CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-334 *and* 21-085/S-010

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDA#: 21-334

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	26-OCT-00
CDER DATE:	27-OCT-00
REVIEW ASSIGN DATE:	10-NOV-00
REVIEW COMPLETE DATE:	22-JAN-01

SPONSOR:
Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON:
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SUBMISSION REVIEWED: Original NDA Submission

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

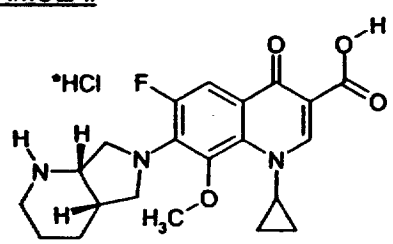
INDICATIONS: Uncomplicated Skin and Skin Structure Infections.

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)

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 that time the Division concluded that the indication of uncomplicated skin and skin structure infections was approvable pending the submission of data confirming the safety of moxifloxacin tablet therapy. This submission represents the sponsor's response concerning the uncomplicated skin and skin structure infections indication and has been given a new NDA number (NDA 21-334).

The approvable letter for NDA 21-085 described post-marketing studies that Bayer was suppose to perform before the skin indication would be granted. The additional data Bayer agreed to provide are comprised of a number of clinical pharmacology studies that would further characterize moxifloxacin related changes in the QT interval on the ECG; two large scale observational studies, one conducted in North America, and one in Europe; and post-marketing surveillance data from at least one million patients. These data have been submitted.

The sponsor is now asking for an indication of uncomplicated skin and skin structure infections caused by *Stapylococcus aureus, Streptococcus pyogenes* or *Streptococcus agalactiae*. No new microbiology issues are involved with the submission of these data. If the indication is granted the only microbiology issue will be the addition of organisms in the labeling for the new indication.

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. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 52-58.

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EXECUTIVE SUMMARY

Most of the older fluoroquinolones such as ciprofloxacin have excellent *in vitro* activity against gram-negative aerobic bacteria. They have limited or no activity, however, against gram-positive aerobic bacteria or anaerobes. Moxifloxacin is the result of searching for a new quinolone that has better activity against gram-positive bacteria and anaerobes while retaining activity against gram-negative pathogens. Moxifloxacin is a C-8-methoxyfluoroquinolone. TABLE A shows mode MIC_{90} values for moxifloxacin against some common pathogens associated with skin infections. Based on the preclinical and clinical data provided in this NDA the susceptible breakpoint for moxifloxacin for non-fastidious organisms was set at ≤2.0 µg/mL. The susceptible breakpoint for *Streptococcus* species was set at ≤1.0 µg/mL.

TABLE A
Moxifloxacin *in vitro* Activity

PATHOGEN	MODE MIC_{90} (µg/mL)*
Staphylococcus aureus (methicillin-susceptible)	0.12
Staphylococcus aureus (methicillin-resistant)	4.0
Staphylococcus epidermidis (methicillin-susceptible)	0.12
Staphylococcus epidermidis (methicillin-resistant)	2.0
Streptococcus agalactiae	0.5
Streptococcus pyogenes	0.25
Viridans Group Streptococci	0.25

TABLE B gives a summary of moxifloxacin's *in vitro* activity compared to other fluoroquinolones.

TABLE B
In vitro Activity of Moxifloxacin compared to other Fluoroquinolones (MIC_{90}s µg/mL)

Organism	MOX	CIPRO	LEVO	TROV
Streptococcus pyogenes	**0.25**	1.0	1.0	0.25
Streptococcus agalactiae	**0.25**	1.0	2.0	0.25
Staphylococcus aureus (MS)	**0.06-0.12**	1.0	0.25	0.06-0.12
Staphylococcus aureus (MR)	**4.0**	≥32	16-64	4-8
Staphylococcus epidermidis (MS)	**0.12**	1.0	0.5	0.12
Staphylococcus epidermidis (MR)	**2.0**	≥32	8-16	0.25-8

MS = Methicillin-susceptible MR = Methicillin-Resistant

The data in the above table demonstrate that moxifloxacin has somewhat better activity against gram-positive bacteria (usually 4- to 8-fold) than does ciprofloxacin or levofloxacin. Moxifloxacin and trovafloxacin had equivalent activity against most gram-positive aerobes. As resistance increased for the older fluoroquinolones in staphylococci, moxifloxacin's MIC also increased but did not reach as high a value as those for the other quinolones.

A limited amount of data are presented on moxifloxacin's activity against bacteria resistant to other agents. It has better activity than most other fluoroquinolones against methicillin/ciprofloxacin resistant *Staphylococcus aureus* but its MIC_{90} value for these organisms is above the susceptible breakpoint. As ciprofloxacin MICs increase for this organism, moxifloxacin's MICs also increase but tend to increase only to a value of 4 µg/mL while the MIC values for most other fluoroquinolones increase to ≥128 µg/mL.

Several studies indicate that moxifloxacin is effective in animal models of infections relating to skin. TABLE C summarizes the results of animal model testing.

TABLE C
Moxifloxacin Effectiveness in Animal Models

Model	Infecting Organism	Results
Mouse Protection Studies (intraperitoneal)	*Staphylococcus aureus*	20 mg/kg moxi= 100% survival (SC) 80 mg/kg cipro or spar = 100 %
	Streptococcus pyogenes	80 mg/kg moxi or spar = 100% (SC) 80 mg/kg cipro = 60 % survival
Thigh Muscle Infections (mice)	*Enterococcus faecalis*	80 mg/kg moxi or spar = 3 log reduction Cipro not effective
Pouch Model (rats)	*Staphylococcus aureus* (Cipro-S)	20 mg/kg moxi 1.5 log reduction Spar not effective 80 mg/kg moxi 2.5 log reduction Spar not effective
	Staphylococcus aureus (Cipro-S)	100 mg/kg moxi=7log reduction in 3 day 50 mg/kg =3log reduction in 6 days
	Staphylococcus aureus (Cipro-Meth-R)	Same as Cipro-S

Cipro-S = Ciprofloxacin-susceptible Cipro-Meth-R = Ciprofloxacin + Methicillin Resistant

The above data indicate that moxifloxacin is effective in selected animal models of infection. In most studies it appears to be more active than ciprofloxacin against gram-positive pathogens.

A single dosage or 400 mg once daily, administered as a 400 mg tablet, is proposed for marketing. Bioavailability is approximately 90%. 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 the feces (~25% of dose). Protein binding is about 50%. Maximum plasma concentration (C_{max}) at steady state with a 400 mg once daily dose is approximately 4.5 µg/mL. The mean steady-state AUC is 48 mg*h/L.

PRECLINCIAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

No new information has been submitted.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

No new information has been submitted. The sections of the original microbiology review that pertain to organisms associated with skin infections is included in this review so that the reader will be reminded of moxifloxacin's activity for these organisms.

MICs were performed on relevant clinical isolates of skin and skin structure infections. Susceptibility testing was performed according to NCCLS guidelines in almost all studies regardless of the methods usually used in the respective country.

The susceptibility breakpoint for moxifloxacin is ≤2.0 µg/mL for *Staphylococcus* species and ≤1 µg/mL for *Streptococcus* species.

The labeling submitted by the applicant proposes to add the shaded organisms to the label in the efficacy list (list #1)

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

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

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The submitted label proposes the following changes to the *in vitro* activity list (list #2):

Aerobic gram-positive microorganisms
Staphylococcus epidermidis
Streptococcus pneumoniae (penicillin-resistant strains)
[redacted]
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

Each of these added organisms will be discussed below along with the reason for including or excluding it from the label.

GRAM-POSITIVE AEROBES

Streptococci

Activity against *Streptococcus pyogenes* is shown in TABLE 1. The mode MIC_{90} for *Streptococcus pyogenes* was 0.25 µg/mL. All studies have MIC_{90}s of 0.125 or 0.25 µg/mL. Well over 100 isolates were tested and many different studies are presented. *Streptococcus pyogenes* may be placed in the clinical efficacy section of the label with Medical Officer concurrence.

TABLE 2 presents data on the activity of moxifloxacin against other streptococci. *Streptococcus agalactiae* was tested in five studies and all MIC_{90} values were 0.25-0.5 µg/mL. Over 100 isolates were tested. *Streptococcus agalactiae* may be placed in the clinical efficacy section of the label if the Medical Officer concurs. In the original NDA 21-085 (Moxifloxacin Tablets) the Medical Officer's review determined that not enough patients had this organism to allow it into list #1. Since no new isolates have been submitted this species should be placed in the *in vitro* activity listing (list #2).

The viridans group of streptococci were tested in about five separate studies. Some of these studies tested individual species (e.g. *S. mitis, S. milleri)* and other studies tested all species together as the viridans group. All MIC_{90} values were 0.25-0.5 µg/mL. Over 100 isolates were tested. Streptococci viridans group may be placed in the *in vitro* activity listing in the label.

TABLE 3 summarizes activity against streptococci other than *Streptococcus pneumoniae.*

Table 1

IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PYOGENES*

Ref.	(No.)	Range	MIC_{50}	MIC_{90}
6	(20)		-	0.25
7	(99)		0.12	0.12
8, 9	(47)		0.25	0.25
10	(1152)		0.125	0.25
18	(120)		0.12	0.25
1	(14)		0.12	0.12
11	(169)		0.125	0.25
12	(26)		-	0.1
4, 5	(60)		0.25	0.25

Table 2

IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER *STREPTOCOCCUS* SPP

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref
S. agalactiae (20)		-	0.5	6
S. agalactiae (96)		0.12	0.5	7
S. agalactiae (38)		0.25	0.5	8, 9
S. agalactiae (12)		0.12	0.25	1, 2
S. agalactiae (25)		0.25	0.25	19, 20, 21
ß-heme *Streptococcus* (70)		-	0.25	19, 20, 21
Streptococcus gp G (22)		0.13	0.13	8, 9
Streptococcus gp C (8)		0.13	-	8, 9
S. milleri gp (22)		0.06	0.06	9, 22
S. milleri (21)		-	0.1	12
S. milleri (30)		0.12	0.5	15, 16, 17
S. equisimilis (89)		0.06	0.125	11
S. mitis (25)		-	0.2	12
S. sanguis (25)		-	0.2	12
S. bovis (25)		-	0.2	12
S. viridans gp (60)		-	0.25	6
S. viridans gp				7
Pen-S (60)		0.12	0.25	
Pen-I (100)		0.12	0.25	
Pen-R (61)		0.12	0.25	
S. viridans gp (16)		0.12	0.25	1, 2
S. viding gp (27)		0.12	0.25	19, 20, 21
S. viridans gp (10)		0.25	0.5	4, 5

Pen-S = Penicillin-susceptible Pen-I = Penicillin-intermediate Pen-R = Penicillin-resistant

Table 3
SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER STREPTOCOCCI

	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Streptococcus pyogenes (1607)		0.25
Streptococcus agalactiae (191)		0.5
Streptococcus viridans gp. (334)		0.25

Staphylococci

TABLE 4 summarizes moxifloxacin's activity against *Staphylococcus aureus*. Susceptibility was evaluated according to the organism's susceptibility to methicillin in most cases. The mode MIC_{90} for methicillin-susceptible *Staphylococcus aureus* was 0.12 µg/mL. The MIC_{90} values ranged from [redacted] Moxifloxacin was not as active against methicillin-resistant strains of *Staphylococcus aureus*. Against these strains the mode MIC_{90} was 4.0 µg/mL with a range of MIC_{90} values from [redacted] *Staphylococcus aureus* may be placed in the clinical activity section of the label (with Medical Officer concurrence) but it must be qualified as methicillin-susceptible strains only.

TABLE 5 shows data from testing of other staphylococci. Once again it appears that methicillin-susceptible strains are more susceptible to moxifloxacin than methicillin-resistant strains. The difference between methicillin-susceptible and –resistant strains of *S. epidermidis* does not seem to be as large as the difference detected with *S. aureus*. All studies with *S. epidermidis* had MIC_{90} values ≤2.0 µg/mL (the susceptible breakpoint). Although it appears that methicillin-resistant *S. epidermidis* had MIC_{90} values below the susceptible breakpoint, less than 100 isolates were tested and the median MIC_{90} value was 2.0 µg/mL (the susceptible breakpoint). Methicillin-resistant staphylococci always have a much higher MIC_{90} than do the methicillin-susceptible strains for all the fluoroquinolones and the methicillin-resistant strains are usually fluoroquinolone-resistant. *Staphylococcus epidermidis* may be listed in the *in vitro* activity listing in the label but should be qualified as *Staphylococcus epidermidis* (methicillin-susceptible strains only).

TABLE 6 summarizes the *in vitro* activity of moxifloxacin against staphylococci.

Table 4 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS AUREUS*

MSSA				MRSA				
(No.)	RANGE	MIC_{50}	MIC_{90}	(No.)	Range	MIC_{50}	MIC_{90}	Ref.
(128)		0.03	0.06	(108)		2	4	7
(90)		0.03	0.06	(63)		0.06	4	8, 9
(34)		0.06	0.06	(20)		2	4	1, 2
(31)		0.06	0.12	(25)		2	4	19, 20, 21
(25)		-	0.1	(25)		-	8	12
-		-	-	(194)		0.5	1	23
(25)		0.06	2	(27)		2	4	24
(100)		0.03	1	-		-	-	14
(54)		0.06	0.12	(20)		2	2	15.16
(39)		0.125	0.125	(21)		2	4	4. 5
(62)*		-	8	-		-	-	6
(322)*		0.06	0.125	-		-	-	10
(131)*		0.06	0.125	-		-	-	11
(18)*		0.03	0.03	-		-	-	25

*No methicillin susceptibility given

APPEARS THIS WAY
ON ORIGINAL

Table 5

IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS* SPP

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref.
S. epidermidis MS[a] (39)		0.06	0.13	8, 9
S. epidermidis MS (23)		0.06	0.12	1, 2
S. epidermidis MS (25)		-	0.1	12
S. epidermidis MR[b] (26)		0.06	0.13	8, 9
S. epidermidis MR (29)		1	2	1, 2
S. epidermidis MR (25)		-	2	12
S. epidermidis (15)		0.06	0.06	25
S. epidermidis (51)		0.12	2	14
S. haemolyticus MS (34)		0.06	0.13	8, 9
S. haemolyticus MR (20)		0.06	0.13	8, 9
S. haemolyticus MR (22)		4	4	1, 2
S. haemolyticus (25)		-	4	12
S. haemolyticus (10)		2	4	14
S. hominis (29)		0.03	0.06	7, 8
S. hominis (10)		0.06	0.5	1, 2
S. hominis (10)		0.06	0.12	14
S. saprophyticus MS (20)		0.03	0.06	8, 9
S. saprophyticus MR (20)		0.06	1	8, 9
S. saprophyticus (16)		0.12	0.25	1, 2
S. simulans (20)		0.03	0.06	8, 9
S. simulans (10)		0.03	0.06	14
S. warneri (7)		0.03	--	8, 9
S. warneri (10)		0.06	0.12	14
S. cohnii (21)		0.03	0.06	8, 9
S. xylosus (6)		0.06	0.06	8, 9
S. lugdunensis		0.12	0.12	14
S. capitis (9)		0.06	0.12	14

[a] Methicillin-Susceptible
[b] Methicillin-Resistant

Table 6 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST STAPHYLOCOCCI

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Staphylococcus aureus		
Meth-S (526)		0.125
Meth-R (309)		4
Staphylococcus epidermidis (233)		0.12

SUMMARY OF IN VITRO ACTIVITY

Assuming that the data submitted is sufficient to approve an indication of uncomplicated skin and skin structure infections caused by *Staphylococcus aureus, Streptococcus pyogenes,* or *Streptococcus agalactiae*, then *Streptococcus pyogenes* may be deleted from the *in vitro* activity listing (list #2 in the Microbiology subsection) and placed into the listing for which clinical efficacy has been shown. *Streptococcus agalactiae* may also be placed in the label. The Medical Officer's review for NDA 21-085 (Moxifloxacin Tablets) stated that there were insufficient numbers of patients with *S. agalactiae* treated with moxifloxacin to determine its efficacy against this organism. *S. agalactiae* should, therefore, be placed in the *in vitro* activity listing (list #2).

Staphylococcus epidermidis may be added to the *in vitro* activity listing (list #2) but it should be qualified as *Staphylococcus epidermidis* (methicillin-susceptible strains). Although the MIC_{90} value in all submitted studies was ≤ 2 µg/mL, less than 100 isolates were tested and the MIC_{90} values for the methicillin-resistant strains was at the susceptible breakpoint. As with all 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.

Streptococcus viridans group may be added to the *in vitro* activity listing.

The list of organisms should, therefore, read as follows: [Shaded organisms are additions to approved labeling and strikeouts are deletions to approved labeling].

Organisms with both clinical efficacy (if this is shown) and *in vitro* activity:

Aerobic gram-positive microorganisms:

Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)
~~*Streptococcus pyogenes*~~

Aerobic gram-negative microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis

Other microorganisms

Chlamydia pneumoniae
Mycoplasma pneumoniae

The *in vitro* activity list with MIC_{90} values of ≤ 2.0 µg/mL includes:

Aerobic gram-positive microorganisms
Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-resistant strains)
[redacted]
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

IN VITRO COMPARISON TO OTHER AGENTS

Moxifloxacin was compared to other agents in many studies. Fluoroquinolones, especially ciprofloxacin, were usually the comparative agent.

IN VITRO COMPARISON AGAINST GRAM-POSITIVE COCCI

Against *Streptococcus pyogenes*, moxifloxacin's MIC_{90} was 0.25 µg/mL. Levofloxacin and ciprofloxacin had MIC_{90} values of 1.0 µg/mL (TABLE 7). The MIC_{90} values of the β-lactams ranged from [redacted] Against *Streptococcus agalactiae* moxifloxacin's MIC_{90} was 0.25 µg/mL, which was fourfold lower than that of ciprofloxacin (TABLE 8). Once again the β-lactams were more active with a MIC_{90} of ≤ 0.06 µg/mL

Against methicillin-susceptible *Staphylococcus aureus*, moxifloxacin MIC_{90} values of 0.06-0.12 µg/mL were comparable to those of trovafloxacin and at least tenfold less than the MIC_{90} values for ciprofloxacin (TABLE 9). The MIC_{90} for vancomycin was 1.0 µg/mL and the MIC_{90}s for cephalosporins were 1.0-4.0 µg/mL. The moxifloxacin MIC_{90} for methicillin-resistant *Staphylococcus aureus* increased to 4.0 µg/mL. Most other drugs had MIC_{90}s ≥ 32 µg/mL for these organisms (TABLE 10). TABLE 11 compares moxifloxacin and other drugs against other staphylococci. Once again moxifloxacin and trovafloxacin had basically equivalent MICs and were lower than those for the other quinolones. Moxifloxacin seemed to have better activity than trovafloxacin against methicillin-resistant strains.

GLOSSARY OF ABBREVIATIONS
[Used in Tables 7-11]

AMC	-	Amoxicillin/Clavulanate
CEF	-	Cephalosporin
CIP	-	Ciprofloxacin
CLA	-	Clarithromycin
CLN	-	Clindamycin
ERY	-	Erythromycin
FOX	-	Cefoxitin
LEV	-	Levofloxacin
MET	-	Metronidazole
MXF	-	Moxifloxacin
OFL	-	Ofloxacin
SPA	-	Sparfloxacin
TRO	-	Trovafloxacin

Table 7 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PYOGENES*

		MIC90 µg/mL						
Ref.	(No.)	MXF	LEV	CIP	TRO	AMC	CEF	ERY
6	(20)	0.25	-	1	-	-	≤0.06[a]	>4
7	(99)	0.12	-	1	-	≤0.01[b]	≤0.01[c]	16
8	(47)	0.25	1	1	0.25	-	-	-
18	(30)	0.25	4[d]	2	-	-	-	-
1	(14)	0.12	1[d]	0.25	-	≤ 0.03	≤ 0.03	0.06[e]
11	(169)	0.25	-	2	0.25	-	-	-
5	(60)	0.25	1	1	-	0.03	0.03[c]	0.125
15, 16, 17	(20)	0.25	-	1	0.25	0.015	0.015	-

[a] cefotaxime
[b] amoxicillin
[c] cefuroxime
[d] ofloxacin
[e] clarithromycin
[f] cefpodoxime

Table 8 - COMPARATIVE ACTIVITY OF MOXIFLOXACIN AGAINST OTHER *STREPTOCOCCUS* SPP

	MIC_{90} µg/mL							
	MXF	LEV	CIP	TROV	AMC	CEF	ERY	Ref.
S. agalactiae (20)	0.25	-	2	-	-	≤ 0.06[a]	>4	6
S. agalactiae (96)	0.25	-	1	-	-	0.03[b]	32	7
S. agalactiae (38)	0.5	1	2	0.5	-	-	-	8
S. agalactiae (12)	0.25	2[b]	1	-	0.06	0.06[c]	1[d]	1
S. agalactiae (25)	0.25	2[b]	-	-	-	-	-	20
S. agalactiae (20)	0.25	-	1	0.25	0.06	0.06[b]	-	17
ß-heme *Streptococcus* (70)	0.25	2[b]	-	-	-	-	-	20
Streptococcus gp G (22)	0.13	1	1	0.13	-	-	-	8
S. milleri (21)	0.1	0.5	0.5	0.1	-	-	-	12
S. milleri gp (22)	0.06	2	2	0.13	-	-	-	8
S. milleri (30)	0.25	-	1	0.25	0.12	0.5[b]	-	17
S. equisimilis (89)	0.125	-	2	0.125	-	-	-	11
S. mitis (25)	0.2	4	16	0.1	-	-	32	12
S. sanguis (25)	0.2	2	8	0.2	-	-	2	12
S. bovis (25)	0.2	2	2	0.5	-	-	32	12

Table 8 - COMPARATIVE ACTIVITY OF MOXIFLOXACIN AGAINST OTHER *STREPTOCOCCUS* SPP (Continued)

	MIC_{90} µg/mL							
	MXF	LEV	CIP	TROV	AMC	CEF	ERY	Ref.
Streptococcus viridans gp (60)	0.25	-	8	-	-	4[a]	>4	6
Streptococcus viridans gp								7
Pen-S (60)	0.25	-	4	-	-	1[b]	>64	
Pen-I (100)	0.25	-	4	-	-	4[b]	>64	
Pen-R (61)	0.25	-	4	-	-	64[b]	>64	
Streptococcus viridans gp (16)	0.25	4[c]	4	-	2	2[b]	1[d]	1
Streptococcus viridans gp (27)	0.25	4[c]	-	-	-	-	-	20
Streptococcus viridans gp (10)	0.5	2	8	-	0.125	0.5[b]	0.25	5

[a] cefotaxime
[b] cefuroxime
[c] ofloxacin
[d] clarithromycin
[e] cefpodoxime

Table 9 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS AUREUS* (METH SUSC)

		MIC_{90} µg/mL							
Ref.	(No.)	MXF	LEV	CIP	TRO	VAN	AMC	CEF	CLA
7	(128)	0.06	-	1	-	-	1	1[a]	-
8	(90)	0.06	0.25	0.5	0.06	-	-	-	-
1	(34)	0.06	0.25[b]	1	-	-	1	2[a]	0.5
20	(31)	0.12	1[b]	-	-	-	-	-	-
12	(25)	0.1	0.2	1	0.1	1	-	-	0.1
13	(100)	1	-	>32	-	1	-	-	-
23	(194)	1	64[b]	128	-	-	-	-	-
17	(54)	0.12	-	1	0.06	-	0.5	4[c]	-
6	(62)[d]	8	-	>16	-	2	>2[e]	>16	-
11	(131)[d]	0.125	-	1	0.125	-	-	-	-
25	(18)[d]	0.03	0.125	0.5	-	-	0.5	1[a]	0.5

[a] Cefuroxime
[b] Ofloxacin
[c] Cefpodoxime
[d] No methicillin susceptibility given
[e] Oxacillin

Table 10 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS AUREUS* / METH RESIST

		MIC_{90} µg/mL							
Ref.	(No.)	MXF	LEV	CIP	TRO	VAN	AMC	CEF	CLA
7	(108)	4	-	64	-	-	64	>64[a]	>64
8	(63)	4	16	32	4	-	-	-	-
1	(20)	4	≥32[b]	≥32	-	-	-	-	≥32
20	(25)	4	64[b]	-	-	-	-	-	-
12	(25)	8	16	32	8	4	-	-	32
17	(20)	2	-	128	2	-	16	>128[c]	-

[a] Cefuroxime
[b] Ofloxacin
[c] Cefpodoxime

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Table 11 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS* SPP

	MIC_{90} µg/mL							
Organism (No.)	MXF	LEV	CIP	TRO	AMC	CLA	VAN	REF.
S. epidermidis MS[a] (39)	0.13	0.5	1	0.13	-	-	-	8
S. epidermidis MS (23)	0.12	0.5[c]	0.5	-	0.25	≥32	-	1
S. epidermidis MS (25)	0.1	4	4	0.1	-	32	2	12
S. epidermidis MR[b] (26)	0.13	1	1	0.25	-	-	-	8
S. epidermidis MR (29)	2	16[c]	≥32	-	-	≥32	-	1
S. epidermidis MR (25)	2	8	32	8	-	32	2	12
S. epidermidis (15)	0.06	0.125	0.125	-	0.5	≥32	-	25
S. epidermidis (51)	2	-	≥32	-	-	2	-	13
S. haemolyticus MS (34)	0.13	1	1	0.13	-	-	-	8
S. haemolyticus MR (20)	0.13	1	1	0.25	-	-	-	8
S. haemolyticus MR (22)	4	≥32[c]	≥32	-	-	≥32	-	1
S. haemolyticus (25)	4	16	32	8	-	0.1	-	12
S. haemolyticus (10)	4	-	≥32	-	≥32	-	2	13

[a] Methicillin-Susceptible [b] Methicillin-Resistant [c] Ofloxacin

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

No new information submitted. From the information submitted with the original NDA it can be concluded that changes in test parameters had little effect on the *in vitro* activity of moxifloxacin. There were some changes when the pH value of the media was 5.6. This lowering of activity is seen with most fluoroquinolones. There was also an increase in MICs for streptococci at pH 8.4. This increase in MICs at high pH is usually not seen when testing fluoroquinolones. As usual with fluoroquinolones increasing the inoculum size (100-fold) to 10^7 cfu/mL also increased the MICs of moxifloxacin. The type of medium used for susceptibility testing did not appear to effect the MICs. In general, the method used for susceptibility testing did not effect moxifloxacin's MICs

BACTERICIDAL ACTIVITY

No new information has been provided. From the data in the original NDA it can be concluded that for most species the MIC and MBC (minimal bactericidal concentration) are equal or within one doubling dilution of each other.

Kill curve studies indicated that moxifloxacin acts much as the other fluoroquinolones do. Bactericidal activity is concentration dependent and is rapid (within 2-4 hours).

POSTANTIBIOTIC EFFECT

No new information is provided. Data submitted in the original NDA showed that the postantibiotic effect (PAE) of moxifloxacin was concentration dependent for all of the species tested. This is true for all other fluoroquinolones also. For most species the PAE ranged from 0 to 2.2 hours at 1 x MIC. The PAE was 1.2 to 3.1 hours at 2 x MIC and 1.4 to 3.3 hours at 10 x MIC.

ANTIBACTERIAL INTERACTION WITH OTHER ANTIMICROBIALS

No new information has been submitted. The results of combination studies with moxifloxacin revealed results much like those seen with most other fluoroquinolones. A few strains and a few combinations yield synergistic results in some studies and indifferent results in other studies. Most combinations show indifferent or additive results at best. Antagonism is often seen with fluoroquinolones and rifampin especially against staphylococci.

INTRACELLULAR ACCUMULATION AND INTERACTION WITH HOST DEFENSE FACTORS

No new information has been provided. Data from the original NDA demonstrated that moxifloxacin concentrates intracellularly in phagocytic and nonphagocytic cells. Concentrations several fold higher than extracellular concentrations were seen (about nine times higher in polymorphonuclear (PMN) leukocytes than in extracellular fluid). Moxifloxacin did not exhibit any adverse effects on killing, ingestion, or burst activity of PMNs.

ASSESSMENT OF RESISTANCE

No new information provided with this submission.

PRECLINICAL EFFICACY (*IN VIVO*)

PHARMACOKINETICS/BIOAVAILABILITY

No new information has been provided. Data from the original NDA (TABLE 12) shows some sample tissue concentration data following administration of 400 mg of moxifloxacin. Moxifloxacin concentrates, as do most other fluoroquinolones, in respiratory tract tissue. Concentrations in most skin tissue, however, are less than in plasma.

Table 12 – Tissue and plasma concentrations of moxifloxacin at 3 hours post-dose

Tissue	Tissue conc. (µg/g)	Plasma conc. (µg/mL)
Bronchial mucosa	5.4	
Alveolar macrophages	56.7	
Maxillary sinus	7.5	
Skin blister fluid	2.6	
Saliva	1.7	
Subcutaneous tissue	0.9	
Skeletal muscle	0.9	
Epithelial lining fluid	20.7	

ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

No new information has been submitted. Studies submitted with the original NDA that pertain to skin and skin structure infections are outlined below.

MOUSE PROTECTION STUDIES

Staphylococcus aureus and *Streptococcus pyogenes* were used to evaluate the efficacy of moxifloxacin in preventing death in a murine intraperitoneal infection model (26). A single dose of 5, 10, 20, 40, or 80 mg/kg body weight of moxifloxacin was administered either orally or subcutaneously in each group of ten mice. The mice were challenged intraperitoneally with 1.53×10^8 cfu/mouse in the *Staphylococcus aureus* group and with 1.14×10^3 cfu/mouse in the *Streptococcus pyogenes* group. Sparfloxacin and ciprofloxacin were used as comparators. Moxifloxacin effected a survival rate of 100% at 20 mg/kg subcutaneously, while 80 mg/kg was needed for the same response in mice treated with ciprofloxacin or sparfloxacin. Moxifloxacin was better than ciprofloxacin against *Streptococcus pyogenes*; however, 80 mg/kg of either sparfloxacin or moxifloxacin subcutaneously was needed for 100% survival. At 80 mg/kg ciprofloxacin effected only 60% survival. Similar results were seen for moxifloxacin and sparfloxacin when 80 mg/kg oral doses were given. Ciprofloxacin had little effect at 80 mg/kg orally.

To evaluate efficacy against gram-negative bacteria, groups of ten mice were infected intraperitoneally with 1.7×10^7 cfu/mouse of either *Escherichia coli* or *Klebsiella pneumoniae* (26). Moxifloxacin, sparfloxacin, or ciprofloxacin were administered in doses of 0.06 to 5.0 mg/kg subcutaneously or orally. When administered subcutaneously, 0.25 mg/kg of ciprofloxacin effected 100% survival, while 0.5 mg/kg subcutaneously of moxifloxacin or sparfloxacin gave the same results. After oral administration, 100% survival was obtained with 1.0 mg/kg moxifloxacin or sparfloxacin and with 0.5 mg/kg ciprofloxacin.

These data show the moxifloxacin is slightly inferior to ciprofloxacin against gram-negative bacteria, but superior against gram-positive bacteria in mouse protection studies.

THIGH MUSCLE INFECTIONS

Groups of five female mice were rendered neutropenic by treating with cyclophosphamide prior to infection. Infection was accomplished by injecting 1.55×10^5 cfu of *Enterococcus faecalis* into the thigh muscles (26). Oral administration of 10, 20, 40, or 80 mg/kg of moxifloxacin, sparfloxacin, or ciprofloxacin resulted in dose dependent reduction in cfu's. Sparfloxacin and moxifloxacin gave similar results at all tested doses. The 80 mg/kg dose for both drugs achieved a 3 $\log_{10}$ reduction in cfu's of *E. faecalis*. Ciprofloxacin had no effect at any dose in this model.

Vesga et al. (27) 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 concitions. 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. The therapeutic efficacy of moxifloxacin correlated best with AUC/MIC compared with C_{max}/MIC or Time above MIC.

POUCH MODEL

A rat pouch model of infection with a ciprofloxacin susceptible strain of *Staphylococcus aureus* was used to evaluate the effect of moxifloxacin on slowly growing or stationary phase organisms (26). An oral dose of 20 mg/kg of moxifloxacin produced an approximate 1.5 $\log_{10}$ reduction of cfu's. Sparfloxacin at this same dosage did not produce any decrease in cfu's. At 80 mg/kg, moxifloxacin effected a 2.5 $\log_{10}$ reduction in cfu's, while sparfloxacin at this dose had little effect. The concentration of moxifloxacin in the pouch was several fold lower than the concentration of sparfloxacin, but moxifloxacin was more active.

Further studies in the granuloma pouch model in rats evaluated activity against a ciprofloxacin susceptible strain of *Staphylococcus aureus* (QSSA); a ciprofloxacin resistant, methicillin resistant strain of *Staphylococcus aureus* (QMRSA); and a strain of *Streptococcus pneumoniae* (28, 29). Once daily doses of 100 mg/kg moxifloxacin, which achieved concentrations in the pouch that simulated those seen in human serum after a 400 mg oral dose, were administered orally. Treatment started either one hour or 24 hours after infecting the animals. A suboptimal dose of 50 mg/kg moxifloxacin was administered orally for six days after infection with a one-step or multiple-step

mutant of each organism. Samples of the pouch exudates were withdrawn daily and cultured on drug free agar and agar containing 2 x MIC or 4 x MIC moxifloxacin in order to determine the extent of emergence of resistance during optimal and suboptimal therapies. A reduction of approximately 7 $\log_{10}$ cfu/mL was achieved in *Streptococcus pneumoniae* after optimal treatment (100 mg/kg, 1 hour after infection) after one day of treatment. This same reduction in cfu/mL was seen after 3 days of optimal treatment in the quinolone sensitive *Staphylococcus aureus* strain. The suboptimal initiation of therapy resulted in much slower reductions in cfu/mL for *Streptococcus pneumoniae*. A 7 $\log_{10}$ reduction in cfu's took six days (instead of 1 day). QSSA was reduced by 3 $\log_{10}$ after six days. No emergence of resistance was seen for either organism regardless of treatment. The results for the QMRSA strain were similar to those for the ciprofloxacin susceptible strain. The suboptimal treatment of 50 mg/kg resulted in a reduction in cfu/mL of approximately 4 $\log_{10}$ after 8 days for *Staphylococcus aureus* and 6 $\log_{10}$ for *Streptococcus pneumoniae*. There was little reduction in cfu/mL for the multiple-step mutants of either organism, but there was no emergence of resistance.

Moxifloxacin appears to be effective in animal models of infection. In most models doses were used that compared to the dose that will be used in humans. According to these models moxifloxacin should be effective against skin and skin structure infections.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

No new information has been presented. In the original NDA the sponsor presented Phase III studies for the indication of skin and skin structure infections. A satisfactory response indicates that the pathogen was eradicated or presumed eradicated at the test of cure visit.

Skin and Skin Structure Infections (SSSI)

The sponsor is requesting an indication of skin and skin structure infections (SSSI) caused by *Staphylococcus aureus, Streptococcus pyogenes,* or *Streptococcus agalactiae*. A total of three studies were conducted. One (D97-005) of the three studies included a moxifloxacin dosing regimen consistent with the proposed labeling (400 mg x 7 days). The other two studies (0131 and 0122) were conducted using a moxifloxacin dosing regimen of 400 mg x 5-14 days. Two of the studies (D97-005 and 0131) were Phase III, adequate and well controlled pivotal studies. The third study (0122) was a pilot, Phase IIa study. Cephalexin was used as the control in both pivotal studies. TABLE 13 shows the eradication rates for these studies. In general eradication rates were comparable between moxifloxacin and cephalexin. There were only a few isolates of *S. pyogenes* in the United States study (D97-005). There also were only a few *Streptococcus agalactiae* isolates.

TABLE 13
Pathogen Eradication Rates for SSSI Studies

Study Number	Duration of Treatment	Moxifloxacin	Cephalexin
Staphylococcus aureus			
D97-005	7 days	57/62 (92%)	50/54 (93%)
0131	5-14 days	55/60 (92%)	50/56 (89%)
Streptococcus pyogenes			
D97-005	7 days	2/2 (100%)	3/4 (75%)
0131	5-14 days	10/11 (91%)	13/14 (93%)
Streptococcus agalactiae			
D97-005	7 days	6/7 (86%)	4/5 (80%)
0131	5-14 days	2/2 (100%)	1/1 (100%)
Streptococcus species			
0131	7 days	4/4 (100%)	6/6 (100%)

MIC/DISK DIFFUSION CORRELATION STUDIES

No new information has been submitted. Since *Streptococcus* species other than *Streptococcus pneumoniae* will now be placed in the clinical efficacy part of the label, breakpoint criteria must be included for these species. In the original NDA preclinical studies were submitted that proposed breakpoints for moxifloxacin for *Streptocuccus* species including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and nonfastidious bacteria. All studies to determine interpretive criteria were performed under the auspices of the [redacted] and directed by Arthur L. Barry. Moxifloxacin 5-µg disks were used for susceptibility testing. All testing was performed according to NCCLS guidelines, M2-A5 for disk tests and M7-A3 for broth microdilution tests. At least one quinolone was included in each study as a drug control. Only the studies that proposed breakpoints for streptococci will be outlined in this review. The numbers on the Figures in this review were not changed from what they were in the original review since they are part of copied figures and changing the numbers would be difficult. The numbers on the figures, therefore, start with number 12 and some numbers are not included.

STREPTOCOCCUS SPECIES INCLUDING *STREPTOCOCCUS PNEUMONIAE*

Two studies were performed at different times. The first study (3) included only *Streptococcus pneumoniae* and did not include any strains with high level resistance to ciprofloxacin. The second study (30) evaluated *Streptococcus* species including *Streptococcus pneumoniae* and included strains that had intermediate and high level resistance to ciprofloxacin.

In the first study, a total of 301 strains of *Streptococcus pneumoniae* were tested by both disk diffusion and broth microdilution methods. Of these strains, 134 were penicillin-susceptible, 106 were penicillin-intermediate, and 61 were penicillin-resistant. *Streptococcus pneumoniae* ATCC 49619 was tested each day for quality control. Ciprofloxacin, levofloxacin, and ofloxacin were included for *in vitro* testing as comparators.

Results of broth tests showed that the range of MICs for moxifloxacin was [redacted] Moxifloxacin was fourfold more active than ciprofloxacin and levofloxacin and eightfold more active than ofloxacin. The range of zone diameters for moxifloxacin was [redacted] Figure 12 shows the scattergram of zone diameters versus MICs. Based on the unimodal population distribution of the MICs and lack of resistant strains, an arbitrary breakpoint of ≥22 mm to indicate organism as susceptible was proposed. This fits the model of using one dilution greater than the highest MIC value for 99% of the population and 3 mm smaller than the smallest zone diameter for 99% of the population. There were five strains with a zone diameter of 25 mm. Three millimeters less would be 22 mm.

In the second study, four laboratories evaluated disk diffusion susceptibility tests against 495 strains of streptococci (30). Each laboratory tested 122-125 clinical strains of streptococci from their respective stock collection. The study was under the direction of Author Barry of the [redacted] The other sites were [redacted] A preliminary study was performed that ensured that the data from the four sites were consistent among the sites and could be pooled. All laboratories used a common lot of broth microdilution panels and susceptibility disks. Each laboratory tested their own set of strains in order to test as many different species of streptococci as possible. In addition, each laboratory tested the quinolone-resistant strains in their collection. TABLE 14 lists the distribution of organisms tested by each site.

TABLE 15 provides the frequency distribution of MICs for β-hemolytic streptococci, the viridans group, and *Streptococcus pneumoniae*. The study strains included 42 ciprofloxacin-intermediate (MIC 4-8 µg/mL) and 21 strains with high level resistance (MIC ≥16 µg/mL) to ciprofloxacin. Fourteen strains of *Streptococcus pneumoniae* had intermediate resistance to ciprofloxacin and 17 strains had high level resistance to ciprofloxacin. Of these 31 *Streptococcus pneumoniae* strains, 4 strains had moxifloxacin MICs of 4 µg/mL.

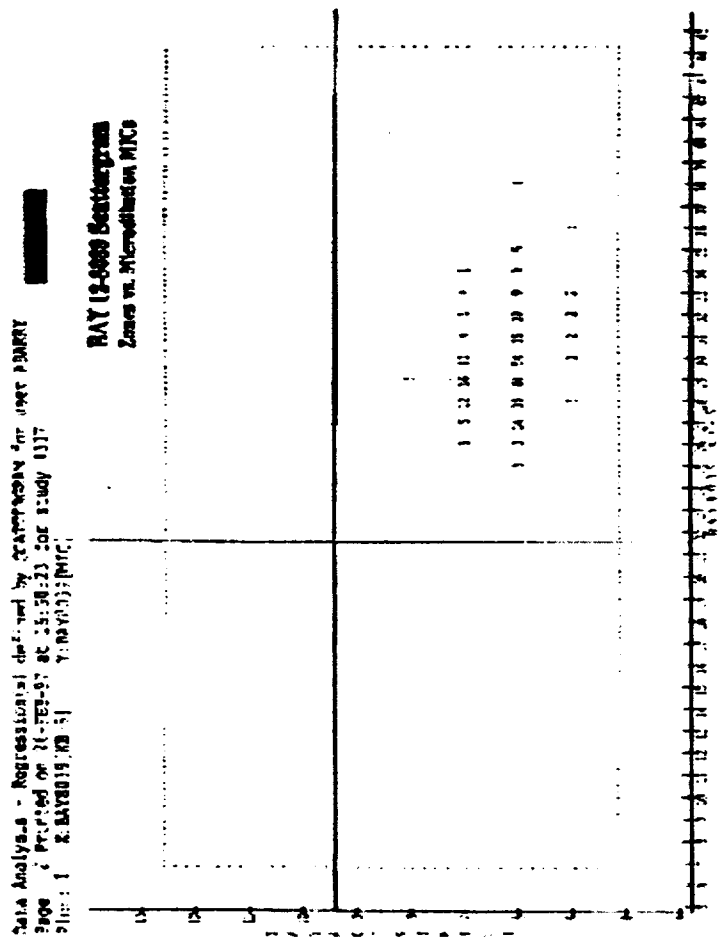

FIGURE 12. STREPTOCOCCUS PNEUMONIAE

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TABLE 14

Description of Isolates Evaluated in a Four-Laboratory Evaluation of Disk Diffusion Susceptibility Tests of Streptococci.

Streptococcus species (total number)	No. of strains tested at each location			
	U of I	MGH	CDC	CMI
Beta hemolytic (144)				
69 *S. pyogenes* (group A)			27	42
33 *S. agalactiae* (group B)			33	
23 Serogroup C			23	
19 Serogroup G			19	
Viridans Group (241)				
46 *S. bovis*		36	10	
52 *S. mitis*	40	11	1	
37 *S. milleri*	20	16	1	
21 *S. mutans*		21		
42 *S. salivarius*	21	21		
43 *S. sanguis*	40	3		
S. pneumoniae (110)	4	15	8	83
All species (495)	125	127	122	125

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TABLE 15

Overall Distribution of Streptococcal MICs

	Number of strains with the following MICs (µg/ml)									
	0.06	0.12	0.25	0.5	1.0	2.0	4.0	8.0	16	>16
Beta Hemolytic (144)										
Bay 12-8039	3	89	44	6	0	0	1			
Ciprofloxacin		1	11	106	19	6	0	0	1	
Ofloxacin				4	80	53	6	0	1	
Viridans Group (241)										
Bay 12-8039	6	104	112	17	0	0	2			
Ciprofloxacin			2	36	98	74	22	6	2	1
Ofloxacin				5	40	131	60	3	1	1
***S. pneumoniae* (110)**										
Bay 12-8039	12	67	3	5	4	15	4			
Ciprofloxacin			3	21	50	5	7	7	8	9
Ofloxacin				1	29	50	5	2	14	9
All Streptococci (495)										
Bay 12-8039	21	260	159	28	4	15	7			
Ciprofloxacin		1	16	163	167	85	29	13	11	10
Ofloxacin				10	149	234	71	5	16	10

The scattergram comparing the MICs and zone diameters of all 495 streptococcal strains is shown in Figure 13A. The scattergrams for the individual groups of streptococci are presented in Figure 14 (*Streptococcus pneumoniae*), Figure 15 (β-hemolytic), and Figure 16 (viridans group). Even including the 63 ciprofloxacin-resistant/intermediate strains, the population distribution was still unimodal for moxifloxacin for each group and for all streptococci combined. Since there was essentially no difference in population distribution among the three groups, criteria were applied for all streptococci including *Streptococcus pneumoniae*. The provisional breakpoints, pending clinical data were Susceptible ≥ 20 mm (MIC ≤ 1.0 µg/mL), Intermediate 17-19 mm (MIC 2.0 µg/mL), and Resistant ≤ 16 mm (≥ 4.0 µg/mL). These criteria resulted in no very major errors, 3 (0.6%) major errors, and 16 (3.2 %) minor errors.

An alternative way to evaluate the data for streptococci is shown in Figure13B. A distinct bimodal population is seen when ciprofloxacin-resistant strains are tested. This bimodality is particularly discernible by disk diffusion. The organisms with zone diameters ≥18 mm are in one population, while organisms with zones ≤ 16 mm are in the other, less susceptible population. A MIC breakpoint of ≤ 1.0 µg/mL and a zone ≥18 mm for susceptible and a MIC of ≥ 4.0 µg/mL and zone ≤ 14 mm for resistant distinguishes the two populations of organisms. This gives us the traditional 3 mm intermediate zone. If ≤ 15 mm is chosen for the resistant breakpoint then only a 2 mm intermediate zone results. There are no very major or major errors and the minor error rate is 1.8%. If a zone of 15 mm was chosen as the resistant breakpoint there would be one major error. These alternative breakpoints also allow all the streptococci having MICs of ≤ 0.25 µg/mL to be categorized as susceptible, rather than some being classified as intermediate as they would be if breakpoints of Susceptible ≥20 mm and Resistant ≤16 mm were used.

It appears that the following are the most appropriate breakpoints for streptococci including *Streptococcus pneumoniae*:

	MIC (µg/mL)	Zone Diameter (mm)
Susceptible	≤ 1.0	≥ 18
Intermediate	2.0	15-17
Resistant	≥ 4.0	≤ 14

The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in this review under the section titled "Correlation of Test Results with Outcome Statistics".

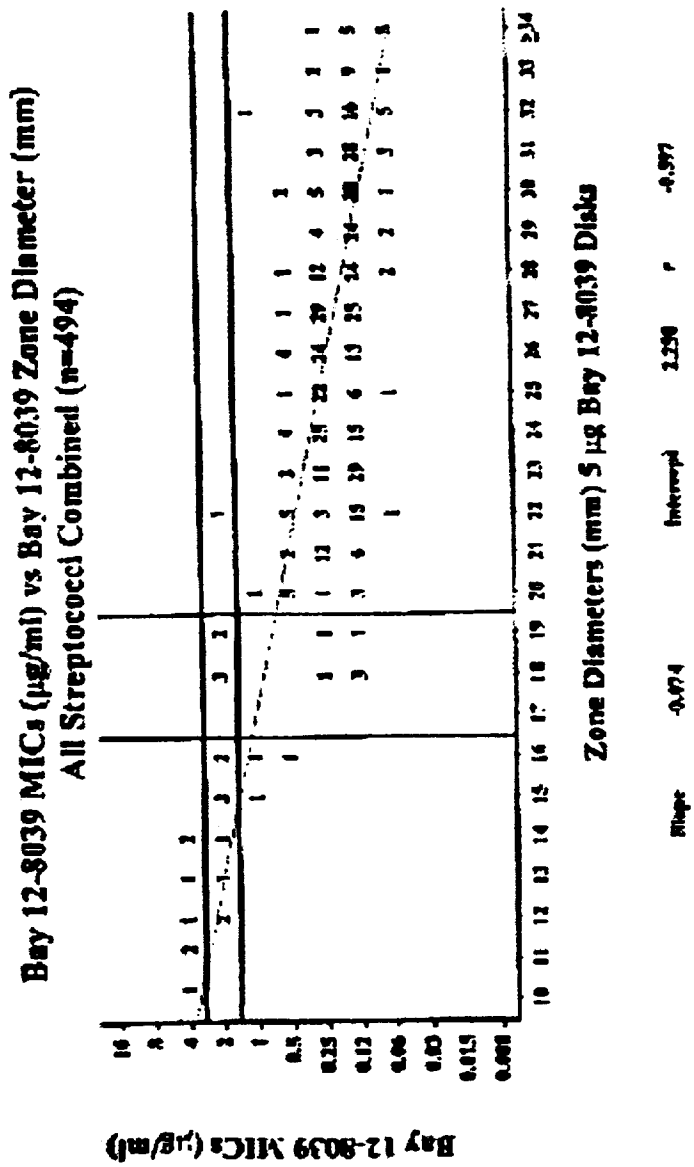

FIGURE 13A. CMI BREAKPOINTS

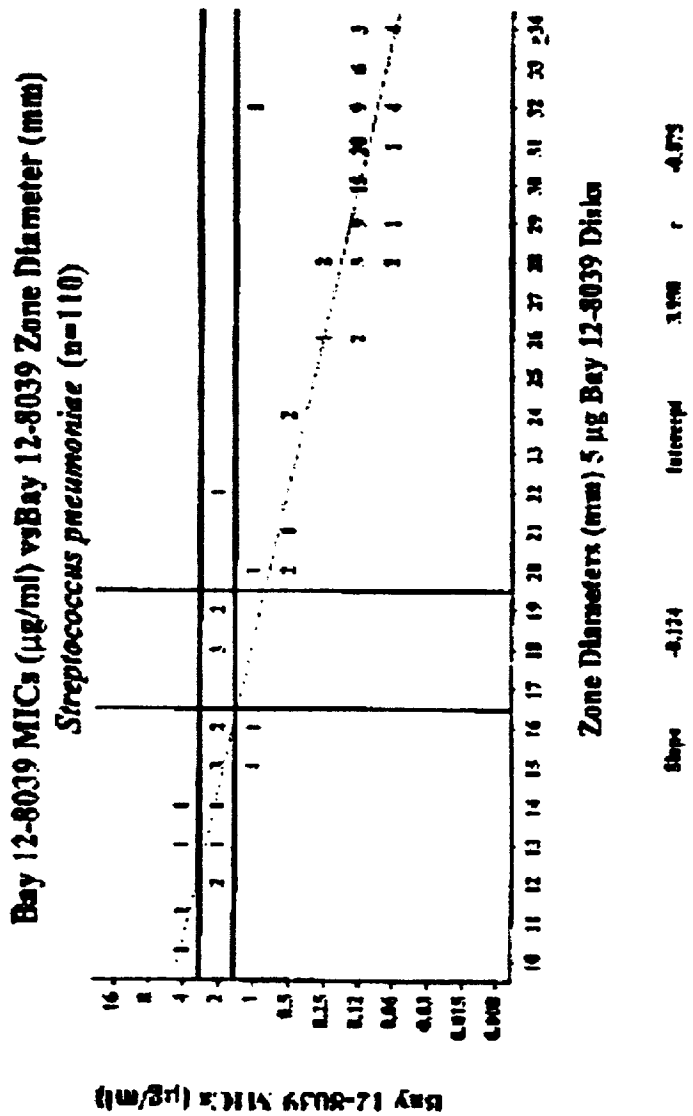
Bay 12-8039 MICs (µg/ml) vsBay 12-8039 Zone Diameter (mm)
Streptococcus pneumoniae (n=110)
Zone Diameters (mm) 5 µg Bay 12-8039 Disks

FIGURE 14

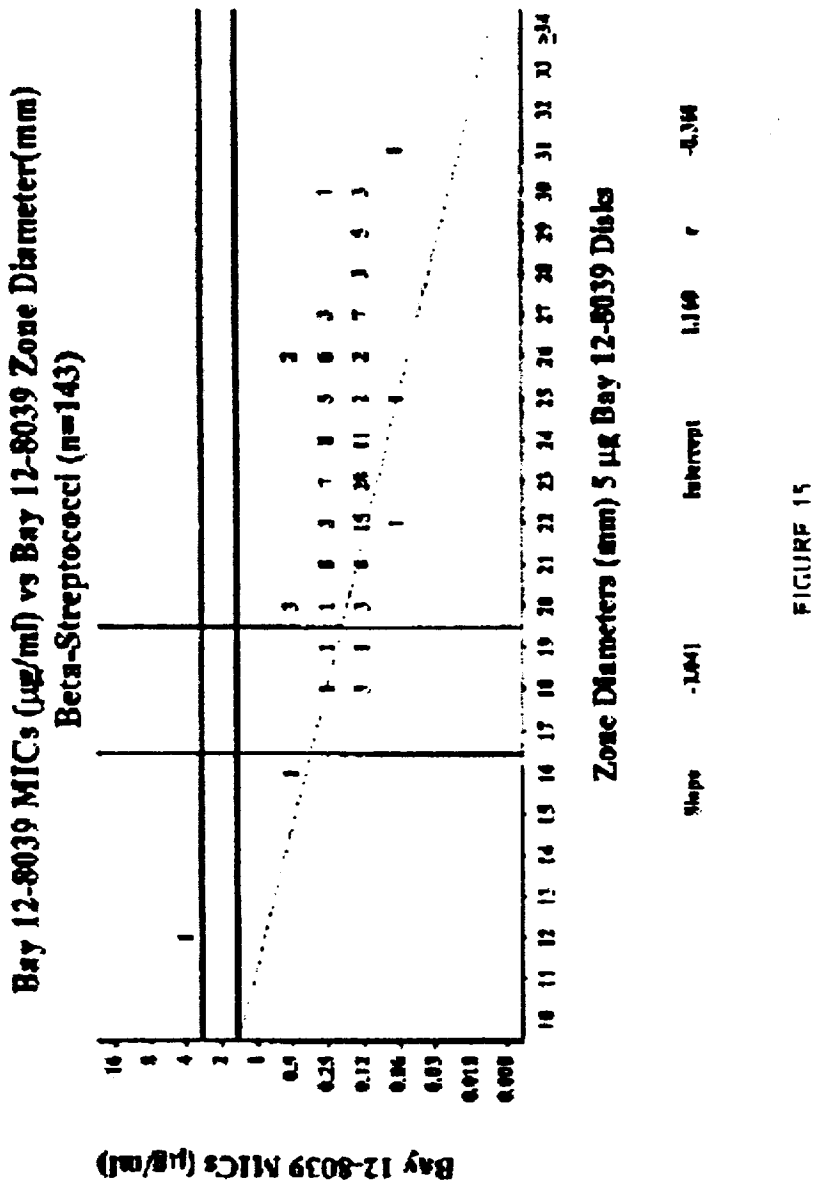
Bay 12-8039 MICs (µg/ml) vs Bay 12-8039 Zone Diameter(mm)
Beta-Streptococci (n=143)
Zone Diameters (mm) 5 µg Bay 12-8039 Disks
Bay 12-8039 MICs (µg/ml)

FIGURE 15

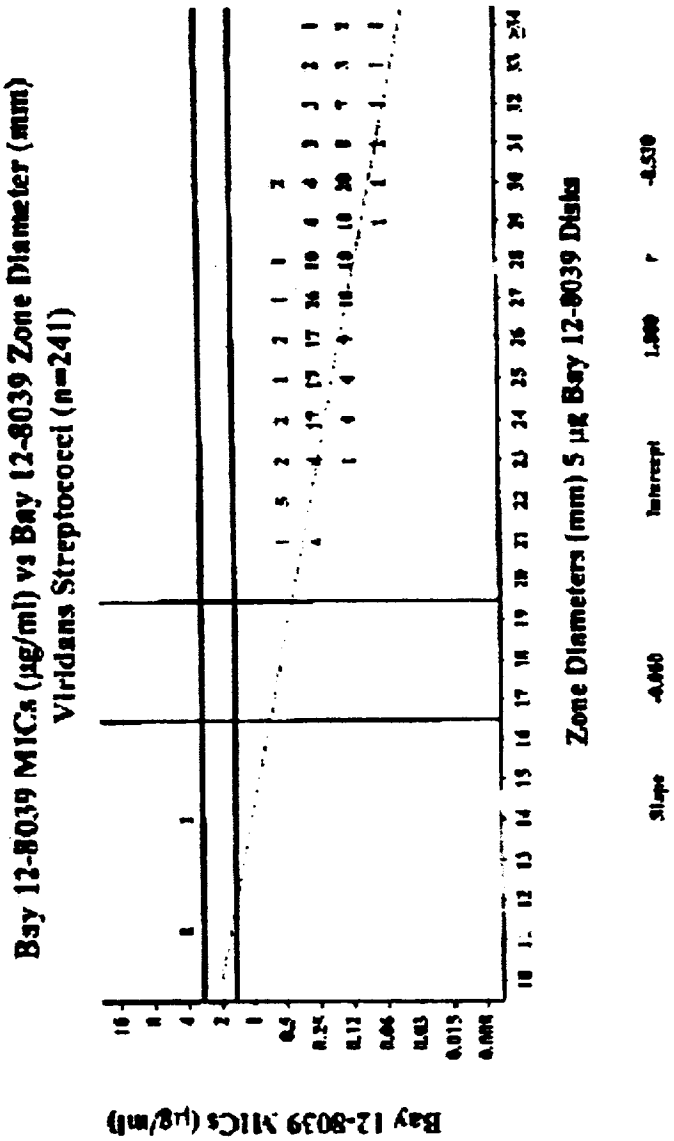
Bay 12-8039 MICs (µg/ml) vs Bay 12-8039 Zone Diameter (mm)
Viridans Streptococci (n=241)
Zone Diameters (mm) 5 µg Bay 12-8039 Disks
Bay 12-8039 MICs (µg/ml)

FIGURE 16

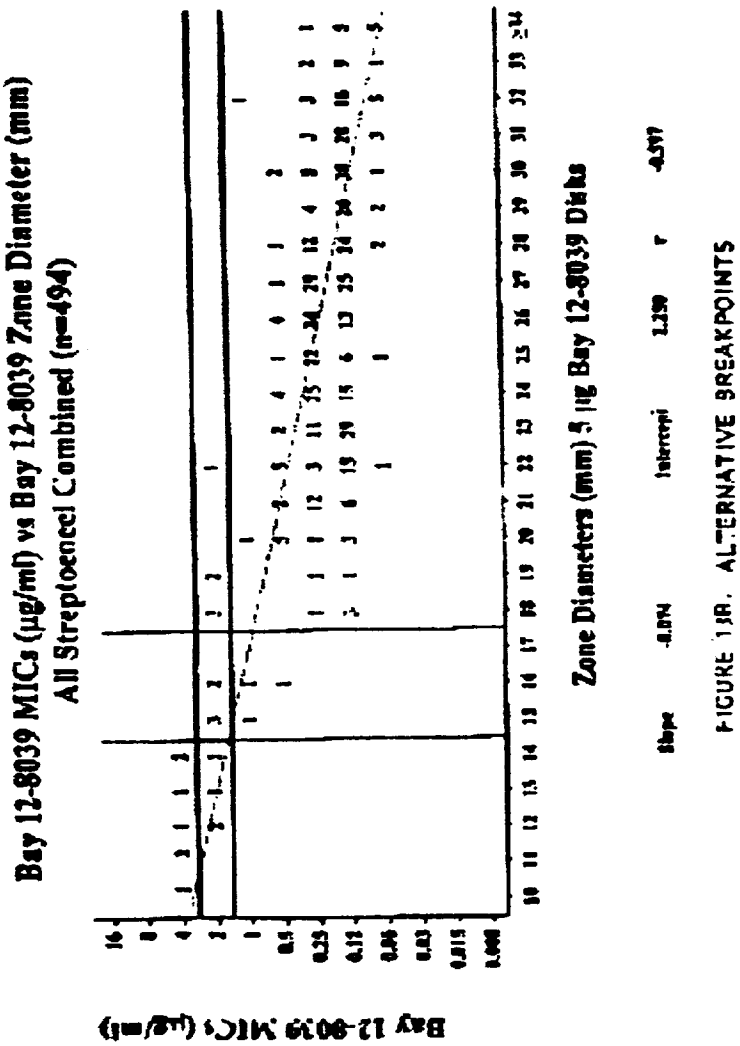

FIGURE 13R. ALTERNATIVE BREAKPOINTS

BACTERIOLOGICAL EFFICACY

CORRELATION OF TEST RESULTS WITH OUTCOME STATISTICS

No new information is provided in this submission. In the original NDA submission clinical trails were conducted for the treatment of respiratory tract infections and uncomplicated skin and soft tissue infections. The respiratory tract infections included sinusitis, acute exacerbations of chronic bronchitis, and community acquired pneumonia.

During each Phase III clinical study with moxifloxacin, the susceptibility of the causative organisms was tested at the clinical trial site by the E-test according to the manufacturer's instructions and by the disk diffusion test as outlined in NCCLS guidelines.

Clinical isolates were sent to the microbiology laboratory at Bayer Corporation, Pharmaceutical Division for confirmation of each organism's identity and for susceptibility testing by both the disk diffusion test and the broth microdilution test. While every effort was made to test all causative organisms isolated during the clinical trials, some organisms were not viable when received. Quality control strains were included in each day's testing. NCCLS methods were used for all testing.

Discrepancies in identification of an isolate between the trial site and the Bayer microbiology laboratory were submitted to the reference laboratory [redacted] In addition, all isolates of *Streptococcus pneumoniae* were submitted to CMI for further confirmation of identification and for repeat microdilution susceptibility testing for both moxifloxacin and penicillin. If test results from [redacted] Bayer were within one doubling dilution of each other, the Bayer test results were used in the analyses. In the interest of obviating any bias, [redacted] results were used to determine penicillin susceptibility of *Streptococcus pneumoniae* isolates.

The Bayer microbiology laboratory tested 526 targeted key pathogens isolated from 458 microbiologically valid patients. The number of patients per indication and the corresponding number of isolates (# patients/# isolates) were sinusitis, 74/76; AECB, 239/294; community acquired pneumonia (CAP), 74/84; skin, 71/72. With the exception of AECB, most patients had only one causative organism.

The clinical responses for the causative organisms that were tested by Bayer microbiology laboratory were grouped by indication and represent USA isolates only. TABLE 16 summarizes the clinical response for each organism for the skin and skin structure infections indication in USA studies. TABLE 17 shows the bacteriological response for each organism in the skin and skin structure infection indication. Since in most cases the clinical response drove the bacteriological response (i. e. most studies reported bacteriological response as presumed eradicated or presumed persisted), the clinical response and bacteriological response are well coordinated.

Table 16- CLINICAL RESPONSE / SKIN (D97-005)

Organism	Test-of-Cure	
	Resolve (%)	Fail (%)
S. aureus	59 (91)	6 (9)
Streptococcus Gp A	2	0
Streptococcus Gp B	6	1
Streptococcus Gp C	1	0

Table 17 - BACTERIOLOGIC RESPONSE / SKIN (D97-005)

Organism	Test-of-Cure			
	Erad (%)	Presume Erad (%)	Persist (%)	Presume Persist (%)
S. aureus	2 (3)	55 (89)	4 (6)	1 (2)
Streptococcus Gp A	0	2	0	0
Streptococcus Gp B	0	6	0	1
Streptococcus Gp C	0	1	0	0

MIC BREAKPOINTS

No new information has been provided. Since *Streptococcus* species beside *Streptococcus pneumoniae* have now been included in the clinical efficacy section of the label breakpoints must be established for them. Only studies from the original NDA submission that propose breakpoints for streptococci will be discussed in this review.

STREPTOCOCCUS SPECIES INCLUDING *STREPTOCOCCUS PNEUMONIAE*

Table 18 shows the relationship between MICs and pathogen response for streptococci treated with 400 mg moxifloxacin.

TABLE 18
Relationship between Moxifloxacin MICs and Bacteriological Outcome at Test-of -Cure

Baseline Pathogen	MIC (µg/mL)	# Isolates	# Eradicated (%)	# Persisted (%)
S. pneumoniae	0.06	12	11 (92)	1 (8)
	0.125	45	45 (100)	0
	0.25	14	13 (93)	1 (7)
	0.5	6	5 (83)	1 (17)
Streptococcus species	0.125	1	0	1 (100)
	0.25	4	4 (100)	0
	0.5	1	1 (100)	0
Group A	0.125	1	1 (100)	0
	0.25	1	1 (100)	0
Group B	0.125	2	2 (100)	0
	0.25	5	4 (80)	1 (20)
Group C	0.06	1	1 (100)	0

The above table shows that all streptococci had MICs between 0.06 and 0.5 µg/mL. Almost all isolates were eradicated. Barry's *in vitro* study (30), which tested 495 strains of streptococci, suggested a susceptible breakpoint of 1.0 µg/mL. This breakpoint seems appropriate, since there were several clinical isolates with MICs of 0.5 µg/mL and one doubling dilution greater than the MIC for 99% of the isolates is often used to set breakpoints when no resistant strains are present. Barry's study included ciprofloxacin-resistant strains and some of these strains had moxifloxacin MICs of 4.0 µg/mL. It would, therefore, appear that there are some moxifloxacin resistant strains. A susceptible breakpoint of 1.0 µg/mL, intermediate breakpoint of 2.0 µg/mL, and a resistant breakpoint of 4.0 µg/mL for moxifloxacin seems appropriate.

The following breakpoints should be in the label for streptococci including *Streptococcus pneumoniae*:

Susceptible = ≤ 1.0 µg/mL
Intermediate = 2.0 µg/mL
Resistant = ≥ 4.0 µg/mL

ZONE DIAMETER BREAKPOINTS

No new information has been provided. Since *Streptococcus* species beside *Streptococcus pneumoniae* have now been included in the clinical efficacy section of the label breakpoints must be established for them. Only studies from the original NDA submission that propose breakpoints for streptococci will be discussed in this review.

STREPTOCOCCUS SPECIES INCLUDING *STREPTOCOCCUS PNEUMONIAE*

Figure 20 show the scattergram of MICs versus zone diameter for streptococci including *Streptococcus pneumoniae*. All isolates had zone diameters of ≥ 20 mm.

TABLE 19 shows the relationship between zone diameter and bacteriological outcome for streptococci treated with 400 mg of moxifloxacin once daily.

TABLE 19
Relationship between Moxifloxacin Zone Diameter and Bacteriological Outcome

Baseline Pathogen	Zone diameter (mm)	# Isolates	# Eradicated (%)	# Persisted (%)
S. pneumoniae	22	3	3 (100)	0
	23	1	1 (100)	0
	24	3	3 (100)	0
	25	2	2 (100)	0
	26	9	9 (100)	0
	27	7	7 (100)	0
	28	9	9 (100)	0
	29	15	14 (93)	1 (7)
	30	8	8 (100)	0
	31	8	7 (88)	1 (12)
	32	5	5 (80)	1 (20)
	33	5	5 (100)	0
	36	1	1 (100)	0
Streptococcus species	20	1	1 (100)	0
	22	1	1 (100)	0
	23	1	1 (100)	0
	26	1	1 (100)	0
	27	1	1 (100)	0
	28	1	0	1 (100)
Group A	21	1	1 (100)	0
	22	1	1 (100)	0
Group B	23	3	3 (100)	0
	25	3	2 (67)	1 (33)
	26	1	1 (100)	0
Group C	33	1	1 (100)	0

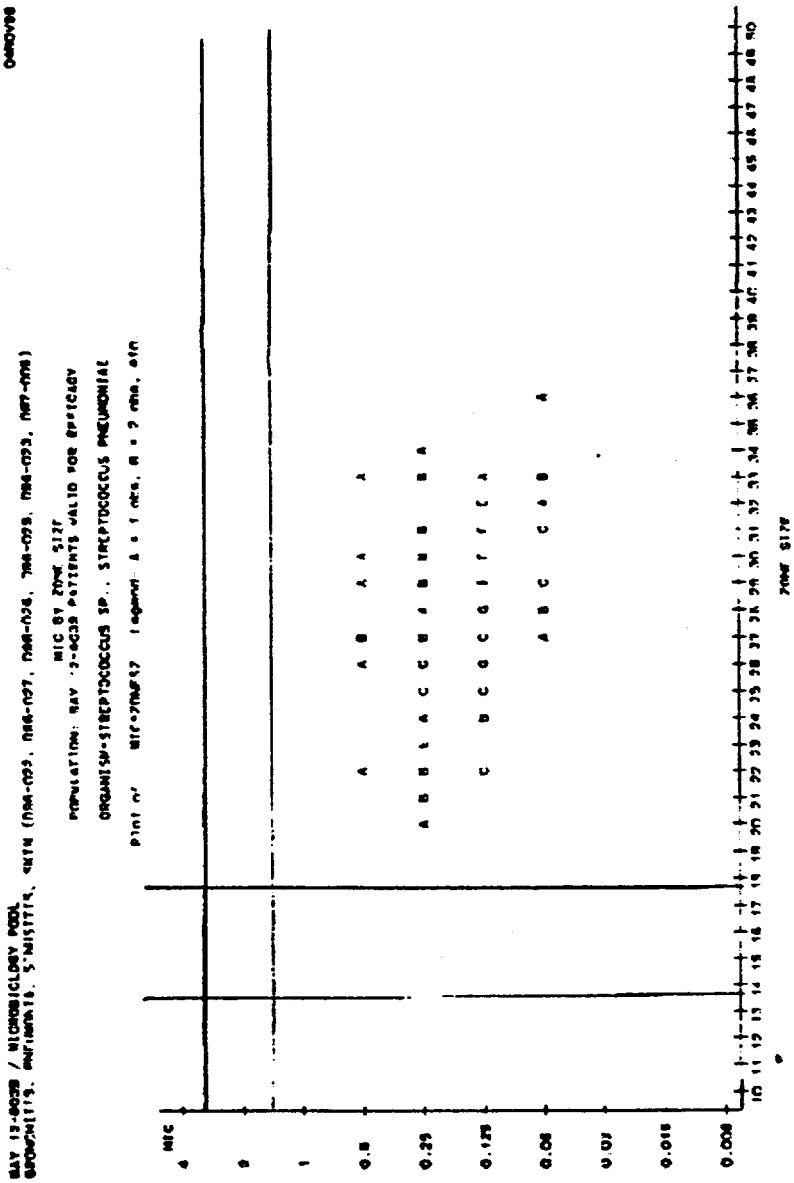

Figure 20

The above table shows that there were no resistant strains in the clinical trials. Almost all isolates were eradicated and there was no correlation between eradication and zone diameter. Barry's study (30) showed a distinct bimodal population, particularly discernible by disk diffusion, when quinolone-resistant strains are tested. The organisms with zone diameter ≥ 18 mm are in one population, while organisms with zones ≤ 14 mm are in the other population. These zone diameters should be used and will be placed in the label.

The following zone diameter breakpoints should be in the label for streptococci including *Streptococcus pneumoniae*:

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

PACKAGE INSERT

ISOLATES APPROVED

The following organisms may be placed in the label. The final decision on whether or not an organism should be in the clinical efficacy list will depend on the Medical Officer's final review of this product. If the clinical picture reveals that some of these genera/species are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.

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 USUAGE** section:

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

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* minimal 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 has 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 microorganism

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Legionella pneumophila
Proteus mirabilis

Anaerobic microorganisms

Fusobacterium species
Prevotella species
Peptostreptococcus species

INTERPRETIVE CRITERIA ESTABLISHED

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

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

For testing *Haemophilus* species:

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

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

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

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

MIC (µg/mL)	Interpretation
≥ 19	(S) Susceptible
16-18	(I) Intermediate
≤ 15	(R) Resistant

For testing *Haemophilus* species:

MIC (µg/Ml)	Interpretation
≥ 18	(S) Susceptible

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

MIC (µg/Ml)	Interpretation
≥ 18	(S) Susceptible
15-17	(I) Intermediate
≤ 14	(R) Resistant

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APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS (To be Communicated)
Changes to the Proposed Label

Assuming that the data submitted is sufficient to approve an indication of uncomplicated skin and skin structure infections:

The applicant should be notified of the following:

1. *Streptococcus pyogenes* may be placed in the clinical efficacy listing in the Microbiology section of the label as long as it is included under the skin and skin structure infections indication.

2. *Streptococcus agalactiae* must be placed in the *in vitro* activity listing (list #2) in the label since it was concluded from data in the original NDA #21-085 (moxifloxacin tablets) that not enough isolates were found in the clinical trials to include it in the clinical efficacy list.

3. *Staphylococcus epidermidis* may be added to the *in vitro* activity listing but it should be qualified as *Stapylococcus epidermidis* (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.

4. *Streptococcus* viridans group may be added to the *in vitro* activity listing.

5. In the Susceptibility Tests subsection the words "For testing *Streptococcus* species including *Streptococcus pneumoniae*" should replace the words "For testing *Streptococcus pneumoniae*" in both the Dilution Techniques and the Diffusion Techniques sections.

6. 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 from the sponsor's proposed labeling are indicated by stikeouts and additions 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 mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin and other quinolones. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

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

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

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

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 [redacted] 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 [ ] (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 diamter 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*:•

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

• 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 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 [redacted] 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 [redacted]

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CONCURRENCES:

HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA #21-334
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/AMeyerhoff
HFD-520/Pharm/AEllis
HFD-590/Chem/DMatecka
HFD-590/CSO/VJensen