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In vitro data for organisms from the preclinical surveillance studies and clinical studies are shown in TABLE 135. All organisms that the applicant has proposed for inclusion in the labeling (indications list) are included.

TABLE 135
Gemifloxacin *In Vitro* Activity Against Selected Pathogens
Preclinical Surveillance Studies and Clinical Studies

Organism	Surveillance Studies		Clinical Studies	
	No. of Times Isolated	MIC ₉₀ (µg/mL)	No. of Times Isolated	MIC ₉₀ (µg/mL)
<i>Escherichia coli</i>	4163	0.25	1170	0.015
<i>Klebsiella pneumoniae</i>	2382	0.5	171	0.06
<i>Enterobacteriaceae</i>	13,806	0.5	1606	0.12
<i>Streptococcus pneumoniae</i>	7896	0.03	372	0.03
<i>Haemophilus</i> species	7582	0.03	372	0.015
<i>Haemophilus influenzae</i>	7145	0.03	287	0.008
<i>Haemophilus parainfluenzae</i>	425	0.06		
Non-Enterobacteriaceae	3761	≥8.0	138	8.0
<i>Staphylococcus</i> species	6021	4.0	245	0.5
MRSA	764	≥8.0		
MSSA	842	0.06		
<i>Staphylococcus aureus</i>			150	0.12
<i>S. saprophyticus</i>	298	0.03	43	0.015
Streptococci (non pneumo)	2710	0.06	77	0.03

These data show that gemifloxacin has very little activity against _____ species. It has good activity against methicillin-susceptible *Staphylococcus aureus*, but limited activity against methicillin-resistant strains. It appears from the MICs encountered that virtually all the *S. aureus* isolates from the clinical trials were methicillin-susceptible. The *Haemophilus* species and streptococci MICs encountered during the clinical trials compared well with those found in the surveillance studies. The enterobacteriaceae MICs found in the clinical trials were considerably lower than those found in the surveillance studies. It appears that some of the more resistant strains found in nature were not found in the clinical trials.

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MIC BREAKPOINTS

ENTEROBACTERIACEAE

TABLES 136 and 137 show the relationship between MICs and pathogen bacteriological response for enterobacteriaceae that the applicant has proposed for the label for respiratory tract infections. TABLE 138 shows the relationship

TABLE 136
Relationship between MICs and Bacteriological Outcome
RTI (excluding AECB)—Bacteriological Intent-to-Treat Population (Enterobacteriaceae)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Enterobacteriaceae</i>	52	81.3	7	10.9	5	7.8
0.004	3	75.0	1	25.0	0	0.0
0.008	15	83.3	3	16.7	0	0.0
0.015	13	100.0	0	0.0	0	0.0
0.03	12	75.0	2	12.5	2	12.5
0.06	6	85.7	0	0.0	1	14.3
0.12	1	50.0	0	0.0	1	50.0
0.25	2	66.7	1	33.3	0	0.0
0.5	0	0.0	0	0.0	1	100.0
<i>Escherichia coli</i>	9	90.0	1	10.0	0	0.0
0.004	1	50.0	1	50.0	0	0.0
0.008	6	100.0	0	0.0	0	0.0
0.015	1	100.0	0	0.0	0	0.0
0.25	1	100.0	0	0.0	0	0.0
<i>Klebsiella pneumoniae</i>	21	75.0	5	17.9	2	7.1
0.008	4	57.1	3	42.9	0	0.0
0.015	9	100.0	0	0.0	0	0.0
0.03	7	63.6	2	18.2	2	18.2
0.06	1	100.0	0	0.0	0	0.0

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TABLE 137
Relationship between MICs and Bacteriological Outcome
RTI –Bacteriological Intent-to-Treat Population (Enterobacteriaceae)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Enterobacteriaceae</i>	106	80.3	17	12.9	9	6.8
≤0.001	0	0.0	0	0.0	1	100.0
0.004	4	66.7	1	16.7	1	16.7
0.008	34	82.9	6	14.6	1	2.4
0.015	28	90.3	2	6.5	1	3.2
0.03	19	79.2	3	12.5	2	8.3
0.06	11	91.7	0	0.0	1	8.3
0.12	5	62.5	2	25.0	1	12.5
0.25	3	50.0	3	50.0	0	0.0
0.5	1	50.0	0	0.0	1	50.0
32	1	100.0	0	0.0	0	0.0
<i>Escherichia coli</i>	22	75.9	5	17.9	2	6.9
≤0.001	0	0.0	0	0.0	1	100.0
0.004	1	33.3	1	33.3	1	33.3
0.008	17	85.0	3	15.0	0	0.0
0.015	3	75.0	1	25.0	0	0.0
0.25	1	100.0	0	0.0	0	0.0
<i>Klebsiella pneumoniae</i>	36	78.3	7	15.2	3	6.5
0.008	5	55.6	3	33.3	1	11.1
0.015	15	93.8	1	6.3	0	0.0
0.03	12	70.6	3	17.6	2	11.8
0.06	3	100.0	0	0.0	0	0.0
32	1	100.0	0	0.0	0	0.0

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Reason:

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_____ b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

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TABLE 139
Comparison of Pharmacokinetic Parameters for Fluoroquinolones

Drug	Dose (mg)	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg•h/mL)	T _{max} (hr)	T _{1/2} (hr)	MIC B.P. (µg/mL)	AUC/MIC Ratio
Ciprofloxacin	500	2.4	23.2	1-2	4	1.0	23.2
Ofloxacin	400	4.6	61.0	1-2	4-5	2.0	30.6
Lomefloxacin	400	3.2	26.1	0.8-1.4	~8	2.0	13.1
Enoxacin	400	2.0	---	1-3	3-6	2.0	---
Norfloxacin	400	1.5	---	~1	3-4	4.0	---
Sparfloxacin	200	1.1	18.7	~4	18-20	1.0	18.7
Levofloxacin	500	5.7	47.5	1-2	6-8	2.0	23.8
Grepafloxacin	400	1.35	14.08	2	7-12	1.0	14.1
	600	2.25	27.51	2	7-12	1.0	27.5
Trovafoxacin	300	3.6	46.1	0.9-1.7	11.2	2.0	23.0
Moxifloxacin	400	4.52	48.0	1-3	12	2.0	24.0
Gatifloxacin	400	4.2	51.3	2	8.4	2.0	25.7
Gemifloxacin	320	1.6	8.4	0.5-2	8	0.25	33.6

A susceptible breakpoint for gemifloxacin of 0.5 would result in an AUC/MIC ratio of 16.8. Although this would be in the range of the AUC/MIC ratio that some of the fluoroquinolones have it is outside of the usual 20-30 range. A breakpoint of 0.25 µg/mL give a more acceptable value of 33.6 which is above the value for all of the other fluoroquinolones. Most of the preclinical studies suggested a susceptible breakpoint of 0.5 µg/mL, but one study (57) suggested a susceptible breakpoint of ≤0.25 µg/mL. In clinical trials there were very few isolates with MICs ≥0.25 µg/mL and most of these were eradicated. There appears to be no correlation between eradication rates and MICs that would allow a definite susceptible breakpoint to be set. Based on the pharmacokinetics of gemifloxacin a susceptible breakpoint of ≤0.25 µg/mL for enterobacteriaceae seems appropriate. The following breakpoints should be in the label for enterobacteriaceae:

Susceptible = ≤0.25 µg/mL

Intermediate = 0.5 µg/mL

Resistant = ≥ 1.0 µg/mL

NON-ENTEROBACTERIACEAE

Neither _____ nor *Acinetobacter* species are indicated for gemifloxacin. Gemifloxacin has limited *in vitro* activity against these organisms.

Since gemifloxacin is not indicated for this group of organisms no breakpoints will be established.

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STAPHYLOCOCCUS SPECIES

TABLES 140 and 141 show the relationship between MICs and bacteriological response for staphylococci for respiratory tract infections. The only *Staphylococcus* species that is indicated is *S. aureus*. Methicillin-resistant strains do not appear to be susceptible from the *in vitro* data. There were only two methicillin-resistant strains in the clinical trials with MICs of 0.5 µg/mL. These two isolates were not eradicated. The breakpoint should, therefore, be set to separate the methicillin-susceptible and -resistant strains. TABLE 142 shows the relationship between MICs and bacteriological outcome for the ———. Most of these strains were *Staphylococcus saprophyticus*, which is not an indicated pathogen.

TABLE 140
Relationship between MICs and Bacteriological Outcome
RTI (excluding AECB)—Bacteriological Intent-to-Treat Population (Staphylococci)

Pathogen Group/	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Staphylococcus</i> species	34	79.1	5	11.6	4	9.3
0.004	3	100.0	0	0.0	0	0.0
0.008	19	82.6	3	13.0	1	4.3
0.015	11	78.6	2	14.3	1	7.1
0.03	1	50.0	0	0.0	1	50.0
2.0	0	0.0	0	0.0	1	100.0
<i>Staphylococcus aureus</i>	34	79.1	5	11.6	4	9.3
0.004	3	100.0	0	0.0	0	0.0
0.008	19	82.6	3	13.0	1	4.3
0.015	11	78.6	2	14.3	1	7.1
0.03	1	50.0	0	0.0	1	50.0
2	0	0.0	0	0.0	1	100.0
MSSA	33	78.6	5	11.9	4	9.5
0.004	3	100.0	0	0.0	0	0.0
0.008	18	81.8	3	13.6	1	4.5
0.015	11	78.6	2	14.3	1	7.1
0.03	1	50.0	0	0.0	1	50.0
2.0	0	0.0	0	0.0	1	100.0

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TABLE 141
Relationship between MICs and Bacteriological Outcome
RTI –Bacteriological Intent-to-Treat Population (Staphylococci)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Staphylococcus species</i>	60	74.1	12	14.8	9	11.1
0.004	3	100.0	0	0.0	0	0.0
0.008	36	80.0	5	11.1	4	8.9
0.015	19	73.1	5	19.2	2	7.7
0.03	1	50.0	0	0.0	1	50.0
0.06	0	0.0	0	0.0	1	100.0
0.5	0	0.0	2	100.0	0	0.0
1.0	1	100.0	0	0.0	0	0.0
2.0	0	0.0	0	0.0	1	100.0
<i>Staphylococcus aureus</i>	60	74.1	12	14.8	9	11.1
0.004	3	100.0	0	0.0	0	0.0
0.008	36	80.0	5	11.1	4	8.9
0.015	19	73.1	5	19.2	2	7.7
0.03	1	50.0	0	0.0	1	50.0
0.06	0	0.0	0	0.0	1	100.0
0.5	0	0.0	2	100.0	0	0.0
1.0	1	100.0	0	0.0	0	0.0
2.0	0	0.0	0	0.0	1	100.0
MRSA	0	0.0	2	100.0	0	0.0
0.5	0	0.0	2	100.0	0	0.0
MSSA	58	75.3	10	13.0	9	11.7
0.004	3	100.0	0	0.0	0	0.0
0.008	34	79.1	5	11.6	4	9.3
0.015	19	73.1	5	19.2	2	7.7
0.03	1	50.0	0	0.0	1	50.0
0.06	0	0.0	0	0.0	1	100.0
1.0	1	100.0	0	0.0	0	0.0
2.0	0	0.0	0	0.0	1	100.0

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TABLE 142
Relationship between MICs and Bacteriological Outcome



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TABLES 143 and 144 show the frequency distributions for baseline pathogen MICs for MSSA and MRSA, respectively, from all indications for the bacteriological intent-to-treat population.

TABLE 143
Frequency Distribution of MICs for Gemifloxacin for *S. aureus* (meth-S)
From the Phase III Clinical Studies (all geographic regions)

N=135	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
Gemi n	7	73	46	5	1	0	0	0	1	1	0	0	1
Cum %	5.2	59.3	93.3	97.0	97.8	97.8	97.8	97.8	98.5	99.3	99.3	99.3	100

TABLE 144
Frequency Distribution of MICs for Gemifloxacin for *S. aureus* (meth-R)
From the Phase III Clinical Studies (all geographic regions)

N=12	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>256
Gemi n	1	1	1	3	2	0	2	1	0	0	0	0	1
Cum %	8.3	16.7	25.0	50.0	66.7	66.7	83.3	91.7	91.7	91.7	91.7	91.7	100

The above TABLES demonstrate that most isolates that were methicillin-susceptible had MICs of $\leq 0.06 \mu\text{g/mL}$. The methicillin-resistant isolates which were not eradicated and thus should be considered resistant to gemifloxacin had MICs of $0.5 \mu\text{g/mL}$. Setting a susceptible breakpoint of $0.12 \mu\text{g/mL}$ would allow one dilution above the highest MIC value usually seen for error and would separate the two populations. The following breakpoints should be in the label for *Staphylococcus* species:

Susceptible = $\leq 0.12 \mu\text{g/mL}$

Intermediate = $0.25 \mu\text{g/mL}$

Resistant = $\geq 0.5 \mu\text{g/mL}$

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STREPTOCOCCUS SPECIES INCLUDING STREPTOCOCCUS PNEUMONIAE

Since *Streptococcus pneumoniae* is the only streptococcal species indicated this is the only species for which a breakpoint criteria will be determined. TABLES 143 and 144 show the relationship between MICs and bacteriological outcome for this species.

TABLE 145
Relationship between MICs and Bacteriological Outcome
RTI (excluding AECB)—Bacteriological Intent-to-Treat Population (Streptococci)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Streptococcus pneumoniae</i>	133	83.1	5	3.1	22	13.8
ND	3	50.0	0	0.0	3	50.0
≤0.001	1	100.0	0	0.0	0	0.0
0.002	2	100.0	0	0.0	0	0.0
0.008	27	93.1	0	0.0	2	6.9
0.015	86	81.9	5	4.8	14	13.3
0.03	14	82.4	0	0.0	3	17.6
Other streptococci	17	77.3	3	13.6	2	9.1
0.004	1	100.0	0	0.0	0	0.0
0.008	1	33.3	0	0.0	2	66.7
0.015	9	75.0	3	25.0	0	0.0
0.03	6	100.0	0	0.0	0	0.0

TABLE 146
Relationship between MICs and Bacteriological Outcome
RTI —Bacteriological Intent-to-Treat Population (Streptococci)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Streptococcus pneumoniae</i>	158	81.0	12	6.2	25	12.8
ND	3	50.0	0	0.0	3	50.0
≤0.001	1	100.0	0	0.0	0	0.0
0.002	2	100.0	0	0.0	0	0.0
0.008	32	86.5	2	5.4	3	8.1
0.015	103	83.1	6	4.8	15	13.1
0.03	17	70.8	3	12.5	4	16.7
0.06	0	0.0	1	100.0	0	0.0
Other streptococci	20	76.9	3	11.5	3	11.5
0.004	1	100.0	0	0.0	0	0.0
0.008	4	66.7	0	0.0	2	33.3
0.015	9	69.2	3	23.1	1	7.7
0.03	6	100.0	0	0.0	0	0.0

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TABLE 147 shows the frequency distribution of baseline pathogen MICs for *Streptococcus pneumoniae* from all indications for the bacteriological intent-to-treat population

TABLE 147
Frequency Distribution of MICs for Gemifloxacin for *S. pneumoniae*
From the Phase III Clinical Studies (all geographic regions)

N=372	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25
Gemi n	6	4	1	63	247	47	1	2	1
Cum %	1.6	2.7	3.0	19.9	86.3	98.9	99.3	99.7	100

Almost all of the clinical isolates had MICs of ≤ 0.03 $\mu\text{g}/\text{mL}$. Over 99% of the population had MICs ≤ 0.06 $\mu\text{g}/\text{mL}$. If the susceptible breakpoint is set at one doubling concentration (to allow for assay error) above the highest MIC concentration for 99% of the population this would give a susceptible concentration of 0.12 $\mu\text{g}/\text{mL}$. *In vitro* studies have shown that some strains that are ciprofloxacin and levofloxacin-resistant have gemifloxacin MICs of 0.5 $\mu\text{g}/\text{mL}$. There is no clinical evidence that these strains are eradicated. Breakpoints of ≤ 0.12 $\mu\text{g}/\text{mL}$ for susceptible, 0.25 $\mu\text{g}/\text{mL}$ for intermediate, and ≥ 0.5 $\mu\text{g}/\text{mL}$ for resistant separate the population into the group that we have seen were clinically eradicated and another group that are resistant to other fluoroquinolones. Until clinical evidence proves otherwise this fluoroquinolone resistant group should be considered gemifloxacin-resistant also. The following breakpoints should be in the label for *Streptococcus pneumoniae*:

Susceptible = ≤ 0.12 $\mu\text{g}/\text{mL}$
Intermediate = 0.25 $\mu\text{g}/\text{mL}$
Resistant = ≥ 0.5 $\mu\text{g}/\text{mL}$

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HAEMOPHILUS SPECIES

TABLES 148 and 149 show the relationship between MICs and bacteriological outcome for this group of organisms.

TABLE 148
Relationship between MICs and Bacteriological Outcome
RTI (excluding AECB)—Bacteriological Intent-to-Treat Population (*Haemophilus*)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Haemophilus</i> species	78	77.2	9	8.9	14	13.9
≤0.001	11	84.6	2	15.4	0	0.0
0.002	37	74.0	4	8.0	9	18.0
0.004	15	88.2	1	5.9	1	5.9
0.008	7	63.6	0	0.0	4	36.4
0.015	7	87.5	1	12.5	0	0.0
0.03	1	50.0	1	50.0	0	0.0
<i>Haemophilus influenzae</i>	66	78.6	6	7.1	12	14.3
≤0.001	9	81.8	2	18.2	0	0.0
0.002	34	72.3	4	8.5	9	19.1
0.004	14	93.3	0	0.0	1	6.7
0.008	4	66.7	0	0.0	2	33.3
0.015	5	100.0	0	0.0	0	0.0

TABLE 149
Relationship between MICs and Bacteriological Outcome
RTI —Bacteriological Intent-to-Treat Population (*Haemophilus*)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Haemophilus</i> species	187	83.1	18	8.0	20	8.9
≤0.001	21	84.0	3	12.0	1	4.0
0.002	74	79.6	7	7.5	12	12.9
0.004	50	90.9	3	5.5	2	3.6
0.008	22	78.6	1	3.6	5	17.9
0.015	14	87.5	2	12.5	0	0.0
0.03	4	66.7	2	33.3	0	0.0
0.06	2	100.0	0	0.0	0	0.0
<i>Haemophilus influenzae</i>	143	82.7	13	7.5	17	9.8
≤0.001	16	84.2	3	15.8	0	0.0
0.002	67	77.9	7	8.1	12	14.0
0.004	43	91.5	2	4.3	2	4.3
0.008	10	76.9	0	0.0	3	23.1
0.015	6	85.7	1	14.3	0	0.0
0.03	1	100.0	0	0.0	0	0.0

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TABLES 150 and 151 show the frequency distribution for baseline pathogen MICs for *Haemophilus* species and *Haemophilus influenzae*, respectively, from all indications for the bacteriological intent-to-treat population

TABLE 150
Frequency Distribution of MICs for Gemifloxacin for *Haemophilus* species
From the Phase III Clinical Studies (all geographic regions)

N=372	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>256
Gemi n	46	148	83	47	26	14	5	1	0	0	0	1	1
Cum %	12.4	52.2	74.5	87.1	94.1	97.8	99.2	99.5	99.5	99.5	99.5	99.7	100 ¹

¹ MIC₁₀₀ = >256 µg/mL—it is likely this is a laboratory error

TABLE 151
Frequency Distribution of MICs for Gemifloxacin for *H. influenzae*
From the Phase III Clinical Studies (all geographic regions)

N=287	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>256
Gemi n	38	137	71	21	11	4	2	1	0	0	0	1	1
Cum %	13.2	61.0	85.7	93.0	96.9	98.3	99.0	99.3	99.3	99.3	99.3	99.7	100 ¹

¹ MIC₁₀₀ = >256 µg/mL—it is likely this is a laboratory error

Almost all of the clinical isolates had MICs of ≤0.06 µg/mL. Over 99% of the population had MICs ≤0.06 µg/mL. There is very little evidence that isolates with MICs greater than 0.12 µg/mL are successfully treated. If the susceptible breakpoint is set at one doubling concentration (to allow for assay error) above the highest MIC concentration for 99% of the population this would give a susceptible concentration of 0.12 µg/mL. Although there were two isolates with MICs >0.12 µg/mL these are very rare and one of the two isolates was probably a laboratory error. All other fluoroquinolones have a susceptible breakpoint only at the present time. *In vitro* surveillance studies indicate that almost all isolates have MIC values of ≤0.12 µg/mL. It appears that the practice of using a susceptible breakpoint only for this group of organisms should be applied to gemifloxacin also. The following breakpoint should be used when testing *Haemophilus* species.

Susceptible = ≤0.12 µg/mL

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

For testing Enterobacteriaceae:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 0.25	(S) Susceptible
0.5	(I) Intermediate
≥ 1.0	(R) Resistant

For testing *Staphylococcus* species:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 0.12	(S) Susceptible
0.25	(I) Intermediate
≥ 0.5	(R) Resistant

For testing *Streptococcus pneumoniae*:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 0.12	(S) Susceptible
0.25	(I) Intermediate
≥ 0.5	(R) Resistant

For testing *Haemophilus* species

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 0.12	(S) Susceptible

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TABLES 152 and 153 show the relationship between zone diameter and pathogen bacteriological response for enterobacteriaceae that the applicant has proposed for the ~~.....~~ TABLE 154 shows the relationship for

TABLE 152
Relationship between Zone Diameters and Bacteriological Outcome
RTI (excluding AECEB)—Bacteriological Intent-to-Treat Population (Enterobacteriaceae)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Enterobacteriaceae</i>	52	81.3	7	10.9	5	7.8
14	0	0.0	0	0.0	1	100.0
17	1	100.0	0	0.0	0	0.0
20	1	100.0	0	0.0	0	0.0
21	1	50.0	0	0.0	1	50.0
23	1	100.0	0	0.0	0	0.0
24	2	40.0	2	40.0	1	20.0
25	5	83.3	0	0.0	1	16.7
26	5	100.0	0	0.0	0	0.0
27	10	90.9	1	9.1	0	0.0
28	4	66.7	1	16.7	1	16.7
29	10	90.9	1	9.1	0	0.0
30	5	100.0	0	0.0	0	0.0
31	3	100.0	0	0.0	0	0.0
32	1	50.0	1	50.0	0	0.0
33	3	100.0	0	0.0	0	0.0
35	0	0.0	1	100.0	0	0.0
<i>Escherichia coli</i>	9	90.0	1	10.0	0	0.0
26	2	100.0	0	0.0	0	0.0
28	1	100.0	0	0.0	0	0.0
29	1	100.0	0	0.0	0	0.0
30	2	100.0	0	0.0	0	0.0
31	1	100.0	0	0.0	0	0.0
32	0	0.0	1	100.0	0	0.0
33	2	100.0	0	0.0	0	0.0
<i>Klebsiella pneumoniae</i>	21	75.0	5	17.9	2	7.1
17	1	100.0	0	0.0	0	0.0
20	1	100.0	0	0.0	0	0.0
24	0	0.0	1	50.0	1	50.0
25	3	75.0	0	0.0	1	25.0
26	3	100.0	0	0.0	0	0.0
27	7	87.5	1	12.5	0	0.0
28	2	66.7	1	33.3	0	0.0
29	2	66.7	1	33.3	0	0.0
31	2	100.0	0	0.0	0	0.0
35	0	0.0	1	100.0	0	0.0

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TABLE 153
Relationship between Zone Diameter and Bacteriological Outcome
RTI –Bacteriological Intent-to-Treat Population (Enterobacteriaceae)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Enterobacteriaceae</i>	106	80.3	17	12.9	9	6.8
14	1	50.0	0	0.0	1	50.0
17	1	100.0	0	0.0	0	0.0
19	1	50.0	1	50.0	0	0.0
20	1	100.0	0	0.0	0	0.0
21	4	66.7	1	16.7	1	16.7
22	2	66.7	1	33.3	0	0.0
23	4	100.0	0	0.0	0	0.0
24	7	70.0	2	20.0	1	10.0
25	8	72.7	2	18.2	1	9.1
26	9	100.0	0	0.0	0	0.0
27	17	94.4	1	5.6	0	0.0
28	11	68.8	3	18.8	2	12.5
29	16	94.1	1	5.9	0	0.0
30	7	77.8	0	0.0	2	22.2
31	6	100.0	0	0.0	0	0.0
32	5	62.5	3	37.5	0	0.0
33	5	100.0	0	0.0	0	0.0
34	1	100.0	0	0.0	0	0.0
35	0	0.0	1	100.0	0	0.0
42	0	0.0	0	0.0	1	100.0
47	0	0.0	1	100.0	0	0.0
<i>Escherichia coli</i>	22	75.9	5	17.2	2	6.9
21	2	100.0	0	0.0	0	0.0
22	0	0.0	1	100.0	0	0.0
24	1	100.0	0	0.0	0	0.0
25	1	100.0	0	0.0	0	0.0
26	3	100.0	0	0.0	0	0.0
27	1	100.0	0	0.0	0	0.0
28	2	66.7	1	33.3	0	0.0
29	2	100.0	0	0.0	0	0.0
30	2	66.7	0	0.0	1	33.3
31	3	100.0	0	0.0	0	0.0
32	2	40.0	3	60.0	0	0.0
33	2	100.0	0	0.0	0	0.0
34	1	100.0	0	0.0	0	0.0
42	0	0.0	0	0.0	1	100.0

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TABLE 153 (continued)
Relationship between Zone Diameter and Bacteriological Outcome
RTI --Bacteriological Intent-to-Treat Population (Enterobacteriaceae)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Klebsiella pneumoniae</i>	36	78.3	7	15.2	3	6.5
17	1	100.0	0	0.0	0	0.0
19	1	100.0	0	0.0	0	0.0
20	1	100.0	0	0.0	0	0.0
21	1	100.0	0	0.0	0	0.0
23	3	100.0	0	0.0	0	0.0
24	2	50.0	1	25.0	1	25.0
25	4	80.0	0	0.0	1	20.0
26	5	100.0	0	0.0	0	0.0
27	8	88.9	1	11.1	0	0.0
28	4	66.7	2	33.3	0	0.0
29	3	75.0	1	25.0	0	0.0
30	0	0.0	0	0.0	1	100.0
31	3	100.0	0	0.0	0	0.0
35	0	0.0	1	100.0	0	0.0
47	0	0.0	1	100.0	0	0.0

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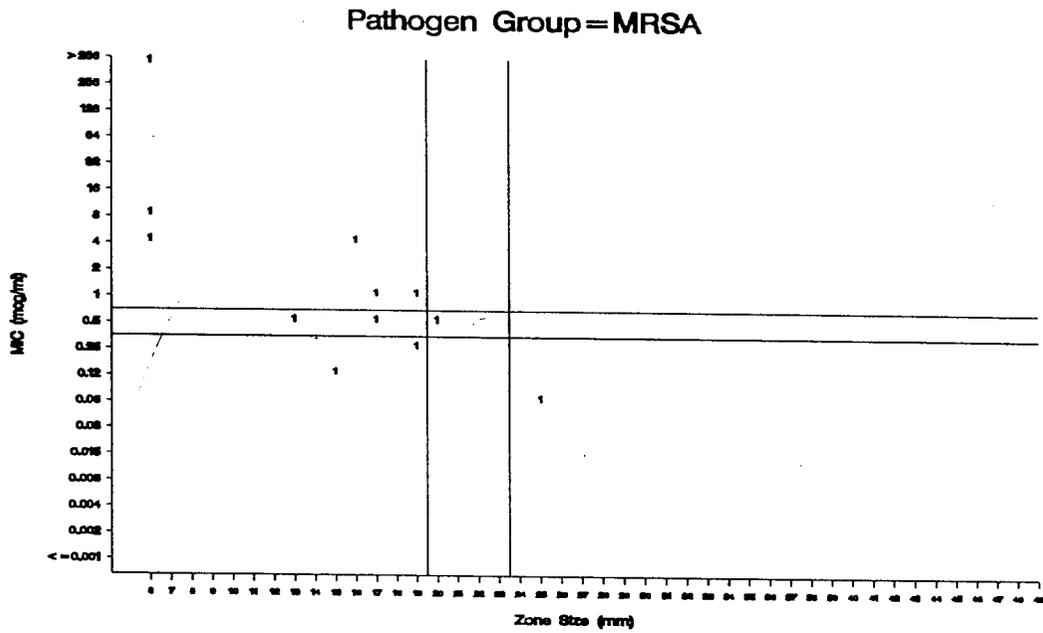
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Figure 40 shows the same scattergram with only the MRSA isolates. Figure 41 shows the scattergram for MSSA isolates only.

Figure 40—Gemifloxacin Scattergram from Phase III Trials (MRSA) (n- 12)



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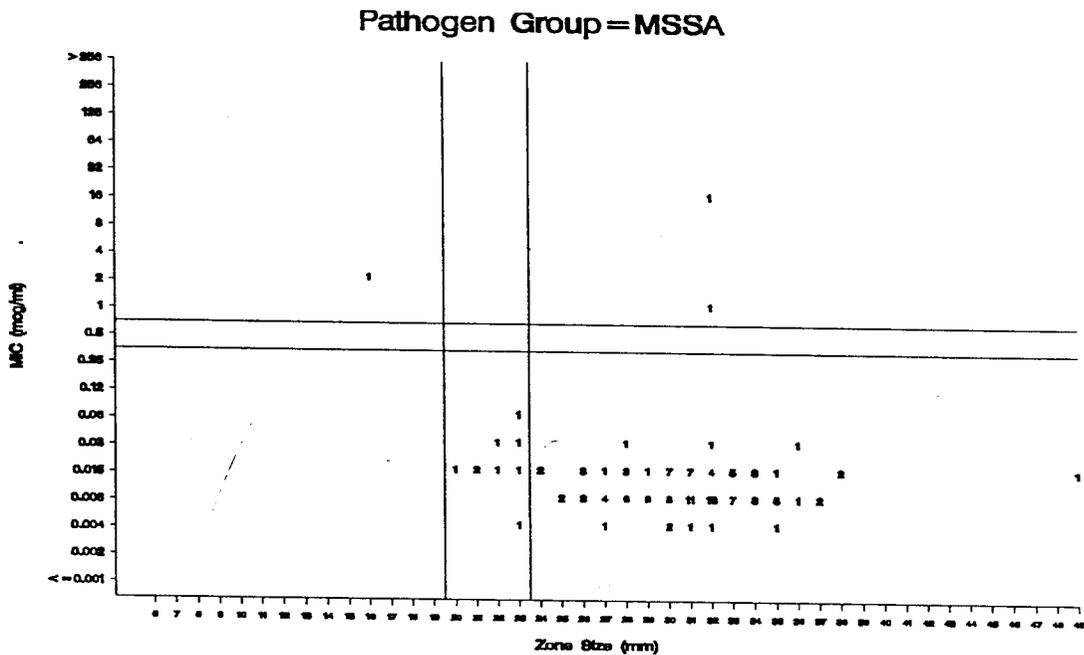
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Figure 41—Gemifloxacin Scattergram from Phase III Trials (MSSA) (n= 134)



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Since there is no evidence that the MRSA are eradicated the breakpoints should separate them from the MSSA isolates, which are eradicated and have zone diameters ≥ 20 mm (except for one isolate). If the susceptible zone diameter breakpoint is set at ≥ 23 mm four more clinical isolates of MSSA would be grouped with the rest as susceptible. The intermediate zone diameters should be 20-22 mm. The resistant zone diameter should be ≤ 19 mm. Using the MIC breakpoints of ≤ 0.12 $\mu\text{g}/\text{mL}$ for susceptible and ≥ 0.5 $\mu\text{g}/\text{mL}$ for resistant leads to 2 very major errors (1.0%), 1 minor error (0.5%), and 7 minor errors (3.5%). These breakpoints separate most of the MRSA from the other susceptible strains. The preclinical studies also suggested that these zone diameter breakpoints may be appropriate for MIC breakpoints of ≤ 0.12 $\mu\text{g}/\text{mL}$ and 0.5 $\mu\text{g}/\text{mL}$.

The following zone diameter breakpoints for *Staphylococcus* species should be in the label:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 23 mm	(S) Susceptible
20-22 mm	(I) Intermediate
≤ 19 mm	(R) Resistant

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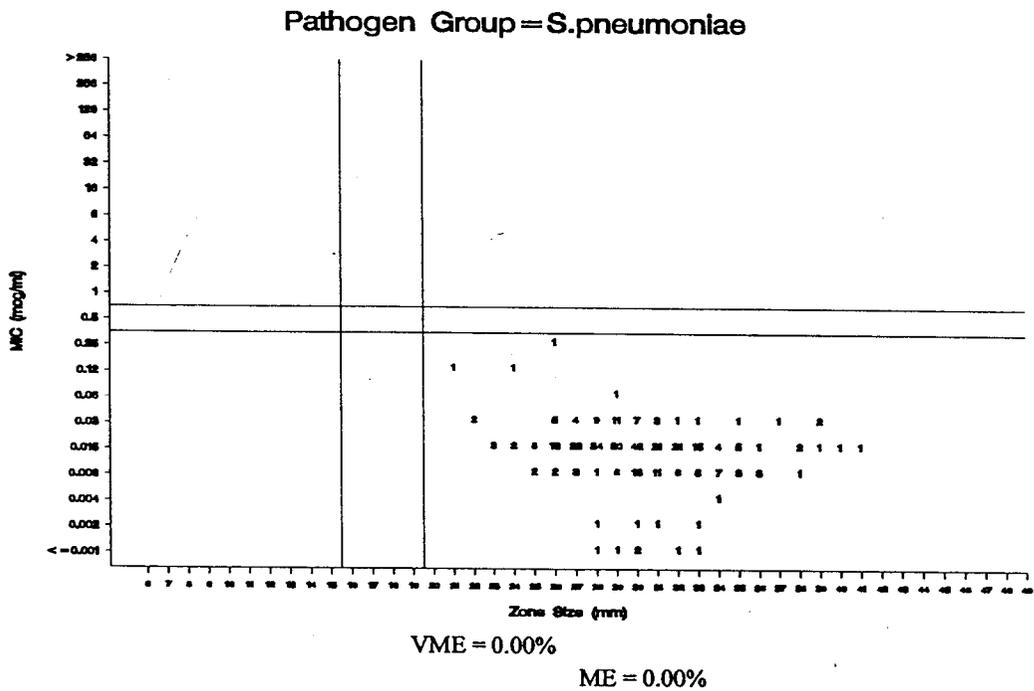
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STREPTOCOCCUS PNEUMONIAE

Figure 42 shows the scattergram of the *Streptococcus pneumoniae* Phase III clinical isolates.

Figure 42—Gemifloxacin Scattergram for Phase III Clinical Isolates of *Streptococcus pneumoniae* (n = 371)

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TABLE 155 shows the relationship between zone diameter and bacteriological outcome for *Streptococcus pneumoniae* in the Phase III clinical trials.

TABLE 155
Relationship between Zone Diameter and Bacteriological Outcome
RTI --Bacteriological Intent-to-Treat Population (*Streptococcus pneumoniae*)

Pathogen Group	Total Eradicated	% Eradicated	Total Persisted	% Persisted	Unable to Determine	% Unable to Determine
<i>Streptococcus pneumoniae</i>	158	81.0	12	6.2	25	12.8
22	0	0.0	1	100.0	0	0.0
23	2	66.7	0	0.0	1	33.3
24	0	0.0	0	0.0	1	100.0
25	2	40.0	1	20.0	2	40.0
26	8	88.9	0	0.0	1	11.1
27	13	81.3	0	0.0	1	18.8
28	11	68.8	2	12.5	3	18.8
29	32	80.0	1	2.5	7	17.5
30	29	93.5	2	6.5	0	0.0
31	15	83.3	2	11.1	1	5.6
32	12	80.0	1	6.7	2	13.3
33	11	84.6	1	7.7	1	7.7
34	8	100.0	0	0.0	0	0.0
35	5	100.0	0	0.0	0	0.0
36	3	100.0	0	0.0	0	0.0
38	2	100.0	0	0.0	0	0.0
39	1	50.0	1	50.0	0	0.0
40	1	100.0	0	0.0	0	0.0
And	3	50.0	0	0.0	3	50.0

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The preclinical study by Jones (137) suggested that a breakpoint of 0.12 µg/mL would separate the *Streptococcus pneumoniae* strains that are ciprofloxacin and levofloxacin-resistant from the susceptible strains. There is no clinical evidence that these resistant strains are eradicated. The preclinical studies also indicated that zone diameter breakpoints of ≥23 mm for susceptible and ≤ 19 mm might be appropriate. It appears that these breakpoints should be used. The following zone diameter breakpoints should be in the label for testing *Streptococcus pneumoniae*:

Zone Diameter (mm)

≥23 mm
20-22 mm
≤ 19 mm

Interpretation

(S) Susceptible
(I) Intermediate
(R) Resistant

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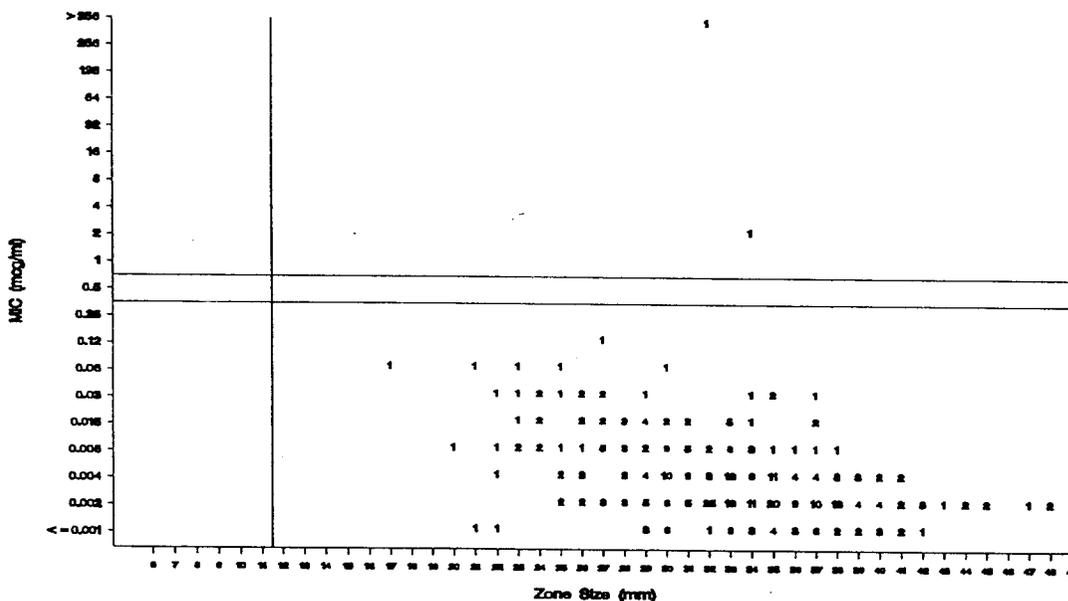
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HAEMOPHILUS SPECIES

Figure 43 shows the scattergram for *Haemophilus* species from the gemifloxacin Phase III clinical trials.

Figure 43—Gemifloxacin Scattergram for *Haemophilus* species from Phase III Trials (n = 372)

Pathogen Group = *Haemophilus* sp.



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Almost all zone diameters were ≥ 20 mm. The smallest zone diameter for 99% of the population is 21 mm. Three milliliters smaller than this zone diameter is 18 mm. This 3 mm zone is to take into account the error of the assay which is one dilution which is equivalent to 3 mm. It appears that a susceptible breakpoint of ≥ 18 mm would include almost all *Haemophilus* species for which clinical efficacy has been shown. There were several *Haemophilus* species with zone diameters from 12-18 mm in the surveillance studies but clinical efficacy has not been shown against these isolates. The following zone diameter breakpoint should be in the label for *Haemophilus* species:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 18 mm	(S) Susceptible

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

For testing Enterobacteriaceae:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥20 mm	(S) Susceptible
16-19 mm	(I) Intermediate
≤ 15 mm	(R) Resistant

For testing *Staphylococcus* species:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥23 mm	(S) Susceptible
20-22 mm	(I) Intermediate
≤ 19 mm	(R) Resistant

For testing *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥23 mm	(S) Susceptible
20-22 mm	(I) Intermediate
≤ 19 mm	(R) Resistant

For testing *Haemophilus* species:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥18 mm	(S) Susceptible

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PACKAGE INSERT

ISOLATES APPROVED

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

Gemifloxacin 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

Streptococcus pneumoniae (penicillin-susceptible strains) may read (including penicillin-resistant strains) if clinical evidence is shown.

Aerobic gram-negative microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae (some strains are only moderately susceptible)
(only in list #1)

Moraxella catarrhalis

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

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

Gemifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.25 µg/mL (0.12 µg/mL for *Streptococcus pneumoniae* and *Staphylococcus* species) or less against most (>90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

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Aerobic gram-positive microorganisms

Aerobic gram-negative microorganisms
Acinetobacter lwoffii
Klebsiella oxytoca

INTERPRETIVE CRITERIA ESTABLISHED

The following MIC interpretive criteria should be used:

For testing Enterobacteriaceae:

MIC ($\mu\text{g/mL}$)
 ≤ 0.25
0.5
 ≥ 1.0

Interpretation
(S) Susceptible
(I) Intermediate
(R) Resistant

For testing *Streptococcus pneumoniae*:

MIC ($\mu\text{g/mL}$)
 ≤ 0.12
0.25
 ≥ 0.5

Interpretation
(S) Susceptible
(I) Intermediate
(R) Resistant

For testing *Haemophilus* species

MIC ($\mu\text{g/mL}$)
 ≤ 0.12

Interpretation
(S) Susceptible

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The following zone diameter criteria should be used:

For testing Enterobacteriaceae:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥20 mm	(S) Susceptible
16-19 mm	(I) Intermediate
≤ 15 mm	(R) Resistant

For testing *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥23 mm	(S) Susceptible
20-22 mm	(I) Intermediate
≤ 19 mm	(R) Resistant

For testing *Haemophilus* species:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥18 mm	(S) Susceptible

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from this document

Reason:

_____ b(2) 'low'

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Attorney Client and Attorney Work
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_____ b(6) Personal Privacy

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Gemifloxacin 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

Streptococcus pneumoniae (penicillin-susceptible strains) may read (including penicillin-resistant strains) if clinical evidence is shown.

Aerobic gram-negative microorganisms

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae (most strains are only moderately susceptible) (only in list #1)

Moraxella catarrhalis

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

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

Gemifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.25 µg/mL (0.12 µg/mL for *Streptococcus* and *Staphylococcus* species) or less against most (>90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Acinetobacter lwoffii

Klebsiella oxytoca

Proteus vulgaris

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SUSCEPTIBILITY TESTS

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1.0	Resistant (R)

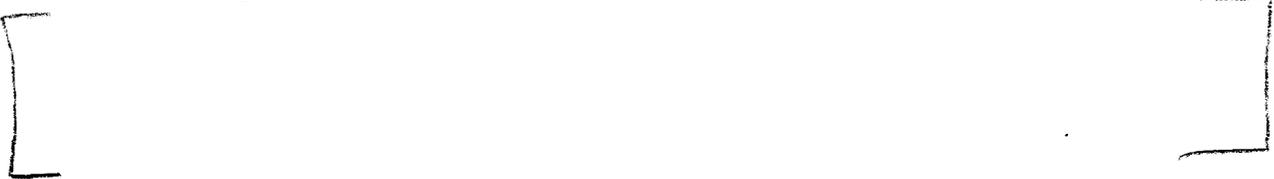
For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^a:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.12	Susceptible (S)

^a This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)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 _____



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For testing *Streptococcus pneumoniae*^b:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.12	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	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 high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

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

<u>Microorganism</u>	<u>MIC Range (µg/mL)</u>
<i>Enterococcus faecalis</i> ATCC 29212	0.016-0.12
<i>Escherichia coli</i> ATCC 25922	0.004-0.016
<i>Haemophilus influenzae</i> ATCC 49247 ^c	0.002-0.008
<hr/>	
<i>Streptococcus pneumoniae</i> ATCC 49619 ^d	0.008-0.03

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

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

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Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5- μ g gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

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

For testing *Enterobacteriaceae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 20	Susceptible (S)
16-19	Intermediate (I)
≤ 15	Resistant (R)

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

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 18	Susceptible (S)

^e This interpretive standard is applicable only to disk diffusion susceptibility testing 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.



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For testing *Streptococcus pneumoniae*^f:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 23	Susceptible (S)
20-22	Intermediate (I)
≤ 19	Resistant (R)

^f These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO₂.

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

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg gemifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	29-36
<i>Haemophilus influenzae</i>	ATCC 49247 ^g	30-37
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^h	28-34

^g This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)².

^h This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO₂.

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.

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/s/

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HFD-590/TLMicro			Signature	<i>6/23/2000</i>	Date

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