CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW

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

NDA#: 21-085

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	09-DEC-98
CDER DATE:	10-DEC-98
REVIEW ASSIGN DATE:	14-DEC-98
REVIEW COMPLETE DATE:	01-MAR-99

SPONSOR: Bayer Pharmaceutical Division
Bayer Corporation
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Deputy Director Regulatory Affairs
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SUBMISSION REVIEWED: Original NDA Submission

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

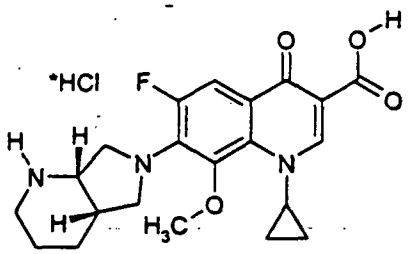
INDICATIONS: Acute Exacerbation of Chronic Bronchitis, Acute Sinusitis, Community Acquired Pneumonia, [redacted]

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]

REMARKS/COMMENTS:
This application is for a new fluoroquinolone, moxifloxacin. The applicant seeks approval for community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, acute sinusitis [redacted]

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 196-204.

APPEARS THIS WAY
ON ORIGINAL

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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. 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 *Haemophilus* species and *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 pneumoniae	0.25
Streptococcus pyogenes	0.25
Viridans Group Streptococci	0.25
Streptococcus agalactiae	0.5
Enterococcus faecalis	0.5-16.0
Enterococcus faecium	2.0-16.0
Acinetobacter species	0.03-8.0
Escherichia coli	0.06
Klebsiella pneumoniae	1.0
Klebsiella oxytoca	0.125
Enterobacter cloacae	0.5
Proteus mirabilis	0.25
Citrobacter freundii	1.0-2.0
Serratia marcescens	2.0-8.0
Pseudomonas aeruginosa	8.0
Stenotrophomonas maltophilia	0.5-4.0
Haemophilus influenzae	0.06
Moraxella catarrhalis	0.06
Neisseria gonorrhoeae	0.03
Legionella pneumoniae	0.125
Mycoplasma pneumoniae	0.06
Chlamydia pneumoniae	1.0
Mycobacterium avium	4.0
Mycobacterium tuberculosis	0.5

* If more than one MIC is given it is a range of MIC_{90} values and not the mode.

TABLE A (continued)
Moxifloxacin *in vitro* Activity

PATHOGEN	MEDIAN MIC_{90} (µg/mL)*
Bacteroides fragilis	2.0
Clostridium perfringens	0.5
Clostridium difficile	2.0
Fusobacterium species	1.0
Prevotella species	0.5
Peptostreptococcus species	0.25

* If more than one MIC is given it is a range of MIC_{90} values and not the median.

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	SPAR	OFL
Streptococcus pneumoniae	**0.25**	2.0	1.0	0.25	0.5	2.0
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	—	—
Enterococcus faecalis	**0.25-16**	1-≥32	1-≥32	0.5-16	—	—
Enterococcus faecium	**2-≥32**	4-≥32	4-≥32	2-32	—	—
Enterococcus faecium (VS)	**16**	>32	>32	8	—	—
Enterococcus faecium (VR)	**16**	>32	>32	16	—	—
Haemophilus influenzae	**0.06**	0.016	0.06	0.016	0.03	—
Moraxella catarrhalis	**0.06**	0.03	0.03	0.06	0.06	—
Escherichia coli	**0.06**	0.015	0.03	0.03	0.015	—
Klebsiella pneumoniae	**1.0**	0.25	0.5	0.13	0.5	—
Enterobacter aerogenes	**1.0**	0.25	2	2	—	—
Serratia marcescens	**4**	2	2	4	—	—
Citrobacter freundii	**1**	0.25	0.5	1	0.5	—
Proteus mirabilis	**0.5**	0.06	0.25	0.25	0.5	—
Morganella morganii	**0.25-16**	0.015-16	0.06-≥32	0.5	0.5	—
Pseudomonas aeruginosa	**2-32**	0.25-8	4-32	2-16	—	—
Bacteroides fragilis	**0.25-4**	8-≥32	—	0.5-1.0	—	2-≥32
Bacteroides ovatus	**2-4**	≥32	—	2	—	16-64
Fusobacterium species	**0.5**	4	—	—	—	4
Prevotella bivia	**2**	16	—	—	—	8
Clostridium difficile	**2**	32	—	1	—	8
Clostridium perfringes	**0.5**	0.5	—	0.125	—	0.5
Mycobacterium tuberculosis	**0.25**	0.5	>0.25	—	0.5	—
Mycoplasma pneumoniae	**0.12**	—	—	—	0.12	2.0
Legionella pneumophila	**0.125**	0.03	0.03	—	—	—

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.

Against gram-negative aerobes, moxifloxacin's activity was typically less than that of ciprofloxacin but was still usually below 1 μg/mL. Most of the other fluoroquinolones were more active.

Moxifloxacin showed some activity against anaerobes but its activity was inferior to that of trovafloxacin in most cases.

A limited amount of data are presented on moxifloxacin's activity against bacteria resistant to other agents. It has activity against penicillin-resistant and macrolide-resistant *Streptococcus pneumoniae*. This is true for all the fluoroquinolones. It has better activity than most other fluoroquinolones against [redacted] 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. Beta-lactamase activity did not affect moxifloxacin's MIC values. This is true for all fluoroquinolones.

There is some evidence that moxifloxacin is bactericidal against *Staphylococcus aureus* at concentrations that are up to 64 times its MIC value while other fluoroquinolones (sparfloxacin) are bactericidal only up to 4 times its MIC value. At the lower concentrations the killing rate is equivalent for both drugs.

Against *Escherichia coli* single mutations in the *parC* gene did not increase ciprofloxacin MICs but did lead to an 8-fold increase in moxifloxacin MIC values. Single mutations in the *gyrA* gene lead to a 32-fold increase in moxifloxacin MIC and a 64-fold rise in ciprofloxacin MIC. This may indicate that both gyrase and topoisomerase are primary targets for moxifloxacin in *Escherichia coli*.

Against *Staphylococcus aureus* single mutations in *grlA* increased ciprofloxacin MICs (2- to 8-fold) but not moxifloxacin's. Double mutants had ciprofloxacin MIC values of 8-256 μg/mL, but moxifloxacin MICs of 0.5 to 2.0 μg/mL. Further mutations did not increase the MIC of moxifloxacin.

The spontaneous mutation rate appears to be about equal for ciprofloxacin and moxifloxacin against gram-negative bacteria. Moxifloxacin appears to have a slightly lower mutation rate than ciprofloxacin for gram-positive bacteria.

Step-wise emergence of resistance to moxifloxacin by *Staphylococcus aureus* and *Streptococcus pneumoniae* developed more slowly and to a much lesser extent compared with ciprofloxacin.

Several studies indicate that moxifloxacin is effective in animal models of infection. 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
	Escherichia coli	0.25 mg/kg cipro = 100% survival (SC) 0.5 mg/kg moxi or spar = 100%
	Klebsiella pneumoniae	1.0 mg/kg moxi or spar = 100% (oralIly) 0.5 mg/kg cipro = 100%
Experimental Pneumonia	*Streptococcus pneumoniae* (Pen-R) In mice	Moxi=Trov=Vanco reduced lung load to 0.5 log cfu/g Cipro=Levo=Spar reduced to 3.9-5.9 log cfu/g
	Haemophilus influenzae (baby rats)	Spar=Cipro 2.5 mg/kg 8 log reduction 10 mg/kg needed for moxi
	Streptococcus pneumoniae (baby rats)	Spar > cipro 50 mg/kg 4 log reduction Moxi not effective in this model
	Mycoplasma pneumoniae (guinea pig)	10 mg/kg moxi effective. 3 mg/kg not effective
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
	Streptococcus pneumoniae	100 mg/kg moxi=7 log reduction in 1day 50 mg/kg = 7 log reduction in 6 days
Tuberculosis (mouse)	*Mycobacterium tuberculosis*	Moxi and Spar effective Clina not effective
Meningitis (Rabbit)	*Streptococcus pneumoniae* (Pen-S)	10 mg/kg moxi effective
	Streptococcus pneumoniae (Pen-R)	40 mg/kg moxi more effective than two 20 mg/kg doses Pen-S and Pen-R results equivalent
	Listeria monocytogenes (mice)	Moxi better than cipro at 2 mg/kg
	Salmonella typhimurium (mice)	Moxi better at 1 day then cipro at 3 days

The above data indicate that moxifloxacin is effective in selected animal models of infection. In most studies it appears to be less active than ciprofloxacin against gram-negative pathogens and 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 34 mg*h/L.

Analysis of drug penetration into human lung tissue (bronchial mucosa, epithelial lining fluid, and alveolar macrophages) indicates that moxifloxacin is more concentrated in these tissues than in serum. At approximately 3 hours postdose, the ratios of moxifloxacin in tissue to that in serum are 1.7, 8.7, and 21.2 for bronchial mucosa, epithelial lining fluid, and alveolar macrophages, respectively. The ratios in sinus tissue to serum were 2.0, 2.2, and 2.6 for maxillary sinus mucosa, anterior ethmoid, and nasal polyps, respectively. In skin and musculoskeletal tissue the ratios were much lower with serum levels being about 2 to 3 times higher that tissue levels.

PRECLINCIAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

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IN VITRO ACTIVITY OF METABOLITES

Acylglucuronide (M2) is the primary metabolite of moxifloxacin; however, it rapidly hydrolyzes to the parent compound in an *in vitro* system and activity can, therefore, not be determined. The N-sulfate congener (M1) is produced in much smaller amounts. Its biological activity was measured against an array of gram-negative and gram-positive bacteria (26). MICs of the N-sulfate compound, moxifloxacin, and ciprofloxacin were determined for 20 organisms. Moderate activity was seen for the N-sulfate metabolite only against the two strains each of *Escherichia coli* and *Klebsiella pneumoniae* for which the MICs were 1.0 µg/mL and 2.0 µg/mL, respectively. The MICs of moxifloxacin were 0.06-0.125 µg/mL and ciprofloxacin's MICs were 0.03-0.06 µg/mL for these four organisms. MICs of the N-sulfate compound for the rest of the tested organisms were ≥ 4.0 µg/mL, which was at least 16-fold higher than the MICs of moxifloxacin and ciprofloxacin for these organisms.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

MICs were performed predominantly on relevant clinical isolates of the respiratory tract, skin and skin structure infections, and anaerobes. A few studies tested other bacteria to characterize the broad spectrum of moxifloxacin. Susceptibility testing was performed according to NCCLS guidelines in almost all studies regardless of the methods usually used in the respective country.

The NDA Holders letter issued January 26, 1993, states that in order to be included in the label a microorganism should be a significant (not anecdotal) pathogen at the body site(s) or in the infection(s) for which clinical effectiveness for other pathogens has been established. Since the applicant is requesting only acute sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, [redacted] only microorganisms usually found at these sites that may be a pathogen for these diseases will be included in the label.

The proposed susceptibility breakpoint for moxifloxacin is 2.0 µg/mL, therefore, in order to be allowed in the *in vitro* list in the label the MIC_{90} value for an organism must be ≤ 2.0 µg/mL.

The labeling submitted by the applicant includes the following organisms in the efficacy list (list #1)

Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae (penicillin-susceptible, [redacted] strains)
[redacted]

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

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

Anaerobic gram-positive microorganisms
Clostridium perfringens
Peptostreptococcus species

Anaerobic gram-negative microorganisms
Fusobacterium species
Prevotella species

Other microorganisms

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

GRAM-POSITIVE AEROBES

Streptococci

Susceptibility to moxifloxacin was evaluated in over 6500 strains of *Streptococcus pneumoniae* that were isolated in the USA, Europe, and other countries. Penicillin susceptibility was determined for most of the strains. To see if any differences in susceptibility to moxifloxacin were related to geographical area, only USA data are shown in TABLE 1 and data from other countries is depicted in TABLE 2. In both tables, susceptibility to moxifloxacin was categorized by the organisms' susceptibility to penicillin. The data in these tables reveal no geographical effects on susceptibility to moxifloxacin. Increasing penicillin MICs did not affect susceptibility to moxifloxacin. Two of the USA studies involved multicentered surveillance studies that were conducted in 1997 (27,28). The MIC_{90} for the 600 strains tested by Barry was 0.25 µg/mL, while the MIC_{90} for the study conducted by Biedenbach was 0.12 µg/mL. Table 3 summarizes the MIC_{90} data obtained from all of the studies. The MIC_{90}s ranged from

The mode MIC_{90} for moxifloxacin and *Streptococcus pneumoniae* was 0.25 µg/mL. All MIC_{90}s were below the susceptible breakpoint of 2.0 µg/mL and well over 100 isolates were tested at numerous sites. *Streptococcus pneumoniae* may be placed in the clinical efficacy section of the label. If enough penicillin-resistant strains were eradicated in clinical trials, this organisms may be listed as including penicillin-resistant strains. If enough penicillin-resistant strains were not eradicated in clinical trails then penicillin-resistant strains may be placed in the *in vitro* activity listing in the package insert.

TABLE 6 summarizes activity against streptococci other than *Streptococcus pneumoniae.*

Table 1- IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE* / USA STUDIES

PEN S			PEN I			PEN R			Ref.
No.	Range	MIC_{90}	No.	Range	MIC_{90}	No.	Range	MIC_{90}	
410		0.25	88		0.25	102		0.25	27
336		0.12	108		0.06	56		0.12	28
154		0.06	150		0.06	100		0.06	29
15		0.25	20		0.25	15		0.25	30, 31
134		0.25	106		0.25	61		0.125	32
18		0.25	4		-	6		-	33, 34
-		-	-		-	27		0.125	35
52		0.5	-		-	7		-	36, 37
53		0.25	76		0.25	76		0.25	38, 39
39		0.25	-		-	-		-	40

* Penicillin susceptibility not given.

Table 2- IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE* / NON USA STUDIES

PEN S			PEN I			PEN R			Ref.
No.	Range	MIC_{90}	No.	Range	MIC_{90}	No.	Range	MIC_{90}	
101		0.12	-		-	-		-	41
107		0.25	80		0.12	76		0.25	42
30		0.25	20		0.25	15		0.25	43, 44
501		0.25	109		0.25	11		0.25	45
336		0.25	16		0.25	2		-	46
99		0.12	-		-	-		-	47
1317		0.25	40		0.25	28		0.25	48, 49
50		0.1	-		-	-		-	50
330		0.12	-		-	-		-	51
60		0.06	60		0.12	60		0.12	52, 53
200		0.25	-		-	-		-	54
267		0.12	21		0.25	6		-	55
92		0.12	-		-	-		-	56
79		0.12	104		0.12	-		-	57
362		0.125	54		1	36		0.25	58
32		0.25	-		-	-		-	59, 60, 61

Table 3 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE*

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Streptococcus pneumoniae (6636)		0.25
Pen-S (5324)		0.25
Pen-I (964)		0.25
Pen-R (348)		0.25

This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.

Staphylococci

TABLE 7 summarizes moxifloxacin's activity against *Staphylococcus aureus*. Susceptibility was evaluated according to the organism's susceptibility to [redacted] in most cases. The mode MIC_{90} for [redacted]-susceptible *Staphylococcus aureus* was 0.12 µg/mL. The MIC_{90} values ranged from [redacted] Moxifloxacin was not as active against [redacted]-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 [redacted] susceptible strains only.

TABLE 8 shows data from testing of other staphylococci. Once again it appears that [redacted] susceptible strains are more susceptible to moxifloxacin than [redacted] resistant strains. The difference between [redacted] susceptible and –resistant strains [redacted] *Staphylococcus epidermidis* may be placed in the *in vitro* activity section of the label.

TABLE 9 summarizes the *in vitro* activity of moxifloxacin against staphylococci.

Table 7 - 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	42
(90)		0.03	0.06	(63)		0.06	4	43, 44
(34)		0.06	0.06	(20)		2	4	30, 31
(31)		0.06	0.12	(25)		2	4	63, 64, 65
(25)		-	0.1	(25)		-	8	50
-		-	-	(194)		0.5	1	67
(25)		0.06	2	(27)		2	4	68
(100)		0.03	1	-		-	-	57
(54)		0.06	0.12	(20)		2	2	59, 60
(39)		0.125	0.125	(21)		2	4	36, 37
(62)[a]		-	8	-		-	-	41
(322)[a]		0.06	0.125	-		-	-	45
(131)[a]		0.06	0.125	-		-	-	46
(18)[a]		0.03	0.03	-		-	-	69

[a] No methicillin susceptibility given

6 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

GRAM-NEGATIVE AEROBES

Haemophilus influenzae

The *in vitro* activity of moxifloxacin against *Haemophilus influenzae* is shown in TABLES 13 and 14. The MIC_{90} was consistent across the 15 geographically diverse studies and β-lactamase production did not give rise to an increase in moxifloxacin MICs. One study that included 499 isolates was a multicenter surveillance of respiratory tract infection isolates in the USA during 1996-1997; the MIC_{90} was 0.03 µg/mL (28). The range of MIC_{90} values for the 1476 strains for which production of β-lactamase was measured was [redacted] the mode MIC_{90} was 0.06 µg/mL irrespective of whether or not the organism produced β-lactamase (see TABLE 14). A mode MIC_{90} of 0.06 µg/mL was also obtained for the total 1892 strains of *Haemophilus influenzae* tested. *Haemophilus influenzae* may be placed in the clinical efficacy section of the package insert with Medical Officer concurrence.

Only one study included *Haemophilus parainfluenzae*. Only 81 isolates were tested. The MIC_{90} value in this study was 0.25 µg/mL and all isolates had MICs ≤ 1.0 µg/mL. There were 39 isolates of *H. parainfluenzae* in the clinical trials. One isolate had a MIC of 8.0 µg/mL. All other isolates had MICs ≤ 0.5 µg/mL. If we include the data from the clinical trials then two studies have been performed and all MIC_{90}s were ≤ 0.5 µg/mL. *Haemophilus parainfluenzae* may stay in the label. If not enough data are available to place it into list #1 (clinical efficacy) then it may be moved to the *in vitro* activity only listing.

Table 13 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *HAEMOPHILUS INFLUENZAE*

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Haemophilus influenzae (1892)[a]		0.06
β-lactamase Pos (477)		0.06
β-lactamase Neg (999)		0.06

[a] Includes 416 strains β-Lactamase unknown

Table 14 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *HAEMOPHILUS INFLUENZAE*

β - Lactamase Positive					β - Lactamase Negative			
Ref.	(No.)	Range	MIC_{50}	MIC_{90}	(No.)	Range	MIC_{50}	MIC_{90}
42	(94)		0.03	0.06	(133)		0.03	0.06
43, 44	(46)[a]		0.016	0.016	(28)[b]		0.016	0.016
28	(173)		0.015	0.03	(326)		0.015	0.03
45	(67)		0.03	0.06	(132)		0.03	0.06
30, 31	(12)		0.03	0.03	(14)		0.03	0.03
63-65	(20)		0.03	0.06	(14)		0.03	0.06
63, 64, 65			-	-	(21)[a]		0.03	0.06
46	(31)		0.03	0.03	(277)		0.03	0.03
33, 34	(14)		0.03	0.06	(16)		0.06	0.06
36, 37	(20)		0.03	0.06	(38)		0.03	0.06
29	(330)[c]		0.03	0.06	-		-	-
70, 75, 72	(19)[c]		0.015	0.03	-		-	-
47	(45)[c]		-	0.12	-		-	-
68	(22)		0.03	0.06	-		-	-
76	(81)[d]		0.016	0.25	-		-	-

[a] Ampicillin - Resistant ≥16 µg/mL
[b] Ampicillin - Susceptible, ≤8 µg/mL
[c] β - Lactamase not given
[d] *H. parainfluenzae*

Moraxella catarrhalis

The *in vitro* activity of moxifloxacin against *Moraxella catarrhalis* is shown in TABLES 15 and 16. The production of β-lactamase did not effect the MIC_{90} value for this organism. A multicenter surveillance study conducted in the USA during 1997 included 251 strains of *M. catarrhalis*, the MIC_{90} was 0.06 µg/mL (28). A mode MIC_{90} of 0.06 µg/mL was obtained for the 1203 strains evaluated (see TABLE 15). *Moraxella catarrhalis* may be placed in the clinical efficacy section of the package insert if the Medical Officer agrees

Table 15 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *MORAXELLA CATARRHALIS*

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Moraxella catarrhalis (1203)[a]		0.06
β-lactamase Pos (712)		0.06
β-lactamase Neg (83)		0.06

[a] Includes 408 strains β-Lactamase unknown

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Table 16 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *MORAXELLA CATARRHALIS*

		β - Lactamase Positive			β - Lactamase Negative			
Ref.	(No.)	Range	MIC_{50}	MIC_{90}	(No.)	Range	MIC_{50}	MIC_{90}
43,44	(52)		0.03	0.03	(8)		0.016	-
28	(251)[a]		0.03	0.06	-		-	-
45	(141)		0.03	0.06	(37)		0.03	0.06
30, 31	(19)		0.06	0.06	-		-	-
63-65	(20)		0.12	0.12	(20)		0.12	0.12
46	(193)		0.03	0.06	(26)		0.03	0.06
47	(10)		-	0.06	-		-	-
33, 34	(26)		0.06	0.125	(3)		-	-
42	(76)[b]		0.06	0.12	-		-	-
29	(250)[b]		0.06	0.06	-		-	-
36, 37	(26)[b]		0.125	0.125	-		-	-
68	(21)[b]		0.06	0.06	-		-	-
59, 60, 61	(35)[b]		0.06	0.12	-		-	-

[a] Includes 28 strains β - Lactamase negative
[b] β - Lactamase not given

Citrobacter diversus was tested in two studies. Only 40 isolates were tested. The MIC_{90} values were 0.25 and 0.06 µg/mL. The applicant has not included this species in their draft labeling. Not enough testing was performed to include this species.

Proteus mirabilis was tested in seven studies. Over 200 isolates were tested and the mode MIC_{90} was 0.25 µg/mL. The MIC_{90} in all seven studies was ≤ 2.0 µg/mL. *Proteus mirabilis* may be placed in the *in vitro* activity section of the package insert.

Morganella morganii was tested in four studies. A total of 92 isolates were tested. The MIC_{90} values ranged from [redacted]. Only 16 isolates were tested in the study with a MIC_{90} value of 16 µg/mL. It appears that some strains are resistant to moxifloxacin. Since only 92 isolates were tested and the MIC_{90} value in one study was 16 µg/mL, this species should be deleted from the package insert.

Providencia stuartii was tested in two studies. Only 40 isolates were tested and one study had a MIC_{90} of 16 µg/mL. Only 10 isolates were tested in this study. Once again it appears that a few isolates of this species are resistant to moxifloxacin. This organism is not in the draft label and will not be allowed into the package insert.

All isolates listed are associated with respiratory tract or skin infections.

Table 17 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST SELECTED GRAM-NEGATIVE BACTERIA

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Escherichia coli (276)		0.06
Klebsiella pneumoniae (138)		1
Enterobacter cloacae (92)		0.5
Proteus mirabilis (236)		0.25
Pseudomonas aeruginosa (371)		8

Table 18 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST ENTEROBACTERIACEAE

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref.
Escherichia coli (30)[a]		0.008	0.008	43
Escherichia coli (34)		0.03	0.06	45
Escherichia coli (24)		0.015	0.015	70, 71, 72
Escherichia coli (31)		0.06	0.06	30, 31
Escherichia coli (22)		0.125	0.25	33
Escherichia coli (84)		0.06	0.06	77
Escherichia coli (12)		0.06	4	68
Escherichia coli (39)		0.06	1	59, 60, 61
Klebsiella pneumoniae (61)[b]		0.03	0.13	43
Klebsiella pneumoniae (21)		0.03	0.25	45
Klebsiella pneumoniae (35)		0.12	1	30, 31
Klebsiella pneumoniae (21)		0.125	1	78
Klebsiella oxytoca (64)[b]		0.003	0.13	43
Klebsiella oxytoca (25)		0.12	0.12	30, 31
Enterobacter aerogenes (42)		0.06	2	43

Table 18 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST ENTEROBACTERIACEAE - (Continued)

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref.
Enterobacter aerogenes (27)		0.12	0.5	30, 31
Enterobacter cloacae (63)		0.03	0.06	43
Enterobacter cloacae (29)		0.06	0.5	30, 31
Serratia marcescens (55)		0.25	8	43
Serratia marcescens (33)		0.25	2	30, 31
Serratia marcescens (22)		0.5	2	78
Citrobacter freundii (52)		0.06	1	43
Citrobacter freundii (33)		0.03	1	70, 71, 72
Citrobacter freundii (28)		0.12	2	30, 31
Citrobacter diversus (20)		0.06	0.25	43
Citrobacter diversus (20)		0.06	0.06	30, 31
Proteus mirabilis (37)		0.06	0.25	43
Proteus mirabilis (30)		0.125	0.5	45
Proteus mirabilis (25)		0.125	0.25	70, 71, 72
Proteus mirabilis (33)		0.25	2	30, 31

Table 18 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST ENTEROBACTERIACEAE - (Continued)

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref.
Proteus mirabilis (19)		0.5	1	78
Proteus mirabilis (27)		0.25	0.5	77
Proteus mirabilis (30)		0.25	0.25	59, 60, 61
Proteus vulgaris (35)		0.25	0.5	43
Proteus vulgaris (24)		0.125	0.5	70, 71, 72
Proteus vulgaris (15)		0.25	0.25	59, 60, 61
Morganella morganii (41)		0.06	0.13	43
Morganella morganii (16)		0.25	16	30, 31
Morganella morganii (20)		0.25	1	78
Morganella morganii (15)		0.12	0.25	59, 60, 61
Providencia stuartii (30)		0.06	0.5	43
Providencia stuartii (10)		4	16	30, 31

[a] Ampicillin MIC ≤8µg/mL
[b] Ceftazidime MIC ≤8µg/mL

3 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Anaerobes

Susceptibility data for a variety of gram-negative and gram-positive anaerobes are presented in TABLES 21-24. Activity against *Bacteroides fragilis* had MIC_{90} values in most studies around the breakpoint of 2 µg/mL. Some studies had slightly lower MIC_{90}s and one study had a MIC_{90} value of 4 µg/mL. Overall, 310 isolates were tested in nine studies and the mode MIC_{90} was 2.0 µg/mL. Most of the other members of the *Bacteroides fragilis* group had MIC_{90} values around the susceptible breakpoint of 2.0 µg/mL. As usual it appears that *Bacteroides thetaiotaomicron* may be more resistant to moxifloxacin with one study having a MIC_{90} of 16 µg/mL. The sponsor has included *Bacteroides fragilis* in the draft package insert. Since this organism is encountered in respiratory tract infections and is occasionally involved in disease production it will be allowed in the *in vitro* activity listing in the label.

The applicant has also included *Fusobacterium* species in the draft label. Most studies did not speciate this genus. There were seven studies that tested this genus and overall about 160 isolates were tested. The mode MIC_{90} was 1.0 µg/mL. One study in which only 15 isolates were tested had a MIC_{90} or 8 µg/mL. Since well over 100 isolates were tested and the MIC_{90} value in all but one study was ≤ 2.0 µg/mL, *Fusobacterium* species will be allowed in the *in vitro* activity section of the package insert.

Prevotella species has also been included in the draft package insert. Most studies did not speciate this genus and a number of studies only tested 3-9 isolates. Four studies tested individual species and all four studies had MIC_{90} values of ≤ 2.0 µg/mL. Only one study had a MIC_{90} value > 2 µg/mL and the mode MIC_{90} was 1.0 µg/mL. *Prevotella* species will be allowed in the *in vitro* activity listing in the label.

All studies that tested *Clostridium difficile* had MIC_{90} values of 1.0 or 2.0 µg/mL. Since this organism is not associated with respiratory or skin infections it has not been included in the label.

All studies that tested *Clostridium perfringens* had MIC_{90} values of 0.25 or 0.5 µg/mL. Just less than 100 isolates (98) were tested in a total of seven studies. This organism is associated with skin infections. *Clostridium perfringes* may remain in the *in vitro* activity section of the label.

Peptostreptococcus species were tested in seven studies. No MIC value was > 2.0 µg/mL. All MIC_{90} values were ≤ 1.0 µg/mL. These organisms have been isolated from infected sinuses and wounds. *Peptostreptococcus* species may remain in the *in vitro* activity listing in the label.

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Table 22 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER GRAM-NEGATIVE ANAEROBES

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref
Fusobacterium nucleatum (21)		1.0	4.0	69
F. nucleatum (7)		0.06	-	84, 85
F. nucleatum (18)		0.12	0.25	87
Fusobacterium spp (23)		0.12	0.5	82, 83
Fusobacterium spp (13)		0.06	0.12	30
Fusobacterium spp (20)		0.25	1.0	63, 64
Fusobacterium spp (15)		4.0	8.0	69
Fusobacterium spp (7)		-	-	33
Fusobacterium spp (50)		0.125	1.0	86
Fusobacterium spp (4)		-	-	87
Prevotella bivia (21)		1.0	2.0	82, 83
Prevotella disiens (19)		0.5	0.5	82, 83
Prevotella heparinolytica (12)		0.125	0.125	69
Prevotella buccae (5)		-	-	84, 85
Prevotella spp (24)		1.0	4.0	63, 64

Table 22 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER GRAM-NEGATIVE ANAEROBES (Continued)

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref
Prevotella spp (26)		0.25	0.5	69
Prevotella spp (9)		1.0	-	33
Prevotella spp (5)		-	-	84, 85
Prevotella spp (74)		0.5	1.0	87
Prevotella spp (3)		-	-	59, 60, 61
Porphyromonas salivosa (11)		0.125	0.125	69
Porphyromonas gingivalis (10)		0.06	0.06	69
Porphyromonas spp (14)		0.25	0.5	69
Veillonella parvula (18)		0.06	0.25	82, 83
Veillonella parvula (10)		0.25	0.25	84, 85

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Table 24 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER GRAM-POSITIVE ANAEROBES

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref.
Eubacterium spp (14)		0.12	0.25	82, 83
Eubacterium spp (7)		0.25	-	85
Bifidobacterium bivius (12)		-	2	88
Bifidobacterium spp (5)		1	-	85
Peptostreptococcus spp (25)		0.06	0.25	82, 83
Peptostreptococcus spp (22)		0.12	0.25	64
Peptostreptococcus spp (28)		0.06	0.25	30, 31
Peptostreptococcus spp (9)		0.25	-	69
Peptostreptococcus spp (30)		0.25	0.5	33
Peptostreptococcus spp (9)		0.25	-	87
Peptostreptococcus spp (20)		0.12	1	73, 89, 61
Propionibacterium acnes (9)		0.25	-	33
Propionibacterium acnes (30)		0.125	0.25	86
Propionibacterium acnes (7)		0.25	-	84
Actinomyces spp (8)		0.03	-	84
Mobiluncus spp (32)		0.25	0.5	63

Table 25 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST SELECTED GRAM-NEGATIVE ANAEROBES

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Bacteroides fragilis (310)		2
Fusobacterium spp. (160)		1
Prevotella spp. (176)		0.5

Table 26 - SUMMARY OF IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST SELECTED GRAM-POSITIVE ANAEROBES

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Clostridium difficile (115)		2
Clostridium perfringens (88)		0.5
Peptostreptococcus spp. (125)		0.25

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Other Respiratory Tract Pathogens

Moxifloxacin's *in vitro* activity against *Chlamydia pneumoniae* is demonstrated in TABLE 27. All MICs were ≤ 1.0 µg/mL. In three studies the MICs were either [redacted] One study had MICs of [redacted] Differences in cell-lines and inocula probably account for these differences since there is no standard method for determining susceptibility of *Chlamydia* species. Although only 19 isolates have been tested, all the data indicates that moxifloxacin's MICs against this species are below 2.0 µg/mL. This organism is hard to culture and do susceptibility studies on so very few isolates are usually tested. *Chlamydia pneumoniae* may remain in the clinical efficacy section of the package insert if the Medical Officer concurs.

Table 27 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *CHLAMYDIA* SPP

Organism (No.)	Range	MIC_{50}	MIC_{90}	Ref
C. pneumoniae (3)	[redacted]	-	-	94
C. pneumoniae (5)		-	-	63-65
C. pneumoniae (10)		1.0	1.0	95, 96
C. pneumoniae (1)		-	-	59, 60, 61
C. trachomatis (27)		0.06	0.06	94
C. trachomatis (20)		0.06	0.12	63-65
C. trachomatis (3)		-	-	59, 60, 61
C. psittaci (10)		0.06	0.125	94

Moxifloxacin's activity against *Legionella* species is summarized in TABLE 28. All MICs were below 0.25 µg/mL and the MIC_{90} were ≤ 0.125 µg/mL. Over 100 isolates of *Legionella pneumophila* were tested in a total of four studies. *Legionella pneumophila* may remain in the *in vitro* activity section of the label.

Table 28 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *LEGIONELLA* SPP

Organism (No.)	Range	MIC50	MIC90	Ref
L. pneumophila (55)		0.015	0.015	63-65
L. pneumophila (12)		0.03	0.125	33
Legionella spp[a] (52)		0.06	0.125	97
Legionella spp[b] (30)		0.03	0.06	98, 99

[a] Includes *L. pneumophila serogroup 1* (21), *L. pneumophila serogroup* 2-14 (18), *L. micdadei* (2), *L. bosemanii* (3), *L. longbeacheae* (2), *L. dumoffili* (1), *L. gormanii* (1), *L. jordanis* (1), *L. feelci* (2), *L. hackeliae* (1).

[b] Includes *L. pneumophila* (21), *L. longbeacheae* (3), *L. bozemanii* (2), *L dumoffii* (2), *L. micdadei* (1), *L. gormanii* (1).

Table 30 - Summary of In Vitro Activity of Moxifloxacin against other RTI Pathogens

Organism (No.)	Range of MIC_{90}s (µg/mL)	Mode MIC_{90}
Legionella spp (149)[a]		0.125
Mycobacterium tuberculosis (276)		0.5
Mycoplasma pneumoniae (131)		0.06
Chlamydia pneumoniae (19)[b]		1

[a] Includes 127 strains of *L pneumophila*
[b] Range of MICs

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The following microorganisms should have qualifiers after their listings:

Aerobic gram-positive aerobes:

Streptococcus pneumoniae (penicillin-susceptible, strains)

Staphylococcus aureus—This organism should be qualified as (methicillin-susceptible strains only). Moxifloxacin was not as active against methicillin-resistant strains. The mode MIC_{90} for these strains was 4.0 µg/mL.

The list of organisms should, therefore, read as follows:

Aerobic gram-positive microorganisms:

Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae

Aerobic gram-negative microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

Aerobic gram-positive microorganisms

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

Anaerobic gram-positive microorganisms
Peptostreptococcus species

Anaerobic gram-negative microorganisms
Fusobacterium 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. Isolates of *Streptococcus pneumoniae* from the USA and Europe were evaluated both separately and by susceptibility to penicillin.

IN VITRO COMPARISON AGAINST GRAM-POSITIVE COCCI

A comparison of moxifloxacin with other quinolones against *Streptococcus pneumoniae* showed that moxifloxacin and trovafloxacin were the most active quinolones. Levofloxacin and ciprofloxacin were at least four- to eightfold less active (see TABLES 31 and 32). The MIC_{90} for moxifloxacin and trovafloxacin was 0.25 µg/mL. The MIC_{90} for ciprofloxacin and levofloxacin were 2.0 and 1.0, respectively. The MIC_{90} for sparfloxacin was 0.5 µg/mL. Susceptibilities were not affected by intercontinental or national geographical locations. MICs for all the tested quinolones were independent of penicillin susceptibility.

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 33). The MIC90 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 34). Once again the β-lactams were more active with a MIC_{90} of ≤ 0.06 µg/mL

Against [redacted] 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 35). 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 [redacted] resistant *Staphylococcus aureus* increased to 4.0 µg/mL. Most other drugs had MIC_{90}s ≥ 32 µg/mL for these organisms (TABLE 36). TABLE 37 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 [redacted] resistant strains.

The MIC_{90} of moxifloxacin was generally fourfold less than the ciprofloxacin MIC_{90} for *Enterococcus faecalis*. Amoxicillin/clavulanate and ampicillin were much more active. None of the quinolones had much activity against *Enterococcus faecium* (TABLE 38).

GLOSSARY OF ABBREVIATIONS

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

Table 31- COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE* / USA STUDIES

	MIC_{90} µg/mL								
Ref. (No.)	**MXF**	**TRO**	**CIP**	**LEV**	**OFL**	**SPA**	**ERY**	**CLA**	**AMC**
PEN-S									
27(410)	0.25	-	2	1	4	0.5	≤0.25	0.125	-
28 (336)	0.12	0.12	1	1	2	0.25	0.06	≤0.03	0.015
29(154)	0.06	0.12	1	1	1	0.12	-	-	-
30(15)	0.25	-	1	-	2	-	-	0.06	0.06
32(134)	0.25	-	1	1	2	-	-	-	-
37(52)	0.5	-	2	2	4	-	0.25	-	0.06
39(53)	0.25	-	4	-	4	0.5	-	-	0.03[d]
PEN-I									
27(88)	0.25	-	2	1	2	0.5	>1	>8	-
28(108)	0.06	0.06	1	1	2	0.25	32	64	2
29(150)	0.06	0.12	1	1	1	0.12	-	-	-
30(20)	0.25	-	1	-	2	-	-	16	1
32(106)	0.25	-	1	1	2	-	-	-	-
39(76)	0.25	-	8	-	4	0.5	-	-	2[d]
PEN-R									
27(102)	0.25	-	1	1	2	0.5	-	≥8	-
28(56)	0.12	0.12	1	1	2	0.25	≥64	≥64	8
29(100)	0.06	0.12	1	1	1	0.12	-	-	-
30(15)	0.25	-	1	-	2	-	-	≥32	4
32(61)	0.125	-	1	1	2	-	-	-	-
102, 35(27)	≤0.125	≤0.125	2	0.5	-	0.25	-	-	-
39(76)	0.25	-	4	-	4	0.5	-	-	4[d]

[a] Ceftriaxone
[b] Cefpodoxime
[c] Cefuroxime
[d] Amoxicillin

Table 32 - COMPARATIVE IN VITRO ACITIVTY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE* / NON-USA STUDIES

		MIC_{90} µg/mL						
Ref.	(No.)	MXF	TRO	CIP	LEV	CLA		AMC
PEN-S								
42	(107)	0.25	-	2	-	4		0.12[b]
43	(30)	0.25	0.25	4	2	-		-
63	(20)	0.12	-	-	1[c]	0.06		0.015
46	(336)	0.25	0.25	2	-	-		-
48	(1317)	0.25	0.25	2	2	-		-
52, 53	(60)	0.06	-	2	1	<0.06		≤ 0.03
54	(174)	0.25	-	4	4[c]	-		-
55	(267)	0.12	0.12	1	-	-		-
56	(92)[d]	0.12	-	2	-	-		-
57	(79)	0.12	-	2	-	-		-
58	(362)	0.125	0.125	2	1	-		-
PEN-I								
42	(80)	0.12	-	1	-	32		2[b]
43	(20)	0.25	0.25	2	2	-		-
63	(20)	0.12	-	-	1	>64		0.5
46	(16)	0.25	0.25	2	-	-		-
48	(40)	0.25	0.25	2	1	-		-
52, 53	(60)	0.12	-	1	1	0.12		1
54	(26)	0.25	-	4	4[c]	-		-
55	(21)	0.25	0.25	2	-	-		-
57	(104)	0.12	-	2	-	-		-
58	(54)	1	0.5	4	4	-		-
PEN-R								
42	(76)	0.25	-	1	-	64		4[b]
43	(15)	0.25	0.25	2	2	-		-
46	(20)	0.12	-	-	2	>64		1
48	(28)	0.25	0.25	2	2	-		-
52, 53	(60)	0.12	-	2	1	0.5		8
58	(36)	0.25	0.25	>4	4	-		-

Table 32 -COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE* / NON-USA STUDIES(Continued)

		MIC_{90} µg/mL					
Ref. (No.)		**MXF**	**TRO**	**CIP**	**LEV**	**CLA**	**AMC**
PEN-Not Designated							
41	(101)	0.12	-	2	-	-	4[g]
47	(99)	0.12	0.12	2	-	0.25	2
50	(50)	0.1	0.1	1	1	0.1	-
61	(32)	0.25	0.25	16	-	-	1
33	(28)	0.25	0.25	2	-	-	-

[a] Cefuroxime
[b] Amoxicillin
[c] Ofloxacin
[d] Includes 2 PEN-R Strains
[e] Ceftriaxone
[f] Cefotaxime
[g] Penicillin
[h] Cefpodoxime

Table 33 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STREPTOCOCCUS PYOGENES*

		MIC90 µg/mL					
Ref.	(No.)	MXF	LEV	CIP	TRO	AMC	ERY
41	(20)	0.25	-	1	-	-	>4
42	(99)	0.12	-	1	-	≤0.01[b]	16
43	(47)	0.25	1	1	0.25	-	-
62	(30)	0.25	4[d]	2	-	-	-
30	(14)	0.12	1[d]	0.25	-	≤ 0.03	0.06[c]
46	(169)	0.25	-	2	0.25	-	-
37	(60)	0.25	1	1	-	0.03	0.125
59, 60, 61	(20)	0.25	-	1	0.25	0.015	-

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

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Table 35 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS AUREUS* (METH SUSC)

		MIC_{90} µg/mL							
Ref.	(No.)	MXF	LEV	CIP	TRO	VAN	AMC		CLA
42	(128)	0.06	-	1	-	-	1		-
43	(90)	0.06	0.25	0.5	0.06	-	-		-
30	(34)	0.06	0.25[b]	1	-	-	1		0.5
64	(31)	0.12	1[b]	-	-	-	-		-
50	(25)	0.1	0.2	1	0.1	1	-		0.1
56	(100)	1	-	>32	-	1	-		-
67	(194)	1	64[b]	128	-	-	-		-
61	(54)	0.12	-	1	0.06	-	0.5		-
41	(62)[d]	8	-	>16	-	2	>2[e]		-
46	(131)[d]	0.125	-	1	0.125	-	-		-
69	(18)[d]	0.03	0.125	0.5	-	-	0.5		0.5

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

Table 36 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *STAPHYLOCOCCUS AUREUS* / METH RESIST

		MIC_{90} µg/mL							
Ref.	(No.)	MXF	LEV	CIP	TRO	VAN	AMC		CLA
42	(108)	4	-	64	-	-	64		>64
43	(63)	4	16	32	4	-	-		-
30	(20)	4	≥32[b]	≥32	-	-	-		≥32
64	(25)	4	64[b]	-	-	-	-		-
50	(25)	8	16	32	8	4	-		32
61	(20)	2	-	128	2	-	16		-

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

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IN VITRO COMPARISON AGAINST GRAM-NEGATIVE BACTERIA

Moxifloxacin's activity against *Haemophilus influenzae* was two- to fourfold less than that of ciprofloxacin and usually twofold less than that of trovafloxacin or sparfloxacin (TABLE 39). This organism was still, however, very susceptible to moxifloxacin. The range of MIC_{90}s for moxifloxacin was [redacted] while the range of MIC_{90}s for ciprofloxacin was [redacted]

The activity of moxifloxacin against *Moraxella catarrhalis* generally was equal to or twofold less than that of ciprofloxacin, trovafloxacin and sparfloxacin (TABLE 40). The ranges of MIC_{90}s were [redacted] moxifloxacin; [redacted] ciprofloxacin; [redacted] trovafloxacin and sparfloxacin.

For most of the Enterobacteriaceae, the activity of moxifloxacin was two- to fourfold lower than that of ciprofloxacin (TABLE 41). With the exception of *Serratia marcescens* [redacted] the majority of the moxifloxacin MIC_{90}s for the Enterobacteriaceae were ≤ 1.0 µg/mL. Against *Klebsiella pneumoniae*, the MIC_{90}s for moxifloxacin were 0.13-1.0 µg/mL, while the MIC_{90}s for ciprofloxacin were 0.06-0.5 µg/mL. The range of MIC_{90}s of moxifloxacin and ciprofloxacin for *Escherichia coli* were [redacted] respectively.

Activity against *Pseudomonas aeruginosa* was four- to eightfold lower for moxifloxacin compared with ciprofloxacin (TABLE 42). MIC_{90}s of moxifloxacin ranged from [redacted]

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Table 39 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *HAEMOPHILUS INFLUENZAE*

			MIC_{90} µg/mL							
Ref.	β-Lac	(No.)	MXF	LEV	CIP	TRO	SPA	AMC	CLA	AMOX
42	Pos	(94)	0.06	-	0.03	-	0.03	2	8	≥64
	Neg	(133)	0.06	-	0.03	-	0.03	2	8	4
43	Pos	(28)[a]	0.06	0.06	0.016	0.016	-	-	-	-
	Neg	(46)[b]	0.06	0.06	0.016	0.016	-	-	-	-
28	Pos	(173)	0.03	≤0.03	≤0.015	≤0.03	≤0.015	2	16	>32
	Neg	(326)	0.03	≤0.03	≤0.015	≤0.03	≤0.015	1	16	1
30	Pos	(12)	0.03	0.06[d]	0.015	-	-	1	4	-
	Neg	(14)	0.03	0.06[d]	0.015	-	-	0.5	8	-
63	Pos	(20)	0.06	0.03[d]	-	-	-	2	16	-
	Neg	(14)	0.06	0.03[d]	-	-	-	0.5	16	-
	Neg	(21)[a]	0.06	0.06[d]	-	-	-	4	16	-
46	Pos	(31)	0.06	-	0.03	0.06	0.06	-	-	-
	Neg	(277)	0.06	-	0.03	0.06	0.06	-	-	-

Table 39 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *HAEMOPHILUS INFLUENZAE* (Continued)

			MIC_{90} µg/mL								
Ref.	β-Lac	(No.)	MXF	LEV	CIP	TRO	SPA	AMC		CLA	AMOX
33	Pos	(14)	0.06	-	-	-	-	-		16	>16[f]
	Neg	(16)	0.06	-	-	-	-	1[f]		16	1[f]
37	Pos	(20)	0.06	0.03	≤0.016	-	-	4		16[g]	-
	Neg	(38)	0.06	0.03	≤0.016	-	-	1		8[g]	-
29	-	(330)	0.06	0.03	0.03	0.03	0.015	-		-	-
72	-	(19)	0.03	-	0.008	-	0.015	16		32	>32
47	-	(45)	≤0.01	-	≤0.01	≤0.01	-	4		32	-
68	-	(22)	0.06	0.06[d]	0.015	-	-	-		-	-
61	-	(36)	0.03	-	0.015	0.015	-	2		-	-
76	-	(81)[h]	0.25	-	0.03	-	-	8		16	128

[a] Ampicillin - Resistant ≥ 16 µg/mL
[b] Ampicillin - Susceptible ≤ 8 µg/mL
[c] Cefpodoxime
[d] Ofloxacin
[e] Cefuroxime
[f] Ampicillin
[g] Erythromycin
[h] *H. parainfluenzae*

Table 40 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *MORAXELLA CATARRHALIS*

			MIC_{90} µg/mL						
Ref.	β- Lac	(No.)	MXF	LEV	CIP	TRO	SPA	AMC	CLA
43	Pos	(52)	0.03	0.03	0.03	0.016	-	-	-
28	Pos	(251)[a]	0.06	≤0.03	0.03	≤0.03	≤0.015	0.25	0.12
30	Pos	(19)	0.06	0.12[c]	0.06	-	-	0.25	0.25
46	Pos	(193)	0.06	-	0.06	0.06	0.06	-	-
	Neg	(26)	0.03	-	0.03	0.03	0.06	-	-
47	Pos	(10)	0.06	-	0.06	0.03	-	0.5	0.5
42	-	(76)	0.12	-	0.12	-	0.03	0.25	0.12
29	-	(250)	0.06	0.06	0.015	0.015	0.015	-	-
33	-	(29)	0.125	-	0.06	0.03	0.03	-	-
37	-	(26)	0.125	0.125	0.125	-	-	0.25	0.25[e]
68	-	(21)	0.06	0.12[c]	0.06	-	-	-	-
61	-	(35)	0.12	-	0.06	0.03	-	0.25	-

[a] Includes 28 β-Lactamase negative strains
[b] Cefpodoxime
[c] Ofloxacin
[d] Cefuroxime
[e] Erythromycin

Table 41 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST ENTEROBACTERIACEAE

	MIC_{90} µg/mL						
Organism (No.)	**MXF**	**CIP**	**TRO**	**LEV**	**SPA**	**AMC**	**REF.**
E. coli (30)[a]	0.008	0.016	0.03	0.03	-	-	43
E. coli (22)	0.015	0.015	-	-	0.015	-	72
E. coli (31)	0.06	0.03	-	0.12[b]	-	16	30
E. coli (22)	0.25	0.06	0.03	0.06	0.06	-	78
E. coli (39)	1	0.5	1	-	-	16	61
K. pneumoniae (61)[a]	0.13	0.06	0.13	0.13	-	-	43
K. pneumoniae (35)	1	0.5	-	1[b]	-	8	30
K. pneumoniae (21)	1	0.25	0.5	0.5	0.5	-	78
K. oxytoca (64)[a]	0.13	0.06	0.13	0.13	-	-	43
K. oxytoca (25)	0.12	0.06	0.12	0.12[b]	-	4	30
E. aerogenes (42)	2	1	2	4	-	-	43
E. aerogenes (27)	0.5	0.12	-	1[b]	-	-	30
E. cloacae (63)	0.06	0.03	0.06	0.06	-	-	43
E. cloacae (29)	0.5	0.25	-	1[b]	-	-	30

Table 41 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST ENTEROBACTERIACEAE (Continued)

	MIC_{90} µg/mL						
Organism (No.)	MXF	CIP	TRO	LEV	SPA	AMC	REF.
S. marcescens (55)	8	4	8	8	-	-	43
S. marcescens (33)	2	1	-	2[b]	-	-	30
S. marcescens (22)	2	1	2	1	2	-	78
C. freundii (52)	1	0.25	1	0.5	-	-	43
C. freundii (33)	1	0.25	-	-	0.5	-	72
C. freundii (28)	2	0.25	-	2[b]	-	-	30
C. diversus (20)	0.25	0.06	0.25	0.13	-	-	43
C. diversus (20)	0.06	0.015	-	0.06[b]	-	4	30
P. mirabilis (37)	0.25	0.06	0.5	0.25	-	-	43
P. mirabilis (25)	0.25	0.06	-	-	0.125	-	72
P. mirabilis (33)	2	0.25	-	1[b]	-	1	30
P. mirabilis (19)	1	0.06	0.25	0.125	0.5	-	78
P. mirabilis (30)	0.25	0.03	0.25	-	-	4	61
P. vulgaris (35)	0.5	0.06	0.5	0.13	-	-	43

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Table 42 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST NONFERMENTATIVE GRAM-NEGATIVE BACTERIA

	MIC_{90} µg/mL					
Organism (No.)	**MXF**	**CIP**	**TRO**	**LEV**	**AMC**	**REF.**
P. aeruginosa (50)	32	8	16	32	-	43
P. aeruginosa (50)	8	1	-	-	-	72
P. aeruginosa (26)	2	0.25	-	4[a]	-	30
P. aeruginosa (22)	8	1	2	4	-	78
P. aeruginosa (15)	8	4	8	-	≥128	61
P. fluorescens (31)	4	2	8	4	-	43
S. maltophilia (50)	4	16	4	8	-	43
S. maltophilia (17)	0.5	4	-	-	-	72
S. maltophilia (10)	4	16	-	16[a]	-	30
S. maltophilia (13)	2	8	2	-	≥128	61
A. baumanii (43)	0.25	1	0.13	0.5	-	43
A. baumanii (15)	8	≥32	-	≥32[a]	16	30
A. lwoffi (30)	0.03	0.13	0.03	0.13	-	43
A. calcoaceticus (20)	0.06	0.13	0.03	0.13	-	43
A. calcoaceticus (30)	0.25	0.5	-	-	-	72

[a] Ofloxacin
[b] Ceftriaxone
[c] Cefpodoxime

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Table 44 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER GRAM-NEGATIVE ANAEROBES

	MIC_{90} µg/mL								
Organism (No.)	**MXF**	**OFL**	**TRO**	**CIP**	**MET**	**CLN**	**FOX**	**PEN**	**REF.**
Fusobacterium spp. (23)[a]	0.5	4	-	4	1	1	4	16	82
Fusobacterium nucleatum (21)	4	>16	-	>16	-	-	-	0.5	69
Fusobacterium nucleatum (18)	0.25	-	0.5	-	0.12	-	-	2	87
Prevotella bivia (21)	2	8	-	16	2	0.03	4	16	82
Prevotella disiens (19)	0.5	2	-	1	2	0.03	2	16	82
Porphyromonas salivosa (11)	0.125	0.5	-	1	-	-	-	1	69
Porphyromonas gingivalis (10)	0.06	0.25	-	0.5	-	-	-	0.03	69
Veillonella parvula (18)	0.25	1	-	0.5	1	0.5	1	2	82
Veillonella parvula (10)	0.25	0.5	0.5	0.25	4	-	0.5	0.12[b]	85

[a] Includes 10 strains of *F nucleatum*
[b] Amoxicillin/clavulanate

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Table 46 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST OTHER GRAM-POSITIVE ANAEROBES

	MIC_{90} µg/mL								
Organism (No.)	**MXF**	**OFL**	**TRO**	**CIP**	**FOX**	**MET**	**CLN**	**AMC**	**REF**
Eubacterium spp (14)	0.25	1	-	-	8	0.25	2	1	82
Bifidobacterium bivius (12)	2	-	4	-	-	32	0.2	0.2	50
Peptostreptococcus spp (25)	0.25	1	-	0.5	0.5	0.5	0.25	0.06[b]	82
Peptostreptococcus spp (22)	0.25	8	-	-	8[c]	-	2	1	65
Peptostreptococcus spp (28)	0.25	4	-	1	2[c]	-	-	0.12	30
Peptostreptococcus spp (30)	0.5	-	0.5	-	0.5	1	1	-	33
Peptostreptococcus magnus (27)	0.25	0.5	0.25	0.5	0.5	0.06	1	0.25	85
Peptostreptococcus spp (20)	1	-	1	2	-	-	-	0.25	61
Propionibacterium acnes (30)	0.25	1[d]	-	-	0.25	≥ 64	0.03	-	86

[a] studies with at least 10 isolates
[b] penicillin
[c] cefuroxime
[d] levofloxacin

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Table 49 - COMPARATIVE IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST *LEGIONELLA* SPP

	MIC_{90} µg/mL						
Organism (No.)	**MXF**	**CIP**	**LEV**	**ERY**	**CLAR**		**REF**
L. pneumophila (55)	0.015	-	0.015[a]	-	-		64
L. pneumophila (12)	0.125	0.03	0.03	-	-		33
Legionella spp[b] (52)	0.125	0.06	-	0.25	-		103
Legionella spp[d] (30)	0.03	-	0.03	0.12	≤ 0.004		98

[a] Ofloxacin
[b] Includes 39 strains of *L pneumophila*
[d] Includes 21 strains of *L pneumophila*

IN VITRO ACTIVITY AGAINST BACTERIA RESISTANT TO OTHER AGENTS

Penicillin-resistance of *Streptococcus pneumoniae* did not effect the MICs of moxifloxacin. The MICs were similar for both penicillin-susceptible and –resistant strains. Macrolide susceptibility also did not affect MICs of moxifloxacin (see TABLE 50). Low level ciprofloxacin resistance (MICs 2-8 µg/mL) did not result in increased MICs of moxifloxacin, however, high level (MIC 64 µg/mL) did result in higher MICs of 4 µg/mL for moxifloxacin. There is cross-resistance between ciprofloxacin and moxifloxacin as there is with other quinolones. Like many of the newer fluoroquinolones, this usually leads to higher MICs but the organism may still be susceptible to the newer agent.

[redacted]esistant strains of *Staphylococcus aureus* had higher MIC_{90}s, usually 4 µg/mL, for moxifloxacin (TABLE 51). Ciprofloxacin –resistant MRSA strains also had moxifloxacin MIC_{90}s of 4 µg/mL. Most studies did not define whether or not their strains of MRSA were ciprofloxacin-susceptible or –resistant, therefore, it is difficult to determine which antibiotic (or both) is contributing to elevated moxifloxacin MICs. Thomson et al (40) did differentiate their strains of *Staphylococcus aureus* according to their susceptibility to either ciprofloxacin or oxacillin. Moxifloxacin's MIC_{90} was 0.12 µg/mL for ciprofloxacin-susceptible and moderately susceptible strains (MIC ≤ 0.5 and 1-4 µg/mL, respectively); however, strains having ciprofloxacin MICs ≥ 8 µg/mL had a moxifloxacin MIC_{90} of 4 µg/mL. When these same strains were evaluated according to their oxacillin [redacted]susceptibility, the moxifloxacin MIC_{90}s for oxacillin-susceptible and –resistant strains were 2 and 4 µg/mL, respectively. The MIC_{90}s for ciprofloxacin were 64 µg/mL for oxacillin-susceptible strains and 128 µg/mL for oxacillin-resistant strains. These results and data showing that the presence of the *mecA* gene only (which causes [redacted]esistance) does not cause an increase in the MIC of moxifloxacin (104) suggest that ciprofloxacin resistance and not [redacted]resistance influences the susceptibility of *Staphylococcus aureus* to moxifloxacin. It does appear, however, that most stains that are ciprofloxacin-resistant are also [redacted]resistant. The Thomson data (40) also suggest that the strains that were evaluated for oxacillin susceptibility were resistant to ciprofloxacin since they had elevated ciprofloxacin and moxifloxacin MICs. It would have been better to test ciprofloxacin-susceptible, [redacted]-resistant strains in order to determine moxifloxacin MICs for this group. There are probably very few ciprofloxacin-susceptible, [redacted]resistant strains. It may be that these strains developed in very sick patients in hospitals where both drugs were heavily used.

Among the gram-negative bacteria, resistance to ampicillin (β-lactamase positive) had no affect on moxifloxacin MICs for *Haemophilus influenzae*. This is true for all fluoroquinolones.

Table 50 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST STREPTOCOCCI RESISTANT TO OTHER AGENTS

Organism (No.)	Resistant To:	Range	MIC_{90}	Ref.
S. pneumoniae (18)	Ciprofloxacin		0.25	72
S. pneumoniae (45)	Ciprofloxacin		4	105
S. pneumoniae (35)	Erythromycin		0.12	63
S. pneumoniae (40)	Erythromycin		0.12	52
S. viridans gp (61)	Penicillin		0.25	42
S. viridans gp (20)	Penicillin		0.25	37
S. pyogenes (10)	Ciprofloxacin		0.5	72
S. pyogenes (30)			0.25	62
S. pyogenes (30)	Erythromycin		0.25	62
S. agalactiae (38)	Ciprofloxacin		0.5	72

Table 51 - IN VITRO ACTIVITY OF MOXIFLOXACIN AGAINST STAPHYLOCOCCI RESISTANT TO OTHER AGENTS

Organism (No.)	Resistant To:	Range	MIC_{90}	Ref.
S. aureus (63)			4	43
S. aureus (20)			4	30
S. aureus (194)			1	67
S. aureus (19)	Ciprofloxacin		4	72
S. aureus (31)	Ciprofloxacin		4	33, 34
S. aureus (70)	Ciprofloxacin		1	106
S. aureus (22)	Ciprofloxacin		4	68
S. aureus (20)	CIP		4	72
S. aureus (59)	CIP		8	105
S. aureus (23)	Oxacillin		2	105
S. epidermidis (26)			0.13	43
S. epidermidis (29)			2	30
S. epidermidis (25)			2	50
Staphylococcus CN (20)			0.06	78
Staphylococcus CN (20)	CIP		8	78
S. haemolyticus (20)			0.13	43
S. haemolyticus (22)			4	30
S. saprophyticus (20)			1	43

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

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 [ ] This lowering of activity is seen with most fluoroquinolones. There was also an increase in MICs for streptococci at pH [ ] This increase at high pH is usually not seen. As usual with fluoroquinolones increasing the inoculum size (100-fold) to 10^7 cfu/mL also increased the MICs of moxifloxacin.

Effect of Test Medium on MICs

MICs of moxifloxacin were determined using various testing media including cation-supplemented Mueller-Hinton broth (CAMHB), Mueller-Hinton broth (MHB), [ ] The organisms tested were five or six strains each of *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis,* [ ] susceptible *Staphylococcus aureus* (MSSA), and [ ] esistant *Staphylococcus aureus* (MRSA). With the exception of varying the test medium, the MICs were performed according to NCCLS guidelines. The MICs obtained against all of the strains except one strain of MRSA were either the same or within one twofold dilution. The MICs for this one strain of MRSA were fourfold higher in [ ] ompared with the other media. The type of medium used for susceptibility testing did not appear to effect the MICs.

Effect of Test Methods on MICs

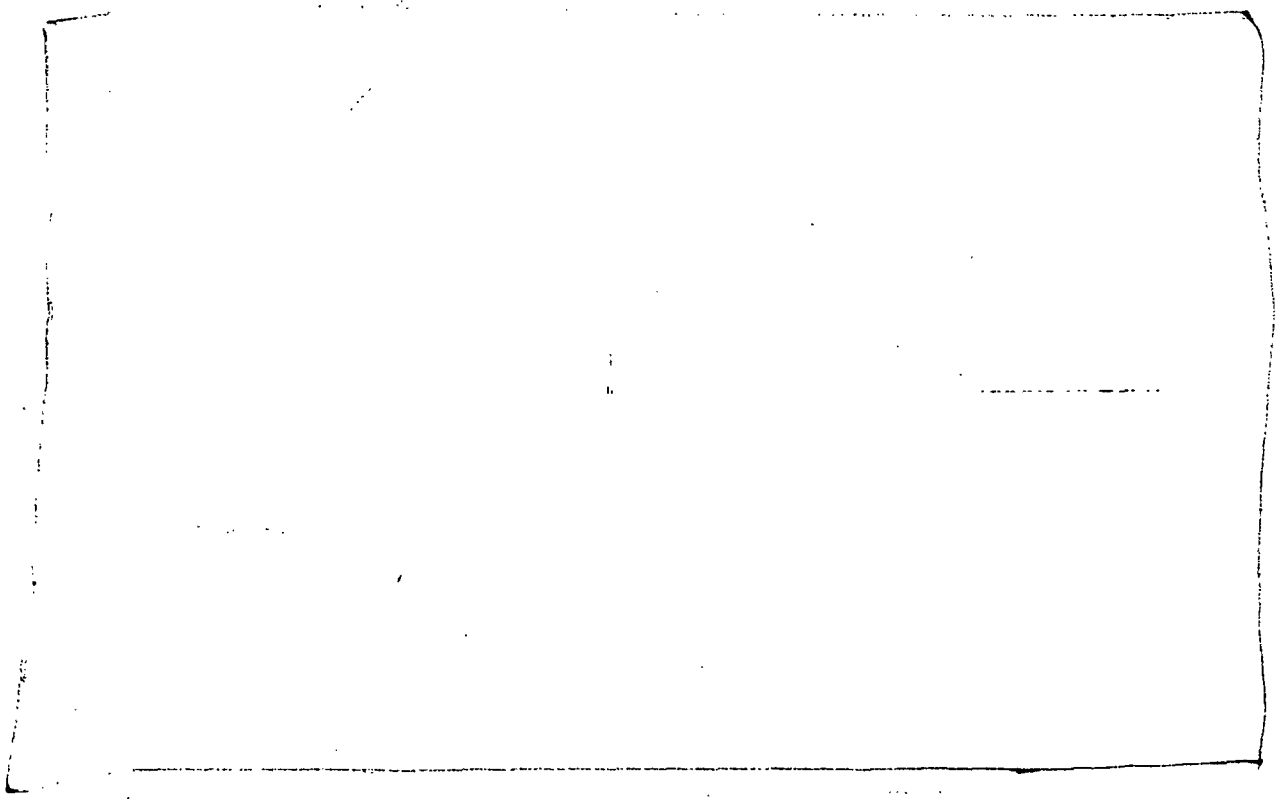
Macrobroth dilution, microbroth dilution, and agar dilution susceptibility test methods were compared against representative respiratory tract infection isolates to determine if the test methods were interchangeable. Good correlation among MICs was obtained by all three methods for all organisms (34). MICs were either the same or within a twofold dilution for all 23 isolates tested. For *Staphylococcus aureus* and *Enterococcus faecalis*, MICs by agar dilution and broth macrodilution were generally within one dilution of the broth microdilution method (78). In one study, however, MICs obtained by broth microdilution were generally two- to as high as -eightfold higher than those seen using agar or broth macrodilution when testing *Escherichia coli* and *Klebsiella pneumoniae*. This increase was not explained and did not seem to fit with most other studies. In general, the method used did not effect moxifloxacin's MICs.

Activity in the Presence or Absence of Oxygen

The activity of moxifloxacin under aerobic and anaerobic conditions was evaluated by time-kill methodology (107, 108, 109). The bactericidal activity against the test strains *Escherichia coli* and *Staphylococcus aureus* was not influenced by the presence or absence of oxygen.

Inoculum Size

An inoculum size of 10^4, 10^5, or 10^6 cfu/mL did not have any effect on the MICs of moxifloxacin for *Moraxella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli*, or *Klebsiella pneumoniae* (78, 34). An appreciable inoculum effect, however, was seen when an inoculum of 10^7 cfu/mL was used. Most MICs increased over eightfold for the majority of strains tested.



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three strains of *Streptococcus pneumoniae* and one strain of *Haemophilus influenzae* tested with 12 hours. A 5-6 $\log_{10}$ reduction was seen for *Moraxella catarrhalis* within 4 hours. Moxifloxacin was more active than grepafloxacin against all strains tested.

Using time-kill curves the bactericidal activity of moxifloxacin was compared with that of other quinolones, β-lactams, and macrolides (70, 72, 113, 51, 34, 114). Against a penicillin-susceptible strain of *Streptococcus pneumoniae*, moxifloxacin was as bactericidal as penicillin, cefprozil, cefuroxime, trovafloxacin, levofloxacin, sparfloxacin, and DU-6859a at 4 X MIC (113, 34). Similar results were seen for a penicillin-resistant strain of *Streptococcus pneumoniae*. Time-kill kinetics for *Streptococcus pyogenes* showed that clarithromycin was the least bactericidal agent. The bactericidal activity of moxifloxacin was comparable to that of cefuroxime, cefprozil, penicillin, DU-6859a, trovafloxacin, and levofloxacin. Bactericidal activity against streptococci was dose dependent (70, 72). With the exception of lomefloxacin, moxifloxacin and the other quinolones were similar in their bactericidal activity against β-lactamase-positive and -negative *Haemophilus influenzae* and *Moraxella catarrhalis* (113, 34). The β-lactam antibiotics were the least active against *Haemophilus influenzae* and β-lactamase positive *Moraxella catarrhalis*.

Bactericidal evaluation of *Staphylococcus aureus* showed that moxifloxacin was as bactericidal as sparfloxacin and more bactericidal than penicillin G, amoxicillin, cefuroxime, and clarithromycin. Bactericidal activity of moxifloxacin was dose dependent. Killing rates determined from time-kill curve experiments demonstrated that against five of the six strains tested, the killing rate was drug concentration dependent for moxifloxacin for up to 64 X MIC. The killing rate for sparfloxacin against these same strains, while similar to that of moxifloxacin, was drug concentration dependent only up to 4 X MIC. In these studies, moxifloxacin was the most bactericidal agent compared with sparfloxacin, penicillin G, amoxicillin, cefuroxime, or clarithromycin.

EFFECT OF SERUM AND COMPONENTS OF PURULENT INFECTION ON BACTERICIAL ACTIVITY

The addition of serum at concentrations of 20% or 70% had minimal effects on the bactericidal activity of moxifloxacin against penicillin-resistant or penicillin-susceptible *Streptococcus pneumoniae*, β-lactamase-positive or -negative *Haemophilus influenzae*, and *Moraxella catarrhalis* as determined by time-kill curves (120). The rate and extent of killing appeared somewhat enhanced in 70% serum for the β-lactamase-positive strain of *Haemophilus influenzae*. Human serum was also shown to have minimal effect on the MICs and MBCs, as determined by broth microdilution, on these same species as well as *Streptococcus pyogenes, Escherichia coli,* and *Klebsiella pneumoniae* (59, 60, 61).

The components of a purulent infection, i.e. albumin, γ-globulin, dead bacteria, and pus were examined for their influence on the bactericidal activity of moxifloxacin and

ciprofloxacin against two strains each of *Staphylococcus aureus, Streptococcus pneumoniae,* and *Escherichia coli* (97). In the presence of 50% albumin or 50% γ-globulin, no effect on killing was seen at 16 X MIC for *Staphylococcus aureus* and *Streptococcus pneumoniae* and at 4 X MIC for *Escherichia coli* by either moxifloxacin or ciprofloxacin. In the presence of either 1 x 10^7 or 5 X 10^7 dead bacteria, there was no effect on the bactericidal activity of moxifloxacin or ciprofloxacin against the aforementioned bacteria and corresponding drug concentrations. Pus did not effect the bactericidal activity of moxifloxacin against *Staphylococcus aureus* at 4-16 X MIC; however, killing by ciprofloxacin was delayed. The components of purulent infection did not have much of an effect, if any, on moxifloxacin's bactericidal activity. Ciprofloxacin was only slightly effected by pus.

POSTANTIBIOTIC EFFECT

Several studies evaluated the postantibiotic effect (PAE) of moxifloxacin on *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae, Escherichia coli,* or *Klebsiella pneumoniae* (111,107,120,121, 115, 109). The PAE was concentration dependent for all of the species tested. This is true for all other fluoroquinolones also.

Vesga and Craig reported that for *Escherichia coli, Klebsiella pneumoniae,* and *Haemophilus influenzae*, the PAE ranged from 0.5 hour-1.9 hours at 2 X MIC, while the range at 8 X MIC was 1.5 hours to 5.7 hours (115).

Other studies evaluating *Escherichia coli, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae,* and *Streptococcus pyogenes* also confirmed the concentration dependence (111,107,120,109) of moxifloxacin's PAE effect. At 1 x MIC, the PAE range was 0 to 2.2 hours. The PAE was 1.2 to 3.1 hours at 2 X MIC and 1.4 to 3.3 hours at 10 X MIC.

Miggiolo et al. (121) used an *in vitro* kinetic model to examine the sub-MIC effect (SME) at 0.5 X MIC against three strains each of *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli,* and *Klebsiella pneumoniae.* The mean PAEs for each group of organisms were 1.01 to 1.91 hours, while the mean SMEs were 8.0 to 11.2 hours. The authors concluded from this comparison that an extended presence of moxifloxacin at subinhibitory concentrations was more effective than a short exposure at a high concentration. Vesga and Craig (110) found the same type of effect.

ANTIBACTERIAL INTERACTION WITH OTHER ANTIMICROBIALS

The combination of a given antimicrobial with another antimicrobial may effect the *in vitro* activity of either one resulting in a synergistic, indifferent, additive, or antagonistic effect. When compared to the bactericidal activity of the most active single drug of a two drug combination by time-kill kinetics, synergy is defined as >2 $\log_{10}$ reduction in cfu/mL; indifference is ≤ 1 $\log_{10}$ reduction; an additive effect is >1-<2 $\log_{10}$; and antagonism is defined as >2 $\log_{10}$ increase in cfu/mL. The effects of moxifloxacin in combination with various other drugs were studied predominately against *Staphylococcus aureus* and enterococci, as well as *Klebsiella pneumoniae, Enterobacter cloacae*, and *Pseudomonas aeruginosa*.

The bactericidal activity of moxifloxacin was compared with ampicillin, [redacted] and gentamicin alone and in combination against six strains each of vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (122). MICs of moxifloxacin were 0.125-2 µg/mL and the concentrations of drug were those that represented the achievable serum C_{max} for each drug. Moxifloxacin alone effected a mean decrease of 3.26 $\log_{10}$ cfu/mL, while the mean decrease of cfu/mL for ampicillin or [redacted] was <1 $\log_{10}$. The cfu/mL for gentamicin actually increased by 4.64 $\log_{10}$. The combination of moxifloxacin plus ampicillin and moxifloxacin plus gentamicin demonstrated a decrease of 3.88 $\log_{10}$ cfu/mL and 3.55 $\log_{10}$, respectively (an indifferent effect). A mean decrease of 1.66 $\log_{10}$ cfu/mL, or antagonism, was observed for 5/12 strains of enterococci for the combination of moxifloxacin plus [redacted] This antagonism has been observed with other quinolones and [redacted] especially against staphylococci.

The bactericidal activity of moxifloxacin alone and in combination with either vancomycin or teicoplanin was determined against nine strains of *Staphylococcus aureus* with reduced susceptibility to teicoplanin (MICs of 2-8 µg/mL) (89). The combination of either teicoplanin or vancomycin against 8 strains of ciprofloxacin and [redacted] esistant *Staphylococcus aureus* resulted in an additive effect at six hours and a synergistic effect at 24 hours. The cfu/mL at the latter time point were reduced 3-3.33 $\log_{10}$ by the combination agents compared with almost no reduction in cfu/mL by any of the agents alone. Synergy was observed for the one strain of ciprofloxacin-susceptible, [redacted] susceptible *Staphylococcus aureus* at 24 hours for either combination.

In another experiment (123), however, an indifferent response was most often seen for the combination of moxifloxacin and vancomycin at various time points against *Staphylococcus aureus* and *Enterococcus faecalis*. This combination was antagonistic for the strain of *Enterococcus faecalis* tested. The combination of moxifloxacin and clindamycin or [redacted] usually resulted in an antagonistic effect against [redacted] resistant strains of *Staphylococcus aureus* and the one strain of ciprofloxacin-, [redacted] susceptible *S. aureus* tested. The combination of moxifloxacin and ampicillin or gentamicin resulted in an indifferent effect against the *Enterococcus faecalis* and

Enterococcus faecium strains tested. The combination of moxifloxacin plus mezlocillin, cefuroxime, or gentamicin was indifferent against one strain each of *Klebsiella pneumoniae, Enterobacter cloacae,* and *Pseudomonas aeruginosa.*

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 [redacted] especially against staphylococci.

INTRACELLULAR ACCUMULATION AND INTERACTION WITH HOST DEFENSE FACTORS

Using a fluorescence fluoroquinolone accumulation assay, Piddock and Jin (124) studied the uptake of moxifloxacin in one strain each of *Escherichia coli, Haemophilus influenzae, Pseudomonas aeruginosa, Streptococcus pneumoniae,* and two strains of *Staphylococcus aureus*, one of which was a NorA mutant. After exposure to 10 μg/mL moxifloxacin or ciprofloxacin, all bacteria accumulated less moxifloxacin than ciprofloxacin. *Escherichia coli* accumulated the least amount of moxifloxacin followed by *Haemophilus influenzae.* In the presence of the efflux inhibitor, CCCP, less effect was seen for *Staphylococcus aureus* and *Streptococcus pneumoniae* than for *Escherichia coli* and *Pseudomonas aeruginosa.* This suggests that moxifloxacin was a poorer substrate for active efflux in the gram-positive organisms and is not pumped out as effectively as in gram-negative bacteria.

The influence of moxifloxacin on phagocytosis, as well as the burst and killing activities of human granulocytes was evaluated in a study using flow cytometry (125). *Candida albicans* and *Staphylococcus aureus* were the control organisms. After exposing heparinized human blood and the organisms to different concentrations of moxifloxacin ranging from [redacted] the organisms were diluted and mixed with the blood to achieve ratios of 1:1 between PMNs and *Candida albicans* and 1:20 between PMNs and *Staphylococcus aureus.* The activities of the phagocytes were measured over time for up to 60 minutes using a fluorescent-activated cell analysis in a flow cytometer. At concentrations of 1-30μg/mL, no effect on phagocytosis or burst activity was seen; however, at concentrations of 50-100 μg/mL, these activities were reduced by approximately 40%. No effect on intracellular killing was observed at concentrations up to 30μg/mL. From these experiments, moxifloxacin does not appear to affect the activities of phagocytes even at higher concentrations than expected to be achieved in serum after once daily dosing with 400 mg tablets.

Al-Nawas and Shah compared the intracellular activity of moxifloxacin in PMNs with that of ciprofloxacin against eight strains of *Staphylococcus aureus* (126, 127). The strains comprised two quality control stains, three [redacted] esistant *Staphylococcus*

aureus (MRSA), and three ciprofloxacin-[redacted]esistant *Staphylococcus aureus* (CMRSA). The MICs of moxifloxacin for the quality control strains and the MRSAs were 0.06 μg/mL and the MICs of ciprofloxacin were 0.5 μg/mL for these organisms. The MICs of ciprofloxacin against the CMRSAs were ≥16μg/mL, while those of moxifloxacin were 2.0μg/mL. Concentrations at 0.1 X MIC and 1 x MIC showed little if any intracellular or extracellular bactericidal activity by either drug against any of these strains. Moxifloxacin at 10 x MIC was only slightly bactericidal against the two quality control strains, while ciprofloxacin, at 10 X MIC, killed 99% of extracellular and 80% of intracellular bacteria. Against MRSA, however, 10 X MIC of both drugs affected approximately 90% intracellular and extracellular killing. At 10 X MIC, > 95% of extracellular and 50% of intracellular CMRSA were killed by moxifloxacin, but no killing was achieved by ciprofloxacin.

The uptake, efflux, and intracellular activity of moxifloxacin in human neutrophils and epithelial cells were evaluated by a fluorometric assay (128). Concentrations of 1-50 μg/mL were studied. The uptake rate was expressed as the intracellular to extracellular concentration ratio, C/E. Killing of intracellular *Staphylococcus aureus* by moxifloxacin (MIC 0.06 μg/mL) was compared with killing by ciprofloxacin (MIC 0.25 μg/mL) and ofloxacin (MIC 0.25 μg/mL). The effect of factors such as pH and metabolic inhibitors, e.g., CCCP or NaCN, on uptake also were examined. Results of these studies showed that the uptake of moxifloxacin was rapid and reached intracellular concentrations ≥9 times the extracellular concentrations. This uptake was reversible. Uptake of moxifloxacin was most affected at [redacted]but the intracellular concentration was still five times that of the extracellular concentration. At [redacted] intracellular concentrations were approximately nine times the extracellular concentrations. The addition of metabolic inhibitors reduced the intracellular concentration to approximately five times the extracellular concentration. Moxifloxacin was more bactericidal intracellularly against *Staphylococcus aureus* at extracellular concentrations of 0.5, 1, and 5 μg/mL compared to ciprofloxacin and ofloxacin. Ciprofloxacin was the most bactericidal at a concentration of 0.125 μg/mL followed by moxifloxacin. At extracellular concentrations of 1 and 5 μg/mL, moxifloxacin affected about 70% and 80% intracellular killing of *Staphylococcus aureus*, respectively.

The intracellular activity within PMNs was also evaluated against two strains of *Salmonella typhimurium* (129). The MICs of these two strains were 0.37 μg/mL and 0.77μg/mL, respectively. The bacteria were added to freshly isolated PMNs that had been exposed to low concentrations, 0.2 μg/mL and 0.4μg/mL, of moxifloxacin. Bacterial killing within the PMNs was measured by bacterial viability (cfu/mL) and PMN burst activity was evaluated using[redacted] The extracellular concentration of moxifloxacin was 0.5 X MIC for both strains. The results showed that the presence of moxifloxacin effected much greater killing of the strain having an MIC of 0.37 μg/mL compared with killing in the absence of moxifloxacin. The killing of the strain having a MIC of 0.77 μg/mL also was greater in the presence of moxifloxacin, but to a lesser

extent, compared with intracellular killing in the absence of moxifloxacin. Moxifloxacin had no effect on burst activity.

These experiments show that moxifloxacin concentrates intracellularly in phagocytic and nonphagocytic cells. Concentrations several fold higher than extracellular concentrations were seen (about nine times higher in PMNs than in extracellular fluid). Moxifloxacin did not exhibit any adverse effects on killing, ingestion, or burst activity of PMNs.

ASSESSMENT OF RESISTANCE

RESISTANCE MECHANISMS

The primary mechanisms of bacterial resistance to fluoroquinolones can be attributed to mutations in the *gyrA* gene in gram-negative bacteria or the *grlA* (*parC*) gene in gram-positive bacteria (130). Mutations in the *gyrB* gene also may confer resistance, but to a lesser extent and less often than mutations in the *gyrA* gene. Another mechanism for decreased activity of quinolones is a reduction in the intracellular accumulation of drug by either a decrease in penetration of the drug or by an active membrane-associated efflux of drug from the cell.

In *Staphylococcus aureus*, high-level resistance to ciprofloxacin requires mutations in both amino acids 80 and 84 of GrlA, as well as amino acid 84 of GyrA. A mutation in the quinolone resistance determining region (QRDR) of each *gryA* and *grlA* suffice in producing a high-level resistance to ciprofloxacin and to a lesser extent levofloxacin and sparfloxacin (131). The *gyrA* codons 84 and 88 and *grlA* codons 80 and 84 are known mutational "hot spots" that confer resistance to fluoroquinolones. Ciprofloxacin resistant isolates usually have serine-to-leucine mutations at *gyrA* codon 84 (Ser84→Leu) plus serine-to-tyrosine or -phenylalanine mutations at *grlA* codon 80 (Ser80→Tyr) or (Ser80→Phe); cross-resistance occurs with levofloxacin and sparfloxacin.

The QRDR in the *gryA* gene in *Escherichia coli* encodes amino acids 67-106 (130). The mutational "hot spots" for most quinolones are the *gyrA* codons 83 and 87. The most frequent mutation results in a serine-to-leucine substitution (Ser83→Leu) or (Asp87→Gly) or both; double mutations result in high level resistance to quinolones. In addition, mutations in the *parC* gene lead to changes at Ser80 or Glu-84, which leads to low level resistance to quinolones such as ciprofloxacin.

The *in vitro* activity of moxifloxacin against defined mutants of gram-positive and gram-negative bacteria was determined in several studies to elucidate mechanisms of resistance or reduced susceptibility in these organisms (132, 104, 133, 134, 106, 135, 136, 68, 40).

Brenwald et al. (132) studied the role of efflux as a mechanism of resistance to fluoroquinolones in *Streptococcus pneumoniae*. Moxifloxacin, sparfloxacin, ciprofloxacin, and norfloxacin were evaluated in efflux mutants. In the presence of reserpine, an efflux inhibitor, MICs of norfloxacin for the wild type strain and mutant strains remained the same, while the MICs of norfloxacin alone for the mutant strains increased four- to eightfold compared to the MIC of the wild type strain. MICs of ciprofloxacin also were four- to eightfold higher in the efflux mutants compared to wild type *Streptococcus pneumoniae*. The MICs of moxifloxacin and sparfloxacin remained unchanged or only increased in MIC by twofold for the efflux mutants compared to the wild type strain. Hooper (133) found that the presence of the NorA efflux pump did not increase the MIC of moxifloxacin for a flqB (NorA hyperexpression) mutant of *Staphylococcus aureus*; however, as expected, the ciprofloxacin MIC increased two- to fourfold for the efflux mutant strain. These data indicate that an efflux mechanism of resistance to moxifloxacin does not appear to be of consequence in single-step efflux mutants of *Streptococcus pneumoniae* and *Staphylococcus aureus*.

Piddock et al. (137) studied ciprofloxacin resistant strains of *Streptococcus pneumoniae*. They found that the *in vitro* activity of moxifloxacin against first-step mutants (parC Ser79→Ala) was only twofold higher than the MIC for the wild type strain. This also was seen with trovafloxacin, grepafloxacin, gatifloxacin, and clinafloxacin, but not with sparfloxacin. MICs of moxifloxacin increased by 16- to 32-fold against second-step (parC Ser79→Ala + putative efflux) mutants compared with the wild type strain. Similar results were seen for the other quinolones.

Genetically characterized fluoroquinolone resistant strains of *Escherichia coli* were used to determine the activity of moxifloxacin compared with that of ciprofloxacin, trovafloxacin, and other quinolones (104). Results are shown in TABLE 52. MICs for single gyrA mutants (Ser83→Leu) of *Escherichia coli* were 1 μg/mL for moxifloxacin and 0.5 μg/mL for ciprofloxacin compared with MICs of 0.03 and 0.008 μg/mL, respectively, for the wild type strains. This is a 32-fold increase for moxifloxacin and a 64-fold increase for ciprofloxacin. MICs of trovafloxacin were the same as moxifloxacin's. MICs for a single parC mutant (Ser80→Ile) were 0.25 μg/mL for moxifloxacin and 0.008 μg/mL for ciprofloxacin. This was an eightfold increase for moxifloxacin, but no increase for ciprofloxacin. The MIC of moxifloxacin against a double gyrA mutant (Ser83→Leu + Asp87→Gly) was 2 μg/mL compared with a MIC of 1 μg/mL for ciprofloxacin. The MICs of moxifloxacin and ciprofloxacin or trovafloxacin were 32 μg/mL and 64 μg/mL or higher against two triple mutants, gyrA (Ser83→Leu + Asp87→Gly) parC (Ser80→Ile) or parC (Glu84→Lys). Since single mutations in either the *gryA* or *parC* gene can cause a significant increase in moxifloxacin's MIC but a single mutation in the *parC* gene does not increase ciprofloxacin's MIC, this may indicate that both gyrase and topoisomerase are primary targets for moxifloxacin in *Escherichia coli*. The primary target for ciprofloxacin and most other fluoroquinolones is gyrase in *E. coli*.

Table 52 - EXAMPLES OF MUTATIONS AND AMINO ACID CHANGES IN GyrA AND ParC IN *ESCHERICHIA COLI*

Gyrase subunit A codons			topo IV subunit A codons			MIC	
81	82/83	87	78	80	84	MXF	CIP
-	-	-	-	-	-	0.03	0.008
-	-	-	-	Ser80→Ile	-	0.25	0.008
-	-	Asp87→Gly	-	-	-	1	0.5
-	Ser83→Leu	-	-	-	-	1	0.5
-	Ser83→Leu	-	-	Ser80→Ile	-	4	1
-	Ser83→Leu	Asp87→Gly	-	Ser80→Ile	-	32	64
-	Ser83→Leu	Asp87→Gly	-	Ser80→Ile	-	128	>256
-	Ser83→Leu	Asp87→Gly	-	-	Glu84→Lys	32	64
-	Ser83→Leu	+marR	-	-	-	4	2

Similar studies were performed using genetically characterized strains of *Staphylococcus aureus* (93, 133, 106, 135). Results are shown in TABLE 53. A single mutation in the *gyrA* gene resulted in no difference in the MIC of moxifloxacin; the MIC of ciprofloxacin increased only minimally by twofold compared to the MIC for the wild type strain. Single mutations in *grlA, grlB,* or *gryA* had no effect on the MICs of moxifloxacin; however, the MICs of ciprofloxacin increased two- to eightfold as a result of a single mutation. High level resistance to ciprofloxacin, MICs of 8-256 μg/mL, occurred in a double mutant grlA(Ser80→Phe)gyrA(Ser84→Leu) or triple mutants grlA(Ser80→Phe)(Ala48→Thr)gyrA(Glu88→Lys); however, the MICs for moxifloxacin were 0.5 to 2 μg/mL. Four-point mutations did not increase the MIC of moxifloxacin any further. Hooper (133) also observed that the MIC for a multiply mutant strain of *Staphylococcus aureus* was the same as that of a double grlAgyrA mutant. Both had a MIC of 4 μg/mL. Hooper also found that serial passage on increasing concentrations of moxifloxacin resulted in a maximum MIC of 4 μg/mL. These data indicate that the primary target of moxifloxacin in *Staphylococcus aureus* is the GrlA subunit of topoisomerase IV and the secondary target is the GyrA subunit of DNA gyrase. All double mutations had a mutation in the *grlA* gene. Single mutations in *grlA* increased MICs for ciprofloxacin, although it appears that moxifloxacin MICs are not increased.

Table 53 - EXAMPLES OF MUTATIONS AND AMINO ACID CHANGES IN GrlA, GrlB, and GyrA of *STAPHYLOCOCCUS AUREUS*

			MIC	
GrlA	**grlB**	**gyrA**	**MXF**	**CIP**
--	--	--	≤ 0.06 - 0.12	0.12
--	--	Ser112→Arg	≤ 0.06	0.25
--	Glu422→Asp	Glu88→Lys	0.12	1
Ser80→Phe	--	--	≤ 0.06	2
Ser80→Phe	--	Ser84→Leu	0.5 - 2	8 - 128
Ser80→Phe Glu84→Val	--	Glu88→Lys	1 - 2	64 - 256
Ser80→Phe Ala48→Thr	Pro451→Ser	Ser84→Leu	1	256

SPONTANEOUS EMERGENCE OF RESISTANCE

To determine the frequency of spontaneous mutation in the presence of moxifloxacin or ciprofloxacin, fluoroquinolone-resistant mutants were selected by spreading an inoculum of 10^9 to 10^{10} cfu/mL over agar plates incorporating the quinolones at 4 X MIC of the test organism. *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae* were tested (70, 71, 72). After overnight incubation the number of colonies growing on the plates are counted. The frequency of appearance of resistant mutants was calculated as the ratio of resistant mutants seen on the plates to the number of cfu/mL in the original inoculum. The frequency of spontaneous mutation by moxifloxacin compared with ciprofloxacin was similar for *Escherichia coli* at 1-3 x 10^{-8} (TABLE 54). The spontaneous mutation rate was higher for *Pseudomonas aeruginosa*, but still similar for both drugs, 2.2 x 10^{-6} for moxifloxacin and 9.6 x 10^{-5} for ciprofloxacin. The rates produced by moxifloxacin and ciprofloxacin were significantly different for *Streptococcus pneumoniae*, <1.5 x 10^{-9} and 2.5 x 10^{-7}, respectively. The mutation frequency of *Staphylococcus aureus* was lower with moxifloxacin at 7 x 10^{-8} compared with 1 x 10^{-7} for ciprofloxacin. These data demonstrate that the spontaneous mutation rates for moxifloxacin were similar to those of ciprofloxacin for gram-negative bacteria, but were lower for gram-positive bacteria. As with other fluoroquinolones the mutation rate was highest with *Pseudomonas aeruginosa*. This high mutation rate for *Pseudomonas aeruginosa* has been seen in some clinical trials in which mutations in this organism have occurred and led to treatment failures.

Thomson et al (134, 40) were unable to select first-step mutants from wild type strains of *Staphylococcus aureus* and *Streptococcus pneumoniae* when exposed to 2-8 x MIC of moxifloxacin. Mutants (at a frequency of 10^{-7}) with increased moxifloxacin MICs were obtained only after exposure to ciprofloxacin. The MIC of moxifloxacin for the first-step mutant was 0.12 µg/mL compared with a MIC of 0.06 µg/mL for the wild type strain. The MICs of moxifloxacin for the second- and third-step mutants were 2 µg/mL and 4 µg/mL, respectively, compared with ciprofloxacin MICs of 64 and >128 µg/mL, respectively. These results indicate that the frequency of spontaneous mutation was <1 x 10^{-9} for these organisms and that moxifloxacin has a lower proclivity for inducing resistance in these gram-positive organisms.

TABLE 54 - IN VITRO SPONTANEOUS MUTATION FREQUENCY FOR MOXIFLOXACIN

Strains	Inoculum cfu/ml)	BAY 12-8039 4 x MIC	Ciprofloxacin 4 x MIC
E. coli Neumann	3.95×10^{9}	2.82×10^{-8}	1.13×10^{-8}
P. aeruginosa Walter	1.02×10^{10}	2.21×10^{-6}	9.59×10^{-5}
S. aureus 133	5.65×10^{9}	7.06×10^{-8}	1.11×10^{-7}
S pneumoniae	1.45×10^{9}	$<1.45 \times 10^{-9}$	2.54×10^{-7}

MULTISTEP RESISTANCE

A multistep emergence of resistance was seen for moxifloxacin and ciprofloxacin for both ciprofloxacin-susceptible and –resistant strains of *Staphylococcus aureus*. The increase in MICs of moxifloxacin, however, was much less than the increase in MICs of ciprofloxacin over the 7-day period. The MICs of moxifloxacin increased about fivefold beginning at day 4, but remained at ≤ 0.5 µg/mL. The MICs of ciprofloxacin increased 100-1000 fold. The MICs of ciprofloxacin against *Streptococcus pneumoniae* increased up to 1000 µg/mL, while the MICs of moxifloxacin remained below 10 µg/mL. Step-wise emergence of resistance to moxifloxacin by *Staphylococcus aureus* and *Streptococcus pneumoniae* developed more slowly and to a much lesser extent compared with ciprofloxacin.

RESISTANCE DEVELOPMENT DURING THERAPY

During the clinical trails performed with moxifloxacin, susceptibility tests were performed on pathogens isolated at baseline, and during post-treatment evaluations. Any post-baseline pathogen that demonstrated a significant decrease in susceptibility (4-fold increase in MIC above that at baseline) was looked at for possible increase in resistance due to treatment.

No pathogen was seen with more than a twofold increase in MIC. It appears that treatment did not induce significant resistance to moxifloxacin in these clinical trials.

EPIDEMIOLOGICAL STUDIES

The only country in which moxifloxacin has been approved is Mexico. Approval was received on December 2, 1998. [redacted] There is, therefore, no epidemiological information to report.

PRECLINICAL EFFICACY (*IN VIVO*)

PHARMACOKINETICS/BIOAVAILABILITY

A single dosage of 400 mg once daily, administered as a 400 mg tablet is proposed for marketing.

The information in this section 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.

Linear absorption kinetics were seen at single doses ranging from 50 to 800 mg and at multiple dose regimens up to 600 mg once daily. Bioavailability is in the range of 90%. Bioavailability is not altered by co-administration of 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 the feces (~25% of dose). Protein binding of moxifloxacin is approximately 50%.

Moxifloxacin has no apparent effects on cytochrome P450 *in vitro*, so metabolic interactions with other drugs that might result from enzyme induction or inhibition are unlikely, and have not been found in *in vivo* studies. Moxifloxacin does interact with Maalox and iron, resulting in a decrease in the bioavailability of moxifloxacin due to the formation of insoluble metal ion complexes.

TABLE 35 summarizes some of the pertinent pharmacokinetic parameters derived from clinical pharmacology studies. It has been postulated that positive clinical