16 μg/mL were not eradicated.

This information does not help much in setting a MIC breakpoint. It appears that isolates with a MIC of 16 μg/mL should be resistant and that a susceptible breakpoint should be somewhere between 1 and 4 μg/mL.

A comparison of the pharmacokinetic parameters for the common fluoroquinolones is presented in TABLE 75. The susceptible breakpoint (MIC B.P.) and the AUC/MIC ratio are included in this table for comparison. Historically, the MIC breakpoints have been set so that at the proposed dose the AUC/MIC ratio would be between 11 and 30. A susceptible breakpoint for moxifloxacin of 2.0 μg/mL would result in an AUC/MIC ratio of 17.0. A susceptible breakpoint of 1.0 μg/mL would result in a ratio of 34.0 and a breakpoint of 4.0 μg/mL would result in a ratio of 8.5. The pharmacokinetics of moxifloxacin suggest that a breakpoint of 2.0 μg/mL could be used. A susceptible breakpoint of 1.0 μg/mL would be just outside the historical range of [redacted] Comparing the C_{max} values of the fluoroquinolones with their breakpoints also suggest that a breakpoint of 2.0 μg/mL should be used. The pre-clinical study performed by Fuchs, Barry, and Brown (150) suggested a susceptible breakpoint of 1.0 or 2.0 μg/mL. Clinical trials showed that most isolates with MICs of 2 and 4 μg/mL were eradicated. A susceptible breakpoint of 2.0 μg/mL should be used for non-fastidious organisms.

TABLE 75
Comparison of Pharmacokinetic Parameters for Fluoroquinolones

Drug	Dose (mg)	C_{max} (μg/mL)	AUC_{0-24} (mg hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	MIC B.P. (μg/mL)	AUC/MIC Ratio
Ciprofloxacin	500	2.4	11.6	1-2	4	1	11.6
Ofloxacin	400	4.6	61.0	1-2	4-5	2	30.5
Lomefloxacin	400	3.2	26.1	0.8-1.4	~8	2	13.1
Enoxacin	400	2.0	—	1-3	3-6	2	—
Norfloxacin	400	1.5	—	~1	3-4	4	—
Sparfloxacin	200	1.1	18.7	~4	18-20	1	18.7
Levofloxacin	500	5.7	47.5	1-2	6.8	2	23.8
Grepafloxacin	400	1.35	14.08	2	7-12	1	14.1
	600	2.25	27.51	2	7-12	1	27.5
Trovafloxacin	100	1.0	9.4	0.5-1.5	9.2	2	4.7
	200	2.1	26.7	0.9-2.7	9.6	2	13.4
	300	3.6	46.1	0.9-1.7	11.2	2	23.0
Moxifloxacin	**400**	**4.52**	**34.0**	**1-3**	**12**	**2**	**17.0**

TABLE 76 shows the bacteriological outcome of non-fastidious organisms with MICs at or near the proposed susceptible breakpoint that were treated with moxifloxacin.

TABLE 76
Bacteriological Outcome for non-fastidious organisms near breakpoint

Organism	MIC	Total	Eradicated	Persisted	% Eradicated
S. aureus	2	1	1	0	100
	4	3	3	0	100
K. pneumoniae	0.5	6	5	1	83
	2	1	1	0	100
	4	1	1	0	100
Serratia marcescens	0.5	2	2	0	100
	8	1	0	1	0
Citrobacter freundii	1	2	2	0	100
	4	1	1	0	100
Pseudomonas aeruginosa	0.5	1	1	0	100
	1	9	5	4	56
	2	5	3	2	60
	4	2	2	0	100
	8	5	4	1	80
	16	2	0	2	0
Stenotrophomonas maltophilia	0.5	2	2	0	100
	1	3	3	0	100
	2	1	1	0	100

Once again this table demonstrates that most isolates with MICs of 1-4 µg/mL were eradicated. Many isolates with a MIC value of 8 µg/mL were also eradicated. Isolates at 16 µg/mL were not eradicated. There were very few isolates with MICs greater than 1.0 µg/mL. Most of these isolates were *Pseudomonas aeruginosa*. A susceptible breakpoint of 2 µg/mL seems justified. The following breakpoints should be in the label for non-fastidious pathogens:

Susceptible = ≤ 2.0 µg/mL
Intermediate = 4.0 µg/mL
Resistant = ≥ 8.0 µg/mL

STREPTOCOCCI INCLUDING *STREPTOCOCCUS PNEUMONIAE*

Table 77 shows the relationship between MICs and pathogen response for streptococci treated with 400 mg moxifloxacin.

TABLE 77
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 (153), 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

HAEMOPHILUS SPECIES

TABLE 78 shows the relationship between MICs and pathogen response for *Haemophilus* species treated with 400 mg of moxifloxacin.

TABLE 78
Relationship between Moxifloxacin MICs and Bacteriological Outcome at Test-of -Cure

Baseline Pathogen	MIC (µg/mL)	# Isolates	# Eradicated (%)	# Persisted (%)
H. influenzae	0.008	1	1 (100)	0
	0.015	32	27 (84)	5 (15)
	0.03	69	61 (88)	8 (12)
	0.06	12	12 (100)	0
	0.125	3	3 (100)	0
	0.25	3	3 (100)	0
H. parainfluenzae	0.015	4	4 (100)	0
	0.03	9	9 (100)	0
	0.06	12	12 (100)	0
	0.125	6	6 (100)	0
	0.25	4	4 (100)	0
	0.5	3	3 (100)	0
	8	1	1 (100)	0
H. parahaemolyticus	0.06	2	2 (100)	0
	0.125	1	1 (100)	0

This table shows that all isolates had MICs ≤ 0.5 µg/mL, except for one *H. parainfluenzae* isolate. All isolates that failed had MICs of 0.03 or less. Barry's study (154) tested only *Haemophilus influenzae* strains and all had MICs of 0.008-0.125 µg/mL. The authors suggested a susceptible breakpoint of 1.0 µg/mL, but this reviewer suggested a breakpoint of 0.25 µg/mL based on the data. It appears from the clinical data that a higher breakpoint is needed. There were three isolates of *Haemophilus parainfluenzae* with MICs of 0.5 µg/mL. If the rule of using one doubling dilution greater than the highest MIC value for 99% of the isolates is applied then a breakpoint of 1.0 µg/mL is justified. No resistant strains were detected in either the pre-clinical or clinical studies, therefore, only a susceptible breakpoint should be used.

The following breakpoint should be in the label for *Haemophilus* species:

Susceptible = ≤ 1.0 µg/mL

The following is a summary of the MIC breakpoints that should be placed in the moxifloxacin label:

For testing aerobes other than *Haemophilus* species and streptococci including *Streptococcus pneumoniae*:

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 streptococci including *Streptococcus pneumoniae*:

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

ZONE DIAMETER BREAKPOINTS

NON-FASTIDIOUS ORGANISMS

Figure 19 shows the scattergram of MICs versus zone diameters for the non-fastidious strains in the clinical trials. This scattergram uses the breakpoints proposed in Fuchs, Barry, and Brown's study (150). The distribution of organisms was similar to that in the pre-clinical study. The organisms having MICs of 4-16 µg/mL were *Pseudomonas aeruginosa* (10), *Serratia marcescens* (1), *Klebsiella pneumoniae* (1), and *Citrobacter freundii* (1). In this scattergram using these breakpoints there is one very major error, no major errors, and nine minor errors.

TABLE 79 shows the relationship between zone diameter and bacteriological response for non-fastidious organisms treated with 400 mg moxifloxacin once daily. Some organisms that are not indicated have been included since they tended to have lower zone diameters in many cases which might help divide the population into susceptible and resistant based on zone diameters and related bacteriological outcome.

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TABLE 79
Relationship between Moxifloxacin Zone Diameter and Bacteriological Outcome

Baseline Pathogen	Zone diameter (mm)	# Isolates	# Eradicated (%)	# Persisted (%)
S. aureus	14	1	1 (100)	0
	16	1	1 (100)	0
	21	1	1 (100)	0
	25	1	1 (100)	0
	27	4	4 (100)	0
	28	5	5 (100)	0
	29	20	19 (95)	1 (5)
	30	15	14 (93)	1 (7)
	31	29	25 (86)	4 (14)
	32	20	18 (90)	2 (10)
	33	8	8 (100)	0
	34	6	6 (100)	0
	35	2	2 (100)	0
	37	1	1 (100)	0
K. pneumoniae	16	2	2 (100)	0
	21	1	1 (100)	0
	22	1	1 (100)	0
	23	2	1 (50)	1 (50)
	24	3	3 (100)	0
	25	7	6 (86)	1 (14)
	26	8	7 (88)	1 (12)
	27	11	11 (100)	0
	28	9	9 (100)	0
	29	1	1 (100)	0
	30	3	3 (100)	0
Serratia marcescens	14	1	0	1 (100)
	24	2	2 (100)	0
	26	1	1 (100)	0
	28	1	1 (100)	0
Citrobacter freundii	17	1	1 (100)	0
	22	1	1 (100)	0
	23	1	1 (100)	0
	25	1	1 (100)	0
	26	1	1 (100)	0
	30	1	1 (100)	0

TABLE 79 (continued)
Relationship between Moxifloxacin Zone Diameter and Bacteriological Outcome

Baseline Pathogen	Zone diameter (mm)	# Isolates	# Eradicated (%)	# Persisted (%)
Pseudomonas aeruginosa	6	4	2 (50)	2 (50)
	12	1	0	1 (100)
	16	1	0	1 (100)
	17	1	0	1 (100)
	19	2	0	2 (100)
	20	2	2 (100)	0
	21	1	1 (100)	0
	22	2	2 (100)	0
	24	1	0	1 (100)
	25	2	2 (100)	0
	27	2	2 (100)	0
	28	2	1 (50)	1 (50)
	29	1	1 (100)	0
	34	1	1 (100)	0
Stenotrophomonas maltophilia	28	3	3 (100)	0
	33	1	1 (100)	0
	34	1	1 (100)	0
	35	1	1 (100)	0
	36	1	1 (100)	0
Moraxella catarrhalis	27	1	1 (100)	0
	28	3	3 (100)	0
	29	2	2 (100)	0
	30	8	7 (88)	1 (11)
	31	8	8 (100)	0
	32	21	16 (76)	5 (24)
	33	13	12 (92)	1 (8)
	34	8	7 (88)	1 (11)
	35	7	6 (86)	1 (14)
	36	5	4 (80)	1 (20)
	37	7	7 (100)	0
	38	2	2 (100)	0

This table shows that there were very few zones below 20 mm. Most of the zones below 20 mm were *Pseudomonas aeruginosa* isolates. It appears that for *Pseudomonas aeruginosa* isolates with zones ≤19 mm were not eradicated and those ≥ 20 mm were eradicated. There are, however, very few isolates at each of these zone diameters (in many cases only one) so a change in only one result can change the outcome from eradicated to persistent. Isolates of *Staphylococcus aureus* and *Klebsiella pneumoniae* at 16 mm were eradicated. An isolate of *Citrobacter freundii* at 17 mm was eradicated. An isolate of *Serratia marcescens* at 14 mm was not eradicated, but an isolate of *Staphylococcus aureus* with a zone of 14 mm was eradicated. These data suggest that a breakpoint should be somewhere between 14 mm and 19 mm. The pre-clinical study and the scattergram of the clinical data suggest a susceptible breakpoint of ≥ 19 mm and a resistant breakpoint of ≤ 15 mm. This allows the usual 3 mm intermediate zone. These breakpoints appear to be acceptable.

The following zone diameter breakpoints for non-fastidious organisms should be in the label.

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

STREPTOCOCCI 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 80 shows the relationship between zone diameter and bacteriological outcome for streptococci treated with 400 mg of moxifloxacin once daily.

TABLE 80
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

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 (153) 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.

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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

HAEMOPHILUS SPECIES

Figure 21 shows the scattergram of MICs versus zone diameter for *Haemophilus influenzae* and *Haemophilus parainfluenzae*. All isolates had zone diameters of ≥ 21 mm except for one *H. parainfluenzae* isolate with a zone diameter of 6 mm.

TABLE 81 shows the relationship between zone diameter and bacteriological outcome for *Haemophilus* species treated with 400 mg moxifloxacin once daily.

TABLE 81
Relationship between Moxifloxacin Zone Diameter and Bacteriological Outcome

Baseline Pathogen	Zone diameter (mm)	# Isolates	# Eradicated (%)	# Persisted (%)
H.. influenzae	21	2	2 (100)	0
	22	2	2 (100)	0
	23	1	1 (100)	0
	24	1	1 (100)	0
	26	1	1 (100)	0
	27	2	2 (100)	0
	28	8	8 (100)	0
	29	5	5 (100)	0
	30	7	7 (100)	0
	31	15	15 (100)	0
	32	17	11 (65)	6 (35)
	33	11	10 (91)	1 (9)
	34	14	13 (93)	1 (7)
	35	13	12 (92)	1 (8)
	36	9	6 (67)	3 (33)
	37	3	2 (67)	1 (33)
	38	2	2 (100)	0
	39	4	4 (100)	0
	40	2	2 (100)	0
	42	1	1 (100)	0

TABLE 81 (continued)
Relationship between Moxifloxacin Zone Diameter and Bacteriological Outcome

Baseline Pathogen	Zone diameter (mm)	# Isolates	# Eradicated (%)	# Persisted (%)
H. parainfluenzae	6	1	1 (100)	0
	22	1	1 (100)	0
	23	2	2 (100)	0
	24	2	2 (100)	0
	25	3	3 (100)	0
	26	4	4 (100)	0
	27	5	5 (100)	0
	28	4	4 (100)	0
	29	1	1 (100)	0
	30	2	2 (100)	0
	31	1	1 (100)	0
	32	4	4 (100)	0
	34	1	1 (100)	0
	35	3	3 (100)	0
	36	2	2 (100)	0
H. parahaemolyticus	24	1	1 (100)	0
	27	1	1 (100)	0
	28	1	1 (100)	0

The data in this table show that except for one isolate with a zone diameter of 6 mm (which was eradicated) all zone diameters were ≥21 mm. There was no correlation between zone diameter and biological outcome in the clinical trials. In the pre-clinical study performed by Fuchs, Barry and Brown (154) the zone diameters ranged from [redacted] No *Haemophilus parainfluenzae* strains were tested. The authors suggested a zone breakpoint of ≥ 22 mm. Using the rule of setting a susceptible breakpoint at 3 mm less than the smallest zone diameter for 99% of the population this reviewer suggested a breakpoint of ≥ 28 mm. Using this rule on the isolates from the clinical population gives us a susceptible breakpoint of ≥ 18 mm. Since no resistant strains were detected in the clinical trails and none were tested in the pre-clinical studies only a susceptible breakpoint should be used.

The following breakpoint should be in the label for *Haemophilus* species:

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

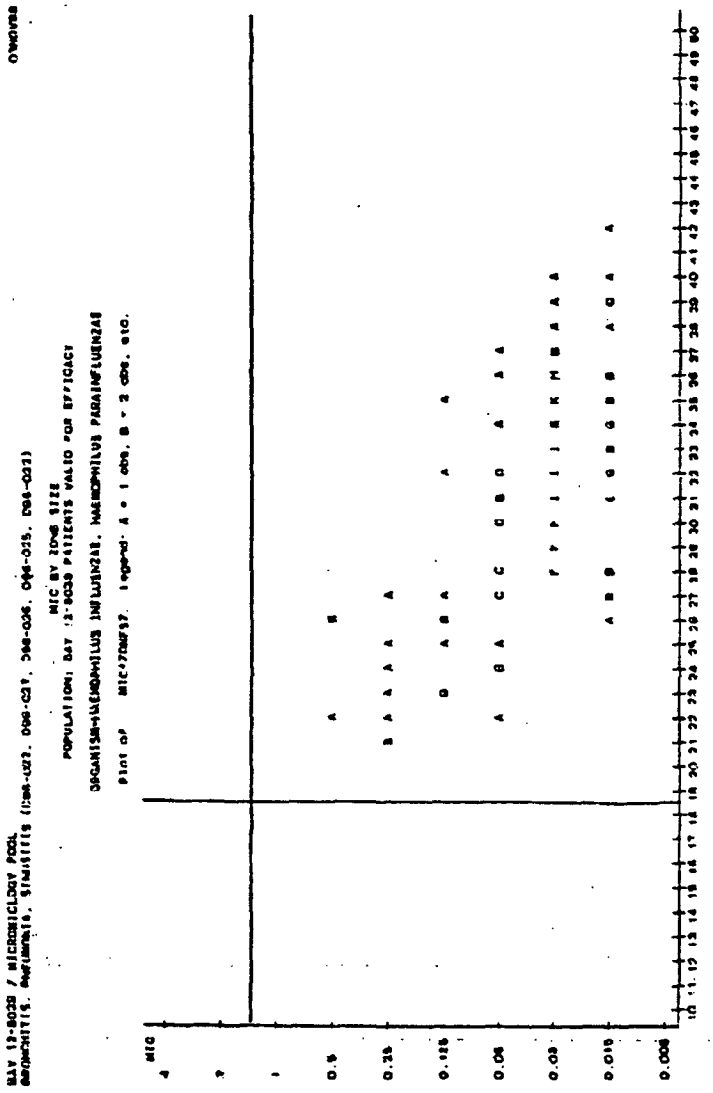


Figure 21

The following is a summary of the zone diameter breakpoints that should be placed in the moxifloxacin label:

For testing aerobes other than *Haemophilus* species and streptococci including *Streptococcus pneumoniae*:

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 streptococci including *Streptococcus pneumoniae*:

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

APPEARS THIS WAY
ON ORIGINAL

PACKAGE INSERT

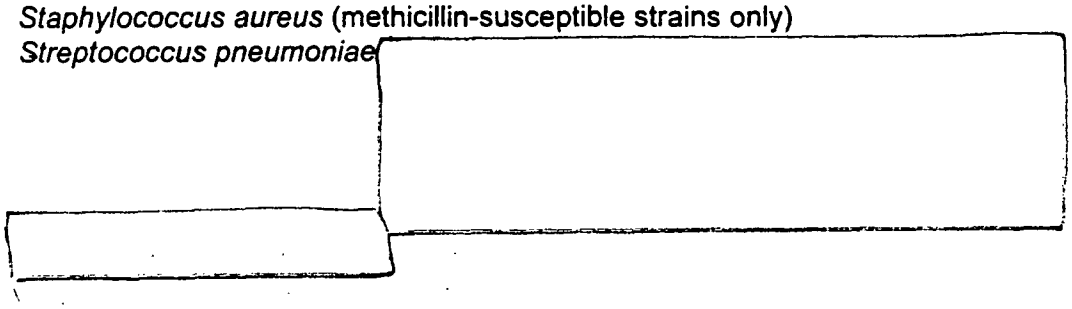
ISOLATES APPROVED

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



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

Aerobic gram-negative microorganism

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

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ON ORIGINAL

INTERPRETIVE CRITERIA ESTABLISHED

The following MIC interpretive criteria should be used for testing aerobes other than *Haemophilus* species and streptococci including *Streptococcus pneumoniae*:

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 streptococci 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 aerobes other than *Haemophilus* species and streptococci including *Streptococcus pneumoniae*:

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 streptococci including *Streptococcus pneumoniae*:

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

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1 pages of revised draft labeling have been redacted from this portion of the document.

2) The following microorganisms should have qualifiers after their listings:

Aerobic gram-positive aerobes

Streptococcus pneumoniae—

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.

3) The last sentence in the introductory paragraph of the Microbiology subsection should be revised to read as follows: "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

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4) The following QC strains and limits should be used for dilution testing:

4) The following QC strains and limits should be used for diffusion testing:

ORGANISM	MOXIFLOXACIN ZONE DIAMETER (mm)
Escherichia coli ATCC 25922	28-35
Staphylococcus aureus ATCC 25923	28-35
Streptococcus pneumoniae ATCC 49619	25-31
Haemophilus influenzae ATCC 49247	31-39

The limits for *Pseudomonas aeruginosa* will not be included in the label since moxifloxacin does not have an indication for this organism and the zone diameter limits for this organism extend into the non-susceptible range. The limits for *E. coli* and *S. aureus* will be included (even though moxifloxacin has no indication for *E. coli*) since at least two quality control organisms should be used for non-fastidious organisms. In order to be consistent with NCCLS, the QC ranges approved by them should be used in labeling if acceptable to FDA. NCCLS QC limits are acceptable and will be placed in the label except for *Pseudomonas aeruginosa* as noted above.

The organisms should be listed in alphabetical order in this list.

5) The disk diffusion susceptible breakpoint for *Haemophilus* species has been changed from ≥ 19 mm to ≥ 18 mm. This breakpoint was set by using the rule of selecting a breakpoint that is 3 mm smaller than the smallest zone diameter for 99% of the data. Using the data from the clinical trials results in the smallest zone diameter for 99% of the data being 21 mm. A breakpoint of 18 mm is 3 mm lower than this diameter.

6) The superscripts in the Microbiology subsection should start with [a] and run through to the end of the section. They should not start over with each new heading as they do in the submitted draft labeling.

The Microbiology subsection of the package insert should, therefore, be revised to read as follows:

Moxifloxacin has *in vitro* activity against a wide range of gram-positive, gram-negative, and anaerobic 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 is responsible for enhanced activity against gram-positive bacteria and lower selection of resistant mutants of gram-positive bacteria.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, arninoglycosides, 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 although MICs are usually higher.

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

[redacted]

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

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

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

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

Aerobic gram-positive microorganisms

[redacted]

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

Anaerobic microorganisms

[redacted]

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 [redacted]

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 [redacted] *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 [redacted] This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

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

Microorganism	MIC Range (µg/mL)
Enterococcus faecalis ATCC 29212	0.06-0.5
Escherichia coli ATCC 25922	[redacted]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:

For testing [redacted]

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

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

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

[e] This zone diameter standard is applicable only to [redacted] 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 [redacted] *Streptococcus pneumoniae*:[f]

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

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

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/S/

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_ /S/ ___Signature 9/30/99 Date
HFD-590/TLMicro ___Signature 9/27/99 Date

CC:
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HFD-590/Division File
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