



NDA 21-061/SLR-026
NDA 21-062/SLR-030
NDA 21-678/SLR-001

Bristol-Myers Squibb
Attention: Amy Jennings, Ph.D.
Manager, Global Regulatory Sciences
5 Research Parkway, P.O. Box 5100
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your supplemental new drug applications (NDAs) dated June 9, 2005, received June 11, 2005 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

<u>NDA Number</u>	<u>Trade Name</u>	<u>Established Name</u>	<u>Dosage Form/Strengths</u>
21-061	TEQUIN [®]	gatifloxacin	Tablet, 200mg and 400 mg
21-062	TEQUIN [®]	gatifloxacin	IV, 200mg and 400 mg
21-678	TEQUIN [®]	gatifloxacin	Powder for Oral Suspension, 1g/25mL, 2g/50mL, 3g/75mL. 4g/100mL

We acknowledge receipt of your submissions dated October 20, and December 7, 2005.

These supplemental new drug applications provide for the following changes to the **CLINICAL PHARMACOLOGY** section, **Microbiology/Susceptibility Tests** subsection and to the **INDICATIONS AND USAGE** section of the package insert. (Note: additions are double underline and deletions are ~~strikethrough~~).

Microbiology subsection:

~~Aerobic gram-positive microorganisms~~ Aerobic Gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pneumoniae (including multidrug-resistant strains [MDRSP])*

Streptococcus pyogenes

*Multidrug-resistant *Streptococcus pneumoniae* (MDRSP) includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*) and are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 mcg/mL), 2nd generation cephalosporins (eg, cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

~~Aerobic gram-negative microorganisms~~ Aerobic Gram-negative microorganisms

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

Other microorganisms

~~*Chlamydia pneumoniae*~~ *Chlamydophila pneumoniae* (previously known as *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 ≤ 2 mcg/mL against most ($\geq 90\%$) 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-positive microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus (Group C/G/F)
Streptococcus agalactiae
Streptococcus viridans group

~~Aerobic gram-negative microorganisms~~ Aerobic Gram-negative microorganisms

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

~~Anaerobic microorganisms~~ 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 β -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 ¹ (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 methicillin-susceptible *Staphylococcus species aureus*:

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

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

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≤1.0	Susceptible (S)

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

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

For testing *Streptococcus pneumoniae*^b:

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

For testing *Streptococcus* species other than *Streptococcus pneumoniae*^b:

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

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

For testing *Neisseria gonorrhoeae*^c:

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

^c 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:

<u>Microorganism</u>	<u>MIC Range (mcg/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 ^d	0.004 – 0.03
<i>Neisseria gonorrhoeae</i> ATCC 49226 ^e	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 ^f	0.12 – 0.5

^d This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.¹

^e 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.¹

^f 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.¹

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg 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- μ g gatifloxacin disk should be interpreted according to the following criteria:

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

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

For testing *Haemophilus influenzae* and *Hemophilus parainfluenzae*^g:

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

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

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

For testing *Streptococcus pneumoniae*^h:

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

For testing *Streptococcus* species other than *Streptococcus pneumoniae*^h:

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

^h These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.²

For testing *Neisseria gonorrhoeae*ⁱ:

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

ⁱ These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO₂.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gatifloxacin.²

As with standardized dilution techniques, 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-mcg gatifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

<u>Microorganism</u>	<u>Zone Diameter Range (mm)</u>
<i>Escherichia coli</i> ATCC 25922	30-37
<i>Haemophilus influenzae</i> ATCC 49247 ^j	33-41
<i>Neisseria gonorrhoeae</i> ATCC 49226 ^k	45-56
<i>Pseudomonas aeruginosa</i> ATCC 27853	20-28
<i>Staphylococcus aureus</i> ATCC 25923	27-33
<i>Streptococcus pneumoniae</i> ATCC 49619 ^l	24-31

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

^k This quality control range is only applicable to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement².

^l 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.

INDICATIONS AND USAGE

TEQUIN (gatifloxacin) is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below (see **DOSAGE AND ADMINISTRATION**).

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or and methicillin-susceptible *Staphylococcus aureus*.

Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae*.

Community-acquired pneumonia due to *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP])* , *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, methicillin-susceptible *Staphylococcus aureus*, *Mycoplasma pneumoniae*, ~~*Chlamydia*~~ *Chlamydia pneumoniae*, or *Legionella pneumophila*. (See **Clinical Studies**.)

We completed our review of these applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the one submitted on December 7, 2005 (text for the package insert and text for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 21-061/SLR- 026, NDA 21-062/SLR- 030 and NDA 21-678/SLR- 001.**" Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

NDA 21-061/SLR- 026
NDA 21-062/SLR- 030
NDA 21-678/SLR- 001
Page 9

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
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