

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-404**

**21-405**

**21-061/s010, s016**

**21-062/s011, s017**

**MICROBIOLOGY REVIEW**

**MICROBIOLOGY REVIEW**  
**DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS**  
**(HFD-590)**

**NDA#:** 21-404  
21-405

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 29-JUN-01  
**CDER DATE:** 02-JUL-01  
**REVIEW ASSIGN DATE:** 14-JUL-01  
**REVIEW COMPLETE DATE:** 14-SEP-01

**SPONSOR:** Bristol-Myers Squibb Company  
5 Research Parkway  
P.O. Box 5100  
Wallingford, CT 06492-7660

**CONTACT PERSON:** Cynthia F. Piccirillo  
Associate Director Regulatory Science  
Phone Number: (203) 677-7625

**SUBMISSION REVIEWED:** Original NDA Submission

**DRUG CATEGORY:** Antimicrobial: Fluoroquinolone

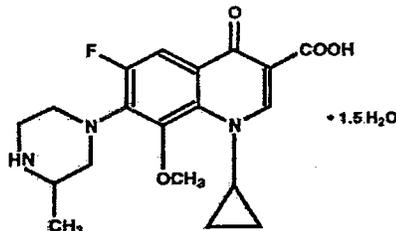
**INDICATIONS:** Uncomplicated Skin and Skin Structure Infections.

**DOSAGE FORM:** 200 and 400 mg Tablet;  
10 mg/mL IV solution; 2 mg/mL in 5% dextrose IV solution

**DRUG PRODUCT NAME**

**PROPRIETARY:** TEQUIN®  
**NONPROPRIETARY/USAN:** Gatifloxacin  
**CODE:** BMS-206584; AM-1155; CG 5501  
**CHEMICAL NAME:** (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate

**STRUCTURAL FORMULA:**



**Molecular Formula:** C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> · 1½ H<sub>2</sub>O  
**Molecular Weight:** 402.42

**NDA # 21-404; # 21-405**  
**Gatifloxacin (skin infections)**  
**Bristol-Myers Squibb Company**

**Page 2 of 44**

**SUPPORTING DOCUMENTS:**

IND # 52,081—Gatifloxacin Tablets

IND # 53,521—Gatifloxacin I.V.

NDA #21-061—Gatifloxacin Tablets (approved 12/17/99)

NDA #21-062—Gatifloxacin IV solution (approved 12/17/99)

**REMARKS/COMMENTS:**

NDA 21-061 and 21-062 for gatifloxacin tablets and IV solution, respectively, were approved in December 1999, with indications of acute sinusitis, acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated and complicated urinary tract infections, pyelonephritis, and gonorrhea. At that time the Division concluded that the indication of uncomplicated skin and skin structure infections was approvable pending the submission of data confirming the safety of gatifloxacin therapy. These submissions represent the sponsor's response concerning the uncomplicated skin and skin structure infections indication and have been given new NDA numbers (NDA 21-404—Tablets and NDA 21-405—IV Solution).

The approvable letter for NDAs 21-061 and 21-062 described post-marketing studies that Bristol-Myers Squibb was suppose to perform before the skin indication would be granted. The additional data Bristol-Myers Squibb agreed to provide are comprised of a number of clinical pharmacology studies that would further characterize gatifloxacin related changes in the QT interval on the ECG; two large scale observational studies, one conducted in North America, and one in Europe; and post-marketing surveillance data from at least one million patients. These data have been submitted.

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

**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 35-43.

TABLE OF CONTENTS

	PAGE
EXECUTIVE SUMMARY .....	4
PRECLINICAL EFFICACY (IN VITRO).....	6
MECHANISM OF ACTION .....	6
ANTIMICROBIAL SPECTRUM OF ACTIVITY .....	6
Streptococci .....	8
Staphylococci.....	9
Summary of <i>In vitro</i> Activity.....	10
IN VITRO COMPARISON TO OTHER AGENTS.....	12
<i>In vitro</i> Comparison Against Streptococci.....	12
<i>In vitro</i> Comparison Against Staphylococci .....	13
EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY .....	14
BACTERICIDAL ACTIVITY.....	14
POSTANTIBIOTIC EFFECT .....	14
ANTIMICROBIAL INTERACTION WITH OTHER ANTIMICROBIALS .....	15
INTRACELLULAR ACCUMULATION .....	15
ASSESSMENT OF RESISTANCE.....	15
PRECLINICAL EFFICACY (IN VIVO).....	16
PHARMACOKINETICS/BIOAVAILABILITY .....	16
CLINICAL EFFICACY (CLINICAL MICROBIOLOGY).....	17
ISOLATES/RELEVANCE TO APPROVED INDICATIONS .....	17
Skin and Skin Structure Infections (SSSI).....	17
MIC/DISK DIFFUSION CORRELATION STUDIES.....	18
BACTERIOLOGICAL EFFICACY .....	25
CORRELATION OF TEST RESULTS WITH OUTCOME STATISTICS.....	25
MIC Breakpoints.....	26
<i>Streptococcus pneumoniae</i> .....	26
<i>Streptococcus</i> Species other than <i>Streptococcus pneumoniae</i> .....	27
Zone Diameter Breakpoints.....	27
<i>Streptococcus pneumoniae</i> .....	27
<i>Streptococcus</i> Species including <i>Streptococcus pneumoniae</i> .....	28
PACKAGE INSERT .....	29
ISOLATES APPROVED.....	29
INTERPRETIVE CRITERIA ESTABLISHED .....	31
NDA REFERENCES.....	33
RECOMMENDATIONS (To be Communicated)	
Changes to the Proposed Label.....	35

**EXECUTIVE SUMMARY**

Gatifloxacin is a synthetic 8-methoxy-fluoroquinolone. It is a racemic mixture of two optical isomers, S- and R-enantiomers. The *in vitro* antimicrobial activity of the racemic mixture is comparable to either of its optical isomers alone. The molecule has a methoxy group at position 8 (C8-OMe) which appears to enhance activity against DNA gyrase in Gram positive bacteria compared to the C-8-H-fluoroquinolones. This methoxy group also appears to decrease the rate of resistance development in Gram positive bacteria.

TABLE A shows mean MIC<sub>90</sub> values for gatifloxacin against some common pathogens associated with skin infections. Based on the preclinical and clinical data provided the susceptible breakpoint for gatifloxacin for non-fastidious organisms and streptococci other than *Streptococcus pneumoniae* was set at ≤2.0 µg/mL. The susceptible breakpoint for *Streptococcus pneumoniae* was set at ≤1.0 µg/mL.

**TABLE A**  
 Gatifloxacin *in vitro* Activity

PATHOGEN	United States	Foreign
	MEAN MIC <sub>90</sub> (µg/mL)	MEAN MIC <sub>90</sub> (µg/mL)
<i>Staphylococcus aureus</i> (methicillin-susceptible)	0.11	0.25
<i>Staphylococcus aureus</i> (methicillin-resistant)	>4	6.2
<i>Staphylococcus epidermidis</i> (methicillin-susceptible)	0.12	1.6
<i>Staphylococcus epidermidis</i> (methicillin-resistant)	1.9	5.9
<i>Streptococcus agalactiae</i>	0.5	0.5
<i>Streptococcus pyogenes</i>	0.5	0.6
Viridans Group Streptococci	0.5	0.25
β-hemolytic streptococci	0.5	0.5
Streptococci (Groups C,G,F)	0.5	0.5

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

**TABLE B**  
*In vitro* Activity of Gatifloxacin compared to other Fluoroquinolones (Mode MICs-µg/mL)

Organism	GATI	SPAR	LEVO	CIPRO	TROV	OFLX	MOXI	CLINA
<i>Streptococcus agalactiae</i>	0.5	0.5	1.0	1.0	0.5	4.0	0.5	0.25
<i>Streptococcus pyogenes</i>	0.5	1.0	1.0	1.0	0.5	2.0	0.25	0.5
Viridans Group streptococci	0.5	0.5	2.0	2.0	0.5	4.0	—	—
<i>Streptococcus</i> groups C, G, F	0.5	0.5	2.0	2.0	0.5	2.0	0.25	0.5
<i>Staphylococcus aureus</i> (MS)	0.25	≤0.25	0.5	1	0.12	2	0.06	0.06
<i>Staphylococcus aureus</i> (MR)	>4	>2	>4	>2	>4	>4	>4	—
<i>Staphylococcus epidermidis</i> (MS)	0.25	0.25	0.5	1.0	0.12	1.0	0.12	0.25
<i>Staphylococcus epidermidis</i> (MR)	4	>4	>2	>2	>4	>4	>2	—
<i>Staphylococcus haemolyticus</i> (MS)	0.5	—	1.0	2.0	0.5	2.0	0.25	0.25
<i>Staphylococcus haemolyticus</i> (MR)	>4	—	>4	>4	>2	>4	>2	>2

MS = Methicillin-susceptible MR = Methicillin-Resistant; GATI = gatifloxacin; SPAR = sparfloxacin;  
 LEVO = levofloxacin; CIPRO = ciprofloxacin; TROV = trovafloxacin; OFLX = ofloxacin; MOXI = moxifloxacin  
 CLINA = clinafloxacin

The data in the above tables demonstrate that against methicillin sensitive staphylococci, gatifloxacin was more active than ciprofloxacin, ofloxacin, and levofloxacin. Gatifloxacin and sparfloxacin had similar anti-staphylococcal activities. Trovafloxacin and moxifloxacin were more active than gatifloxacin versus staphylococci. As with other quinolones, gatifloxacin has poor activity against methicillin resistant *Staphylococcus* species.

Against streptococci gatifloxacin was more active than ofloxacin, ciprofloxacin, and levofloxacin. Gatifloxacin was equal to sparfloxacin and trovafloxacin. Moxifloxacin was more active.

Against *Escherichia coli* single point mutations in the *gryA* gene led to a 3-fold increase in gatifloxacin MIC and a 10-fold increase in ciprofloxacin MIC. In *Pseudomonas aeruginosa* a single-point mutation in *nfxA* (*gryA* equivalent) led to a 4-fold increase in gatifloxacin MIC and an 8-fold increase in the MICs of ciprofloxacin, norfloxacin, and ofloxacin. It appears that single step mutations do not increase gatifloxacin MICs as much as those of older quinolones.

Single-point mutations in the *gryA* gene resulted in a 2-fold increase in gatifloxacin MICs in pneumococci. In comparison the *gryA* single mutation did not change the MIC of trovafloxacin, levofloxacin, or ciprofloxacin. Sparfloxacin's MIC was increased 2-fold. This may indicate that the primary target in pneumococci for gatifloxacin and sparfloxacin is DNA gyrase and not topoisomerase IV which is the primary target for the other quinolones.

Alterations in both topoisomerase IV and DNA gyrase resulted in gatifloxacin MICs that were usually around 2-4 µg/mL. These mutants would be considered to have borderline susceptibility to gatifloxacin. The rate of increase appears to be about the same for gatifloxacin as it is for other quinolones. Ciprofloxacin MICs, however, are usually in the range of 12.5 to 25 µg/mL.

Against Gram positive bacteria single-step mutational rates were lower for gatifloxacin than comparator quinolones. At gatifloxacin concentrations equal to 2 times the MIC, the frequencies of mutation were generally  $10^{-7}$  to  $\leq 10^{-8}$ . This compared to rates 100-fold higher with ciprofloxacin and 10-fold higher with ofloxacin. These rates were about equal to those with sparfloxacin. At 4 times the MIC no mutants were selected with gatifloxacin. Against Gram negative bacteria the mutational selection rates were comparable for gatifloxacin, ciprofloxacin, and ofloxacin.

Serial passage of staphylococci in the presence of gatifloxacin led to an 8-fold increase in gatifloxacin's MIC against *Staphylococcus aureus* after 8 passages. The MIC increased to 0.4 µg/mL, a value still within the drug's susceptible range. In contrast when exposed to serial passages in ciprofloxacin, the MIC value increased 500-fold to a value of 100 µg/mL. It appears that step-wise emergence of resistance to gatifloxacin by *Staphylococcus aureus* develops more slowly and to a much lesser extent compared to ciprofloxacin.

The mean steady-state peak and trough plasma concentrations attained following a oral dosing regimen of 400 mg once daily are approximately 4.0 µg/mL and 0.36 µg/mL, respectively. For intravenous dosing of 400 mg once daily the peak and trough plasma concentrations were 4.5 µg/mL and 0.40 µg/mL, respectively.

After a 400 mg single oral dose the  $C_{max}$  was 3.4 µg/mL,  $T_{max}$  was 2 hours and the plasma half-life ( $T_{1/2}$ ) was between 7 to 8 hours. The absolute availability was 96%. Serum protein binding was 20%. Gatifloxacin was primarily eliminated by the kidney in urine (82-88%) as unchanged drug. The  $AUC_{0-\infty}$  was 32.4 µg.h/mL.

## PRECLINICAL EFFICACY (IN VITRO)

### MECHANISM OF ACTION

No new information has been submitted.

### ANTIMICROBIAL SPECTRUM OF ACTIVITY

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

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

The susceptibility breakpoint for gatifloxacin is  $\leq 2.0$  µg/mL for *Staphylococcus* species and *Streptococcus* species other than *Streptococcus pneumoniae*. The susceptible breakpoint for *Streptococcus pneumoniae* is  $\leq 1.0$  µg/mL.

The labeling submitted by the applicant proposes the addition of *Streptococcus pyogenes* to the clinical efficacy listing (list #1) in the Microbiology subsection of the label. This section of the label is presented below with the sponsor's proposed additions presented as double-underlines and deletions to the present label indicated by a strikeout.

#### **Aerobic gram-positive microorganisms**

*Staphylococcus aureus* (methicillin-susceptible strains only)

*Streptococcus pneumoniae* (penicillin-susceptible strains)

*Streptococcus pyogenes*

**Aerobic gram-negative microorganisms**

*Escherichia coli*  
*Haemophilus influenzae*  
*Haemophilus parainfluenzae*  
*Klebsiella pneumoniae*  
*Moraxella catarrhalis*  
*Neisseria gonorrhoeae*  
*Proteus mirabilis*

**Other microorganisms**

*Chlamydia pneumoniae*  
*Legionella pneumophila*  
*Mycoplasma pneumoniae*

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

**Aerobic gram-positive microorganisms**

*Staphylococcus saprophyticus*  
*Staphylococcus epidermidis* (methicillin-susceptible strains only)

*Streptococcus pneumoniae* (penicillin-resistant strains)

*Streptococcus agalactiae*  
*Streptococcus* (Group C/G/F)  
~~*Streptococcus pyogenes*~~  
Viridans group streptococci

**Aerobic gram-negative microorganisms**

*Acinetobacter lwoffii*  
*Citrobacter koseri*  
*Citrobacter freundii*  
*Enterobacter aerogenes*  
*Enterobacter cloacae*  
*Klebsiella oxytoca*  
*Morganella morganii*  
*Proteus vulgaris*

**Anaerobic microorganisms**

*Peptostreptococcus* species

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

**STREPTOCOCCI**

TABLE 1 gives a summary of gatifloxacin's *in vitro* activity against streptococci. These data were presented in the original NDAs 21-061 and 21-062.

**TABLE 1**  
**Gatifloxacin Activity Against Streptococci**

Bacterial Species	United States Studies			Foreign Studies			Total Number Tested
	Total Number of Strains Tested	Number of Investigators	Geometric Mean MIC <sub>90</sub> (µg/mL)	Total Number of Strains Tested	Number of Investigators	Geometric Mean MIC <sub>90</sub> (µg/mL)	
<i>S. agalactiae</i>	169	3	0.5	85	4	0.5	254
<i>S. pyogenes</i>	141	3	0.5	202	4	0.6	343
<i>S. sanguis</i>	34	3	0.9	0			34
Viridans streptococci	655	3	0.5	92	1	0.25	747
β-streptococci	148	1	0.5	106	2	0.5	254
Groups C, G, F	82	3	0.5	82	2	0.5	164

The geometric mean MIC<sub>90</sub> value for all streptococci species tested was ≤1.0 µg/mL in both United States and Foreign studies. Over 100 isolates of *S. agalactiae* were tested in seven studies. This species will be allowed in the *in vitro* activity listing in the label. Over 100 isolates of *S. pyogenes* were tested, *Streptococcus pyogenes* will be allowed in the clinical efficacy section if the Medical Officer determines that there is enough clinical evidence to allow this species into the indications section. If *S. pyogenes* is not allowed in the clinical efficacy listing then it may be placed in the *in vitro* activity listing (list #2) in the Microbiology subsection.

Viridans group streptococci were tested in four studies. Over 700 isolates were tested. The MIC range was 0.12 to 16.0 µg/mL. The MIC<sub>90</sub> range was 0.25 to 0.5 µg/mL. The geometric mean MIC<sub>90</sub> was 0.5 µg/mL and 0.25 µg/mL for United States and foreign studies, respectively. Viridans group streptococci will be allowed in the *in vitro* activity listing in the label.

*Streptococcus* Groups C/G/F were tested in four studies. The MIC range was 0.13-1.0 µg/mL. The MIC<sub>90</sub> range was 0.12-0.5 µg/mL. The geometric mean MIC<sub>90</sub>s were 0.5 µg/mL for both United States and foreign studies. *Streptococcus* Groups C/G/F will be allowed into the *in vitro* activity listing (list #2) in the label.

### STAPHYLOCOCCI

TABLE 2 summarizes gatifloxacin's activity against *Staphylococcus* species. These data were presented in the original NDAs 21-061 and 21-062 for gatifloxacin tablets and IV, respectively. Susceptibility was evaluated according to the organism's susceptibility to methicillin in most cases. The geometric mean MIC<sub>90</sub> for methicillin-susceptible *Staphylococcus aureus* was 0.11 µg/mL for United States studies and 0.25 µg/mL for foreign studies. Gatifloxacin was not very active against methicillin-resistant strains of *Staphylococcus aureus*. Against these strains the geometric mean MIC<sub>90</sub> was >4.0 µg/mL in United States studies and 6.2 µg/mL in foreign studies. *Staphylococcus aureus* is already in the clinical activity section of the label and is qualified as methicillin-susceptible strains only.

The geometric mean MIC<sub>90</sub>s for methicillin-susceptible *Staphylococcus epidermidis* were 0.12 µg/mL and 1.6 µg/mL in United States and foreign studies, respectively. Once again methicillin-susceptible strains are more susceptible to gatifloxacin than methicillin-resistant strains. The geometric mean MIC<sub>90</sub>s for methicillin-resistant strains of *S. epidermidis* were 1.9 µg/mL and 5.9 µg/mL in United States and foreign studies, respectively. Since a total of over 100 isolates of *S. epidermidis* were tested and the MIC<sub>90</sub> value is ≤2.0 µg/mL (susceptible breakpoint), this species will be allowed in the *in vitro* activity listing (list #2) in the label. The listing will be qualified as methicillin-susceptible strains only.

The geometric mean MIC<sub>90</sub>s for methicillin-susceptible *Staphylococcus haemolyticus* were 0.12 µg/mL and 0.5 µg/mL in United States and foreign studies, respectively. Once again methicillin-susceptible strains are more susceptible to gatifloxacin than methicillin-resistant strains. The geometric mean MIC<sub>90</sub>s for methicillin-resistant strains of *S. haemolyticus* were 6.9 µg/mL and 2.0 µg/mL in United States and foreign studies, respectively. There were only a total of 45 methicillin-susceptible isolates (11 US and 34 foreign) tested.

---

---

---

TABLE 2  
 Gatifloxacin Activity Against Staphylococci

Bacterial Species	United States Studies			Foreign Studies			Total Number Tested
	Total Number of Strains Tested	Number of Investigators	Geometric Mean MIC <sub>90</sub> (µg/mL)	Total Number of Strains Tested	Number of Investigators	Geometric Mean MIC <sub>90</sub> (µg/mL)	
<i>S. aureus</i> (MS)	368	2	0.11	1389	5	0.25	1757
<i>S. aureus</i> (MR)	2744	2	>4	1642	6	6.2	4386
<i>S. epidermidis</i> (MS)	32	1	0.12	101	2	1.6	133
<i>S. epidermidis</i> (MR)	307	2	1.9	198	2	5.9	505
<i>S. haemolyticus</i> (MS)	11	1	0.12	34	1	0.5	45
<i>S. haemolyticus</i> (MR)	36	1	6.9	45	1	2	81
Coagulase-Negative (MS)	0			233	1	0.9	233
Coagulase-Negative (MR)	653	2	3.8	475	2	>2	1128

(MS) = methicillin-susceptible; (MR) = methicillin-resistant

#### SUMMARY OF IN VITRO ACTIVITY

Assuming that the data submitted is sufficient to approve an indication of uncomplicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*, then *Streptococcus pyogenes* may be deleted from the *in vitro* activity listing (list #2 in the Microbiology subsection) and placed into the listing for which clinical efficacy has been shown.

*Staphylococcus epidermidis* (methicillin-susceptible strains only) may be added to the *in vitro* activity listing (list #2). *Streptococcus agalactiae*, *Streptococcus* (Group C/G/F) and Viridans group streptococci may be added to the *in vitro* activity listing (list #2). The MIC<sub>90</sub> values for each of these species or groups were below the susceptible breakpoint and over 100 isolates were tested in several different studies. Each of these organisms are associated with skin infections.

Only one United States and one foreign study were performed. Only a total of 45 isolates were tested.

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

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

#### Aerobic gram-positive microorganisms:

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

**Aerobic gram-negative microorganisms**

*Escherichia coli*  
*Haemophilus influenzae*  
*Haemophilus parainfluenzae*  
*Klebsiella pneumoniae*  
*Moraxella catarrhalis*  
*Neisseria gonorrhoeae*  
*Proteus mirabilis*

**Other microorganisms**

*Chlamydia pneumoniae*  
*Legionella pneumophila*  
*Mycoplasma pneumoniae*

The *in vitro* activity list with MIC<sub>90</sub> values of  $\leq 2.0$   $\mu\text{g/mL}$  includes:

**Aerobic gram-positive microorganisms**

*Staphylococcus saprophyticus*  
*Staphylococcus epidermidis* (methicillin-susceptible strains only)  
*Streptococcus agalactiae*  
*Streptococcus* (Group C/G/F)  
*Streptococcus pneumoniae* (penicillin-resistant strains)  

---

*Streptococcus viridans* group

**Aerobic gram-negative microorganisms**

*Acinetobacter lwoffii*  
*Citrobacter koseri*  
*Citrobacter freundii*  
*Enterobacter aerogenes*  
*Enterobacter cloacae*  
*Klebsiella oxytoca*  
*Morganella morganii*  
*Proteus vulgaris*

**Anaerobic microorganisms**

*Peptostreptococcus* species

## IN VITRO COMPARISON TO OTHER AGENTS

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

### IN VITRO COMPARISON AGAINST STREPTOCOCCI

Against *Streptococcus pyogenes*, gatifloxacin's MIC<sub>90</sub> was 0.5 µg/mL. Sparfloxacin, levofloxacin and ciprofloxacin had modal MIC values that were 2-fold greater (1.0 µg/mL) (see TABLE 3). Ofloxacin's MICs were 4-fold higher. Trovafloxacin and clinafloxacin had MICs that were equivalent to those seen with gatifloxacin. Moxifloxacin's MICs were 2-fold less (0.25 µg/mL).

Against *Streptococcus agalactiae* gatifloxacin's MIC<sub>90</sub> was 0.5 µg/mL. Sparfloxacin, trovafloxacin, and moxifloxacin had comparable MICs. Levofloxacin and ciprofloxacin MICs were 2-fold higher (1.0 µg/mL) and ofloxacin MICs were 8-fold higher (4.0 µg/mL). Clinafloxacin had MICs that were 2-fold lower (0.25 µg/mL) compared to gatifloxacin MIC values.

Against *Streptococcus* groups C,G,F gatifloxacin's MIC<sub>90</sub> was 0.5 µg/mL. Sparfloxacin, trovafloxacin, and clinafloxacin had similar MIC to those of gatifloxacin. Levofloxacin, ofloxacin, and ciprofloxacin had MICs that were 4-fold higher (2.0 µg/mL). Moxifloxacin had 2-fold lower MICs (0.25 µg/mL).

Against viridans group streptococci gatifloxacin's MIC<sub>90</sub> was 0.5 µg/mL. Sparfloxacin and trovafloxacin had MICs comparable to those for gatifloxacin. Levofloxacin and ciprofloxacin had MICs that were 4-fold higher (2.0 µg/mL) and ofloxacin had MICs 8-fold higher (4.0 µg/mL). Moxifloxacin and clinafloxacin were not tested.

TABLE 3

*In vitro* Activity of Gatifloxacin compared to other Fluoroquinolones (Mode MICs-µg/mL)  
Streptococci

Organism	GATI	SPAR	LEVO	CIPRO	TROV	OFLX	MOXI	CLINA
<i>Streptococcus agalactiae</i>	0.5	0.5	1.0	1.0	0.5	4.0	0.5	0.25
<i>Streptococcus pyogenes</i>	0.5	1.0	1.0	1.0	0.5	2.0	0.25	0.5
Viridans Group streptococci	0.5	0.5	2.0	2.0	0.5	4.0	--	--
<i>Streptococcus</i> groups C, G, F	0.5	0.5	2.0	2.0	0.5	2.0	0.25	0.5

GATI = gatifloxacin; SPAR = sparfloxacin; LEVO = levofloxacin; CIPRO = ciprofloxacin;  
TROV = trovafloxacin; OFLX = ofloxacin; MOXI = moxifloxacin; CLINA = Clinafloxacin

**IN VITRO COMPARISON AGAINST STAPHYLOCOCCI**

Against methicillin-susceptible *Staphylococcus aureus*, gatifloxacin's MIC<sub>90</sub> value was 0.25 µg/mL which was comparable to that of sparfloxacin and trovafloxacin. Levofloxacin MICs were 2-fold higher (0.5 µg/mL) and ciprofloxacin MICs were 4-fold higher (1.0 µg/mL). Ofloxacin MICs were 8-fold higher (2.0 µg/mL). Moxifloxacin and clinafloxacin MICs were 4-fold lower (0.06 µg/mL) (see TABLE 4). None of the tested fluoroquinolones had activity against methicillin-resistant strains of *Staphylococcus aureus*.

Against methicillin-susceptible *Staphylococcus epidermidis*, gatifloxacin's MIC<sub>90</sub> value was 0.25 µg/mL. Sparfloxacin and clinafloxacin had similar MIC values. Levofloxacin had 2-fold higher MICs (0.5 µg/mL). Ciprofloxacin and ofloxacin had 4-fold higher values (1.0 µg/mL). Trovafloxacin and moxifloxacin had 2-fold lower MICs (0.12 µg/mL) (see TABLE 4). None of the tested fluoroquinolones had activity against methicillin-resistant strains of *Staphylococcus epidermidis*.

Against methicillin-susceptible *Staphylococcus haemolyticus*, gatifloxacin's MIC<sub>90</sub> was 0.5 µg/mL (only 45 isolates were tested). Trovafloxacin had similar MIC values. Levofloxacin had MICs 2-fold higher (1.0 µg/mL). Ciprofloxacin and ofloxacin had MICs 4-fold higher (2.0 µg/mL). Moxifloxacin and clinafloxacin had 2-fold lower MICs (0.25 µg/mL). Sparfloxacin was not tested. None of the tested fluoroquinolones showed much activity against methicillin-resistant strains.

TABLE 4

*In vitro* Activity of Gatifloxacin compared to other Fluoroquinolones (Mode MICs-µg/mL)  
 Staphylococci

Organism	GATI	SPAR	LEVO	CIPRO	TROV	OFLX	MOXI	CLINA
<i>Staphylococcus aureus</i> (MS)	0.25	≤0.25	0.5	1	0.12	2	0.06	0.06
<i>Staphylococcus aureus</i> (MR)	>4	>2	>4	>2	>4	>4	>4	—
<i>Staphylococcus epidermidis</i> (MS)	0.25	0.25	0.5	1.0	0.12	1.0	0.12	0.25
<i>Staphylococcus epidermidis</i> (MR)	4	>4	>2	>2	>4	>4	>2	—
<i>Staphylococcus haemolyticus</i> (MS)	0.5	—	1.0	2.0	0.5	2.0	0.25	0.25
<i>Staphylococcus haemolyticus</i> (MR)	>4	—	>4	>4	>2	>4	>2	>2

MS = methicillin-susceptible; MR = methicillin-resistant

GATI = gatifloxacin; SPAR = sparfloxacin; LEVO = levofloxacin; CIPRO = ciprofloxacin;

TROV = trovafloxacin; OFLX = ofloxacin; MOXI = moxifloxacin; CLINA = Clinafloxacin

## EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

No new information was submitted. From the information submitted with the original NDAs it can be concluded that changes in test parameters had little effect on the *in vitro* activity of gatifloxacin (1,2,3,4). The effect of pH on gatifloxacin activity was notable only against Gram negative bacteria (1,2,3). With Gram negative bacteria, gatifloxacin MICs were about 8-fold lower at pH 7 than at pH 6. This lowering of activity at low pH is seen with most fluoroquinolones. Generally, no more than a 2-fold difference was noted in gatifloxacin MICs using bacterial inocula sizes of  $10^4$  to  $10^8$  CFU/mL (1,2,3). For the most part, the presence of 50% serum had little to no effect on gatifloxacin's MICs (1,2,3). The type of medium used for susceptibility testing did not appear to effect the MICs (3,4). Like other quinolones, the presence of magnesium antagonized the activity of gatifloxacin (2,3). There were 4- to 8-fold increases in gatifloxacin MICs tested in medium containing  $MgCl_2$  concentrations of 3 to 9 mM. This  $Mg^{++}$  effect (usually around concentrations of 9-10 mM) is seen with almost all fluoroquinolones. This effect at high  $Mg^{++}$  concentrations may be due to competition between  $Mg^{++}$  and the drugs for binding sites on the broken single-stranded DNA. Unsupplemented Mueller-Hinton medium is 0.3 mM in  $Mg^{++}$  concentration and normal human serum is about 1.1 mM. Changes in activity due to  $Mg^{++}$  only occur at much greater concentrations than those that would be seen clinically. No significant changes in gatifloxacin MICs were seen at  $Ca^{++}$  concentrations of 5 mM.  $Ca^{++}$  has been shown to also effect quinolone activity but usually only at concentrations of 50 mM or more. It is thus not surprising to see that 5 mM of  $Ca^{++}$  did not have any effect.

## BACTERICIDAL ACTIVITY

No new information has been provided. From the data in the original NDAs it can be concluded that for most species the MIC and MBC (minimal bactericidal concentration) are equal or within one doubling dilution of each other (2,5).

Kill curve studies indicated that gatifloxacin acts much as the other fluoroquinolones do (5,6,7,8,9). Bactericidal activity is concentration dependent and is rapid (within 2-4 hours).

## POSTANTIBIOTIC EFFECT

No new information is provided. Data submitted in the original NDA showed that the postantibiotic effect (PAE) of gatifloxacin was concentration dependent for all of the species tested. This is true for all other fluoroquinolones also. For most species the PAE ranged from 0.5 to 4.8 hours at 10 x MIC.

## ANTIBACTERIAL INTERACTION WITH OTHER ANTIMICROBIALS

No new information has been submitted. The results of combination studies with gatifloxacin revealed results much like those seen with most other fluoroquinolones (8,10). A few strains and a few combinations yield synergistic results in some studies and indifferent results in other studies. Most combinations show indifferent or additive results at best. Antagonism is often seen with fluoroquinolones and rifampin especially against staphylococci.

## INTRACELLULAR ACCUMULATION

No new information has been provided. Data from the original NDA demonstrated that gatifloxacin concentrates intracellularly in phagocytic and nonphagocytic cells (69,70). Concentrations several fold higher than extracellular concentrations were seen (about seven times higher in polymorphonuclear (PMN) leukocytes than in extracellular fluid). Gatifloxacin killed intracellular staphylococcal cells to a greater extent than ciprofloxacin or ofloxacin.

## ASSESSMENT OF RESISTANCE

No new information was provided with this submission. Data from the original NDA's show that single-point mutations in *gyrA* result in a 2-fold increase in gatifloxacin MICs against pneumococci (7,13,14). In comparison, the *gyrA* single mutation in pneumococci resulted in either no change in MIC (trovafloxacin, levofloxacin, ciprofloxacin) or a 2-fold increase in MIC (sparfloxacin). This increase in sparfloxacin and gatifloxacin MICs indicates that DNA gyrase is the primary target of gatifloxacin and sparfloxacin in pneumococci, but topoisomerase IV is the primary target for other quinolones. In contrast, single mutations in topoisomerase IV (*parC*) in pneumococci had essentially no effect on gatifloxacin or sparfloxacin MICs. Single mutations in both DNA gyrase and topoisomerase IV generally resulted in gatifloxacin MICs  $\geq 4$   $\mu\text{g/mL}$ . These MICs would be classified in the resistant range.

Overexpression of the staphylococcal NorA efflux pump resulted in gatifloxacin MIC increases of 2- to 8-fold (7). This increase is less than the 15- to 60-fold increase observed with ciprofloxacin, norfloxacin, or ofloxacin. Sparfloxacin only had a 3-fold increase.

At 2 and 4 times the MIC, gatifloxacin selected resistant mutants of Gram positive bacteria (staphylococci and pneumococci) at 10- and 100-fold lower rates than ciprofloxacin or ofloxacin (5,6,7,14,15). Selection rates were about equal for Gram negative bacteria.

Serial passage of staphylococci in the presence of gatifloxacin led to slower MIC increases compared to passage in the presence of ciprofloxacin (6). Gatifloxacin MICs did not increase as high as those for ciprofloxacin.

## PRECLINICAL EFFICACY (IN VIVO)

### PHARMACOKINETICS/BIOAVAILABILITY

No new information has been provided. The usual dose of gatifloxacin is 400 mg once daily. The absolute bioavailability of gatifloxacin is 96%. Peak plasma concentrations usually occur 1-2 hours after oral dosing. The pharmacokinetics after a 1-hour intravenous infusion are similar to those seen after oral administration of an equal dose. The mean pharmacokinetic parameters of gatifloxacin are summarized in TABLE 5.

TABLE 5  
Gatifloxacin Pharmacokinetic Parameters

Dose	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	AUC <sup>a</sup> (µg.h/mL)	T <sub>1/2</sub> (hr)	UR (%)
400 mg single oral	3.8	1.00	33.0	7.8	72.4
400 mg multiple oral	4.2	1.50	34.4	7.1	80.2
400 mg infected patients	4.2	—	51.3	—	—
400 mg single dose IV	5.5	1.00	35.1	7.4	62.3
400 mg multiple dose IV	4.6	1.0	35.4	13.9	83.5

<sup>a</sup> Single dose: AUC(0-∞), Multiple dose: AUC (0-24); C<sub>max</sub>: maximum serum concentration; T<sub>max</sub>: time to C<sub>max</sub>; AUC: area under concentration versus time curve; T<sub>1/2</sub>: Serum half-life, UR: urinary recovery

**Appears This Way  
On Original**

Data from the original NDA (TABLE 6) shows some tissue to serum ratios of gatifloxacin after oral dosing. Gatifloxacin concentrates, as do most other fluoroquinolones, in respiratory tract tissue. Concentrations in skin, however, is about equal to that in plasma.

TABLE 6  
Tissue Distribution of Gatifloxacin Following Oral Dosing

Tissue	Tissue/Fluid: Serum Ratio*
Bronchial mucosa	1.65
Alveolar macrophages	26.5
Lung epithelial lining fluid	1.67
Lung parenchyma	4.09
Sinus mucosa	1.78
Skin blister fluid	1.00
Bone	0.62
Saliva	0.88
Cerebrospinal fluid (CSF)	0.36

\* Mean Values over 24 hours following single and multiple doses  
Mean AUC ratio is presented for skin blister fluid and saliva

## CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

### ISOLATES/RELEVANCE TO APPROVED INDICATIONS

No new information has been presented. In the original NDA the sponsor presented Phase III studies for the indication of skin and skin structure infections.

#### Skin and Skin Structure Infections (SSSI)

The sponsor is requesting an indication of uncomplicated skin and skin structure infections (i.e., simple abscessed, furuncles, folliculitis, wound infections, and cellulitis) due to methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*. The sponsor conducted one double-blind, comparative trial (A1420-005) that compared gatifloxacin (400 mg once daily) with levofloxacin (500 mg once daily) for 7-10 days.

In this study, 120 pathogens were obtained from 95 evaluable subjects treated with gatifloxacin. The main pathogens were  $\beta$ -hemolytic streptococci [1 *Streptococcus pyogenes* (monomicrobial) + 5 *S. pyogenes* (polymicrobial); 2 *S. agalactiae* (polymicrobial), *Staphylococcus aureus* (53 monomicrobial + 16 polymicrobial), and *Acinetobacter* species [3 *A. lwoffii* (monomicrobial) + 2 *A. baumannii* (monomicrobial) + 3 *A. lwoffii* (polymicrobial) + 1 *A. baumannii* (polymicrobial)]. Moderate numbers of *Pseudomonas* species (5 monomicrobial + 3 polymicrobial + 1 *P. aeruginosa*) were also isolated.

## MIC/DISK DIFFUSION CORRELATION STUDIES

No new information has been submitted. Since *Streptococcus* species other than *Streptococcus pneumoniae* will now be placed in the clinical efficacy part of the label, breakpoint criteria must be included for these species. In the original NDA preclinical studies were submitted that proposed breakpoints for various organisms. In a study by Bonner (16), 301 *Streptococcus pneumoniae*, 150 viridans group streptococci, and 148  $\beta$ -hemolytic streptococci were tested. The authors proposed a MIC susceptible breakpoint of  $\leq 2.0$   $\mu\text{g/mL}$  for all the streptococci.

Figure 1 shows the scattergram of MIC versus zone diameter data for *Streptococcus pneumoniae* from this study. The error rate-bounded method was used to calculate the zone diameter criteria corresponding to MIC breakpoints. For MIC breakpoints of  $\leq 2.0$   $\mu\text{g/mL}$  (susceptible) and  $\geq 8.0$   $\mu\text{g/mL}$  (resistant), the corresponding zone diameter breakpoints were  $\geq 18$  mm (susceptible) and  $\leq 14$  mm (resistant), respectively. There were no very major or major errors in this study when these breakpoints were used. There were 7 (1.2%) minor errors. Looking at the data from this study it can be seen that there are two distinct populations. One population has MICs  $\leq 1.0$   $\mu\text{g/mL}$  and zone diameters  $\geq 20$  mm. The other population has MICs  $\geq 4.0$   $\mu\text{g/mL}$  and zone diameters  $\leq 14$  mm. If a susceptible breakpoint is set at  $\leq 1.0$   $\mu\text{g/mL}$  and a resistant breakpoint at  $\geq 4.0$   $\mu\text{g/mL}$ , then the two populations are separated from each other. A susceptible zone diameter breakpoint could be set at  $\geq 20$  mm and a resistant at  $\leq 14$  mm. This would leave a large intermediate category (15-19 mm), however.

Appears This Way  
On Original

Figure 1  
*Streptococcus pneumoniae* Scattergram (Reference 16)

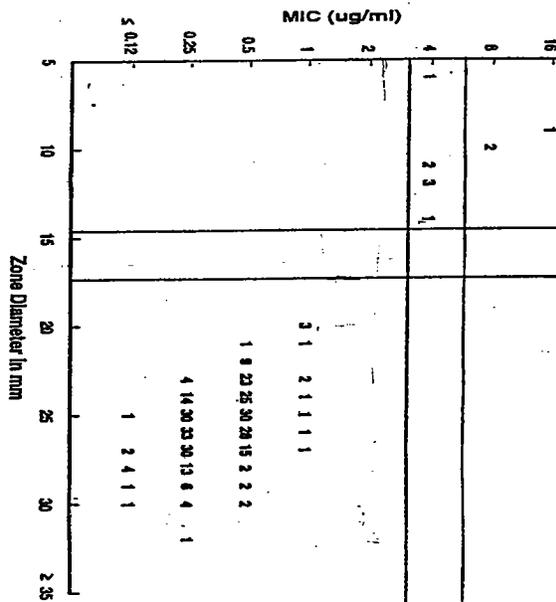


Figure 2 shows the scattergram of *Streptococcus pneumoniae* from the clinical trials submitted in the original NDAs. In these trials there appears to be only one population of isolates and all of them have MICs  $\leq 0.5 \mu\text{g/mL}$  and zone diameters  $\geq 19 \text{ mm}$ . From the data in this scattergram MIC breakpoints for *S. pneumoniae* were originally set at  $\leq 1.0 \mu\text{g/mL}$  (susceptible),  $2.0 \mu\text{g/mL}$  (intermediate), and  $\geq 4.0 \mu\text{g/mL}$  (resistant). These breakpoints are in the approved label and have also been approved by NCCLS. At the time of the original NDA approval zone diameter breakpoints were set at  $\geq 18 \text{ mm}$  (susceptible),  $15\text{-}17 \text{ mm}$  (intermediate), and  $\leq 14 \text{ mm}$  (resistant). These zone diameter breakpoints are different from those approved by NCCLS. A reevaluation of the data by this reviewer indicates that more appropriate zone diameter breakpoints would be those chosen by NCCLS  $\geq 21 \text{ mm}$  (susceptible),  $18\text{-}20 \text{ mm}$  (intermediate), and  $\leq 17 \text{ mm}$  (resistant). These new zone diameter breakpoints would still lead to no very major or major errors but would increase minor errors to 3 (1.1%).

Figure 2  
Gatifloxacin MIC versus Gatifloxacin Zone Diameters (Clinical Trials)  
*Streptococcus pneumoniae*

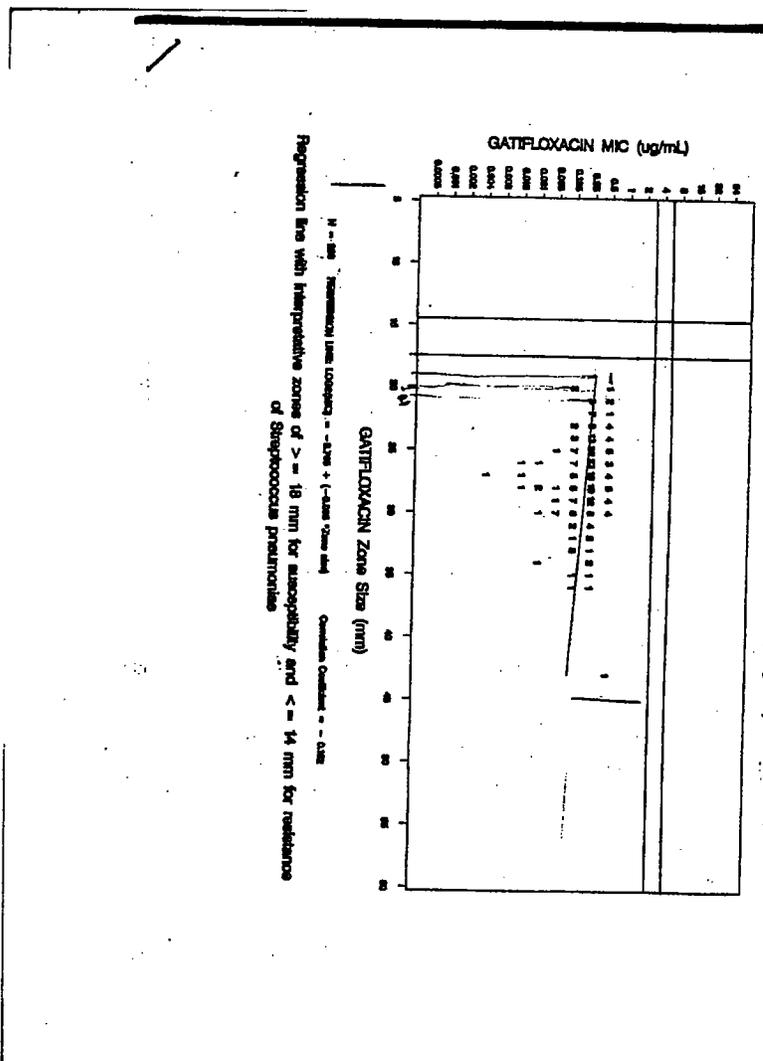


Figure 3 shows the scattergram from Bonner's study (16) for  $\beta$ -hemolytic streptococci. There was one isolate with an MIC of 1.0  $\mu\text{g/mL}$ . All other MICs were  $\leq 0.5 \mu\text{g/mL}$ . Zone diameters were  $\geq 20 \text{ mm}$ .

Figure 4 shows the scattergram from Bonner's study for viridans group streptococci. As with *Streptococcus pneumoniae* there are two distinct populations. One population has MICs  $\leq 1.0 \mu\text{g/mL}$  and zone diameters  $\geq 19 \text{ mm}$  and the other population has MICs  $\geq 4.0 \mu\text{g/mL}$  and zone diameters  $\leq 14 \text{ mm}$ .

Figure 5 shows the scattergram for streptococci other than *S. pneumoniae* from the clinical trials submitted with the original NDAs. There are several isolates with MICs of 1.0  $\mu\text{g/mL}$ . If the susceptible breakpoint is set at 2.0  $\mu\text{g/mL}$  this will allow these isolates to be susceptible if the error of the assay is taken into account. From the scattergram it appears that a susceptible breakpoint of  $\geq 18 \text{ mm}$  is needed so that the vast majority of isolates will be classified as susceptible.

If *Streptococcus pneumoniae* criteria are set as follow:

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\leq 1.0$	$\geq 21$	(S) Susceptible
2.0	18-20	(I) Intermediate
$\geq 4.0$	$\leq 17$	(R) Resistant

and the criteria for streptococci other than *Streptococcus pneumoniae* are set as follow:

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\leq 2.0$	$\geq 18$	(S) Susceptible
4.0	15-17	(I) Intermediate
$\geq 8.0$	$\leq 14$	(R) Resistant

then the criteria for streptococci other than *S. pneumoniae* will be the same as that for staphylococci and Enterobacteriaceae. The zone diameter criteria for *S. pneumoniae* will be 3 mm larger than those for other streptococci which will correspond to a one dilution difference in MIC criteria.

Appears This Way  
On Original

Figure 3  
Scattergram for  $\beta$ -hemolytic streptococci (Reference 16)

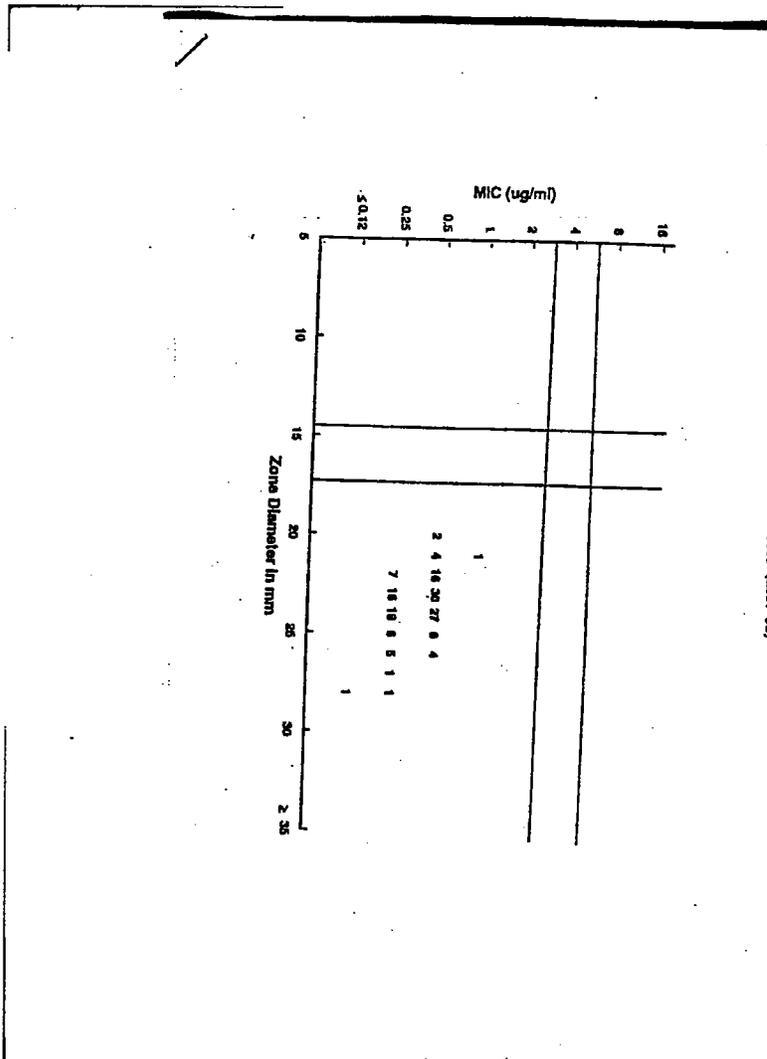


Figure 4  
 Scattergram of Viridans Streptococci (Reference 16)

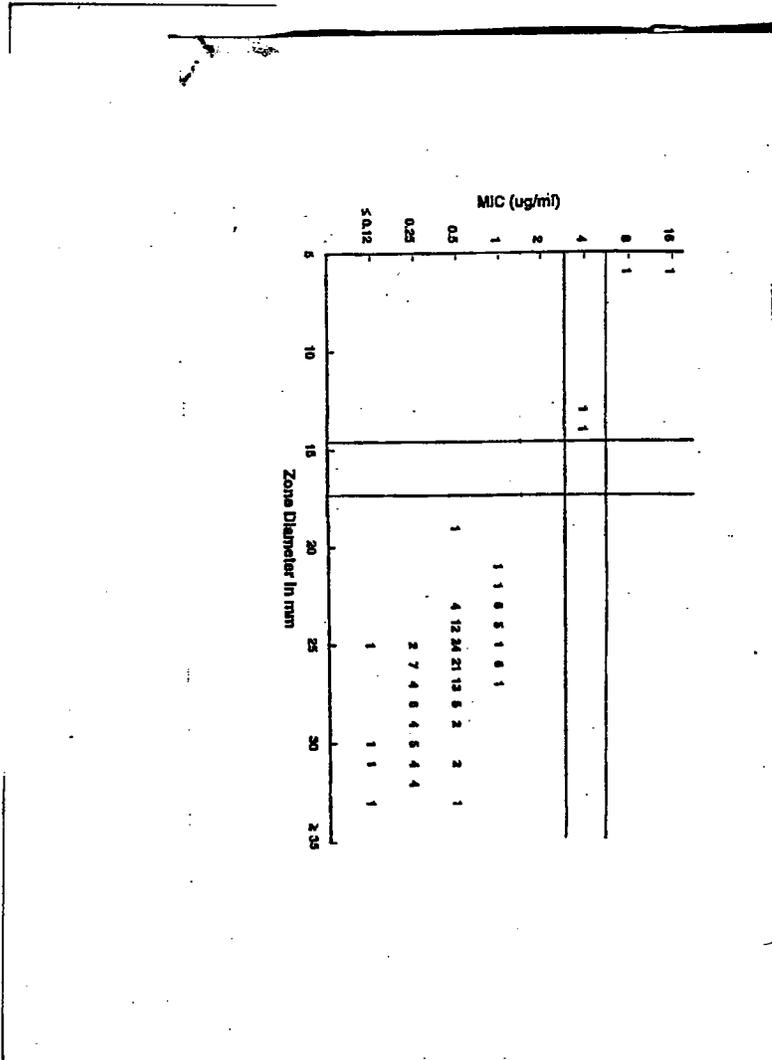
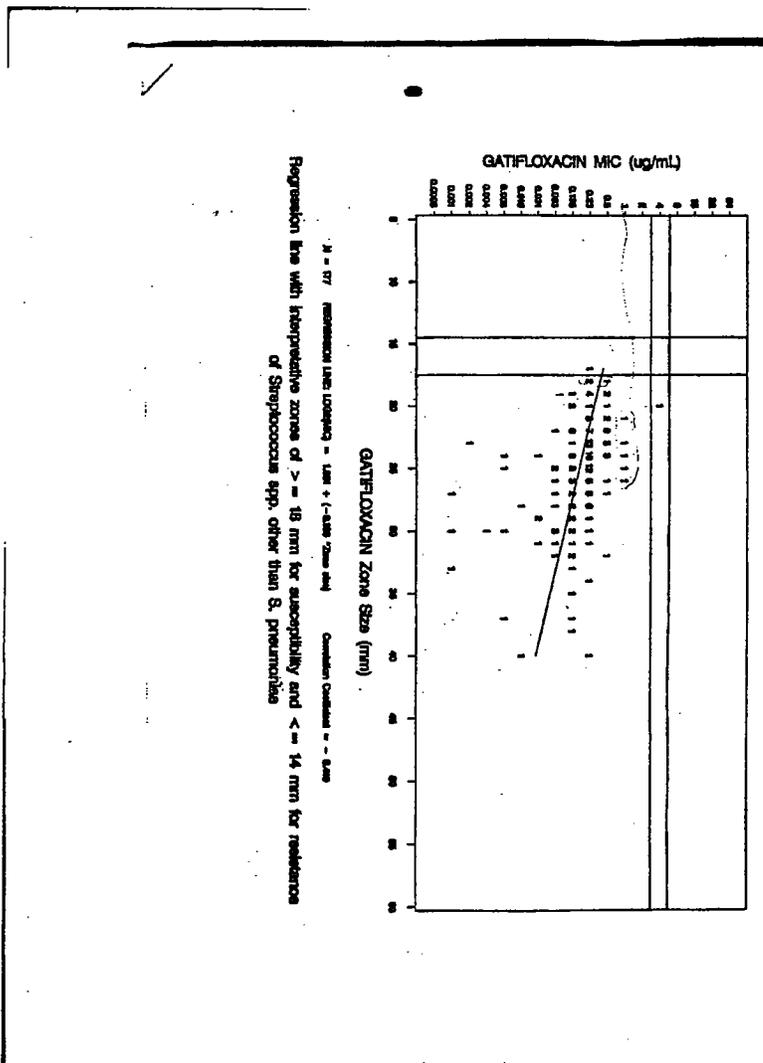


Figure 5  
Scattergram of Gatifloxacin MIC versus Zone Diameter (Clinical Trials)  
Streptococci Other Than *Streptococcus pneumoniae*



**BACTERIOLOGICAL EFFICACY**

**CORRELATION OF TEST RESULTS WITH OUTCOME STATISTICS**

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

Clinical isolates were identified to the species level and susceptibility testing by both the disk diffusion test and the broth microdilution test was performed. Quality control strains were included in each day's testing. NCCLS methods were used for all testing.

There were a total of 2113 strains isolated from 1817 microbiologically evaluable patients that were treated with gatifloxacin (Table 7). Most infections involved only one pathogen.

In uncomplicated skin and skin structure infections there were 120 pathogens which were obtained from 95 evaluable patients who were treated with gatifloxacin. Most infections were caused by *Staphylococcus aureus* and  $\beta$ -hemolytic streptococci.

**TABLE 7**  
 Number of Microbiologically Evaluable Subjects and Pathogens by Infection Type

Infection Type	Single Pathogens		Multiple Pathogens		Total	
	# of Micro Eval Patients	# of Pathogens	No. of Micro Eval Patients	# of Pathogens	No. of Micro Eval Patients	# of Pathogens
ABECB	198	198	80	175	278	373
CAP	223	223	85	197	308	420
Complicated UTI	163	163	14	32	177	195
Uncomplicated UTI	379	379	24	49	403	428
Sinusitis	92	92	20	41	112	133
<b>Uncomplicated SSSI</b>	<b>72</b>	<b>72</b>	<b>23</b>	<b>48</b>	<b>95</b>	<b>120</b>
Uncomplicated Gonorrhea	444	444	0	0	444	444
<b>Total</b>	<b>1571</b>	<b>1571</b>	<b>246</b>	<b>542</b>	<b>1817</b>	<b>2113</b>

Eval = Evaluable; Micro = Microbiologically; ABECB = Acute bacterial exacerbations of chronic bronchitis;  
 CAP = Community acquired pneumonia; UTI = Urinary tract infections;  
 SSSI = Skin and skin structure infections.

TABLE 8 shows the main pathogens in the skin infection study.

TABLE 8  
 Main pathogens in Skin Study

Organism	Main pathogens in Skin Study	
	Single Pathogen	Multiple Pathogen
<i>Staphylococcus aureus</i>	53	16
<i>Streptococcus pyogenes</i>	1	5
<i>Streptococcus agalactiae</i>	0	2
<i>Acinetobacter lwoffii</i>	3	3
<i>Acinetobacter baumannii</i>	2	1

### MIC BREAKPOINTS

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

#### STREPTOCOCCUS PNEUMONIAE

Data from Bonner's pre-clinical study (16) showed that there were two distinct populations of *Streptococcus pneumoniae* isolates (see Figure 1). One population had gatifloxacin MIC values of  $\leq 1.0$   $\mu\text{g/mL}$  and the other population had gatifloxacin MICs of  $\geq 4.0$   $\mu\text{g/mL}$ . The approved label for gatifloxacin has MIC criteria for *S. pneumoniae* as follow:

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 1.0$	(S) Susceptible
2.0	(I) Intermediate
$\geq 4.0$	(R) Resistant

Figure 2 shows the scattergram of *Streptococcus pneumoniae* from the clinical trials submitted in the original NDAs. In these trials there appears to be only one population of isolates and all of them have MICs  $\leq 0.5$   $\mu\text{g/mL}$ . From the data in this scattergram breakpoints for *S. pneumoniae* were originally set at  $\leq 1.0$   $\mu\text{g/mL}$  (susceptible), 2.0  $\mu\text{g/mL}$  (intermediate), and  $\geq 4.0$   $\mu\text{g/mL}$  (resistant). These breakpoints are in the approved label and have also been approved by NCCLS. Setting the susceptible breakpoint at  $\leq 1.0$   $\mu\text{g/mL}$  allows for a one dilution error rate in the assay and prevents isolates at 1.0  $\mu\text{g/mL}$  (which because of the assay error might really be 0.5  $\mu\text{g/mL}$ ) from being classified as "non-susceptible".

STREPTOCOCCUS SPECIES OTHER THAN STREPTOCOCCUS PNEUMONIAE

Figure 5 shows the scattergram of the clinical trial isolates of streptococci other than *S. pneumoniae*. There were several isolates with gatifloxacin MICs of 1.0 µg/mL. Setting the susceptible breakpoint at 2.0 µg/mL will allow for a one dilution assay error. The MIC criteria for streptococci other than *Streptococcus pneumoniae* should be as follow:

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

**ZONE DIAMETER BREAKPOINTS**

No new information has been provided. Since *Streptococcus* species beside *Streptococcus pneumoniae* have now been included in the clinical efficacy section of the label, breakpoints must be established for them.

STREPTOCOCCUS PNEUMONIAE

Figure 2 shows the scattergram of *Streptococcus pneumoniae* from the clinical trials submitted in the original NDAs. In these trials there appears to be only one population of isolates and all of them have zone diameters ≥19 mm. At the time of the original NDA approval zone diameter breakpoints were set at ≥18 mm (susceptible), 15-17 mm (intermediate), and ≤14 mm (resistant). A reevaluation of the data by this reviewer indicates that more appropriate zone diameter breakpoints would be those chosen by NCCLS; ≥21 mm (susceptible), 18-20 mm (intermediate), and ≤17 mm (resistant). These new zone diameter breakpoints would still lead to no very major or major errors but would increase minor errors to 3 (1.1%). The following zone diameter criteria should be used for *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥21	(S) Susceptible
18-20	(I) Intermediate
≤17	(R) Resistant

STREPTOCOCCUS SPECIES OTHER THAN STREPTOCOCCUS PNEUMONIAE

Figure 5 shows the scattergram of the clinical trial isolates of streptococci other than *S. pneumoniae*. From the scattergram it appears that a susceptible breakpoint of  $\geq 18$  mm is needed so that the vast majority of isolates will be classified as susceptible.

If *Streptococcus pneumoniae* criteria are set as follow:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\geq 21$	(S) Susceptible
18-20	(I) Intermediate
$\leq 17$	(R) Resistant

and the criteria for streptococci other than *Streptococcus pneumoniae* are set as follow:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\geq 18$	(S) Susceptible
15-17	(I) Intermediate
$\leq 14$	(R) Resistant

then the criteria for streptococci other than *S. pneumoniae* will be the same as that for staphylococci and Enterobacteriaceae. The zone diameter criteria for *S. pneumoniae* will be 3 mm larger than those for other streptococci which will correspond to a one dilution difference in MIC criteria.

**Appears This Way  
On Original**



4 Page(s) Withheld

           § 552(b)(4) Trade Secret / Confidential

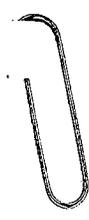
           § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

## NDA REFERENCES

1. Hosaka, M, Kinoshita A, Toyama, M, Otsuki M, and Nishino T. (1995). Antibacterial properties of AM-1155, a new 8-methoxy quinolone. *Journal of Antimicrobial Chemotherapy*. **36**:293-301.
2. DenBleyker K, Minassian B, and Fung-Tomc J. (May, 1998). Test factor effects on gatifloxacin antibacterial inhibitory (MIC) and bactericidal (MBC) activities. BMS Report No. 910068725.
3. Kessler RE, Tomizawa H, Hosaka M, and Hirai, K. (August, 1996) Influences of various factors on *in vitro* antibacterial activity of AM-1155. BMS Report No. 910058252.
4. Wise R, Brenwald NP, Andrews JM, and Boswell F. (1997). The activity of the methylpiperazinyl fluoroquinolone CG 5501: a comparison with other fluoroquinolones. *Journal of Antimicrobial Chemotherapy*. **39**:447-452.
5. Wakabayashi E and Mitshuhashi S. (1994). *In vitro* antibacterial activity of AM-1155, a novel 6-fluoro-8-methoxy quinolone. *Antimicrobial Agents and Chemotherapy*. **38**:594-601.
6. Hosaka M, Yasue T, Fukuda H, Tomizawa H, Aoyama H, and Hirai K. (1992). *In vitro* and *in vivo* antibacterial activities of AM-1155, a new 6-fluoro-8-methoxy quinolone. *Antimicrobial Agents and Chemotherapy*. **36**:2180-2117.
7. Bonner DP and Hooper DC. (August, 1998). Studies on the mechanism of action and resistance to gatifloxacin in *Staphylococcus aureus*. BMS Report No. 910068993.
8. Gradelski E, Kolek B, Bonner D, and Fung-Tomc J. (August, 1998). The mechanisms of antibacterial killing with gatifloxacin (GAT), trovafloxacin (TRO), ciprofloxacin (CIP), and norfloxacin (NOR). BMS Report No. 910069119.
9. Bonner DP, Torres-Viera C, Wennersten B, Moellering Jr. RC, and Eliopoulos GM. (October, 1998). Comparative *in vitro* activity of gatifloxacin, a new fluoroquinolone antimicrobial, against Gram-positive bacteria. BMS Report No. 910070819.
10. Kolek B, Gradelski E, Minassian B, Fung-Tomc J, and Bonner D. (November, 1998). Synergy/antagonism determination of gatifloxacin and other antimicrobial agents. BMS Report No. 910070953.
11. Warr, G. and Ryan B. (August 1998). Gatifloxacin intracellular penetration into leukocytes. BMS Report No. 910069167.

12. Yamamoto T, Kusajima H, Hosaka M, Fukuda H, Oomori Y, and Shinoda H. (1996). Uptake and intracellular activity of AM-1155 in phagocytic cells. *Antimicrobial Agents and Chemotherapy*. **40:2756-2759**.
13. Bonner DP, Fukuda H, and Hiramatsu K. (October, 1998). Antibacterial activity of gatifloxacin, an 8-methoxy fluoroquinolone, against target-altered *Streptococcus pneumoniae*. BMS Report No. 910070909.
14. Fukuda H, Hori S, and Hiramatsu K. (1998). Antibacterial activity of gatifloxacin (AM-1155, CG 5501, BMS-206584), a newly developed fluoroquinolone, against sequentially acquired quinolone-resistant mutants and the *norA* transformant of *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*. **42:1917-1922**.
15. Gradelski E, Bonner D, and Fung-Tomc J. (August, 1998). Differential selection for variants with decreased susceptibility to gatifloxacin (GAT), ciprofloxacin (CIP), and ofloxacin (OFL). BMS Report No. 910068994.
16. Bonner DP, Jones RN, Johnson M, Erwin E, Beach ML, Biedenbach DJ, Pfaller MA, and the Quality Control Study Group. (August, 1998). Comparative antimicrobial activity of gatifloxacin tested against *Streptococcus* species including quality control guidelines and E-test method variation. BMS Report No. 910070980.



  9   Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

  ✓   § 552(b)(5) Draft Labeling

**NDAs # 21-404; # 21-405  
Gatifloxacin (skin infections)  
Bristol-Myers Squibb Company**

**Page 44 of 44**

---

Peter A. Dionne  
Microbiologist HFD-590

**CONCURRENCES:**

HFD-590/Div Dir \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_  
HFD-590/TLMicro \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

**CC:**

HFD-590/Original NDAs #21-404 and #21-405  
HFD-590/Division File  
HFD-590/Micro/PDionne  
HFD-590/MO/EIbia  
HFD-520/Pharm/SHundley  
HFD-590/Chem/NSchmuff  
HFD-590/CSO/DWillard

---

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

---

/s/

-----  
Peter Dionne  
10/17/01 03:17:14 PM  
MICROBIOLOGIST

Shukal signed on ?--Ken signed on 10/12/01

Shukal Bala  
10/17/01 03:31:08 PM  
MICROBIOLOGIST

Kenneth Hastings  
10/22/01 11:10:46 AM  
PHARMACOLOGIST