (YES) NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO (NA)
- Patent information included with authorized signature? (YES) NO
- Exclusivity requested? YES; If yes, _____years (NO)

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? (YES) NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."
- Financial Disclosure included with authorized signature? (YES) NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested: [N/A]
- Field Copy Certification (that it is a true copy of the CMC technical section)? [N/A] YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? (YES) NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date_____ (NO)
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s)__ 7/17/00 and 10/03/00_____ NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? (YES) NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES (NO)

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO (NA)

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO (NA)

Advisory Committee Meeting needed? YES, date if known _____ (NO)

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES (NO) N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES (NO)
  If no, did sponsor submit a complete environmental assessment? YES (NO)
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES (NO)
  Claim for categorical exclusion as required under 21 CFR 314.50(d)(1)(iii) not submitted 17-Dec-2002; was submitted 5-Feb-2003

- Establishment Evaluation Request (EER) package submitted? YES (NO) N/A

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES (NO) N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 31, 2003

BACKGROUND:

NDA 21-085 for Avelox Tablets was approved December 10, 1999; indications included Community Acquired Pneumonia (CAP) and Acute Bacterial Sinusitis (ABS). NDA 21-277 for Avelox IV was approved November 30, 2001; indications included CAP and ABS.

NDA 21-085/S-009 and NDA 21-085/S-011 were filed on January 30, 2001, and February 16, 2001, respectively. These supplemental new drug applications proposed the following changes:

- Add "(including penicillin-resistant strains, MIC penicillin ≥ 2µg/ml)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Community Acquired Pneumonia** (NDA 21-085/S-009).

- Add "(including penicillin-resistant strains, MIC penicillin ≥ 2µg/ml)" to *Streptococcus peumoniae* in **INDICATIONS AND USAGE, Acute Bacterial Sinusitis** (NDA 21-085/S-011).

They were withdrawn by Bayer on September 28, 2001.

ATTENDEES: Rosemary Johann-Liang, Dorota Matecka, Stephen Hundley, Peter Dionne, Dakshina Chilukuri, Ellen Frank, Rigoberto Roca, Shukal Bala, Karen Higgins, Philip Colangelo

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Rosemary Johann-Liang
Secondary Medical:	Rigoberto Roca
Statistical:	Karen Higgins
Pharmacology:	Steven Hundley
Chemist:	Dorota Matecka
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Dakshina Chilukuri
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	Peter Dionne
DSI:	N/A
Project Manager:	Susan Peacock
Other Consults:	N/A

Per reviewers, all parts in English, or English translation? YES_X___ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES_____NO__X_____

MICROBIOLOGY CLINICAL – File____X_____ Refuse to file_____

STATISTICAL – File ___X_____ Refuse to file _____

BIOPHARMACEUTICS – File ____X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____NO __X_____

PHARMACOLOGY – File ___X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES___N/A?X__NO_____ File__X___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

__X_____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

Susan Peacock
Regulatory Project Manager
HFD-590

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Susan Peacock
2/13/03 08:53:24 AM
CSO

Susan Peacock
2/13/03 08:59:05 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-085/S-009
NDA 21-085/S-011

Bayer Corporation
Attention: Andrew Verderame
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

We received your September 28, 2001, correspondence on September 28, 2001, notifying us that you are withdrawing your unapproved supplemental new drug applications for Avelox (moxifloxacin hydrochloride) Tablets. These supplemental new drug applications were filed on January 30, 2001 (NDA 21-085/S-009) and February 16, 2001 (NDA 21-085/S-011).

These supplemental new drug applications proposed the following changes:

- Add "(including penicillin-resistant strains, MIC penicillin $\geq 2\mu g/ml$)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Community Acquired Pneumonia** (NDA 21-085/S-009)
- Add "(including penicillin-resistant strains, MIC penicillin $\geq 2\mu g/ml$)" to *Streptococcus peumoniae* in **INDICATIONS AND USAGE, Acute Bacterial Sinusitis** (NDA 21-085/S-011).

In accordance with 21 CFR 314.65, these supplemental applications are withdrawn as of September 28, 2001. This withdrawal does not prejudice refiling of these applications. You may reference information contained in these withdrawn applications in any future submission.

If you have any questions, call Yoon J. Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, 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

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

/s/

Ellen Frank
3/13/02 11:21:23 AM
NDA 21-085/S-009 and NDA 21-085/S-011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-085/S-009

PRIOR APPROVAL SUPPLEMENT

Bayer Corporation
Pharmaceutical Division
Attention: Andrew Verderame
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Mr. Verderame:

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

Name of Drug Product: Avelox® (moxifloxacin hydrochloride) 400 mg Tablets

NDA Number: 21-085

Supplement Number: S-009

Review Priority Classification: Standard (S)

Date of Supplement: November 30, 2000

Date of Receipt: December 1, 2000

This supplement proposes the following change(s):

Add " (including penicillin-resistant strains, MIC penicillin ≥ 2 μg/ml)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Community Acquired Pneumonia.**

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 30, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 1, 2001 and the secondary user fee goal date will be December 1, 2001.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the

date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division 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: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Valerie Jensen, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Ellen C. Frank, 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

/s/

Ellen Frank
1/25/01 12:20:24 PM
NDA 21-085/S-009

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-085/S-011

PRIOR APPROVAL SUPPLEMENT

Bayer Corporation
Attention: Andrew Verderame
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

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

Name of Drug Product: Avelox® (moxifloxacin hydrochloride) 400 mg Tablets

NDA Number: 21-085

Supplement Number: S-011

Review Priority Classification: Standard (S)

Date of Supplement: December 14, 2000

Date of Receipt: December 18, 2000

This supplement proposes the following change(s):

Add "(including penicillin-resistant strains, MIC penicillin ≥ 2 μg/mL)" to *Streptococcus pneumoniae* in **INDICATIONS AND USAGE, Acute Bacterial Sinusitis.**

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 18, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 18, 2001 and the secondary user fee goal date will be December 18, 2001.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt

of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division 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: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Valerie Jensen, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Ellen C. Frank, 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

APPEARS THIS WAY
ON ORIGINAL

/s/

Ellen Frank
1/25/01 12:22:47 PM
NDA 21-085/S-011

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 27, 2001

To: Andrew Verderame	**From:** Yoon J. Kong, Pharm.D.
Company: Bayer Corporation	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** (301) 827-2475
Phone number: 203-812-5172	**Phone number:** (301) 827-2127
Subject: Avelox NDA 21-085,S-009/S-011 (PRSP)	
Total no. of pages including cover: 2	
Comments:	

Document to be mailed: ☐ YES ☑ NO

Dear Andy,

Pursuant to our teleconference on September 25, 2001, we have the following comments to fax regarding Study 200036.

1. Compared to the double-blind comparative studies in which the efficacy of moxifloxacin was shown to be comparable to the efficacy of the control regimen, the results of this study appear inconsistent with those findings. Specifically, the efficacy of moxifloxacin in this open-label trial is reported to be numerically higher (up to 10%) in most of the analyses. Please comment on this apparent inconsistency.

2. In Study 100039 there were approximately 30% of patients classified as severe and approximately 40% classified as microbiologically-evaluable patients. In Study 200036 approximately 50% of patients classified as severe, yet only 20% classified as microbiologically-evaluable. The presumption would be that patients classified as severe would be patients with bacterial infections, therefore, the lower rate of microbiological documentation in Study 200036 is surprising. Please comment on the differences.

3. **In Study 100039 the microbiological outcome for moxifloxacin is numerically lower compared to the control. In Study 200036, the microbiological outcome is numerically is higher. Please comment on these findings.**

If you have any questions or concerns regarding this fax, please contact me @ (301) 827-2127.

Thank you.

Yoon Kong, Pharm.D.

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

/s/

Yoon Kong
9/28/01 03:45:44 PM
CSO

Already ok'd by Dr. Albrecht and faxed to company 092801. Thanks..

Rigoberto Roca
10/1/01 12:29:33 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM

DATE: August 17, 2000

TO: Andrew Verderame
Associate Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(203) 812-5172
(203) 812-5029(fax)

FROM: Valerie Jensen RPh., Project Manager
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Plans for a supplemental new drug application to add penicillin resistant strains of *Streptococcus pneumoniae* as an approved pathogen under the Acute Bacterial Sinusitis indication in the package insert for Avelox ™.

BACKGROUND: NDA 21-085 for Avelox, moxifloxacin HCl 400mg tablets, was approved on December 10th, 1999. Bayer sent a proposal for a supplemental new drug application for the addition of penicillin resistant strains of *S. pneumoniae* as an approved pathogen under the Acute Bacterial Sinusitis indication along with questions to the Division regarding this proposal on May 1, 2000. Bayer requested a teleconference in the May 1, 2000 submission in order to discuss the Division's answers to the two questions contained in the submission.

The questions which were contained in the May 1, 2000 submission are duplicated below along with the Division's responses to these questions.

Question 1):

Is the body of data presented in this package (with the two Sinusitis Medical reports from which the data are obtained to be included in the formal supplement) sufficient to achieve approval of Acute Bacterial Sinusitis caused by PRSP? Bayer can provide additional details, wherever possible, to the Division to aid in the answer of this question.

Response:

Among the elements to be included in an application such as the one proposed, is demonstration of clinical efficacy in infections due to penicillin sensitive *S. pneumoniae* as well as penicicillin resistant *S. pneumoniae.* We would request that the entire case report forms for each of these fifteen isolates be included with the submission.

Question 2)

Should the draft labeling in the Clinical Studies section to be submitted with the formal supplement include a discussion of the Sinusitis PRSP isolates as 15 or 12 in total?

We would consider this an issue which would be decided upon during the review of the submission.

Please call Valerie Jensen R.Ph., if you have any questions related to this correspondence at (301) 827-2374.

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
Meyerhoff/MO
Roca/Medical Team Leader
Dionne/Micro. Reviewer
ShenL/Stat. Reviewer
Meyer/Biopharm. Reviewer

Distribution:
HFD-590/Jensen/PM
HFD-590/Division File
HFD-590/Meyerhoff/MO
NDA 21-085

APPEARS THIS WAY
ON ORIGINAL

HFD-590
Jensen

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

MEMORANDUM

DATE: September 25, 2000

TO: Andrew Verderame
Associate Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(203) 812-5172
(203) 812-5029(fax)

FROM: Valerie Jensen RPh., Project Manager
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Preparation for Teleconference scheduled for October 6, 2000

BACKGROUND: NDA 21-085 for Avelox™, moxifloxacin HCl 400mg tablets, was approved on December 10th, 1999. Bayer sent a proposal for a supplemental new drug application for the addition of penicillin- resistant strains of *S. pneumoniae* as an approved pathogen under the Acute Bacterial Sinusitis indication along with questions to the Division regarding this proposal on May 1, 2000. Bayer requested a teleconference in the May 1, 2000 submission in order to discuss the Division's answers to the two questions contained in the submission. A facsimile was sent to Bayer on August 17, 2000 in response to the May 1, 2000 submission. A submission dated August 23, 2000 was received from Bayer which again informed the Division of Bayer's plans to submit a supplement for the treatment of Acute Bacterial Sinusitis caused by penicillin resistant strains of *S. pneumoniae*. A teleconference is planned for October 6, 2000.

Please refer to the correspondence dated August 23, 2000 notifying us of your intent to submit the supplemental application for the treatment of Acute Bacterial Sinusitis (ABS) caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP) to NDA 21-085 for Avelox™. Several factors regarding a PRSP claim in Acute Bacterial Sinusitis were discussed in recent Inter-Divisional meetings and are summarized as follows:

For a PRSP claim in Acute Bacterial Sinusitis, it may be important to demonstrate the efficacy of the drug in more serious indications first (i.e. CAP due to PRSP including bacteremic /severely ill cases) for the following reasons:

1. A claim for PRSP in ABS could result in practitioners extrapolating efficacy against PRSP from a less serious (approved) indication (e.g.ABS) to other more serious (unapproved) indications (e.g. CAP) where efficacy has not been demonstrated.

2. Although ABS is typically not a serious disease, rare, serious complications of ABS can occur (e.g., meningitis, brain abscess, or cavernous sinus thrombosis) and evidence must be available for efficacy in more serious indications.

The issue of indications that merit approval for resistant organisms remains a subject of intense discussion within the Division. In this regard we will probably address the following during our scheduled teleconference:
Does Bayer intend to pursue a claim for PRSP in CAP?
Does Bayer intend to provide additional efficacy in bacteremic PRSP infections?

Please call Valerie Jensen R.Ph., if you have any questions related to this correspondence at (301) 827-2374.

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
Meyerhoff/Medical Officer
Roca/Medical Team Leader
Navarro/Medical Officer

Distribution:
HFD-590/Jensen/PM
HFD-590/Division File
HFD-590/Meyerhoff/MO
NDA 21-085
HFD-590/Roca/Medical TL
HFD-590/Navarro/MO

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELECONFERENENCE

DATE OF TELECONFERENCE: July 17, 2000

APPLICATION: [redacted]

DRUG: AVELOX® (moxifloxacin hydrochloride) IV Solution

SPONSOR: Bayer Corporation
Pharmaceutical Division

SUBJECT: Pre-NDA meeting

SPONSOR ATTENDEES:
Paul MaCarthy, M.D., Medical Affairs
Deborah Church, M.D., Medical Affairs
Shurjeel Choudhri, M.D., Medical Affairs
Barbara Painter, Ph.D., Microbiology
Ed Huguenel, Ph.D., Project Management
John Lettieri, Ph.D., Clinical Pharmacology
Pamela Gilles, Ph.D., Preclinical
Dan Haverstock, Ph.D., Statistics
Dennis Devonshuk, NDA Support Services
Charles Hobbs, Data Systems
Robin Christoforides, Regulatory
Andy Verderame, Regulatory

FDA ATTENDEES:
Sandra Kweder, M.D., Acting Director, ODE IV
Renata Albrecht, M.D., Acting Director, DSPIDP
Rigoberto Roca, M.D., Medical Team Leader
Andrea Meyerhoff, M.D., Medical Officer
Leonard Sacks, M.D., Medical Officer
Eileen Navarro, M.D., Medical Officer
Phillip Colangelo, Pharm.D., Ph.D., Clin. Pharm.& Biopharm. Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Liji Shen, Ph.D., Statistical Reviewer
Joette Meyer, Pharm.D., Clin. Pharm. & Biopharm Reviewer
Funmi Ajayi, Ph.D., Clin. Pharm. & Biopharm Team Leader
John Powers, M.D., Medical Officer

NDA 21-277

Brad Leissa, M.D., Medical Team Leader
Kenneth Hastings, Ph.D., Pharm-tox Team Leader
Karen Higgins, Ph.D., Statistical Team Leader
Ed Cox, M.D., Medical Reviewer
David Roeder, Acting Assoc. Director for Regulatory Affairs, ODE IV
Valerie Jensen, R.Ph., Project Manager

BACKGROUND:

Bayer requested a teleconference with the Division of Special Pathogen and Immunologic Drug Products to discuss issues regarding the planned November, 2000 submission of NDA 21-277 for Avelox™ IV Solution. Avelox™ IV Solution has been studied under [redacted]. Bayer also asked for a separate pre-NDA CMC teleconference which was held on August 4, 2000. Bayer sent a background package dated June 22, 2000 in preparation for the pre-NDA teleconference held on July 17, 2000. A separate submission entitled, "Summary of Cardiac Safety" was submitted on June 30, 2000 in preparation for this July 17, 2000 teleconference. A facsimile was sent to Bayer on July 14, 2000 in response to Bayer's June 22 and June 30, 2000 submissions. Since the data regarding safety and efficacy from the Avelox™ IV studies were not yet available at the time of the teleconference on July 17th, 2000, a third pre-NDA meeting is scheduled for October 3, 2000. The points for discussion which were used to facilitate the meeting are duplicated below. Division comments are duplicated below in italics.

DISCUSSION:

Item (1) from facsimile sent by the Division to Bayer on July 14, 2000 is as follows:

> With respect to section 6 of the table of contents of the planned NDA submission, human pharmacology and bioavailability/bioequivalence studies, we understand that you plan to submit two studies evaluating the absolute bioavailability of moxifloxacin. Study 0136 evaluates a 100 mg oral and intravenous dose, which is lower than the clinically relevant dose. Study 0139 evaluates the proposed 400 mg intravenous dose in relation to the approved 400 mg oral dose. The results of study 0139 show that the two formulations do not have the same rate and extent of systemic exposure. Following intravenous administration of moxifloxacin 400 mg, the mean Cmax is approximately 45% higher than the mean Cmax for the same dose administered orally.
>
> We request that you address the findings of Study 0139 in the context of the planned NDA submission, with focus on establishing the safety profile of moxifloxacin intravenous 400mg.

Item (2) from July 14, 2000 facsimile is as follows:

> The pre-meeting background package does not seem to adequately address the potential Cmax for a repeated IV dose of 400mg. Since the Cmax was the parameter most strongly associated with prolongation of the QT interval, this would be one item of concern. If the Cmax from a 400 mg dose IV is found to be substantially higher than from the corresponding oral dose, the risk/benefit analysis of each indication will be considered separately.

The Division advises Bayer that since the mean Cmax is higher following IV administration of moxifloxacin than it is for the same dose following oral administration, this may have implications for the strategy of Bayer's NDA submission for the IV formulation regarding what this submission tells us about the safety profile of the IV formulation.

Bayer states that over 550 patients were treated with moxifloxacin in the clinical trials. Bayer estimates that about half of the patients given moxifloxacin have blood levels associated with EKG data. Bayer states that the background submission for the pre-NDA meeting scheduled for October 3, 2000 will include clean data and analyses and we will plan to discuss what the data show during the October 3, 2000 pre-NDA meeting. Bayer also states that multiple 400mg dose data will be included.

The Division states that it will not be determined a priori whether indications may or may not be granted. The overall risk-benefit for each indication will be determined once the data are available and reviewed.

Item (4) from facsimile sent July 14, 2000 is as follows:

> Because the Special Summary of Cardiac Safety was only received quite recently, we request that you present your submission plans for this part of the NDA at the pre-NDA meeting. We have concerns about commenting on the adequacy of the cardiac safety analysis without having the data to evaluate.

Bayer agrees that the data will be submitted with the background information sent in preparation for the October 3, 2000 pre-NDA meeting and that the plans for this submission will be discussed in more detail during the October 3, 2000 meeting.

Item (5) from facsimile sent July 14, 2000 is as follows:

> We note that Study 100039 stratified patients according to disease severity. We would like to know the following:
>
> (a) the number of patients enrolled who met the criteria of severe disease, and

(b) the number of patients enrolled who were bacteremic. Efficacy data from a small number of patients with *S. pneumoniae* bacteremia in NDA 21-085 suggested that the efficacy profile of moxifloxacin in patients with pneumococcal bacteremia and/or more severe disease be better characterized

Bayer estimates that 30% of patients enrolled were classified as having severe disease. Bayer states that there are 45 cases of bacteremia in the US study.

The pediatric development plan for Avelox IV was discussed. As of April 1, 1999, 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 (*21 CFR 314.55*). Submissions dated December 2, 2000 or later will be required to provide pediatric data unless a waiver or deferral is requested in the submission. The Division will agree to defer the study of Avelox IV in pediatric patients and Bayer plans to request a deferral of pediatric studies in the submission of NDA 21-277.

Item (7) from facsimile dated July 14, 2000 is as follows:

> The data definition tables displayed in the pre-NDA meeting briefing package do not cover the completed information of study 100039. Please plan to submit in the data sets regarding efficacy the reason for discontinuation, dose, and evaluability.

Bayer agrees with this request.

Item (8) from the July 14, 2000 facsimile is as follows:

> We request that the safety database be presented in two parts:
> (a)safety data from patients enrolled in North American centers, and
> (b)safety data from patients enrolled in all centers.

Bayer agrees that the North American data will be analyzed separately.

Item (10) from the July 14, 2000 facsimile is as follows:

[redacted]

Bayer agrees with this plan.

Item (11) from the July 14, 2000 facsimile is as follows:

> The microbiology section should include a line listing for each patient in the clinical trial. This listing should include patient ID number, study number, visit day the isolate was detected, species of the isolate detected, the drug the patient was receiving, the MIC of the isolate to moxifloxacin and to comparator, clinical outcome and bacteriological outcome. An example of what this listing could look like is below:

Patient#	Study#	Visit#	Organism Detected	Study Drug	Moxi MIC	Comp. MIC	Clin. Outcome	Bact. Outcome
1204	100039	Visit 1(Screening)	*S. pneum.*	Moxi	0.25	1.0	Cured	Eradic.
1343	100039	Visit 3(TOC)	*S.pneum.*	Levo.	0.5	8.0	Failed	Persist.

Bayer plans to send in a "sham" dataset in mid-August in SAS JMP format.

Item (3) from Bayer's June 22, 2000 submission is as follows:

> The methodology for Study 100039 calls for all ECG tracings to be sent to a central, expert facility (GDXI) for interpretation and calculation of the relevant intervals such as the QT and QTc. All ECGs submitted to GDXI are reviewed by one Cardiologist who manually determines the QT and QTc intervals using a standardized database. This approach was chosen to ensure that the same methodology would be used to interpret all ECGs obtained during the trial and to minimize the issue of inter-observer variability. Although the ECGs have been interpreted, centrally, Bayer has also collected ECG interpretation data from the sites themselves. The data from the sites have been collected for information purposes only and will not be coded or cleaned. We will be suppressing this data from submission since it will not be used in any of the analyses for this study. Does the agency agree to this approach?

In addition to the centrally-interpreted data, the Division would like to have the raw data submitted so that in case there is a question about a particular patient's data, the raw ECG interpretation data from the sites may be looked at.

Signature, minutes preparer:_____ **Date:**_____

Conference Chair:_____ **Date:**_____

NDA 21-277

Concurrence:
Sandra Kweder, MD, Acting Director,
ODE IV
Renata Albrecht, MD, Acting Director, DSPIDP
Rigoberto Roca, MD, Medical Team Leader
Andrea Meyerhoff, MD, Medical Officer
Leonard Sacks, MD, Medical Officer
Eileen Navarro, MD, Medical Officer
Phillip Colangelo, Pharm.D., Ph.D.,
Clin. Pharm.& Biopharm. Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Liji Shen, Ph.D., Statistical Reviewer
Joette Meyer, Pharm.D., Clin. Pharm. & Biopharm Reviewer
Funmi Ajayi, Ph.D., Clin. Pharm. & Biopharm Team Leader
John Powers, MD, Medical Officer
Brad Leissa, MD, Medical Team Leader
Kenneth Hastings, Ph.D., Pharm-tox
Team Leader
Karen Higgins, Ph.D., Statistical Team Leader
Ed Cox, MD, Medical Reviewer
David Roeder, Acting Assoc. Director for Regulatory Affairs, ODE IV

Distribution:

HFD-590/Jensen/PM
HFD-590/Division File

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/s/

Renata Albrecht
5/7/01 03:58:22 PM
for Sandra Kweder

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RECORD OF MEETING

DATE OF MEETING:	October 3, 2000
APPLICATION:	[redacted]
DRUG:	AVELOX® (moxifloxacin hydrochloride) IV Solution
SPONSOR:	Bayer Corporation Pharmaceutical Division
SUBJECT:	Pre-NDA meeting
SPONSOR ATTENDEES:	Carl Calcagni, R.Ph., Vice President Regulatory Affairs Paul MaCarthy, M.D., Vice President, Medical Affairs Deborah Church, M.D., Director, Anti-Infective Medical Affairs Shurjeel Choudhri, M.D., Medical Affairs Barbara Painter, Ph.D., Microbiology Ed Huguenel, Ph.D., Project Management John Lettieri, Ph.D., Clinical Pharmacology Alan Hollister, M.D., Ph.D., Clinical Pharmacology Pamela Gilles Ph.D., Preclinical Friedrich Jekat, Ph.D., Toxicology Dan Haverstock, Ph.D., Statistics Robin Christoforides, Regulatory Affairs Andy Verderame, Regulatory Affairs
FDA ATTENDEES:	Sandra Kweder, M.D., Deputy Director, ODE IV Renata Albrecht, M.D., Acting Director, DSPIDP Rigoberto Roca, M.D., Medical Team Leader Andrea Meyerhoff, M.D., M.Sc., D.T.M.H. Medical Officer Leonard Sacks, M.D., Medical Officer Eileen Navarro, M.D., Medical Officer Phillip Colangelo, Pharm.D., Ph.D., Clin. Pharm.& Biopharm. Reviewer Peter Dionne, M.S., Microbiology Reviewer David Roeder, ADRA, ODE IV

[redacted]
NDA 21-277

Joette Meyer, Pharm.D., Clin. Pharm. & Biopharm Reviewer
Funmi Ajayi, Ph.D., Clin. Pharm. & Biopharm Team Leader
Brad Leissa, M.D., Medical Team Leader
Karen Higgins, Ph.D., Statistical Team Leader
Ed Cox, M.D., Medical Reviewer
Joyce Korvick, M.D., Medical Reviewer
Qian Li, Ph.D., Statistical Reviewer
Jouhayna Saliba, R.Ph., Project Manager
Valerie Jensen, R.Ph., Project Manager

BACKGROUND:

A pre-NDA teleconference was held July 17, 2000 between Bayer and the Division of Special Pathogen and Immunologic Drug Products to discuss issues regarding the planned November, 2000 submission of NDA 21-277 for Avelox™ IV Solution. Avelox™ IV Solution has been studied under [redacted] Bayer also asked for a separate pre-NDA CMC teleconference which was held on August 4, 2000. Bayer sent a background package dated June 22, 2000 in preparation for the pre-NDA teleconference held on July 17, 2000. A separate submission entitled, "Summary of Cardiac Safety" was submitted on June 30, 2000 in preparation for this July 17, 2000 teleconference. A facsimile was sent to Bayer on July 14, 2000 in response to Bayer's June 22 and June 30, 2000 submissions. Since the data regarding safety and efficacy from the Avelox™ IV studies were not yet available at the time of the teleconference on July 17th, 2000, a third pre-NDA meeting was scheduled for October 3, 2000. In preparation for the October 3, 2000 meeting, Bayer submitted a background package dated September 8, 2000 containing some safety and efficacy data from the two Avelox IV (one in the US, one in EU) studies. This package also contained some results from three Clinical Pharmacology Phase 4 studies which were requested in the December 10, 1999 approval letter for the Avelox tablet NDA (21-085). These three studies will be submitted in response to Phase 4 commitments numbered #4, #5, #6, and #7 of the December 10, 1999 approval letter and will be referenced in NDA 21-277. Bayer sent a list of discussion items dated September 25, 2000 which helped to facilitate the meeting. Discussion items are duplicated below. Division comments are duplicated below in italics.

DISCUSSION:

Bayer presented preliminary data from their two Avelox IV studies as well as preliminary data from the three Clinical Pharmacology Phase 4 studies.

The Division asks whether Bayer has looked at how the duration of the infusion may affect the QTc interval since in a hospital setting, the drug may not always be infused over exactly sixty minutes. The Division requests an analysis be included in the NDA which examines the effect of infusion durations on the QT interval. The Division requests Bayer show how the ΔQTc is correlated with plasma concentration and with infusion

duration.

Bayer responds that the Phase I studies all involved standardized infusion times as per the protocols and in the Phase III studies, the times are recorded for when the infusion was started and for when it was stopped and this data will be available with the NDA submission.

The Division asks about differences seen in the numbers included with the June 30, 2000 submission compared to data presented during this meeting. The Division requests that the NDA include with the analyses presented, an identification of the subsets of patients which were studied which may have contributed to the results seen. The Division requests that Bayer present data in the NDA regarding effects of age and gender on Cmax values.

Bayer states that the numbers presented during this meeting are closer to the final numbers which will be submitted in the NDA upon final analysis. Bayer also states that in the NDA submission, they will identify what studies have been pooled for the data presented. Bayer states that they will have age and gender information associated with PK from their studies which will be submitted in the NDA.

The Division asks Bayer about the differences seen in ΔQTc in the Phase IV commitment clinical pharmacology studies, particularly the mean ΔQTc of 15 msec seen in Study#100263 and the mean ΔQTc of 6 msec in Study #100264. The Division requests that Bayer help the Division to understand the bridge between this data and the clinical data. The Division refers Bayer to the minutes of the March 7, 2000 teleconference in which the Division recommended options regarding determination of baseline QTc interval.

Bayer states that post-approval data has identified a mean ΔQTc of 10 msec at Cmax for the Avelox tablets and for the IV formulation the ΔQTc has been identified to be 9msec after the first dose. The ΔQTc seen on day 3 after infusion is less impressive. Bayer states that this may suggest a decrease in the ΔQTc occurs over time of exposure. Bayer states that a clear dose response curve is seen with 800mg and 1200mg doses. Bayer states that there is the possibility of diurnal variation affecting the QTC measurements as well as day to day variability in individuals affecting this measurement.

The Division expects that since the times of infusion and EKG measurement will be provided with the NDA, effects such as diurnal variation can be accounted for

The Division asks about outliers and interpretation of the results regarding outliers and also asks Bayer to comment on the range of Cmax values seen in these studies.

Bayer comments that it may be determined that infusion rates were faster in outliers. Bayer states that the clinical studies give the best prediction of effects on Cmax and the data which will be included in the NDA from patients gives a range of possibilities regarding the results seen.

The Division states that there may be additional analyses we requested during the review of the NDA to help us understand the data and what it means in terms of safety.

The following discussion points in bolded text were provided by Bayer and were addressed as follows:

1. **Bayer believes there is adequate information regarding plasma level data, ECG data and safety experience with the IV formulation to make an appropriate risk benefit assessment.**

   The Division responds that the data which is planned to be included in the NDA and the additional data from the Phase 4 studies which will be referenced in the NDA, will be reviewable. Over the review period, the Division plans to work closely with Bayer to determine additional analyses of the data which may be required for determination of safety.

2. **Bayer proposes to pool microorganism data from the previously reported moxifloxacin tablet studies for community acquired pneumonia and the European sequential moxifloxacin IV to PO Community Acquired Pneumonia Study (200036) with the organism data from the North American Study (100039) in or in order to get approval for selected organisms such as *K. pneumoniae* and *S. aureus*.**

   The Division agrees with Bayer's plan to pool data but with some caveats such as the organisms must be determined to be the pathogen and must be gleaned from the appropriate studies and the Division would assess the validity of the cases. A mild case may not be able to be pooled to support a serious case.

   Bayer asks about the use of IV Amoxicillin/Clavulanate as a comparator since it is not an approved drug in the U.S. Bayer will plan on a superiority claim with regards to this comparator.

   The Division responds that the adequacy of the study that uses this unapproved comparator would be determined during the review. The Division requests that Bayer articulate in the NDA their position regarding the adequacy of this comparator. The Division noted that the test of cure visit for study #200036 was somewhat shorter than usually recommended. The test of cure for this study was 5 – 7 days following the end of treatment and the Division usually recommends that test of cure in Community Acquired Pneumonia studies take place 7 – 14 days post-end of treatment (EOT).

   The Division asks Bayer about their plans to pursue Legionella pneumophila as an additional organism to be included in this NDA.

Bayer responds that they plan to pool data from NDA 21-085 into data included with NDA 21-277 for the addition of *L. pneumophila, K. pneumoniae,* and *S. aureus.*

The Division requests that it be clear in the NDA, for example, that a pneumonia reported to be caused by S. aureus be consistent clinically with a case of this type of pneumonia.

3. **Based upon the bioequivalence of IV and PO moxifloxacin, Bayer proposes that the moxifloxacin IV formulation be approved for all indications for which the moxifloxacin tablet formulation already has approval. In addition, we would like to reach agreement that as additional tablet or IV indications become approved, that reciprocal approvals for the alternate formulation be standard practice.**

The Division has not yet determined that the IV and oral formulations are bioequivalent. The Division will consider this request but cannot make this determination until the data are reviewed and a determination is made regarding safety. A package insert common to both the IV and oral formulations is, however achievable although this common PI may not have all indications granted to both formulations. The Division would agree to consider additional indications for reciprocal approval for the alternate formulation on a case by case basis.

4. **Regarding item 2.e from the Division's July 14, 2000 facsimile,**

   For PATHOGEN, do you prefer one record per organism, or a list of variables PATHOGEN 1 – PATHOGEN X?

   Do you prefer a variable for infection site? Bacteriological responses will be calculated for respiratory, blood, and pleural cavity sites.

   For both questions above, do you wish one record per infection site and/or one record per pathogen, if so do you wish the other variable blank or duplicated? A good example is that the clinical response will not be evaluated for blood sites, so would you prefer the clinical response blank or duplicated from the respiratory sites for these records?

   The Division agrees with Bayer that these questions can be followed-up at a future time. The Division requests that Bayer provide a sham dataset for the Division to comment on.

   Bayer states that in follow-up to the July 17, 2000 teleconference, they are planning to ask for deferral of pediatric studies involving Avelox in NDA 21-277.

Signature, minutes preparer:_____ **Date:**_____

Conference Chair:_____ **Date:**_____

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/s/

Renata Albrecht
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for Sandra Kweder

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF TELECONFERENCE

DATE: January 29, 2001

NDA: 21-085/S-009

DRUG: Avelox® (moxifloxacin HCl) 400 mg Tablets

BAYER ATTENDEES:
Deborah Church, MD, Director Anti-Infective Medical Affairs
Barbara Painter, Ph.D., Microbiology
Shurjeel Choudhri, MD, Medical, Anti-Infectives
Janet Herrington, Ph.D., Microbiology
Amy Straub, Ph.D., Project Management
Robin Christoforides, Assistant Director, Regulatory Affairs
Andrew Verderame, Deputy Director, Regulatory Affairs

FDA ATTENDEES:
Andrea Meyerhoff, M.D., M.Sc., D.T.M.H., Medical Officer
Shukal Bala, Ph.D., Microbiology Team Leader
Peter Dionne, M.S., Microbiology Reviewer
Valerie Jensen, R.Ph., Project Manager

BACKGROUND:
NDA 21-085/S-009 was submitted on November 30, 2000 and received on December 1, 2000. This supplemental NDA proposes to add *S. pneumoniae* (including penicillin-resistant strains, MIC penicillin ≥ 2 µg/ml) to the list of microorganisms under the community acquired pneumonia (CAP) indication for Avelox®. The data to support this supplemental NDA were submitted to NDA 21-277 for Avelox® IV Solution on November 2, 2000. NDA 21-085/011 was submitted on December 14, 2000 and received on December 18, 2000. This supplemental NDA proposes to add *S. pneumoniae* (including penicillin-resistant strains, MIC penicillin ≥ 2 µg/ml) to the list of microorganisms under the acute bacterial sinusitis (ABS) indication and the data to support this supplemental NDA were submitted to NDA 21-277. The Division of Special Pathogen and Immunologic Drug Products requested a teleconference to discuss issues regarding these two supplemental NDAs. Discussion items from the teleconference are duplicated below.

- The Division asked Bayer to confirm whether the isolates of international origin utilized the penicillin E-test without the dilutional method to back up the MIC. Bayer confirmed

that they were unable to ship the isolates in order to retest them using the dilutional method. The U.S. isolates underwent E-testing in the field and underwent E-testing as well as dilutional testing at the central laboratory.

- The Division stated that the dilutional method is the preferred test and noted that approximately one-half (7 out of 13) of the isolates were not worked up beyond the E-test. The Division noted that the isolate found to have a value of 6.0 µg/ml from the E-test would be considered to be penicillin resistant but the isolates having values near 2.0 µg/ml from E-testing alone may not be penicillin resistant.

- Bayer stated that they will be sending data from 6 additional isolates which were reference-tested with the dilutional method as a submission to NDA 21-277 by the 4 month safety update for this NDA. Bayer stated that all 6 isolates were from patients who were cured and 2 were from bacteremic patients. Bayer stated that with these 6 additional isolates, 12 resistant isolates which underwent both E-testing and dilutional method testing will now be the basis for the pencillin-resistant *S. pneumoniae* claim for the community-acquired pneumonia indication.

- Bayer asked how the sinusitis and CAP data help each other. The Division responded that as discussed previously, penicillin-resistance data in CAP is necessary in order to consider a penicillin resistance claim for ABS. The Division reiterated that efficacy needs to be demonstrated in a more serious indication such as pneumonia before a less serious indication such as sinusitis may be considered for the resistance claim.

- Bayer plans to provide additional information regarding isolates that underwent E-testing as well as dilutional method testing when they submit the data from the additional 6 isolates.

- The Division stated that there is no specific number of penicillin-resistant isolates for which data must be submitted in order to gain approval for penicillin resistant *S. pneumoniae* but the more isolates that can be submitted, the better and that this would be a review issue. The Division stated that the efficacy for *S. pneumoniae* in general will be looked at when considering efficacy for penicillin-resistant *S. pneumoniae*. The 20-30 cases of bacteremia in NDA 21-277 will also expand on the knowledge about the efficacy of Avelox® in these types of infections.

Signature, minutes preparer: _____ Date: _____

Conference Chair (or designated signatory): _____ Date: _____

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/s/

Andrea Meyerhoff
4/25/01 10:56:42 AM

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Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

September 20, 2001

Mark Goldberger, M.D., MPH, Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 21-085/S-009
AVELOX ® (moxifloxacin hydrochloride) Tablets
PRSP in Community Acquired Pneumonia
Response to FDA Request for Information

Dear Dr. Goldberger:

Bayer Corporation hereby responds to a verbal request communicated by Valerie Jensen, Project Manager, and Yoon Kong, Project Manager, made on September 19, 2001. The Division requested an updated environmental assessment evaluation for the two labeling supplements seeking to add PRSP claims to the package insert.

Find attached Bayer's response to NDA 21-085/S-009, which requests the PRSP claim in the Community Acquired Pneumonia indication.

If any questions arise with regard to this information, please do not hesitate to contact me at (203) 812-5172.

Sincerely yours,

Andrew S. Verderame
Deputy Director, Regulatory Affairs

Enclosure

Desk Copy : Valerie Jensen, R.Ph, Project Manager
Yoon Kong, Pharm.D., Project Manager

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA#: 21-085/SE1-016
21-277/SE1-008

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 17-DEC-02
CDER DATE: 18-DEC-02
REVIEW ASSIGN DATE: 18-DEC-02
REVIEW COMPLETE DATE: 07-FEB-03

SPONSOR:
Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON:
Robin M. Christoforides
Associate Director Regulatory Affairs
Phone Number: (203) 812-2112

SUBMISSION REVIEWED: NDA supplement to add penicillin-resistant *S. pneumoniae* to acute bacterial sinusitis indication

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

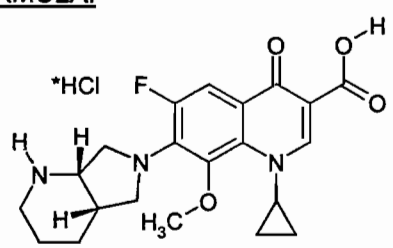
INDICATIONS: Community-acquired pneumonia (CAP), acute sinusitis, and acute bacterial exacerbations of chronic bronchitis (ABECB)

DOSAGE FORM: 400 mg intravenous solution, 400 mg tablets

DRUG PRODUCT NAME

PROPRIETARY: Avelox™
NONPROPRIETARY/USAN: Moxifloxacin Hydrochloride
CODE: BAY 12-8039
CHEMICAL NAME: (1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo(4.3.0)non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride

STRUCTURAL FORMULA:



Molecular Formula: $C_{21}H_{24}FN_3O_4 \bullet HCl$
Molecular Weight: 437.9

SUPPORTING DOCUMENTS:

NDA #21-085—Moxifloxacin Tablets (approved 12/10/99)
NDA #21-277—Moxifloxacin I.V. (approved 11/30/2001)

REMARKS/COMMENTS:

NDA 21-085 for Moxifloxacin Tablets was approved in December 1999, with indications of acute sinusitis, acute exacerbation of chronic bronchitis, and community acquired pneumonia. NDA 21-277 for Moxifloxacin I.V. was approved in November, 2001, for the same indications. At the time of approval not enough evidence was provided to include penicillin-resistant *Streptococcus pneumoniae* in the acute bacterial sinusitis (ABS) indication. Bayer has submitted this supplement for penicillin-resistant *S. pneumoniae* in the indication of acute bacterial sinusitis.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. Combining the isolates from the two moxifloxacin tablet acute sinusitis studies there were 15 patients with penicillin-resistant (MIC ≥2 µg/mL) *Streptococcus pneumoniae* isolates if the MIC data from the reference laboratory is used. One of these 15 patients failed therapy. If the MIC data from Bayer Laboratory is used then there were 12 patients with penicillin-resistant *Streptococcus pneumoniae*, All 12 patients were cured. The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in ABS. The changes needed in the microbiology labeling are presented at the end of this review. These revisions are listed as notification to the sponsor at the end of this review on pages 18-23.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Moxifloxacin hydrochloride tablets NDA 21-085 was approved in December 1999, for acute sinusitis, community-acquired pneumonia, and acute bacterial exacerbations of chronic bronchitis. Moxifloxacin I.V. NDA 21-277 was approved in November 2001, for the same indications. This supplement is for the addition of penicillin-resistant *Streptococcus pneumoniae* to the acute bacterial sinusitis indication.

Data from the original tablet NDA 21-085 and from two multicenter surveillance studies performed by [redacted] in 1997-1998 and 1999 have been included in this submission to show moxifloxacin's *in vitro* activity against *Streptococcus pneumoniae*. These data demonstrate that activity against *Streptococcus pneumoniae* has not changed and that moxifloxacin's activity is not altered by penicillin susceptibility. Table A summarizes these data.

TABLE A
Activity of Moxifloxacin against *Streptococcus pneumoniae*

Organism	Study	# Isolates	MIC Range (µg/mL)	MIC_{90} (µg/mL)
Streptococcus pneumoniae—ALL	NDA	6636	0.06-1	0.25
Penicillin-Susceptible		5324	0.06-0.5	0.25
Penicillin-Intermediate		964	0.06-1	0.25
Penicillin-Resistant		348	0.06-0.25	0.25
Streptococcus pneumoniae—ALL	Focus 1997-1998	5640	≤0.002-4	0.25
Penicillin-Susceptible		3603	≤0.002-2	0.25
Penicillin-Intermediate		1267	≤0.002-4	0.25
Penicillin-Resistant		770	0.015-4	0.25
Streptococcus pneumoniae—ALL	Focus 1999	4940	≤0.008-4	0.125
Penicillin-Susceptible		3189	≤0.008-4	0.125
Penicillin-Intermediate		952	0.03-4	0.125
Penicillin-Resistant		799	0.06-4	0.125

A murine model of pneumonia showed that moxifloxacin was effective against a penicillin-resistant strain of *Streptococcus pneumoniae*. In this model moxifloxacin, trovafloxacin, and vancomycin were more effective than amoxicillin, ciprofloxacin, levofloxacin, or sparfloxacin in reducing the load of bacteria in lungs. Moxifloxacin was the most effective agent tested in sterilizing the lungs.

Moxifloxacin was effective against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* in normal and neutropenic mouse thigh models. Moxifloxacin was also effective against a penicillin-intermediate (MIC = 1 µg/mL) *Streptococcus pneumoniae* strain in experimental meningitis in rabbits.

At steady-state following multiple doses of 400 mg moxifloxacin's AUC is 48.0 mg x hr/L and C_{max} is 4.52 µg/mL. Moxifloxacin concentrations in bronchial mucosa, alveolar macrophages, and maxillary sinus tissue exceed plasma concentrations.

There were 15 patients with penicillin-resistant *Streptococcus pneumoniae* isolates if the MIC data from the reference laboratory are used. Fourteen of the fifteen patients had a clinical response of resolution and a bacteriological response of presumed eradication at the Test-of-Cure visit. If the Bayer Laboratory MIC data are used there were 12 patients with penicillin-resistant *Streptococcus pneumoniae* isolates. All 12 patients had clinical resolution and a bacteriological outcome of presumed eradication at the Test-of-Cure visit.

PRECLINCIAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

No new information has been submitted.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Table 1 summarizes the *in vitro* activity of moxifloxacin against strains of *Streptococcus pneumoniae* that were isolated and evaluated and presented in the original tablet NDA (21-085) submission. The MIC_{90} for all isolates, regardless of the degree of susceptibility to penicillin, was 0.25 µg/mL.

Recently, [redacted]) conducted two multicenter surveillance studies of respiratory pathogens, including *Streptococcus pneumoniae*, in the years 1997-1998 (1) and 1999 (2). The data from these studies are shown in Tables 2 and 3. The MIC_{90}s of moxifloxacin for *Streptococcus pneumoniae* during the two time periods were 0.25 µg/mL for 5,640 isolates and 0.125 µg/mL for 4,940 isolates, respectively. A comparison of moxifloxacin with levofloxacin against *S. pneumoniae* isolated during the two surveillance studies showed that moxifloxacin was four- to eightfold more active *in vitro* than levofloxacin. The MIC_{90}s for moxifloxacin and levofloxacin against *Streptococcus pneumoniae* were independent of penicillin susceptibility.

TABLE 1
Summary of Activity of Moxifloxacin Against All *S. pneumoniae* (Original Tablet NDA)

Organism (No.)	Range of MICs (µg/mL)	Mode MIC_{90}
All (6636)	0.06-1	0.25
Pen-S (5324)	0.06-0.5	0.25
Pen-I (964)	0.06-1	0.25
Pen-R (348)	0.06-0.25	0.25

Summary Table from the original moxifloxacin tablet NDA #21-085
Pen = penicillin; S= susceptible; I = Intermediate; R = resistant

TABLE 2
Surveillance Study of Moxifloxacin against *S. pneumoniae* in 1997-1998

	Moxifloxacin		Levofloxacin	
Organism (No.)	Range of MICs (μg/mL)	MIC_{90}	Range of MICs (μg/mL)	MIC_{90}
All (5640)	≤0.002-4	0.25	≤0.004->8	1
Pen-S (3603)	≤0.002-2	0.25	≤0.004->8	1
Pen-I (1267)	≤0.002-4	0.25	≤0.004->8	1
Pen-R (770)	0.015-4	0.25	0.12->8	1

Reference 1
Pen = penicillin; S= susceptible; I = Intermediate; R = resistant

TABLE 3
Surveillance Study of Moxifloxacin against *S. pneumoniae* in 1999

	Moxifloxacin		Levofloxacin	
Organism (No.)	Range of MICs (μg/mL)	MIC_{90}	Range of MICs (μg/mL)	MIC_{90}
All (4940)	≤0.008-4	0.12	≤0.008->32	1
Pen-S (3189)	≤0.008-4	0.12	≤0.008-16	1
Pen-I (952)	0.03-4	0.12	0.25-16	1
Pen-R (799)	0.06-4	0.12	0.25>32	1

Reference 2
Pen = penicillin; S= susceptible; I = Intermediate; R = resistant

The studies presented in this submission demonstrate that moxifloxacin's activity against *Streptococcus pneumoniae* is approximately the same as that reported in the original tablet NDA. Moxifloxacin MIC values were independent of penicillin susceptibility.

ASSESSMENT OF BACTERIAL RESISTANCE

The primary mechanisms of bacterial resistance to most fluoroquinolones can be attributed to mutations in the *gyrA* gene in *Escherichia coli* or the *grlA (parC)* gene in gram-positive bacteria. Mutations in the *gryB* gene may also confer quinolone resistance, but to a lesser extent and less often than mutations in the *gyrA* gene. An additional mechanism for decreased activity of quinolones is a reduction in the intracellular accumulation of drug through decreased permeability, or by an active membrane-associated efflux of drug from the cells.

No new information has been provided in this supplement.

PRECLINICAL EFFICACY *(IN VIVO)*

PHARMACOKINETICS/BIOAVAILABILITY

Moxifloxacin hydrochloride is a C-8-methoxyfluoroquinolone that has been developed for treatment of respiratory tract and skin infections. A single dosage of 400 mg once daily, administered as a 400-mg intravenous solution or a 400-mg tablet is the usual dosing regimen.

The mean (±SD) C_{max} and AUC values at steady state with a 400 mg once daily oral dosage regimen are 4.5 ± 0.53 µg/mL and 48 ± 2.7 µg•h/mL, respectively. C_{max} is attained 1 to 3 hours after oral dosing. The mean (±SD) trough concentration is 0.95 ± 0.10 µg/mL. Following intravenous administration of 400 mg, steady state C_{max} and AUC values are 4.2-6.1 µg/mL and 37.9-48.2 µg•h/mL, respectively. Concentrations in plasma increase proportionately with the dose up to the highest dose tested (1200 mg single oral dose). The mean (±SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

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. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma. Some sample tissue concentration data following administration of 400 mg moxifloxacin are presented in Table 4.

TABLE 4
Tissue and Plasma Concentrations of Moxifloxacin At 3 Hours Post-Dose

Tissue	Tissue Concentration (µg/g)	Plasma Concentration (µg/mL)
Bronchial mucosa	5.4	3.2
Alveolar macrophages	56.7	3.2
Maxillary sinus	7.5	3.6

Table 5 summarizes some of the pertinent pharmacokinetic parameters derived from clinical pharmacology studies. This table includes the pharmacodynamic parameters AUIC (area under the inhibition curve, calculated as AUC/MIC) and the ratio C_{max} /MIC. Studies have been performed that relate these two parameters to clinical efficacy. Most studies seem to indicate that at target values for AUIC and C_{max}/MIC of ≥100-125 and ≥8-10, respectively, positive clinical efficacy is expected. Some studies indicate that the AUIC value of 100-125 is needed for infections caused by Gram-negative organisms but a much lower AUIC of around 20-25 is needed for Gram-positive infections. As can be seen in the table, these target values are reached with a 400 mg dose of moxifloxacin for *Streptococcus pneumoniae*.

TABLE 5
Pharmacokinetic/Pharmacodynamic Values for Moxifloxacin
Following Single and Multiple Doses of 400 mg PO Once Daily

Variable	Day 1	Day 10
AUC (mg x hr/L)	30.2	48.0
C_{max} (µg/mL)	3.36	4.52
T1/2 (hr)	9.3	12.0
C_{min} (µg/mL)	0.52	0.94
AUIC (*S. pneumoniae*) *	120.8	192
C_{max}/MIC (*S. pneumoniae*) *	13.4	18.1

* MIC_{90} = 0.25 µg/mL

Bioavailability is in the range of 90%. Bioavailability is not altered by coadministration with food.

The terminal elimination half-life is approximately 12 hours. Moxifloxacin is eliminated in part by renal excretion (~20% of dose), and by sulfate (~34% of dose) and glucuronide (~17% of dose) conjugation. Unchanged drug is also eliminated in feces (~25% of dose), reflecting either biliary secretion or direct secretion into the intestinal tract.

ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

Several new studies have been included in this submission. These studies are summarized in the following sections.

MURINE MODEL OF PNEUMONIA

An immunocompetent mouse model of pneumonia was used to assess the clearance of a strain of penicillin-resistant *Streptococcus pneumoniae* (3,4). Therapy was initiated four hours after the lungs of mice were intratracheally inoculated with 3 x 10^7 cfu/mL of pneumococci. The mice were treated with moxifloxacin, 100 mg/kg orally; trovafloxacin, 15 mg/kg orally; sparfloxacin, 50 mg/kg orally; levofloxacin, 50 mg/kg orally, ciprofloxacin 100 mg/kg orally; amoxicillin, 20 mg/kg orally; or vancomycin, 20 mg/kg, intravenously. The drugs were administered every six hours for four doses, the mice were killed, and cfu/g of lung tissue was obtained. As seen in Table 6, moxifloxacin, trovafloxacin, and vancomycin were equally effective in reducing the lung load to a median $\log_{10}$ cfu/g lung tissue of 0.5 to 1.0. Moxifloxacin, trovafloxacin, and vancomycin were more effective than amoxicillin, ciprofloxacin, levofloxacin, and sparfloxacin, which reduced the lung load to a median $\log_{10}$ cfu/g of 3.9-5.9. Moxifloxacin was the most effective agent in sterilizing 11/15 lungs followed by trovafloxacin at 8/15, and vancomycin at 4/14.

TABLE 6
Efficacy of Moxifloxacin Against Penicillin-Resistant *S. pneumoniae* in Murine Experimental Pneumonia

Treatment Regimen	30-min serum conc (µg/mL)	No. Sterile/ No. Total	Median Log10 CFU/g Lung	Range 25th-75th Percentile
None	---	0/17	8.1	7.3 – 8.6
Moxifloxacin	2.0	11/15	0.5	0.5 – 1.0
Trovafloxacin	5.3	8/15	0.5	0.5 – 2.8
Levofloxacin	5.3	1/10	4.3	4.0 – 4.5
Ciprofloxacin	5.4	0/9	5.9	5.6 – 6.2
Amoxicillin	12	0/14	5.4	5.2 – 5.8
Vancomycin	32	4/14	1.0	0.8 – 2.6

MOUSE THIGH MODEL

Vesga et al. (5) evaluated the pharmacokinetic parameters and therapeutic efficacy of moxifloxacin against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* in normal and neutropenic mouse thigh models. The moxifloxacin MICs of the test organisms were 0.015-0.25 µg/mL. Thigh muscles were injected with 7.77 $\log_{10}$ cfu/mL two hours prior to the initiation of treatment. To determine the effect of various dosing intervals on therapeutic efficacy, moxifloxacin was administered subcutaneously with total daily doses ranging in fourfold increments from 0.586 to 2400 mg/kg given in 1, 2, 4, or 8 doses over a 24 hour period. Efficacy was equivalent for each tested dose for time intervals q3h, q6h, q12h, or q24h for all organisms in neutropenic mice, which suggests the feasibility of once daily dosing. Against *Klebsiella pneumoniae* moxifloxacin showed the same efficacy at 24 hours for the q12h dosing for both neutropenic and normal mice. This indicates that neutropenia had no effect on the activity of moxifloxacin against *K. pneumoniae* at 24 hours after initiation of infection under these experimental conditions. However, at 24 hours after the initiation of infection and the same dosing interval in mice infected with *S. pneumoniae*, moxifloxacin was about 4 times more effective in normal mice. Pharmacokinetic parameters after administration of single subcutaneous doses of 6.25, 25, or 100 mg/kg to uninfected mice resulted in respective AUCs of 4.96, 24.0, and 58.7 mg.h/L. The C_{max} was 3.05, 9.09, and 15.5 µg/mL, respectively. The half-life increased from 1.1 hours after the 6.25 mg/kg dose to 2.14 hours after the 100 mg/kg dose. The therapeutic efficacy of moxifloxacin correlated best with AUC/MIC compared with C_{max}/MIC or Time above MIC.

RABBIT MENINGITIS MODEL

Ostergaard et al. (6,7) evaluated moxifloxacin against penicillin-resistant (MIC was actually 1.0 μg/mL so it was a penicillin-intermediate strain) and penicillin-susceptible *Streptococcus pneumoniae* type 9V in experimental meningitis in rabbits. The efficacy of moxifloxacin was compared with that of ceftriaxone and vancomycin. The pharmacokinetics of moxifloxacin in infected and noninfected rabbits were evaluated. New Zealand White rabbits were challenged intracisternally with 0.2 mL of 1×10^6 to 2×10^6 cfu/mL of *Streptococcus pneumoniae* type 9V. Table 7 shows the Minimal Inhibitory Concentrations (MICs) and Minimal Bactericidal Concentrations (MBCs) for the two strains.

TABLE 7
MICs and MBCs for the two *S. pneumoniae*
Type 9V strains used in the meningitis model

Agent	Strain 1 (1395)		Strain 2 (3058)	
	MIC (μg/mL)	MBC (μg/mL)	MIC (μg/mL)	MBC (μg/mL)
Penicillin	1	1	≤0.031	≤0.031
Ceftriaxone	0.5	1	≤0.031	≤0.031
Vancomycin	0.5	0.5	0.5	0.5
Moxifloxacin	0.125	0.25	0.125	0.25

Approximately 10 hours after inoculation with the penicillin-intermediate strain, six rabbits were administered two doses of moxifloxacin 40 mg/kg iv, five hours apart and eight rabbits were administered two doses of moxifloxacin 20 mg/kg iv, five hours apart. Two groups of five rabbits each were given either one dose of ceftriaxone 125 mg/kg iv or two doses of vancomycin 20 mg/kg iv, five hours apart. The three rabbits infected with the penicillin-susceptible pneumococcus were administered two doses of moxifloxacin 40 mg/kg iv. Ten hours post-treatment, the $\log_{10}$ cfu/mL in cerebrospinal fluid (CSF) was below the detection limit (1.7 $\log_{10}$ cfu/mL) for all treatment groups. Changes in $\log_{10}$ cfu/mL in CSF at 3 and 5 hours post treatment were significantly higher for moxifloxacin dosed at 40 mg/kg (-3.99 ± 1.30; -5.15 ± 1.40) than for vancomycin dosed at 20 mg/kg (-2.10 ± 1.07; -3.3 ± 1.09) but not higher than for ceftriaxone (-3.09 ± 2.09; -4.51 ± 1.53). The two dose 40 mg/kg moxifloxacin regimen was better than the two dose 20 mg/kg moxifloxacin regimen at the 3 hour timepoint. Table 8 shows how many rabbits had sterile CSF at various timepoints with each treatment.

TABLE 8
Number of Rabbits with CSF Bacterial Concentrations
Under the Detection Limit at Various Timepoints

Agent and Dose	No. of rabbits with sterile CSF (n) at :			
	3 hour	5 hour	10 hour	24 hour
Untreated	0 (5)	0 (4)	0 (1)	ND
Ceftriaxone 125 mg/kg x 1	2 (5)	3 (5)	4 (5)	4 (4)
Vancomycin 20 mg/kg x 2	0 (5)	0 (5)	2 (3)	3 (3)
Moxifloxacin				
20 mg/kg x 2	0 (8)	0 (8)	1 (6)	5 (5)
40 mg/kg x 2	1 (9)	3 (9)	6 (6)	5 (5)

Moxifloxacin at 40 mg/kg was the only treatment group in which all rabbits had sterile CSF at 10 hours post treatment. Ceftriaxone was almost as good. At 24 hours post treatment all treatment groups produced sterile CSF in all animals.

There were no significant differences seen when the efficacies of moxifloxacin for treatment of the penicillin-susceptible and penicillin-resistant strains were compared.

This study demonstrated that moxifloxacin was effective in the treatment of both penicillin-intermediate and –susceptible pneumococcal meningitis in rabbits.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN ACUTE BACTERIAL SINUSITIS

During each Phase III sinusitis clinical trial the susceptibility of the causative organisms was tested at the clinical trial site by the E-test method and by the disk diffusion test using NCCLS guidelines. Clinical isolates were sent to the microbiology laboratory at Bayer Corporation for confirmation of each organism's identity and for concurrent susceptibility testing by both the disk diffusion test and broth microdilution test. All isolates of *Streptococcus pneumoniae* were submitted to a reference laboratory, [redacted] for additional confirmation of identification and for repeat susceptibility testing for penicillin using broth microdilution test methodology. All aspirate specimens in the acute sinusitis clinical trials in the USA were obtained by antral puncture. The Bayer microbiology laboratory tested 61 isolates of *Streptococcus pneumoniae* from microbiologically evaluable patients.

Table 9 shows the range of moxifloxacin MICs for the 61 strains of *Streptococcus pneumoniae* isolated from the two acute sinusitis studies, D96-023 and D96-023A (aka 100131). The range of MICs was 0.06-0.5 µg/mL and the MIC_{90} was 0.25 µg/mL.

TABLE 9
MICs for Pre-Treatment Isolates of All *Streptococcus pneumoniae*

Study	No. Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
D96-023	29	0.06-0.5	0.125	0.25
D96-023A	32	0.06-0.25	0.125	0.25
Total	61	0.06-0.5	0.125	0.25

The clinical response and the bacteriological response for all 61 isolates of *Streptococcus pneumoniae* are summarized in Tables 10 and 11. Resolution occurred in 53/61 (86.9%) of patients at the Test-of-Cure visit, while 52/60 (86.7%) organisms were presumed eradicated.

TABLE 10
Clinical Response for All *Streptococcus pneumoniae*

	End of Therapy (%)			Test-of-Cure (%)	
Study	Resolve	Fail	Indeterminate	Resolve	Fail
D96-023	28 (97)	1 (3)	0 (0)	28 (97)	1 (3)
D96-023A	26 (81.3)	5 (15.6)	1 (3.1)	25 (78.1)	7 (21.9)
Total	54 (88.5)	6 (9.8)	1 (1.6)	53 (86.9)	8 (13.1)

TABLE 11
Bacteriological Response for All *Streptococcus pneumoniae*

	End of Therapy (%)				Test-of-Cure (%)		
Study	Erad	Pres Erad	Pres Persist	Indet	Pres Erad	Pres Persist	Erad/Recur
D96-023	1 (4)	27 (96)	0 (0)	0 (0)	27 (96)	1 (4)	0 (0)
D96-023A	3 (9.4)	26 (81.3)	2 (6.2)	1 (3.1)	25 (78.1)	5 (15.6)	2 (6.3)
Total	4 (6.7)	53 (88.3)	2 (3.3)	1 (1.7)	52 (86.7)	6 (10)	2 (3.3)

Erad = Eradicated; Pres Erad = Presumed Eradicated; Pres Persist = Presumed Persistent
Erad/Recur = Eradicated and then Recurred at Follow-Up

Fifteen penicillin-resistant strains of *Streptococcus pneumoniae* were isolated during the two sinusitis studies. The penicillin MICs were 2.0-4.0 µg/mL. At the Test-of-Cure visit, resolution and presumed eradication occurred at a rate of 93.3% for penicillin-resistant strains of *S. pneumoniae* (see Table 12) compared with resolution and presumed eradication rates of 84.8% and 84.4%, respectively, in the group of *Streptococcus pneumoniae* that excluded penicillin-resistant strains (Table 13). These 15 penicillin-resistant isolates represented 24.6% of the total of 61 microbiologically evaluable sinusitis isolates of *Streptococcus pneumoniae* that were tested prior to therapy.

TABLE 12
Bacteriological and Clinical Response by MIC at Test-of-Cure
Penicillin-Resistant *Streptococcus pneumoniae*

MIC (µg/mL)	Clinical Response		Bacteriological Response	
	Resolve	Fail	Pres Erad	Pres Persist
D96-023				
0.06	1	0	1	0
0.125	3	0	3	0
0.25	2	1	2	1
D96-023A				
0.06	1	0	1	0
0.125	7	0	7	0
Total	14 (93.3%)	1 (6.7%)	14 (93.3%)	1 (6.7%)

Pres Erad = Presumed Eradicated; Pres Persist = Presumed Persistent

TABLE 13
Bacteriological and Clinical Response by MIC at Test-of-Cure
Excluding Penicillin-Resistant *Streptococcus pneumoniae*

MIC (µg/mL)	Clinical Response		Bacteriological Response		
	Resolve	Fail	Pres Erad	Pres Persist	Erad/Recur
D96-023					
0.06	6	0	6	0	0
0.125	13	0	12	0	0
0.25	2	0	2	0	0
0.5	1	0	1	0	0
Total	22 (100%)	0 (0%)	21 (100%)	0 (0%)	0 (0%)
D96-023A					
0.06	2	0	2	0	0
0.125	12	6	12	5	1
0.25	3	1	3	0	1
Total	17 (70.8%)	7 (29.2%)	17 (70.8%)	5 (20.8%)	2 (8.3%)
GRAND TOTAL	39 (84.8%)	7 (15.2%)	38 (84.4%)	5 (11.1%)	2 (4.4%)

Pres Erad = Presumed Eradicated; Pres Persist = Presumed Persistent
Erad/Recur = Eradicated and then Recurred at Follow-Up

The MICs of penicillin from both the Bayer laboratory and the [redacted], as well as moxifloxacin MICs are provided by patient in Table 14. The MICs of penicillin obtained in both the Bayer laboratory and [redacted] were either equal or within the broth microdilution experimental error of one doubling dilution.

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TABLE 14
MICs for Penicillin-Resistant *Streptococcus pneumoniae*
Isolated from Sinusitis

		Penicillin MIC (µg/mL)		MXF MIC (µg/mL)
	Patient No.	Bayer	[redacted]	
D96-023				
	2009	2.0	2.0	0.125
	2013	2.0	2.0	0.125
	3008	2.0	2.0	0.125
	7003*	1.0	2.0	0.25
	7014	4.0	2.0	0.25
	7017	4.0	2.0	0.25
	23024	2.0	2.0	0.06
D96-023A				
	2118	2.0	4.0	0.125
	2122	4.0	4.0	0.125
	2130	2.0	4.0	0.125
	6114	1.0	2.0	0.125
	14107	4.0	4.0	0.125
	31126	2.0	4.0	0.06
	36109	4.0	>4.0	0.125
	41158	1.0	2.0	0.125

* Patient failed
MXF = Moxifloxacin

If the Bayer laboratory penicillin susceptibility results are used there are twelve (12) penicillin-resistant isolates and 12/12 are cured and presumed eradicated. If the reference laboratory results are used (usually the reference laboratory is used if there are conflicting results) there are 15 penicillin-resistant isolates and 14/15 (93.3%) are cured and presumed eradicated.

Bayer was told by the Agency that in order to obtain approval of *Streptococcus pneumoniae* (penicillin-resistant strains) in the indication of Acute Bacterial Sinusitis that it would be necessary for them to show efficacy for penicillin-resistant *S. pneumoniae* in a more serious indication such as Community Acquired Pneumonia. Bayer has submitted another supplement to NDA 21-085 with data for this organism in Community Acquired Pneumonia.

The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in ABS with these fifteen (or 12 if Bayer data used) patients. If this indication is approved, list #1 (clinical efficacy shown) in the Microbiology subsection of the package insert may be revised to include *Streptococcus pneumoniae* (including penicillin-resistant strains) instead of reading *Streptococcus pneumoniae* (penicillin-susceptible strains). *Streptococcus pneumoniae* (penicillin-resistant strains) would then be deleted from list #2 (*in vitro* activity) in the Microbiology subsection.

NDA REFERENCES

1. Sahm D, Thornsberry C, Hickey M. *In vitro* comparison of BAY 12-8039 against 1997-1998 respiratory season isolates. West Haven, CT: Bayer Corporation; 1998.

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3. Rouse MS PK, Patel R, Wilson WR, Steckelberg JM. *In vitro* and *in vivo* activity of BAY 12-8039 or trovafloxacin against penicillin-resistant *Streptococcus pneumoniae* experimental pneumonia in immunocompetent mice. *36th Interscience Conference on Antimicrobial Agents and Chemotherapy.* New Orleans, LA; 1996. Abstract Number: abstract. p: 29.

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5. Vesga O CR, Stanstad T, Craig WA. Pharmacodynamic activity of BAY 12-8039. *36th Interscience Conference on Antimicrobial Agents and Chemotherapy.* New Orleans, LA; 1996. Abstract Number: abstract. p: 102.

6. Ostergaard C ST, Knudsen JD, Frimodt-Moller N. Evaluation of a new 8-methoxyquinolone-BAY 12-8039-against a penicillin-resistant *Streptococcus pneumoniae* type 9V in experimental meningitis in rabbits. *37th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Toronto, Canada: 1997. Abstract Number: abstract. p: 40.

7. Ostergaard C ST, Knudsen JD, Moller NF. Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. *Antimicrobial Agents and Chemotherapy.* 1998; **42**:1706-1712.

RECOMMENDATIONS (To be Communicated)
Changes to the Proposed Label

The applicant should be notified of the following:

1. The addition of penicillin-resistant *Streptococcus pneumoniae* to the clinical efficacy listing will be allowed if enough evidence is provided to show that these isolates are eradicated in the indication of community acquired pneumonia. From the microbiological viewpoint using the data from ——— there are 15 patients penicillin-resistant isolates. Fourteen of these 15 patients were cured and the bacteriological outcome was eradication or presumed eradication. If data from Bayer Laboratories are used then there were 12 patients with penicillin-resistant isolates. All 12 patients were cured.

2. The NCCLS references should be updated to the January 2003 versions.

The Microbiology subsection of the package insert should, therefore, be revised to read as follows: Deletions to the current labeling are indicated by a strikeout. Additions to the current labeling are indicated by a double underline.

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 C-8-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 ~~suceptible~~ strains* only)
Streptococcus pyogenes

* Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC ≥2 µg/mL.

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 pneumoniae* (penicillin-resistant strains)~~
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 method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* species:

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

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

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

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

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

For testing *Streptococcus* species including *Streptococcus pneumoniae*:[b]

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

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration 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 concentration usually achievable; other therapy should be selected.

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

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

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

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

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

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

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

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

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

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

[e] This zone diameter standard is applicable only to disk diffusion 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)	Interpretation	
≥ 18	Susceptible	(S)
15-17	Intermediate	(I)
≤ 14	Resistant	(R)

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

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

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

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	28-35
Haemophilus influenzae ATCC 49247[g]	31-39
Staphylococcus aureus ATCC 25923	28-35
Streptococcus pneumoniae ATCC 49619[h]	25-31

[g] These quality control limits are applicable only to *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2].

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

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—~~Fifth~~ Sixth Edition. Approved Standard NCCLS Document M7-A~~5~~ 6 , Vol. ~~20~~ 23, No. 2, NCCLS, Wayne, PA, January ~~2000~~ 2003.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—~~Seventh~~ Eighth Edition. Approved Standard NCCLS Document M2-A~~7~~ 8, Vol. ~~20~~ 23, No. 1, NCCLS, Wayne, PA, January ~~2000~~ 2003.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA #21-085/SE1-015
HFD-590/Original NDA #21-277/SE1-007
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/RJohann-Liang
HFD-590/Pharm/SHundley
HFD-590/BioPharm/DChilukuri
HFD-590/Chem/DMatecka
HFD-590/CSO/SPeacork

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/s/

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Shukal signed 2/13/03; Ken signed 2/24/03

Shukal Bala
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-085/S-015
21-277/S-007

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDA#: 21-085/SE1-009

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	30-NOV-00
CDER DATE:	01-DEC-00
REVIEW ASSIGN DATE:	11-DEC-00
REVIEW COMPLETE DATE:	06-MAR-01

SPONSOR: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON: Andrew S. Verderame
Associate Director Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Supplemental Application to add penicillin-resistant *Streptococcus pneumoniae* to the indication of Community Acquired Pneumonia

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

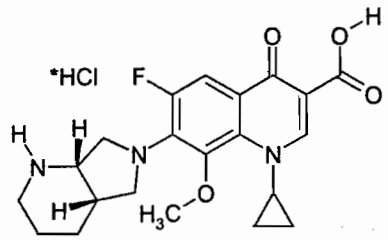
INDICATIONS: Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB), Community Acquired Pneumonia

DOSAGE FORM: 400 mg Tablet

DRUG PRODUCT NAME

PROPRIETARY: Avelox™
NONPROPRIETARY/USAN: Moxifloxacin Hydrochloride
CODE: BAY 12-8039
CHEMICAL NAME: (1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo(4.3.0)non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride

STRUCTURAL FORMULA:



Molecular Formula: $C_{21}H_{24}FN_3O_4 \bullet HCl$
Molecular Weight: 437.9

SUPPORTING DOCUMENTS:

NDA #21-085—Moxifloxacin Tablets (approved 12/10/99)
NDA #21-277—Moxifloxacin I.V. (submitted 3/6/2001)

REMARKS/COMMENTS:

NDA 21-085 for Moxifloxacin Tablets was approved in December 1999, with indications of acute sinusitis, acute exacerbation of chronic bronchitis, and community acquired pneumonia. At the time of approval not enough evidence was provided to include penicillin-resistant *Streptococcus pneumoniae* in the Community Acquired Pneumonia indication. Bayer has now submitted this supplement to NDA 21-085 to include this organism. All data for this supplement have been included in NDA 21-277, Avelox I.V. solution. No data has been submitted with this supplement.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. These revisions are listed as notification to the sponsor at the end of this review on pages 4-11.

All data for this supplement were submitted to NDA 21-277 (moxifloxacin I.V.) In the original NDA 21-277 submission, combining the I.V. and Tablet community-acquired pneumonia studies (CAP) there were 13 penicillin-resistant (MIC ≥2 µg/mL) *Streptococcus pneumoniae* isolates. A four month safety update (dated March 6, 2001) added six more penicillin-resistant *Streptococcus pneumoniae* isolates that were treated with moxifloxacin in CAP studies. Combining all studies there were 19 penicillin-resistant *Streptococcus pneumoniae* isolates according to the sponsor. Seven of these isolates, however, had penicillin susceptibility determined only by the E-test method. These isolates were all from centers outside the United States and the penicillin MIC could not be determined by broth microdilution. Six of the seven isolates had penicillin MICs of 1.5 or 2.0 µg/mL by the E-test method. Since the E-test method may give a MIC that is one dilution higher than the broth method, these six isolates may not truly be penicillin-resistant.

Bayer has included several literature references to try and show that the E-test method is equivalent to the broth dilution method in determining penicillin resistance in *Streptococcus pneumoniae*. These studies indicate that the results obtained by the two methods are usually within one doubling dilution of each other (equivalent to the error of the assay) for over 90% of the isolates tested, which indicates that the two methods may be considered equivalent. All of the studies, however, indicate that there may be many minor errors (susceptible or resistant by one method and intermediate by the other method). This means that isolates tested by E-test methods that have MICs close to the penicillin resistant breakpoint criteria (≥2 µg/mL) might actually be in the intermediate range and not truly resistant. If these six isolates are not allowed there are 12 isolates with broth dilution MIC results and one isolate with an E-test result of 6.0 µg/mL that can be considered to be truly penicillin resistant. The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in CAP with these thirteen isolates.

For more details and an analysis of the results see the microbiology review for NDA 21-277 dated March 2, 2001 and the four month safety update microbiology review dated March 27, 2001.

RECOMMENDATIONS (To be Communicated)
Changes to the Proposed Label

The applicant should be notified of the following:

Assuming that the data submitted is sufficient to approve an indication of uncomplicated skin and skin structure infections:

1. The statement reading '

   should be revised to read "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 evidence present was related to mechanisms associated with these genes in *S. pneumoniae* and *S. aureus*.

2. The statement reading

   should be revised to read "*In vitro* resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency between 1.8×10^{-9} to $<1 \times 10^{-11}$ for Gram-positive bacteria. The mutation rates for Gram-negative bacteria are somewhat higher at 1×10^{-8} for *Escherichia coli* and 1×10^{-6} for *Pseudomonas aeruginosa*. This higher mutation rate for *Pseudomonas aeruginosa* is seen with most fluoroquinolones." Mutation rates from Gram-negative bacteria, especially *Pseudomonas aeruginosa* were higher than those for Gram-positive bacteria. This should be reflected in the label.

3. The section of the Microbiology subsection of the label that

   should be deleted. This information has never been allowed in the labeling before. We usually do not even allow the MIC values to be in the label. Although studies have shown that efficacy seems to be related to these pharmacodynamic parameters the addition of this information in the microbiology section does not really add any useful information since clinical trials have been performed and the drug has been shown to be effective against the organisms listed in the table. Different studies have used slightly different values for the AUC/MIC ratio that leads to efficacy. Most studies seem to indicate that once this value has been reached higher values do not add to the efficacy of the drug. Most studies also have used individual MIC values for each pathogen and not the MIC_{90} value. If this information is allowed into the label it will not really be adding useful information since efficacy against these pathogens has been shown. An AUC/MIC ratio greater than the value needed for good efficacy does not mean the drug has better efficacy against that organism.

4. The addition of penicillin-resistant *Streptococcus pneumoniae* to the clinical efficacy listing will be allowed if enough evidence is provided to show that these isolates are eradicated in the indication of community acquired pneumonia. From the microbiological viewpoint there are 13 penicillin-resistant isolates. Twelve of the thirteen patients were cured and the organisms were presumed to be eradicated.

5. The placement of *Streptococcus pyogenes* in the clinical efficacy list (list #1) is acceptable if the skin indication is approved. From the microbiological viewpoint not enough isolates of *Streptococcus agalactiae* were tested in the skin clinical trials to allow this organism into the efficacy list. *Streptococcus agalactiae* may, however, be added to the *in vitro* activity list (list #2) if the skin indication is approved.

6. From the microbiological viewpoint not enough isolates of *Legionella pneumoniae* were studied in the clinical trials to allow this organism into the clinical efficacy list (list #1).

7. *Staphylococcus epidermidis* may be added to the *in vitro* activity listing (list #2) if the skin indication is approved. It should be qualified as (methicillin-susceptible strains only). Although the MIC_{90} values for methicillin-resistant isolates was ≤ 2 µg/mL in all submitted studies, less than 100 methicillin-resistant isolates were tested and the MIC_{90} value was at the susceptible breakpoint. As with other fluoroquinolones the MIC values for methicillin-resistant strains was higher than for methicillin-susceptible strains and methicillin-resistant staphylococci are normally resistant to all fluoroquinolones.

8. *Streptococcus* viridans group and *Streptococcus agalactiae* may be added to the *in vitro* activity listing (list #2) if the skin indication is approved.

9. Since from the microbiological viewpoint not enough isolates of *Legionella pneumophila* were treated in the clinical trials this organism should remain in the *in vitro* activity listing (list #2) instead of being moved to the clinical efficacy list (list #1).

10. In the Susceptibility Tests subsection the words "For testing *Streptococcus* species including *Streptococcus pneumoniae*" should replace the words [redacted] in both the Dilution Techniques and the Diffusion Techniques sections.

11. The NCCLS references should be updated to the January 2000 versions.

The Microbiology subsection of the package insert should, therefore, be revised to read as follows: Deletions to the sponsor's proposed labeling are indicated by a strikeout. Additions to the sponsor's proposed labeling are indicated by a double underline.

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 C-8-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, [redacted] 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. The mutation rates for Gram-negative bacteria are higher at 1×10^{-8} for *Escherichia coli* and 1×10^{-6} for *Pseudomonas aeruginosa*. This higher mutation rate for *Pseudomonas aeruginosa* is seen with most fluoroquinolones.

[redacted]

[redacted]

[redacted]

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)
Streptococcus pyogenes

* Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC ≥2 µg/mL.

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 method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* species:

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

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

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

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

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

For testing *Streptococcus* species including *Streptococcus pneumoniae*:[b]

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

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration 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 concentration usually achievable; other therapy should be selected.

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

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

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

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

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

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

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

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

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

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

[e] This zone diameter standard is applicable only to disk diffusion 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)	Interpretation	
≥ 18	Susceptible	(S)
15-17	Intermediate	(I)
≤ 14	Resistant	(R)

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

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

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

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	28-35
Haemophilus influenzae ATCC 49247[g]	31-39
Staphylococcus aureus ATCC 25923	28-35
Streptococcus pneumoniae ATCC 49619[h]	25-31

[g] These quality control limits are applicable only to *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2].

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

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—~~Fourth~~ Fifth Edition. Approved Standard NCCLS Document M7~~-A4~~ 5 , Vol. ~~17~~ 20, No. 2, NCCLS, Wayne, PA, January ~~1997~~ 2000.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--~~Sixth~~ Seventh Edition. Approved Standard NCCLS Document M2-A~~6~~ 7, Vol. ~~17~~ 20, No. 1, NCCLS, Wayne, PA, January ~~1997~~ 2000.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

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HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA #21-085/SE1-009
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/AMeyerhoff
HFD-520/Pharm/AEllis
HFD-590/Chem/DMatecka
HFD-590/CSO/VJensen

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Kenneth Hastings
4/17/01 10:20:11 AM
PHARMACOLOGIST

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA#: 21-085/SE1-011

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	12-DEC-00
CDER DATE:	18-DEC-00
REVIEW ASSIGN DATE:	08-JAN-01
REVIEW COMPLETE DATE:	28-MAR-01

SPONSOR:
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Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON:
Andrew S. Verderame
Associate Director Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Supplemental Application to add penicillin-resistant *Streptococcus pneumoniae* to the indication of Acute Bacterial Sinusitis

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

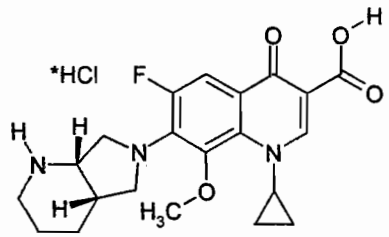
INDICATIONS: Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB), Community Acquired Pneumonia

DOSAGE FORM: 400 mg Tablet

DRUG PRODUCT NAME

PROPRIETARY: Avelox™
NONPROPRIETARY/USAN: Moxifloxacin Hydrochloride
CODE: BAY 12-8039
CHEMICAL NAME: (1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo(4.3.0)non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride

STRUCTURAL FORMULA:



Molecular Formula: $C_{21}H_{24}FN_3O_4 \bullet HCl$
Molecular Weight: 437.9

SUPPORTING DOCUMENTS:

[redacted]

NDA #21-085—Moxifloxacin Tablets (approved 12/10/99)
NDA #21-277—Moxifloxacin I.V.

REMARKS/COMMENTS:

NDA 21-085 for Moxifloxacin Tablets was approved in December 1999, with indications of acute sinusitis, acute exacerbation of chronic bronchitis, and community acquired pneumonia. At the time of approval not enough evidence was provided to include penicillin-resistant *Streptococcus pneumoniae* in the sinusitis indication. Bayer has been told by the Agency that in order to get penicillin-resistant *S. pneumoniae* in the indication of acute sinusitis they would be required to show efficacy for this organism in a more serious disease such as community acquired pneumonia. Bayer has submitted another supplement for penicillin-resistant *S. pneumoniae* in the indication of community acquired pneumonia. Bayer has now submitted this supplement to NDA 21-085 to include this organism in the acute sinusitis indication. All data for this supplement have been included as an amendment to NDA 21-277, Avelox I.V. solution. No data has been submitted with this supplement.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. These revisions are listed as notification to the sponsor at the end of this review on pages 22-29.

All data for this supplement were submitted to NDA 21-277 (moxifloxacin I.V.). In the original NDA 21-277 submission, combining the I.V. and tablet community-acquired pneumonia studies (CAP) there were 13 penicillin-resistant (MIC ≥2 µg/mL) *Streptococcus pneumoniae* isolates. A four month safety update (dated March 6, 2001) added six more penicillin-resistant *Streptococcus pneumoniae* isolates that were treated with moxifloxacin in CAP studies. Combining all studies there were 19 penicillin-resistant *Streptococcus pneumoniae* isolates according to the sponsor. Seven of these isolates, however, had penicillin susceptibility determined only by the E-test method. These isolates were all from centers outside the United States and the penicillin MIC could not be determined by broth microdilution. Six of the seven isolates had penicillin MICs of 1.5 or 2.0 µg/mL by the E-test method. Since the E-test method may give a MIC that is one dilution higher than the broth method, these six isolates may not truly be penicillin-resistant.

Bayer has included several literature references to try and show that the E-test method is equivalent to the broth dilution method in determining penicillin resistance in *Streptococcus pneumoniae*. These studies indicate that the results obtained by the two methods are usually within one doubling dilution of each other (equivalent to the error of the assay) for over 90% of the isolates tested, which indicates that the two methods may be considered equivalent. All of the studies, however, indicate that there may be many minor errors (susceptible or resistant by one method and intermediate by the other method). This means that isolates tested by E-test methods that have MICs close to the penicillin resistant breakpoint criteria (≥2 µg/mL) might actually be in the intermediate range and not truly resistant. If these six isolates are not allowed there are 12 isolates with broth dilution MIC results and one isolate with an E-test result of 6.0 µg/mL that can be considered to be truly penicillin resistant. The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in CAP with these thirteen isolates.

In the indication of acute sinusitis, there were fifteen penicillin-resistant *S. pneumoniae* isolates tested by the broth microdilution method by a reference laboratory. After treatment fourteen of the fifteen isolates were presumed to be eradicated. When tested in Bayer's laboratory, three of these fifteen isolates had a pencillin MIC of 1.0 µg/mL (classified as penicillin-intermediate). Using Bayer laboratory results 12 of 12 penicillin-resistant isolates were presumed eradicated after treatment with moxifloxcin.

For more details and an analysis of the results see the microbiology review for NDA 21-277 dated March 2, 2001 and the four month safety update microbiology review dated March 27, 2001.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Moxifloxacin hydrochloride tablets NDA 21-085 was approved in December 1999, for acute sinusitis, community-acquired pneumonia, and acute bacterial exacerbations of chronic bronchitis. This supplement is for the addition of penicillin-resistant *Streptococcus pneumoniae* to the acute bacterial sinusitis indication. Bayer was told by the Agency that in order for *Streptococcus pneumoniae* (penicillin-resistant strains) to be approved in the indication of acute sinustitis efficacy for penicillin-resistant *S. pneumoniae* would have to be shown in a more serious infection such as community acquired pneumonia.

Data from the tablet NDA and from two multicenter surveillance studies performed by [redacted]. in 1997-1998 and 1999 have been included in this submission to show moxifloxacin's *in vitro* activity against *Streptococcus pneumoniae*. These data demonstrate that activity against *Streptococcus pneumoniae* has not changed and that moxifloxacin's activity is not altered by penicillin susceptibility. Table A summarizes these data.

TABLE A
Activity of Moxifloxacin against *Streptococcus pneumoniae*

Organism	Study	# Isolates	MIC Range (µg/mL)	MIC_{90} (µg/mL)
Streptococcus pneumoniae—ALL	NDA	6636	0.06-1	0.25
Penicillin-Susceptible		5324	0.06-0.5	0.25
Penicillin-Intermediate		964	0.06-1	0.25
Penicillin-Resistant		348	0.06-0.25	0.25
Streptococcus pneumoniae—ALL	Focus 1997-1998	5640	≤0.002-4	0.25
Penicillin-Susceptible		3603	≤0.002-2	0.25
Penicillin-Intermediate		1267	≤0.002-4	0.25
Penicillin-Resistant		770	0.015-4	0.25
Streptococcus pneumoniae—ALL	Focus 1999	4940	≤0.008-4	0.125
Penicillin-Susceptible		3189	≤0.008-4	0.125
Penicillin-Intermediate		952	0.03-4	0.125
Penicillin-Resistant		799	0.06-4	0.125

A murine model of pneumonia showed that moxifloxacin was effective against a penicillin-resistant strain of *Streptococcus pneumoniae*. In this model moxifloxacin, trovafloxacin, and vancomycin were more effective than amoxicillin, ciprofloxacin, levofloxacin, or sparfloxacin in reducing the load of bacteria in lungs. Moxifloxacin was the most effective agent tested in sterilizing the lungs.

Moxifloxacin was effective against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* in normal and neutropenic mouse thigh models. Moxifloxacin was also effective against a penicillin-intermediate (MIC = 1 µg/mL) *Streptococcus pneumoniae* strain in an experimental meningitis in rabbits.

At steady-state following multiple doses of 400 mg moxifloxacin's AUC is 48.0 mg x hr/L and C_{max} is 4.52 µg/mL. Moxifloxacin concentrations in bronchial mucosa, alveolar macrophages, and maxillary sinus tissue exceeds plasma concentrations.

There were fifteen penicillin-resistant *Streptococcus pneumoniae* (reference laboratory results) with penicillin MICs tested by the broth dilution method from sinusitis studies submitted with the tablet NDA. All but one was cured. If Bayer laboratory results are used then 12/12 isolates were presumed eradicated. Three isolates had penicillin MICs of 1.0 µg/mL when tested by Bayer but had MICs of 2.0 µg/mL when tested by the reference laboratory.

There were four penicillin-resistant *Streptococcus pneumoniae* isolates in the IV community acquired study performed in the United States. These four isolates had penicillin-susceptibility results from both E-test and broth dilution methods. There were two additional penicillin-resistant isolates from the tablet studies that had broth dilution penicillin susceptibility results. All six of these isolates were from patients who showed clinical resolution and the organisms were presumed to be eradicated upon treatment. There were seven *Streptococcus pneumoniae* isolates from foreign studies that the sponsor concludes are penicillin-resistant. Six of these isolates are from the IV study and one from a study submitted with the tablet NDA. These isolates were tested for penicillin susceptibility by the E-test only. Most of these isolates had penicillin MICs of 1.5 or 2.0 µg/mL by the E-test method. Since the E-test can produce MIC results that are one dilution higher than those produced by the broth dilution test, which is the gold standard for this testing, these isolates may not truly be penicillin-resistant. Two of the patients with these isolates failed therapy.

In the four-month safety update for NDA 21-277 (moxifloxacin I.V.) six additional isolates of penicillin-resistant *S. pneumoniae* were included from a tablet community-acquired pneumonia (CAP) study. These six isolates were tested for penicllin susceptibility by the broth microdilution method. All six isolates had penicillin MICs of 2.0 or 4.0 µg/mL. All six isolates were presumed eradicated upon moxifloxacin treatment.

PRECLINCIAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

No new information has been submitted.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Table 1 summarizes the *in vitro* activity of moxifloxacin against strains of *Streptococcus pneumoniae* that were isolated and evaluated and presented in the tablet NDA submission. The MIC_{90} for all isolates, regardless of the degree of susceptibility to penicillin, was 0.25 µg/mL.

Recently, [redacted]) conducted two multicenter surveillance studies of respiratory pathogens, including *Streptococcus pneumoniae*, in the years 1997-1998 (1) and 1999 (2). The data from these studies are shown in Tables 2 and 3. The MIC_{90}s of moxifloxacin for *Streptococcus pneumoniae* during the two time periods were 0.25 µg/mL for 5,640 isolates and 0.125 µg/mL for 4,940 isolates, respectively. A comparison of moxifloxacin with levofloxacin against *S. pneumoniae* isolated during the two surveillance studies showed that moxifloxacin was four- to eightfold more active *in vitro* than levofloxacin. The MIC_{90}s for moxifloxacin and levofloxacin against *Streptococcus pneumoniae* were independent of penicillin susceptibility.

TABLE 1
Summary of Activity of Moxifloxacin Against All *S. pneumoniae* (Tablet NDA)

Organism (No.)	Range of MICs (µg/mL)	Mode MIC_{90}
All (6636)	0.06-1	0.25
Pen-S (5324)	0.06-0.5	0.25
Pen-I (964)	0.06-1	0.25
Pen-R (348)	0.06-0.25	0.25

Summary Table from moxifloxacin tablet NDA #21-085
Pen = penicillin; S= susceptible; I = Intermediate; R = resistant

TABLE 2
Surveillance Study of Moxifloxacin against *S. pneumoniae* in 1997-1998

	Moxifloxacin		Levofloxacin	
Organism (No.)	Range of MICs (µg/mL)	MIC_{90}	Range of MICs (µg/mL)	MIC_{90}
All (5640)	≤0.002-4	0.25	≤0.004->8	1
Pen-S (3603)	≤0.002-2	0.25	≤0.004->8	1
Pen-I (1267)	≤0.002-4	0.25	≤0.004->8	1
Pen-R (770)	0.015-4	0.25	0.12->8	1

Reference 1
Pen = penicillin; S= susceptible; I = Intermediate; R = resistant

TABLE 3
Surveillance Study of Moxifloxacin against *S. pneumoniae* in 1999

	Moxifloxacin		Levofloxacin	
Organism (No.)	Range of MICs (µg/mL)	MIC_{90}	Range of MICs (µg/mL)	MIC_{90}
All (4940)	≤0.008-4	0.12	≤0.008->32	1
Pen-S (3189)	≤0.008-4	0.12	≤0.008-16	1
Pen-I (952)	0.03-4	0.12	0.25-16	1
Pen-R (799)	0.06-4	0.12	0.25>32	1

Reference 2
Pen = penicillin; S= susceptible; I = Intermediate; R = resistant

The studies presented in this submission demonstrate that moxifloxacin's activity against *Streptococcus pneumoniae* is approximately the same as that reported in the original tablet NDA. Moxifloxacin MIC values were independent of penicillin susceptibility.

ASSESSMENT OF BACTERIAL RESISTANCE

The primary mechanisms of bacterial resistance to most fluoroquinolones can be attributed to mutations in the *gyrA* gene in *Escherichia coli* or the *grlA (parC)* gene in gram-positive bacteria. Mutations in the *gryB* gene may also confer quinolone resistance, but to a lesser extent and less often than mutations in the *gyrA* gene. An additional mechanism for decreased activity of quinolones is a reduction in the intracellular accumulation of drug through decreased permeability, or by an active membrane-associated efflux of drug from the cells.

No new information has been provided in this supplement.

PRECLINICAL EFFICACY *(IN VIVO)*

PHARMACOKINETICS/BIOAVAILABILITY

Moxifloxacin hydrochloride is a C-8-methoxyfluoroquinolone that has been developed for treatment of respiratory tract and skin infections. A single dosage of 400 mg once daily, administered as a 400-mg intravenous solution or a 400-mg tablet is the usual dosing regimen.

The information in this section pertaining to the intravenous formulation is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

The mean (±SD) C_{max} and AUC values at steady state with a 400 mg once daily oral dosage regimen are 4.5 ± 0.53 µg/mL and 48 ± 2.7 µg•h/mL, respectively. C_{max} is attained 1 to 3 hours after oral dosing. The mean (±SD) trough concentration is 0.95 ± 0.10 µg/mL. Following intravenous administration of 400 mg, steady state C_{max} and AUC values are 4.2-6.1 µg/mL and 37.9-48.2 µg•h/mL, respectively. Concentrations in plasma increase proportionately with the dose up to the highest dose tested (1200 mg single oral dose). The mean (±SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

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. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma. Some sample tissue concentration data following administration of 400 mg moxifloxacin are presented in Table 4.

TABLE 4
Tissue and Plasma Concentrations of Moxifloxacin At 3 Hours Post-Dose

Tissue	Tissue Concentration (µg/g)	Plasma Concentration (µg/mL)
Bronchial mucosa	5.4	3.2
Alveolar macrophages	56.7	3.2
Maxillary sinus	7.5	3.6

Table 5 summarizes some of the pertinent pharmacokinetic parameters derived from clinical pharmacology studies. This table includes the pharmacodynamic parameters AUIC (area under the inhibition curve, calculated as AUC/MIC) and the ratio C_{max} /MIC. Studies have been performed that relate these two parameters to clinical efficacy. Most studies seem to indicate that at target values for AUIC and C_{max}/MIC of ≥100-125 and ≥8-10, respectively, positive clinical efficacy is expected. Some studies indicate that the AUIC value of 100-125 is needed for infections caused by Gram-negative organisms but a much lower AUIC of around 20-25 is needed for Gram-positive infections. As can be seen in the table, these target values are reached with a 400 mg dose of moxifloxacin for *Streptococcus pneumoniae*.

TABLE 5
Pharmacokinetic/Pharmacodynamic Values for Moxifloxacin
Following Single and Multiple Doses of 400 mg PO Once Daily

Variable	Day 1	Day 10
AUC (mg x hr/L)	30.2	48.0
C_{max} (µg/mL)	3.36	4.52
T1/2 (hr)	9.3	12.0
C_{min} (µg/mL)	0.52	0.94
AUIC (*S. pneumoniae*) *	120.8	192
C_{max}/MIC (*S. pneumoniae*) *	13.4	18.1

* MIC_{90} = 0.25 µg/mL

Bioavailability is in the range of 90%. Bioavailability is not altered by coadministration with food.

The terminal elimination half-life is approximately 12 hours. Moxifloxacin is eliminated in part by renal excretion (~20% of dose), and by sulfate (~34% of dose) and glucuronide (~17% of dose) conjugation. Unchanged drug is also eliminated in feces (~25% of dose), reflecting either biliary secretion or direct secretion into the intestinal tract.

ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

Several new studies have been included in this submission. These studies are summarized in the following sections.

MURINE MODEL OF PNEUMONIA

An immunocompetent mouse model of pneumonia was used to assess the clearance of a strain of penicillin-resistant *Streptococcus pneumoniae* (3,4). Therapy was initiated four hours after the lungs of mice were intratracheally inoculated with 3 x 10^7 cfu/mL of pneumococci. The mice were treated with moxifloxacin, 100 mg/kg orally; trovafloxacin, 15 mg/kg orally; sparfloxacin, 50 mg/kg orally; levofloxacin, 50 mg/kg orally, ciprofloxacin 100 mg/kg orally; amoxicillin, 20 mg/kg orally; or vancomycin, 20 mg/kg, intravenously. The drugs were administered every six hours for four doses, the mice were killed, and cfu/g of lung tissue was obtained. As seen in Table 6, moxifloxacin, trovafloxacin, and vancomycin were equally effective in reducing the lung load to a median log_{10} cfu/g lung tissue of 0.5. Moxifloxacin, trovafloxacin, and vancomycin were more effective than amoxicillin, ciprofloxacin, levofloxacin, and sparfloxacin, which reduced the lung load to a median log_{10} cfu/g of 3.9-5.9. Moxifloxacin was the most effective agent in sterilizing 11/15 lungs followed by trovafloxacin at 8/15, and vancomycin at 4/14.

TABLE 6
Efficacy of Moxifloxacin Against Penicillin-Resistant *S. pneumoniae* in Murine Experimental Pneumonia

Treatment Regimen	30-min serum conc (µg/mL)	No. Sterile/ No. Total	Median Log10 CFU/g Lung	Range 25th-75th Percentile
None	---	0/17	8.1	7.3 – 8.6
Moxifloxacin	2.0	11/15	0.5	0.5 – 1.0
Trovafloxacin	5.3	8/15	0.5	0.5 – 2.8
Levofloxacin	5.3	1/10	4.3	4.0 – 4.5
Ciprofloxacin	5.4	0/9	5.9	5.6 – 6.2
Amoxicillin	12	0/14	5.4	5.2 – 5.8
Vancomycin	32	4/14	1.0	0.8 – 2.6

MOUSE THIGH MODEL

Vesga et al. (5) evaluated the pharmacokinetic parameters and therapeutic efficacy of moxifloxacin against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* in normal and neutropenic mouse thigh models. The moxifloxacin MICs of the test organisms were 0.015-0.25 µg/mL. Thigh muscles were injected with 7.77 $\log_{10}$ cfu/mL two hours prior to the initiation of treatment. To determine the effect of various dosing intervals on therapeutic efficacy, moxifloxacin was administered subcutaneously with total daily doses ranging in fourfold increments from 0.586 to 2400 mg/kg given in 1, 2, 4, or 8 doses over a 24 hour period. Efficacy was equivalent for each tested dose for time intervals q3h, q6h, q12h, or q24h for all organisms in neutropenic mice, which suggests the feasibility of once daily dosing. Against *Klebsiella pneumoniae* moxifloxacin showed the same efficacy at 24 hours for the q12h dosing for both neutropenic and normal mice. This indicates that neutropenia had no effect on the activity of moxifloxacin against *K. pneumoniae* at 24 hours after initiation of infection under these experimental conditions. However, at 24 hours after the initiation of infection and the same dosing interval in mice infected with *S. pneumoniae*, moxifloxacin was about 4 times more effective in normal mice. Pharmacokinetic parameters after administration of single subcutaneous doses of 6.25, 25, or 100 mg/kg to uninfected mice resulted in respective AUCs of 4.96, 24.0, and 58.7 mg.h/L. The C_{max} was 3.05, 9.09, and 15.5 µg/mL, respectively. The half-life increased from 1.1 hours after the 6.25 mg/kg dose to 2.14 hours after the 100 mg/kg dose. The therapeutic efficacy of moxifloxacin correlated best with AUC/MIC compared with C_{max}/MIC or Time above MIC.

RABBIT MENINGITIS MODEL

Ostergaard et al. (6,7) evaluated moxifloxacin against penicillin-resistant (MIC was actually 1.0 µg/mL so it was a penicillin-intermediate strain) and penicillin-susceptible *Streptococcus pneumoniae* type 9V in experimental meningitis in rabbits. The efficacy of moxfloxacin was compared with that of ceftriaxone and vancomycin. The pharmacokinetics of moxifloxacin in infected and noninfected rabbits were evaluated. New Zealand White rabbits were challenged intracisternally with 0.2 mL of 1 x 10^6 to 2 x 10^6 cfu/mL of *Streptococcus pneumoniae* type 9V. Table 7 shows the Minimal Inhibitory Concentrations (MICs) and Minimal Bactericidal Concentrations (MBCs) for the two strains.

TABLE 7
MICs and MBCs for the two *S. pneumoniae*
Type 9V strains used in the meningitis model

Agent	Strain 1 (1395)		Strain 2 (3058)	
	MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MBC (µg/mL)
Penicillin	1	1	≤0.031	≤0.031
Ceftriaxone	0.5	1	≤0.031	≤0.031
Vancomycin	0.5	0.5	0.5	0.5
Moxifloxacin	0.125	0.25	0.125	0.25

Approximately 10 hours after inoculation with the penicillin-resistant strain, six rabbits were administered two doses of moxifloxacin 40 mg/kg iv, five hours apart and eight rabbits were administered two doses of moxifloxacin 20 mg/kg iv, five hours apart. Two groups of five rabbits each were given either one dose of ceftriaxone 125 mg/kg iv or two doses of vancomycin 20 mg/kg iv, five hours apart. The three rabbits infected with the pencillin-susceptible pneumococcus were administered two doses of moxifloxacin 40 mg/kg iv. Ten hours post-treatment, the $\log_{10}$ cfu/mL in cerebrospinal fluid (CSF) was below the detection limit (1.7 $\log_{10}$ cfu/mL) for all treatment groups. Changes in $\log_{10}$ cfu/mL in CSF at 3 and 5 hours post treatment were significantly higher for moxifloxacin dosed at 40 mg/kg (-3.99 ± 1.30; -5.15 ± 1.40) than for vancomycin dosed at 20 mg/kg (-2.10 ± 1.07; -3.3 ± 1.09) but not higher than for ceftriazone (-3.09 ± 2.09; -4.51 ± 1.53). The two dose 40 mg/kg moxifloxacin regimen was better than the two dose 20 mg/kg moxifloxacin regimen at the 3 hour timepoint. Table 8 shows how many rabbits had sterile CSF at various timepoints with each treatment.

TABLE 8
Number of Rabbits with CSF Bacterial Concentrations
Under the Detection Limit at Various Timepoints

Agent and Dose	No. of rabbits with sterile CSF (n) at :			
	3 hour	5 hour	10 hour	24 hour
Untreated	0 (5)	0 (4)	0 (1)	ND
Ceftriaxone 125 mg/kg x 1	2 (5)	3 (5)	4 (5)	4 (4)
Vancomycin 20 mg/kg x 2	0 (5)	0 (5)	2 (3)	3 (3)
Moxifloxacin				
20 mg/kg x 2	0 (8)	0 (8)	1 (6)	5 (5)
40 mg/kg x 2	1 (9)	3 (9)	6 (6)	5 (5)

Moxifloxacin at 40 mg/kg was the only treatment group in which all rabbits had sterile CSF at 10 hours post treatment. Ceftriaxone was almost as good. At 24 hours post treatment all treatment groups produced sterile CSF in all animals.

There were no significacnt differences seen when the efficacies of moxifloxacin for treatment of the penicillin-susceptible and penicillin-resistant strains were compared.

This study demonstrated that moxifloxacin was effective in the treatment of both penicillin-intermediate and –susceptible pneumococcal meningitis in rabbits.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN ACUTE SINUSITIS

During each Phase III clinical study the susceptibility of the causative organisms was tested at the clinical trial site by the E-test method and by the disk diffusion test using NCCLS guidelines. Clinical isolates were sent to the microbiology laboratory at Bayer Corporation for confirmation of each organism's identity and for concurrent susceptibility testing by both the disk diffusion test and broth microdilution test. All isolates of *Streptococcus pneumoniae* were submitted to a reference laboratory, [redacted], for additional confirmation of identification and for repeat susceptibility testing for penicillin using broth microdilution. All aspirate specimens in the acute sinusitis clinical trials in the USA were obtained by antral puncture. The Bayer microbiology laboratory tested 61 isolates of *Streptococcus pneumoniae* from microbiologically evaluable patients.

Table 9 shows the range of moxifloxacin MICs for the 61 strains of *Streptococcus pneumoniae* isolated from the two acute sinusitis studies, D96-023 and D96-023A (aka 100131). The range of MICs was 0.06-0.5 µg/mL and the MIC_{90} was 0.25 µg/mL.

TABLE 9
MICs for Pre-Treatment Isolates of All *Streptococcus pneumoniae*

Study	No. Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
D96-023	29	0.06-0.5	0.125	0.25
D96-023A	32	0.06-0.25	0.125	0.25
Total	61	0.06-0.5	0.125	0.25

The clinical response and the bacteriological response for all 61 isolates of *Streptococcus pneumoniae* are summarized in Tables 10 and 11. Resolution occurred in 53/61 (86.9%) of patients at the Test-of-Cure visit, while 52/60 (86.7%) organisms were presumed eradicated.

TABLE 10
Clinical Response for All *Streptococcus pneumoniae*

	End of Therapy (%)			Test-of-Cure (%)	
Study	Resolve	Fail	Indeterminate	Resolve	Fail
D96-023	28 (97)	1 (3)	0 (0)	28 (97)	1 (3)
D96-023A	26 (81.3)	5 (15.6)	1 (3.1)	25 (78.1)	7 (21.9)
Total	54 (88.5)	6 (9.8)	1 (1.6)	53 (86.9)	8 (13.1)

TABLE 11
Bacteriological Response for All *Streptococcus pneumoniae*

	End of Therapy (%)				Test-of-Cure (%)		
Study	Erad	Pres Erad	Pres Persist	Indet	Pres Erad	Pres Persist	Erad/Recur
D96-023	1 (4)	27 (96)	0 (0)	0 (0)	27 (96)	1 (4)	0 (0)
D96-023A	3 (9.4)	26 (81.3)	2 (6.2)	1 (3.1)	25 (78.1)	5 (15.6)	2 (6.3)
Total	4 (6.7)	53 (88.3)	2 (3.3)	1 (1.7)	52 (86.7)	6 (10)	2 (3.3)

Erad = Eradicated; Pres Erad = Presumed Eradicated; Pres Persist = Presumed Persistent
Erad/Recur = Eradicated and then Recurred at Follow-Up

Fifteen penicillin-resistant strains of *Streptococcus pneumoniae* were isolated during the two sinusitis studies. The penicillin MICs were 2.0-4.0 µg/mL. At the Test-of-Cure visit, resolution and presumed eradication occurred at a rate of 93.3% for penicillin-resistant strains of *S. pneumoniae* (see Table 12) compared with resolution and presumed eradication rates of 84.8% and 84.4%, respectively, in the group of *Streptococcus pneumoniae* that excluded penicillin-resistant strains (Table 13). These 15 penicillin-resistant isolates represented 24.6% of the total of 61 microbiologically evaluable sinusitis isolates of *Streptococcus pneumoniae* that were tested prior to therapy.

TABLE 12
Bacteriological and Clinical Response by MIC at Test-of-Cure
Penicillin-Resistant *Streptococcus pneumoniae*

MIC (µg/mL)	Clinical Response		Bacteriological Response	
	Resolve	Fail	Pres Erad	Pres Persist
D96-023				
0.06	1	0	1	0
0.125	3	0	3	0
0.25	2	1	2	1
D96-023A				
0.06	1	0	1	0
0.125	7	0	7	0
Total	14 (93.3%)	1 (6.7%)	14 (93.3%)	1 (6.7%)

Pres Erad = Presumed Eradicated; Pres Persist = Presumed Persistent

TABLE 13
Bacteriological and Clinical Response by MIC at Test-of-Cure
Excluding Penicillin-Resistant *Streptococcus pneumoniae*

MIC (µg/mL)	Clinical Response		Bacteriological Response		
	Resolve	Fail	Pres Erad	Pres Persist	Erad/Recur
D96-023					
0.06	6	0	6	0	0
0.125	13	0	12	0	0
0.25	2	0	2	0	0
0.5	1	0	1	0	0
Total	22 (100%)	0 (0%)	21 (100%)	0 (0%)	0 (0%)
D96-023A					
0.06	2	0	2	0	0
0.125	12	6	12	5	1
0.25	3	1	3	0	1
Total	17 (70.8%)	7 (29.2%)	17 (70.8%)	5 (20.8%)	2 (8.3%)
GRAND TOTAL	39 (84.8%)	7 (15.2%)	38 (84.4%)	5 (11.1%)	2 (4.4%)

Pres Erad = Presumed Eradicated; Pres Persist = Presumed Persistent
Erad/Recur = Eradicated and then Recurred at Follow-Up

The MICs of penicillin from both the Bayer laboratory and the [redacted], as well as moxifloxacin MICs are provided by patient in Table 14. The MICs of penicillin obtained in both the Bayer laboratory and [redacted] were either equal or within the broth microdilution experimental error of one doubling dilution.

TABLE 14
MICs for Penicillin-Resistant *Streptococcus pneumoniae*
Isolated from Sinusitis

		Penicillin MIC (µg/mL)		MXF MIC (µg/mL)
	Patient No.	Bayer	CMI (Ref)	
D96-023				
	2009	2.0	2.0	0.125
	2013	2.0	2.0	0.125
	3008	2.0	2.0	0.125
	7003*	1.0	2.0	0.25
	7014	4.0	2.0	0.25
	7017	4.0	2.0	0.25
	23024	2.0	2.0	0.06
D96-023A				
	2118	2.0	4.0	0.125
	2122	4.0	4.0	0.125
	2130	2.0	4.0	0.125
	6114	1.0	2.0	0.125
	14107	4.0	4.0	0.125
	31126	2.0	4.0	0.06
	36109	4.0	>4.0	0.125
	41158	1.0	2.0	0.125

* Patient failed
MXF = Moxifloxacin

If the Bayer laboratory penicillin susceptibility results are used there are twelve (12) penicillin-resistant isolates and 12/12 are cured and presumed eradicated. If the reference laboratory results are used (usually the reference laboratory is used if there are conflicting results) there are 15 penicillin-resistant isolates and 14/15 (93.3%) are cured and presumed eradicated.

Bayer was told by the Agency that in order to obtain approval of *Streptococcus pneumoniae* (penicillin-resistant strains) in the indication of Acute Bacterial Sinusitis that it would be necessary for them to show efficacy for penicillin-resistant *S. pneumoniae* in a more serious indication such as Community Acquired Pneumonia. Bayer has submitted another supplement to NDA 21-085 with data for this organism in Community Acquired Pneumonia.

PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN COMMUNITY ACQUIRED PNEUMONIA

The sponsor has combined all of the penicillin-resistant *Streptococcus pneumoniae* isolates from all community acquired pneumonia studies. These studies include both the IV and tablet studies. The sponsor claims that they have data from 13 penicillin-resistant isolates. North American studies account for 6 of the 13 isolates. The studies were 100039 IV (n=4), D96-025 Tablet (n=1), and D96-026 Tablet (n=1). Five of these six isolates were cultured from sputum, while the sixth isolate was recovered from both sputum and blood. The clinical response for these six isolates at the end of therapy and at Test-of-Cure was resolution and all six organisms were presumed eradicated.

Penicillin susceptibility testing of the six North American isolates was performed concomitantly by E-test and broth microdilution at the Bayer microbiology laboratory. Table 15 summarizes the clinical and bacteriological results along with susceptibility testing results for these isolates.

TABLE 15
Moxifloxacin Patients Valid for Efficacy
With Penicillin-Resistant *Streptococcus pneumoniae* (U.S. Studies)

Patient #	Organism	Penicillin-MIC E-test	Penicillin-MIC Broth	Moxifloxacin MIC	Clinical Response	Bacteriological Response
STUDY 100039—I.V.						
13007	*S. pneumoniae*	3.0	2.0	0.06	Resolution	Pres-Erad
13025	*S. pneumoniae*	4.0	4.0	0.125	Resolution	Pres-Erad
48013	*S. pneumoniae*	1.5	2.0	0.125	Resolution	Pres-Erad
48013	*S. pneumoniae**	1.5	2.0	0.06	Resolution	Pres-Erad
71001	*S. pneumoniae*	3.0	4.0	0.125	Resolution	Pres-Erad
STUDY D96-025—Tablet						
4006	*S. pneumoniae*	2.0	2.0	0.125	Resolution	Pres-Erad
STUDY D96-026—Tablet						
248	*S. pneumoniae*	4.0	4.0	0.125	Resolution	Pres-Erad

* Isolate recovered from blood specimen
Pres-Erad = Presumed Eradicated

Bayer has included two studies (8,9) to try and show that the E-test method and broth microdilution give equivalent results. Although these studies showed that over 90% of the results by both methods were within one-dilution of each other, the E-test method can produce results one dilution higher than those seen with the broth microdilution method, which is the reference method. Since many of these isolates have penicillin MIC values of 1.5 or 2.0 µg/mL by the E-test method, these may really be isolates with MICs of 1.0 µg/mL when tested by broth dilution. These isolates may, therefore, not be truly penicillin-resistant. All six North American isolates have broth microdilution MIC results ≥2.0 µg/mL and are truly penicillin-resistant. All six were presumed eradicated.

There were seven *S. pneumoniae* isolates from foreign studies. These isolates were only tested by the E-test method and are no longer available. They were not tested by broth dilution. Six isolates were from tablet study 0140 and one isolate was from the foreign IV study 200036. Table 16 summarizes the clinical and bacteriological results along with susceptibility testing results for these isolates.

TABLE 16
Moxifloxacin Patients Valid for Efficacy
With Penicillin-Resistant *Streptococcus pneumoniae* (Foreign Studies)

Patient #	Organism	Penicillin MIC–E-test	CNTY	Moxifloxacin MIC	Clinical Response	Bacteriological Response
STUDY 140—Tablet						
10011	*S. pneumoniae*	2.0	FR	0.125	Fail	Pres-Persist
10099	*S. pneumoniae*	1.5	FR	1.0	Resolution	Eradication
10370	*S. pneumoniae*	1.5	MEX	0.125	Resolution	Pres-Erad
10304	*S. pneumoniae*	2.0	SPA	0.250	Resolution	Pres-Erad
10434	*S. pneumoniae*	2.0	HK	0.125	Resolution	Pres-Erad
10674	*S. pneumoniae*	6.0	RUS	0.50	Fail	Pres-Persist
STUDY 200036—I.V.						
38101	*S. pneumoniae*	2.0	SPA	0.125	Resolution	Pres-Erad

Pres-Erad = Presumed Eradicated
Pres-Persist = Presumed Persistent
CNTY = Country; FR = France; MEX = Mexico; SPA = Spain; HK = Hong Kong; RUS = Russia

Since all but one of these foreign isolates had E-test penicillin MICs of 1.5 or 2.0 µg/mL and were not tested by the reference broth dilution method they can not be considered to be truly penicillin-resistant isolates. Only the isolate with a penicillin MIC of 6.0 µg/mL will be included as penicillin-resistant.

There are, therefore, only seven truly penicillin-resistant isolates. Six of the seven were eradicated or presumed eradicated. This number of isolates may not be enough to allow the inclusion of penicillin-resistant *S. pneumoniae* in the community acquired pneumonia indication. The sponsor has indicated that four to six more isolates will be submitted at the four month safety update for this NDA.

In the four month safety update submitted for NDA 21-277 (Moxifloxacin I.V.) there were six additional isolates of *S. pneumoniae* that were resistant to penicillin (MICs of 2.0 to 4.0 µg/mL). These isolates were from an additional tablet community-acquired pneumonia study. The isolates were from the sputum of patients 1012, 1019, 1028, 1032, and 604001 and from blood of patient 614002 (TABLE 17). The responses for these six isolates at the Test-of-Cure visit were all resolution and presumed eradication.

TABLE 17
Penicillin MICs of Penicillin-Resistant *S. pneumoniae*
Isolated from CAP Study 100224[a]

Site Number / Country	Patient Number	Source	Broth MIC	Etest MIC
1 / USA	1012	Sputum	2.0	3.0
1 / USA	1019	Sputum	4.0	8.0
1 / USA	1028	Sputum	4.0	3.0
1 / USA	1032	Sputum	2.0	1.5
604 / Spain	604001	Sputum	2.0	2.0
614 / Spain	614002	Blood	2.0	1.0

[a] Enrichment study for isolation of *S pneumoniae*

Including these six additional isolates, there are now twelve penicllin-resistant *S. pneumonia* isolates with pencillin MICs determined by broth microdilution. If the isolate with an E-test penicillin MIC of 6.0 µg/mL is included there are thirteen isolates that were penicillin-resistant that were cultured from patients in CAP studies. Twelve of the thirteen were presumed eradicated after moxifloxacin treatment. The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in CAP with these thirteen isolates.

NDA REFERENCES

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7. Ostergaard C ST, Knudsen JD, Moller NF. Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. *Antimicrobial Agents and Chemotherapy.* 1998; **42:**1706-1712.

8. Tenover F, Baker C, Swenson J. Evaluation of commercial methods for determining antimicrobial susceptibility of *Streptococcus pneumoniae. J Clin Microbiol.* 1996;**34:**10-14.

9. Skulnick M, Small G, Lo P, Patel MP, Porter CR, Low DE, Matsumura S, and Mazzulli T. Evaluation of accuracy and reproducibility of E test for susceptibility testing of *Streptococcus pneumoniae* to penicillin, cefotaxime, and ceftriaxone. *J Clin Microbiol.* 1995;**33:**2334-2337.

RECOMMENDATIONS (To be Communicated)
Changes to the Proposed Label

The applicant should be notified of the following:

Assuming that the data submitted is sufficient to approve an indication of uncomplicated skin and skin structure infections:

1. The statement reading "

   should be revised to read "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 evidence present was related to mechanisms associated with these genes in *S. pneumoniae* and *S. aureus.*

2. The statement reading "

   should be revised to read "*In vitro* resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency between 1.8×10^{-9} to $<1 \times 10^{-11}$ for Gram-positive bacteria. The mutation rates for Gram-negative bacteria are higher at 1×10^{-8} for *Escherichia coli* and 1×10^{-6} for *Pseudomonas aeruginosa*. This higher mutation rate for *Pseudomonas aeruginosa* is seen with most fluoroquinolones." Mutation rates from Gram-negative bacteria, especially *Pseudomonas aeruginosa* were higher than those for Gram-positive bacteria. This should be reflected in the label.

3. The section of the Microbiology subsection

   should be deleted. This information has never been allowed in the labeling before. We usually do not even allow Although studies have shown that efficacy seems to be related to these pharmacodynamic parameters the addition of this information in the microbiology section does not really add any useful information since clinical trials have been performed and the drug has been shown to be effective against the organisms listed in the table. Different studies have used slightly different values for the AUC/MIC ratio that leads to efficacy. Most studies seem to indicate that once this value has been reached higher values do not add to the efficacy of the drug. Most studies also have used individual MIC values for each pathogen and not the MIC_{90} value. If this information is allowed into the label it will not really be adding useful information since efficacy against these pathogens has been shown. An AUC/MIC ratio greater than the value needed for good efficacy does not mean the drug has better efficacy against that organism.

4. The addition of penicillin-resistant *Streptococcus pneumoniae* to the clinical efficacy listing will be allowed if enough evidence is provided to show that these isolates are eradicated in the indication of community acquired pneumonia. From the microbiological viewpoint there are 13 penicillin-resistant isolates. Twelve of the thirteen patients were cured and the organism is presumed to be eradicated.

5. The placement of *Streptococcus pyogenes* in the clinical efficacy list (list #1) is acceptable if the skin indication is approved. From the microbiological viewpoint not enough isolates of *Streptococcus agalactiae* were tested in the skin clinical trials to allow this organism into the efficacy list. *Streptococcus agalactiae* may, however, be added to the *in vitro* activity list (list #2) if the skin indication is approved.

6. From the microbiological viewpoint not enough isolates of *Legionella pneumoniae* were studied in the clinical trials to allow this organism into the clinical efficacy list (list #1).

7. *Staphylococcus epidermidis* may be added to the *in vitro* activity listing (list #2) if the skin indication is approved. It should be qualified as (methicillin-susceptible strains only). Although the MIC_{90} values for methicillin-resistant isolates was ≤ 2 µg/mL in all submitted studies, less than 100 methicillin-resistant isolates were tested and the MIC_{90} value was at the susceptible breakpoint. As with other fluoroquinolones the MIC values for methicillin-resistant strains was higher than for methicillin-susceptible strains and methicillin-resistant staphylococci are normally resistant to all fluoroquinolones.

8. *Streptococcus* viridans group and *Streptococcus agalactiae* may be added to the *in vitro* activity listing (list #2) if the skin indication is approved.

9. Since from the microbiological viewpoint not enough isolates of *Legionella pneumophila* were treated in the clinical trials this organism should remain in the *in vitro* activity listing (list #2) instead of being moved to the clinical efficacy list (list #1).

10. In the Susceptibility Tests subsection the words "For testing *Streptococcus* species including *Streptococcus pneumoniae*" should replace the words ' " in both the Dilution Techniques and the Diffusion Techniques sections.

11. The NCCLS references should be updated to the January 2000 versions.

The Microbiology subsection of the package insert should, therefore, be revised to read as follows: Deletions to the sponsor's proposed labeling are indicated by a strikeout. Additions to the sponsor's proposed labeling are indicated by a double underline.

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 C-8-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. The mutation rates for Gram-negative bacteria are higher at 1×10^{-8} for *Escherichia coli* and 1×10^{-6} for *Pseudomonas aeruginosa*. This higher mutation rate for *Pseudomonas aeruginosa* is seen with most fluoroquinolones.

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)
Streptococcus pyogenes

* Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC ≥2 µg/mL.

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 method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* species:

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

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

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

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

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

For testing *Streptococcus* species including *Streptococcus pneumoniae*:[b]

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

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration 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 concentration usually achievable; other therapy should be selected.

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

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

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

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

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

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

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

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

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

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

[e] This zone diameter standard is applicable only to disk diffusion 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)	Interpretation	
≥ 18	Susceptible	(S)
15-17	Intermediate	(I)
≤ 14	Resistant	(R)

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

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

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

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	28-35
Haemophilus influenzae ATCC 49247[g]	31-39
Staphylococcus aureus ATCC 25923	28-35
Streptococcus pneumoniae ATCC 49619[h]	25-31

[g] These quality control limits are applicable only to *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2].

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

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—~~Fourth~~ Fifth Edition. Approved Standard NCCLS Document M7-~~A4~~ 5 , Vol. ~~17~~ 20, No. 2, NCCLS, Wayne, PA, January ~~1997~~ 2000.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--~~Sixth~~ Seventh Edition. Approved Standard NCCLS Document M2-A~~6~~ 7, Vol. ~~17~~ 20, No. 1, NCCLS, Wayne, PA, January ~~1997~~ 2000.

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