

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**21-061 and 21-062**

**MICROBIOLOGY REVIEW**

REVIEW FOR HFD-590  
OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF  
MICROBIOLOGIST'S REVIEW #2 OF NDA 21-062  
11 August 1999

AUG 27 1999

- A. 1. NDA 21-062 BI  
APPLICANT: Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, CT 06492
2. PRODUCT NAMES: Tequin™ (gatifloxacin) I.V.
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
The product is provided in single-use vials for intravenous administration as a sterile preservative-free solution in 5% dextrose. It is supplied in two fill volumes (20 and 40 mL) both containing 10 mg/mL of the active drug. It is also manufactured in 100 mL (200 mg active) and 200 mL (400 mg active) flexible infusion bags in 5% dextrose.
4. METHODS OF STERILIZATION:  
The products are terminally sterilized.
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:  
The product is indicated for the treatment of bacterial infections.
- B. 1. DATE OF INITIAL SUBMISSION: 28 December 1998
2. DATE OF AMENDMENT: 16 June 1999 (Subject of this review)
3. RELATED DOCUMENTS:  
NDA 21-061, [REDACTED]
4. ASSIGNED FOR REVIEW: 5 April 1999
- C. REMARKS:  
The vial products will be manufactured by:  
Bristol Laboratories Corporation

State Road PR#114, km 3.2  
Foreign Trade Zone #7  
Mayaguez, Puerto Rico 00680

The product formulation packaged in flexible bags will be manufactured by:

: Abbott Laboratories, Inc.  
100 Abbott Park Road  
Abbott Park, IL 60064-3500

The application seeks parametric release of the terminally sterilized flexible containers.

- D. CONCLUSIONS: The application is recommended of approval on the basis of sterility assurance.

/S/

11 August 1999

Paul Stinavage, Ph.D.

cc: Original NDA 21-062 and NDA 21-061  
HFD-590/Div. Files/J. Smith/B. Atkins  
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 11 August 1999  
R/D initialed by P. Cooney

/S/

8-27-99

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

Comments on Microbiology Label Dated 12/03/99

**NDA#:** 21-061, 21-062

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 03-DEC-99  
**CDER DATE:** 03-DEC-99  
**REVIEW ASSIGN DATE:** 03-DEC-99  
**REVIEW COMPLETE DATE:** 09-DEC-99

**SPONSOR:** Bristol-Myers Squibb Company  
Five Research Parkway  
Wallingford, CT 06492

**CONTACT PERSON:** Douglas C. Kriesel, Ph. D.  
Director Worldwide Regulatory Affairs  
Phone Number: (203) 677-6883

**SUBMISSION REVIEWED:** Microbiology Labeling

**DRUG CATEGORY:** Antimicrobial: Fluoroquinolone

**INDICATIONS:** Acute Exacerbation of Chronic Bronchitis, Acute Sinusitis,  
Community Acquired Pneumonia, Urinary Tract Infections and  
Gonorrhea.

**DOSAGE FORM:** 200 and 400 mg Tablet; 2 and 10 mg/mL solution

**DRUG PRODUCT NAME**

**PROPRIETARY:**

TEQUIN™

**NONPROPRIETARY/USAN:**

Gatifloxacin

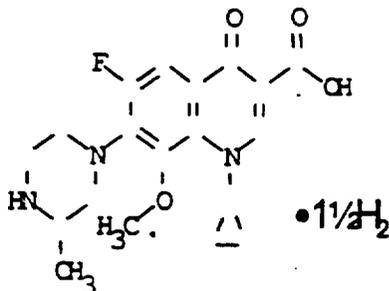
**CODE:**

BMS-206584; AM-1155, CG 5501

**CHEMICAL NAME:**

(±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperaziny)-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

SUPPORTING DOCUMENTS:



BACKGROUND:

Since the indication of Skin and Skin Structure infections will not be approved at this time the following revisions must be made to the Microbiology subsection of the label submitted December 3, 1999:

1. Page 8—*Streptococcus pyogenes* must be deleted from list #1 since it is no longer included in an approved indication. It may be moved to list #2 since gatifloxacin MIC values for this organism are  $\leq 2 \mu\text{g/mL}$ , a large amount of *in vitro* data are available, and it is associated with acute sinusitis.
2. Page 8—*Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Streptococcus* (Group C/G/F), and Viridans group streptococci must be deleted from list #2 since these organisms are associated with skin and skin structure infections and are not associated with any of the indications that will be approved.
3. Page 9 and Page 11—Since the only streptococci species now indicated is *Streptococcus pneumoniae*, the testing criteria for other *Streptococcus* species must be deleted under dilution techniques (page 9) and diffusion techniques (page 11)

The microbiology subsection of the label should read as follows:

Gatifloxacin is an 8-methoxyfluoroquinolone with *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the non-methoxy C-8 moiety.

The mechanism of action of fluoroquinolones including gatifloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between gatifloxacin and the mentioned classes of antibiotics.

From *in vitro* synergy tests, gatifloxacin, as with other fluoroquinolones is antagonistic with rifampin against enterococci.

Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutation. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between  $1 \times 10^{-7}$  to  $10^{-10}$ . Although cross-resistance has been observed between gatifloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gatifloxacin.

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

**Aerobic gram-positive microorganisms**

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

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

Gatifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of  $\leq 2 \mu\text{g/mL}$  ( $\leq 1 \mu\text{g/mL}$  for *Streptococcus pneumoniae*) against most (90%) strains of the following microorganisms; however, the safety and effectiveness of gatifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between gatifloxacin and the mentioned classes of antibiotics.

From *in vitro* synergy tests, gatifloxacin, as with other fluoroquinolones, is antagonistic with rifampin against enterococci.

Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutations. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between  $1 \times 10^{-7}$  to  $10^{-10}$ . Although cross-resistance has been observed between gatifloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gatifloxacin.

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

*Aerobic gram-positive microorganisms*

*Staphylococcus aureus* (methicillin-susceptible strains only)

*Streptococcus pneumoniae* (penicillin-susceptible strains)

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

Gatifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of  $\leq 2 \mu\text{g/mL}$  ( $\leq 1 \mu\text{g/mL}$  for *Streptococcus pneumoniae*) against most (90%) strains of the following microorganisms; however, the safety and effectiveness of gatifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

*Aerobic gram-positive microorganisms*

*Staphylococcus saprophyticus*

*Streptococcus pneumoniae* (penicillin-resistant strains)

*Streptococcus pyogenes*

*Aerobic gram-negative microorganisms*

*Acinetobacter lwoffii*

*Citrobacter koseri*

*Citrobacter freundii*

*Enterobacter aerogenes*

*Enterobacter cloacae*

*Klebsiella oxytoca*

*Morganella morganii*

*Proteus vulgaris*

*Anaerobic microorganisms*

*Peptostreptococcus* species

NOTE: The activity of gatifloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum* (see **WARNINGS**).

**Aerobic gram-positive microorganisms**

*Staphylococcus saprophyticus*  
*Streptococcus pneumoniae* (penicillin-resistant strains)

**Aerobic gram-negative microorganisms**

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

**Anaerobic microorganisms**

*Peptostreptococcus* species

NOTE: The activity of gatifloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum* (see **WARNINGS**).

NOTE: Extended-spectrum  $\beta$ -lactamase producing gram-negative microorganisms may have reduced susceptibility to quinolones.

**Susceptibility Tests**

**Dilution techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gatifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* species:

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 2.0$	Susceptible (S)
4.0	Intermediate (I)
$\geq 8.0$	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* <sup>a</sup>:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.5	Susceptible (S)

<sup>a</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM) <sup>1</sup>.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae* <sup>b</sup>:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

<sup>b</sup> These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Neisseria gonorrhoeae* <sup>c</sup>:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

<sup>c</sup> These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement.

NOTE: Extended-spectrum  $\beta$ -lactamase producing gram-negative microorganisms may have reduced susceptibility to quinolones.

#### *Susceptibility Tests*

*Dilution techniques:* Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gatifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* species:

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 2.0$	Susceptible (S)
4.0	Intermediate (I)
$\geq 8.0$	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>a</sup>

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 0.5$	Susceptible (S)

<sup>a</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)<sup>1</sup>.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*<sup>b</sup>:

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

<sup>b</sup> These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Neisseria gonorrhoeae*<sup>c</sup>:

<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Interpretation</u>
$\leq 0.125$	Susceptible (S)
0.25	Intermediate (I)
$\geq 0.5$	Resistant (R)

<sup>c</sup> These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement.

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 gatifloxacin powder should provide the following MIC values:

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 gatifloxacin powder should provide the following MIC values:

<u>Microorganism</u>		<u>MIC Range (µg/mL)</u>
<i>Enterococcus faecalis</i>	ATCC 29212	0.12-1.0
<i>Escherichia coli</i>	ATCC 25922	0.008-0.03
<i>Haemophilus influenzae</i>	ATCC 49247 <sup>d</sup>	0.004-0.03
<i>Neisseria gonorrhoeae</i>	ATCC 49226 <sup>e</sup>	0.002-0.016
<i>Pseudomonas aeruginosa</i>	ATCC 27853	0.5-2.0
<i>Staphylococcus aureus</i>	ATCC 29213	0.03-0.12
<i>Streptococcus pneumoniae</i>	ATCC 49619 <sup>f</sup>	0.12-0.5

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

<sup>e</sup> This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement<sup>1</sup>.

<sup>f</sup> This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood<sup>1</sup>.

**Diffusion Techniques:** Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg gatifloxacin to test the susceptibility of microorganisms to gatifloxacin.

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

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

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

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* <sup>g</sup>:

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

<sup>g</sup> This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).<sup>2</sup>

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding [redacted] results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae* <sup>h</sup>:

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

<sup>h</sup> These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% [redacted] sheep blood incubated in 5% CO<sub>2</sub>.<sup>2</sup>

For testing *Neisseria gonorrhoeae* <sup>i</sup>:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 38	Susceptible (S)
34-37	Intermediate (I)
≤ 33	Resistant (R)

<sup>i</sup> These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO<sub>2</sub>.<sup>2</sup>

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 gatifloxacin.

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- $\mu$ g gatifloxacin 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	30-37
<i>Haemophilus influenzae</i>	ATCC 49247 <sup>j</sup>	33-41
<i>Neisseria gonorrhoeae</i>	ATCC 49226 <sup>k</sup>	45-56
<i>Pseudomonas aeruginosa</i>	ATCC 27853	20-28
<i>Staphylococcus aureus</i>	ATCC 25923	27-33
<i>Streptococcus pneumoniae</i>	ATCC 49619 <sup>l</sup>	24-31

<sup>j</sup> This quality control range applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

<sup>k</sup> This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 performed by a disk diffusion using GC agar base with 1% defined growth supplement<sup>2</sup>.

<sup>l</sup> This quality control range is only applicable to tests conducted with *S. pneumoniae* ATCC 49619 performed by a disk diffusion Mueller-Hinton agar supplemented with 5% defibrinated sheep blood<sup>2</sup>.

#### References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.

APPEARS THIS WAY  
ON ORIGINAL

/S/

Peter A. Dionne  
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir \_\_\_\_\_ /S/ \_\_\_\_\_ Signature 12/15/99 Date  
HFD-590/TLMicro \_\_\_\_\_ Signature 12/13/99 Date

CC:

HFD-590/Original NDA # 21-061, #21-062  
HFD-590/Division File  
HFD-590/Micro/PDionne  
HFD-590/MO/JKorvick  
HFD-520/Pharm/AEllis  
HFD-590/Chem/JSmith  
HFD-590/CSO/DBernato

Division of Anti-Infective Drug Products  
Clinical Microbiological Review

NDA NUMBER:

21061

21062

REVIEW DATE:

10-31-99

SUBMISSION/TYPE:

Original NDA

DOCUMENT DATE

12-28-98

CDER DATE

12-29-98

ASSIGNED DATE

3-2-99

NAME & ADDRESS OF APPLICANT:

Bristol-Myers Squibb Company  
5 Research Parkway  
Willingford, CT 06492

CONTACT PERSON:

Douglas C. Kriesel, Ph.D., Director  
Worldwide Regulatory Affairs  
Bristol-Myers Squibb Company  
5 Research Parkway  
Willingford, CT 06492  
Phone: (203) 677-6883

DRUG PRODUCT NAME

Proprietary:

TEQUIN™ Tablets

Nonproprietary/USAN:

TEQUIN™ I.V.

Code Names/#'s:

Gatifloxacin

Therapeutic Class:

BMS-206584, AM-1155, and CG-5501  
1 S

PHARMACOLOGICAL CATEGORY:

Fluoroquinolone

DOSAGE FORM:

Tablets

STRENGTHS:

Aqueous solution injection

200 and 400 mg tablet

2 and 10 mg/mL, solution

ROUTE OF ADMINISTRATION:

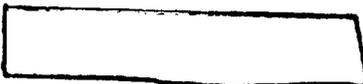
Oral

DISPENSED:

Intravenous infusion

Rx  OTC

RELATED DOCUMENTS (if applicable):



REMARKS/COMMENTS:

This application is for a fluoroquinolone, Gatifloxacin. The application is for the treatment of patients with community acquired pneumonia; acute bacterial exacerbation of chronic bronchitis;

acute sinusitis; uncomplicated skin and skin structure infections; uncomplicated urinary tract infections; complicated urinary tract infections and pyelonephritis, uncomplicated urethral, pharyngeal and rectal gonorrhea in males and endocervical, pharyngeal, and rectal gonorrhea in females.

**CONCLUSIONS & RECOMMENDATIONS:**

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY section 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 150-160. The recommended revisions are the opinion of this consultant. Mr. Peter Dionne, the microbiologist in the Division of Special Pathogens and Immunological Drug Products, will make the final recommendations.

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ON ORIGINAL**

**APPEARS THIS WAY  
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**MICROBIOLOGY REVIEW**  
**DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS**  
**(HFD-590)**

Comments on Microbiology Label Submitted 11/22/99

**NDA#:** 21-061, 21-062

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 22-NOV-99  
**CDER DATE:** 23-NOV-99  
**REVIEW ASSIGN DATE:** 23-NOV-99  
**REVIEW COMPLETE DATE:** 01-DEC-99

**SPONSOR:** Bristol-Myers Squibb Company  
Five Research Parkway  
Wallingford, CT 06492

**CONTACT PERSON:** Douglas C. Kriesel, Ph. D.  
Director Worldwide Regulatory Affairs  
Phone Number: (203) 677-6883

**SUBMISSION REVIEWED:** Microbiology Labeling

**DRUG CATEGORY:** Antimicrobial: Fluoroquinolone

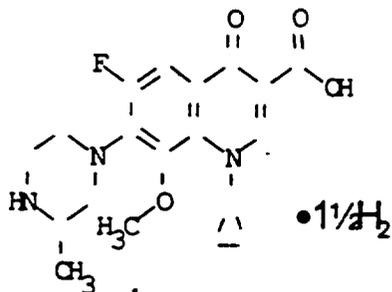
**INDICATIONS:** Acute Exacerbation of Chronic Bronchitis, Acute Sinusitis,  
Community Acquired Pneumonia, Skin and Skin Structure  
Infections, Urinary Tract Infections and Gonorrhea.

**DOSAGE FORM:** 200 and 400 mg Tablet; 2 and 10 mg/mL 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:**

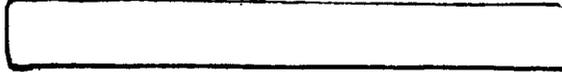


**Molecular Formula:** C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub>•1½ H<sub>2</sub>O  
**Molecular Weight:** 402.42

**NDA # 21-061; #21-062  
Bristol-Myers Squibb  
Gatifloxacin Tablets and IV**

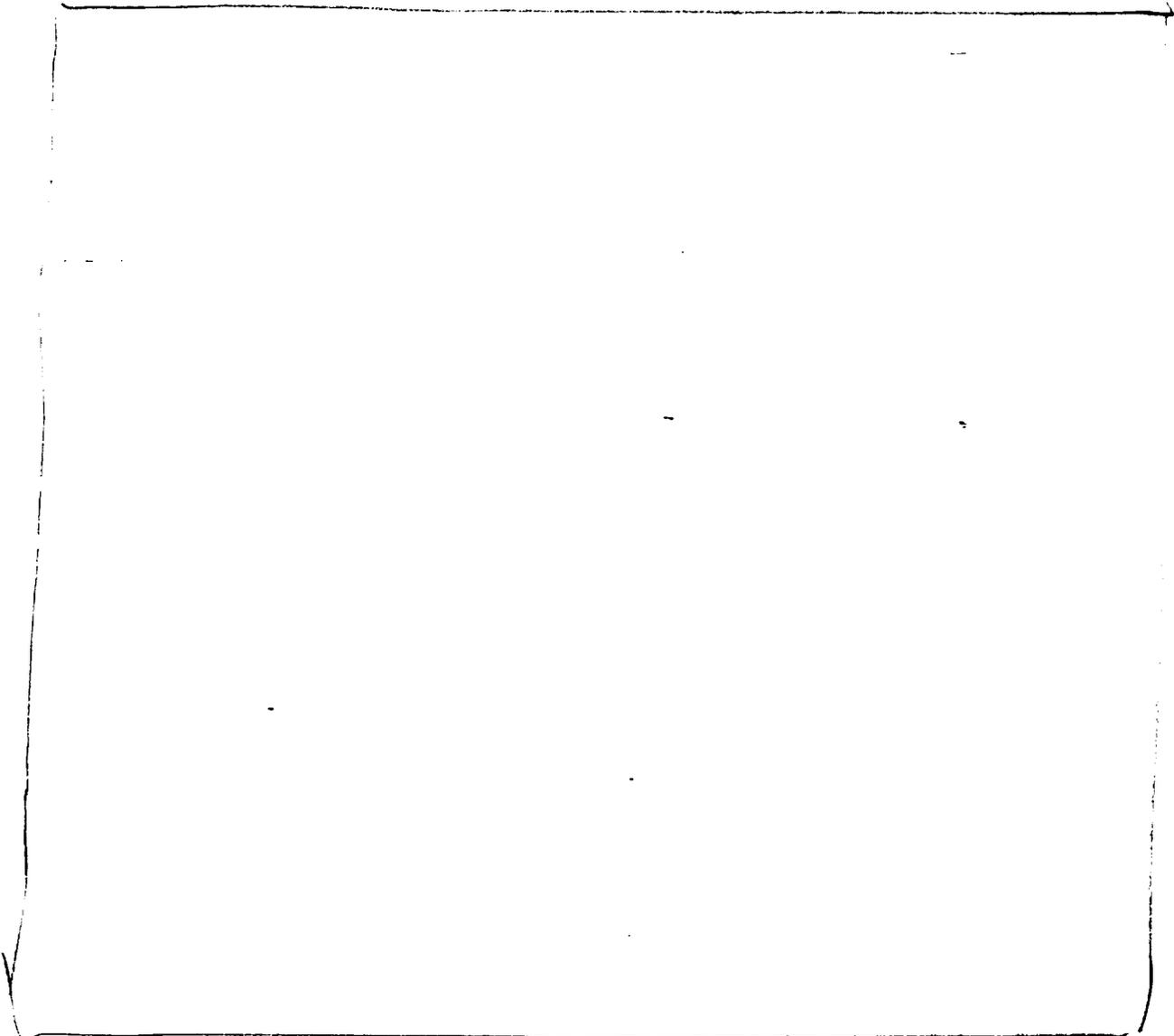
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**SUPPORTING DOCUMENTS:**

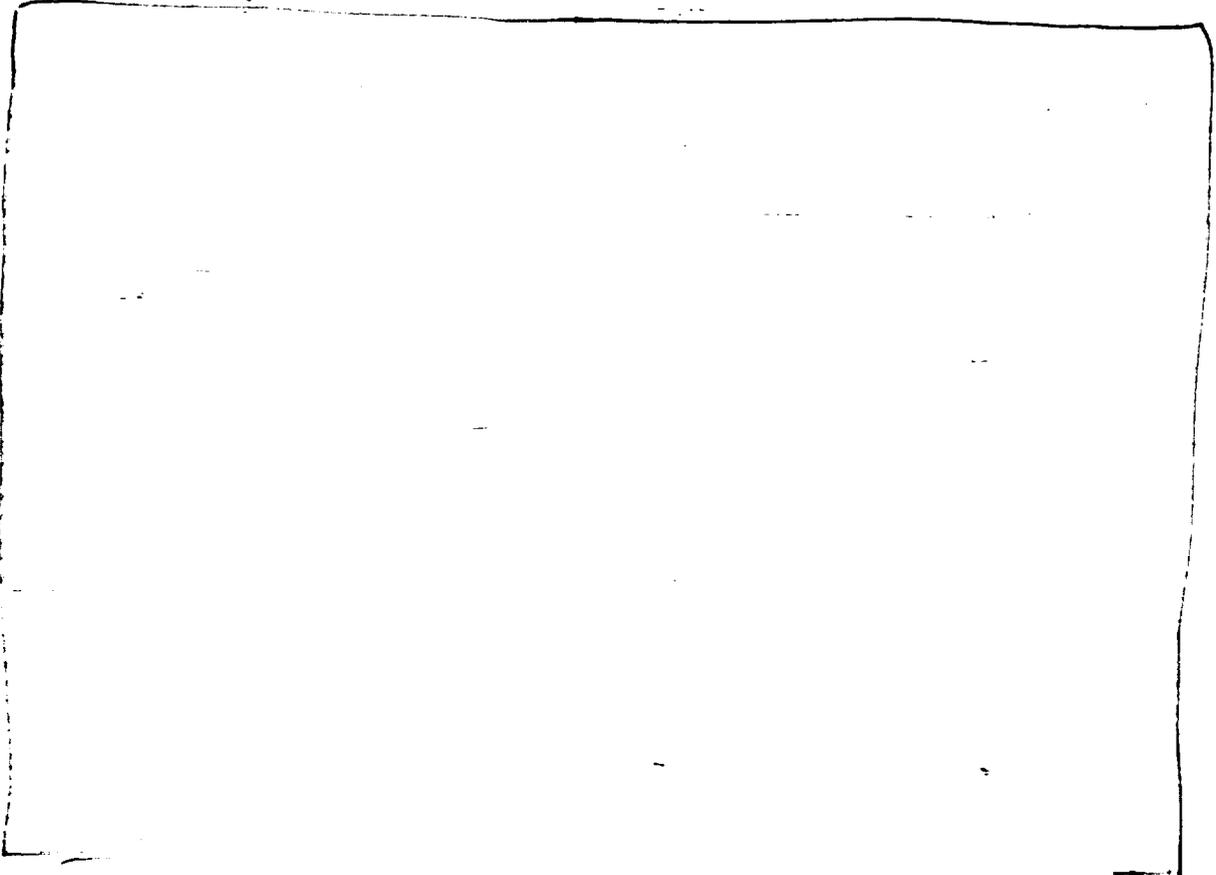


**BACKGROUND:**

The sponsor has reviewed the microbiology subsection of the label provided by FDA as a facsimile on October 29, 1999. The label faxed to them was identical to that in the Microbiology review dated 17-NOV-99. The sponsor has made several revisions to the faxed label. Each revision will be discussed below.



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



The microbiology subsection of the label should read as follows:

Gatifloxacin is an 8-methoxyfluoroquinolone with *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the non-methoxy C-8 moiety.

The mechanism of action of fluoroquinolones including gatifloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between gatifloxacin and the mentioned classes of antibiotics.

From *in vitro* synergy tests, gatifloxacin, as with other fluoroquinolones is antagonistic with rifampin against enterococci.

Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutation. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between  $1 \times 10^{-7}$  to  $10^{-10}$ . Although cross-resistance has been observed between gatifloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gatifloxacin.

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

**Aerobic gram-positive microorganisms**

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

**Aerobic gram-negative microorganisms**

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

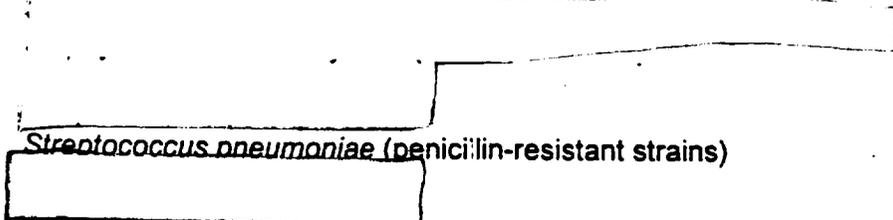
**Other microorganisms**

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

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

Gatifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of  $\leq 2 \mu\text{g/mL}$  against most (90%) strains of the following microorganisms; however, the safety and effectiveness of gatifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Aerobic gram-positive microorganisms**



**Aerobic gram-negative microorganisms**

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

**Anaerobic microorganisms**

- Peptostreptococcus* species

NOTE: The activity of gatifloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum* (see **WARNINGS**).

NOTE: Extended-spectrum  $\beta$ -lactamase producing gram-negative microorganisms may have reduced susceptibility to quinolones.

**Susceptibility Tests**

**Dilution techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gatifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* species:

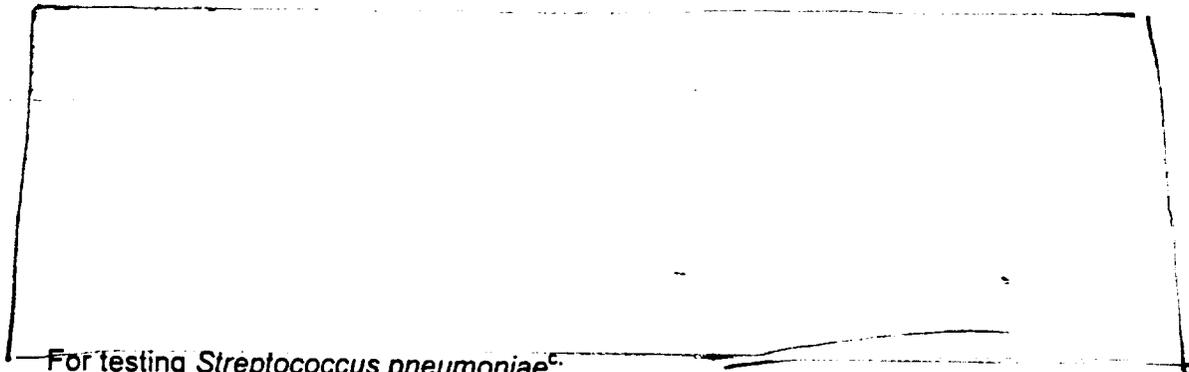
<u>MIC (<math>\mu</math>g/mL)</u>	<u>Interpretation</u>
$\leq 2.0$	Susceptible (S)
4.0	Intermediate (I)
$\geq 8.0$	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* <sup>a</sup>:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.5	Susceptible (S)

<sup>a</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium<sup>1</sup>.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.



For testing *Streptococcus pneumoniae* <sup>c</sup>:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

<sup>c</sup> These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

For testing *Neisseria gonorrhoeae* <sup>d</sup>:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

<sup>d</sup> These interpretive standards are applicable only to agar dilution tests with GC agar base and 1% defined growth supplement<sup>1</sup>.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations 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 gatifloxacin powder should provide the following MIC values:

<u>Microorganism</u>		<u>MIC (<math>\mu\text{g/mL}</math>)</u>
<i>Enterococcus faecalis</i>	ATCC 29212	0.12-1.0
<i>Escherichia coli</i>	ATCC 25922	0.008-0.03
<i>Haemophilus influenzae</i>	ATCC 49247 <sup>e</sup>	0.004-0.03
<i>Neisseria gonorrhoeae</i>	ATCC 49226 <sup>f</sup>	0.002-0.016
<i>Pseudomonas aeruginosa</i>	ATCC 27853	0.5-2.0
<i>Staphylococcus aureus</i>	ATCC 29213	0.03-0.12
<i>Streptococcus pneumoniae</i>	ATCC 49619 <sup>g</sup>	0.12-0.5

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

<sup>f</sup> This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement<sup>1</sup>.

<sup>g</sup> This quality control range is applicable to only *S. pneumoniae* ATCC 49616 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

**Diffusion Techniques:** Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5- $\mu\text{g}$  gatifloxacin to test the susceptibility of microorganisms to gatifloxacin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5- $\mu\text{g}$  gatifloxacin disk should be interpreted according to the following criteria:

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

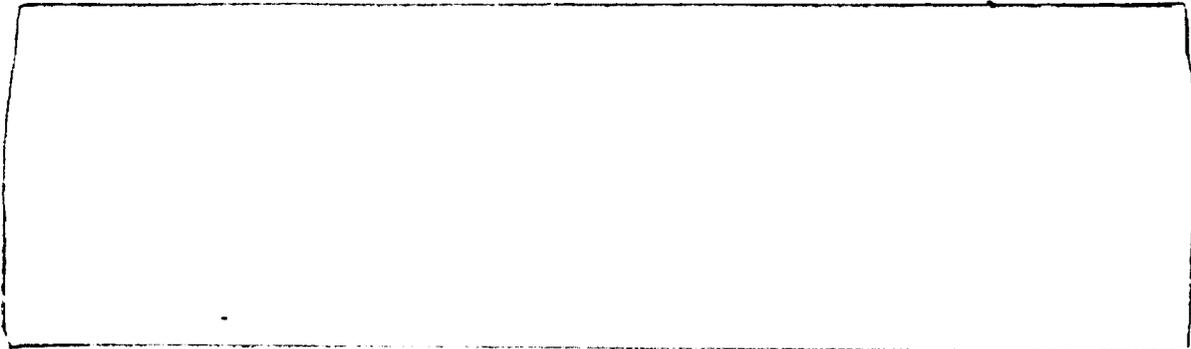
<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 18	Susceptible (S)
15 - 17	Intermediate (I)
≤ 14	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>h</sup> :

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

<sup>h</sup> This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.



For testing *Streptococcus pneumoniae*<sup>i</sup>:

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

<sup>i</sup> These  using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.

For testing *Neisseria gonorrhoeae*<sup>k</sup>:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 38	Susceptible (S)
34-37	Intermediate (I)
≤ 33	Resistant (R)

<sup>k</sup> These interpretive standards are applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement<sup>2</sup> incubated in 5% CO<sub>2</sub>.

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 gatifloxacin.

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 gatifloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	30-37
<i>Haemophilus influenzae</i>	ATCC 49274 <sup>l</sup>	33-41
<i>Neisseria gonorrhoeae</i>	ATCC 49226 <sup>m</sup>	45-56
<i>Pseudomonas aeruginosa</i>	ATCC 27853	20-28
<i>Staphylococcus aureus</i>	ATCC 25923	27-33
<i>Streptococcus pneumoniae</i>	ATCC 49619 <sup>n</sup>	24-31

<sup>l</sup> This quality control range is applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

<sup>m</sup> This quality control range is applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement<sup>2</sup>.

<sup>n</sup> This quality control range is applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

NDA # 21-061; #21-062  
Bristol-Myers Squibb  
Gatifloxacin Tablets and IV

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References:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997

APPEARS THIS WAY  
ON ORIGINAL

/S/

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\_\_\_\_ Signature 12/15/99 Date  
\_\_\_\_ Signature 12/9/99 Date

CC:

HFD-590/Original NDA #21-061, #21-062  
HFD-590/Division File  
HFD-590/Micro/PDionne  
HFD-520/Micro/ASheldon  
HFD-520/Micro/SAItaie  
HFD-590/MO/JKorvick  
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