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APPLICATION NUMBER:

21-061/SE2-007

21-062/SE2-008

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)
Amendment to Original Review

NDA #: 21-061/SE2-007

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 28-MAR-01
CDER DATE: 29-MAR-01
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REVIEW COMPLETE DATE: 03-APR-01

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SUBMISSION REVIEWED: Supplement with information to support an alternative duration of treatment (i.e. 5 days) for patients with acute bacterial exacerbations of chronic bronchitis (ABECB).
Analysis of data excluding sites 23 and 24 in Study AI420-064

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: ABECB, Acute Sinusitis, Community Acquired Pneumonia, Urinary Tract Infections and Gonorrhea.

DOSAGE FORM: 200 mg and 400 mg Tablets

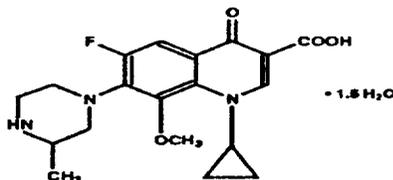
DRUG PRODUCT NAME

PROPRIETARY: TEQUIN®

NONPROPRIETARY/USAN: Gatifloxacin

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: C₁₉H₂₂FN₃O₄ · 1½ H₂O

Molecular Weight: 402.42

SUPPORTING DOCUMENTS: NDA 21-062—Gatifloxacin IV solution

BACKGROUND:

This supplement requests an alternative duration of treatment for acute bacterial exacerbations of chronic bronchitis (ABECB). Gatifloxacin was approved for the treatment of ACECB due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus* on December 17, 1999. The approved treatment was 400 mg once daily for 7-10 days. In this submission the sponsor seeks approval of a 400 mg once daily for 5 days dosage.

Data from two clinical trials are submitted for this new treatment duration. The combined accrual in these two studies was 624 patients. Three hundred and sixty-nine (369) patients received gatifloxacin; two hundred and fifty-six (256) received a 5-day course and 113 received a 7-day course. Two hundred and fifty-five patients received a comparator agent (108 clarithromycin, 147 azithromycin). Study AI420-064 compared the safety and efficacy of gatifloxacin, given orally at a dose of 400 mg once daily, to a standard regimen of clarithromycin, 500 mg BID for 10 days. Gatifloxacin was dosed for 5 or 7 days in this study. Study AI420-065 compared gatifloxacin, given orally at a dose of 400 mg once daily for 5 days to azithromycin, 500 mg on Day 1, followed by 250 mg QD for 4 days.

This review amends the Microbiology Review dated January 31, 2001 by excluding data from two sites (#23 and #24) in Study AI420-064. All patients enrolled by Drs C. Andrew DeAbate (site #23—97 patients) and C. P. Mathew (site #24—100 patients) have been excluded from the tables and the discussion in this amended review.

CONCLUSIONS & RECOMMENDATIONS:

This NDA supplemental application requests approval of an alternative duration of treatment (i.e. 5 days) for acute bacterial exacerbations of chronic bronchitis. Data from two clinical trials were submitted.

Over 60% of patients had a pre-treatment pathogen identified. Of the three key respiratory pathogens *Moraxella catarrhalis* was the most frequently identified pathogen (71 isolates, all but two of which produced β -lactamase). There were 58 isolates of *Haemophilus influenzae* (one-third produced a β -lactamase), 49 *Streptococcus pneumoniae* isolates of which 10 were penicillin-intermediate and only two were penicillin-resistant. There were also 92 *Staphylococcus aureus* isolates and 61 *Haemophilus parainfluenzae* isolates recovered pre-treatment.

Streptococcus pneumoniae had the highest gatifloxacin MIC₉₀ value of the three key respiratory pathogens. Gatifloxacin eradicated 18 of 20 *S. pneumoniae* isolates.

No new microbiological pre-clinical information is provided in the supplement. The supplement may be approved from the microbiological viewpoint. There are no microbiological points to convey to the sponsor. No changes are needed in the Microbiology subsection of the label.

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EXECUTIVE SUMMARY

This supplemental application contains information in support of a request for an alternative duration of treatment (i.e. 5 days) for adult patients with acute bacterial exacerbations of chronic bronchitis (ABECB). No new preclinical microbiological information has been included with this application.

Two randomized, double-blind, multicenter studies were performed to compare the safety and efficacy of gatifloxacin, given orally at a dose of 400 mg once daily, to a standard regimen of either clarithromycin, 500 mg BID for 10 days (Study AI420-064), or azithromycin, 500 mg on Day 1, followed by 250 mg QD for 4 days (AI420-065). Gatifloxacin was dosed for 5 days; study AI420-064 also had a 7-day gatifloxacin arm.

The overall microbiological eradication rates in the pooled arms were comparable (91% gatifloxacin, 88% comparators). For *Streptococcus pneumoniae*, the comparators eradicated 14 of 15 isolates, while gatifloxacin eradicated 18 of 20. Eradication rates for *Haemophilus influenzae* and *Moraxella catarrhalis* were favorable in both treatment groups. Only three organisms (two isolates of methicillin-resistant *S. aureus* and one of *Pseudomonas putida*) were not susceptible to gatifloxacin. Only 61% and 68% of the isolated pathogens were susceptible to clarithromycin and azithromycin, respectively. Eighty-four percent of *S. pneumoniae* isolates were susceptible to the macrolides. Clarithromycin was not as active as the other two drugs against *Haemophilus* isolates.

PRECLINICAL EFFICACY (IN VITRO)

MECHANISM OF ACTION

No new information has been submitted. Like other quinolones, gatifloxacin inhibits the activity of the 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.

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ANTIMICROBIAL SPECTRUM OF ACTIVITY

(FIVE PATHOGENS INVOLVED IN THIS INDICATION)

No new pre-clinical information has been presented. Susceptibility data presented in the original NDA 21-061 are shown in TABLE 1 for the pathogens that are approved for ABECB. The data in TABLE 1 demonstrate that *Streptococcus pneumoniae* will probably be the pathogen that will be the most affected by a shorter duration of treatment. The MIC₉₀ value (0.5 µg/mL) for this pathogen is close to the susceptible breakpoint of 1 µg/mL. The MIC₉₀ values for the other pathogens are well below the susceptible breakpoints. *Staphylococcus aureus* has the second highest MIC₉₀ at 0.1-0.25 µg/mL. Methicillin-resistant *S. aureus* isolates usually have a much higher MIC value and are usually resistant to gatifloxacin.

TABLE 1

Activity of Gatifloxacin Against ABECB Organisms (Summary data from Original NDA)

Organism	No. of Isolates in NDA	Country	Geometric Mean MIC ₉₀ (µg/mL)	
<i>Streptococcus pneumoniae</i>	2039	USA	0.5	
	524	ex-USA	0.7	
	PEN-S	101	USA	0.5
		64	ex-USA	0.7
	PEN-I	91	USA	0.5
		70	ex-USA	0.5
	PEN-R	65	USA	0.5
		33	ex-USA	0.5
<i>Staphylococcus aureus</i>	Meth-S	368	USA	0.11
		1389	ex-USA	0.25
	Meth-R	2744	USA	>4
		1642	ex-USA	6.2
<i>Haemophilus influenzae</i>	1422	USA	≤0.03	
	410	ex-USA	0.01	
<i>H. parainfluenzae</i>	54	USA	0.09	
<i>Moraxella catarrhalis</i>	679	USA	<0.03	
	245	ex-USA	0.06	

Susceptibility data generated for pre-treatment isolates in the two clinical studies submitted with this supplement are presented in TABLE 2.

TABLE 2
 Susceptibility Results for Causative Pathogens (excluding 7-day Gatifloxacin Treated)

Pathogen	Total Isolated	Gatifloxacin			Azithromycin			Clarithromycin		
		S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
<i>S. pneumoniae</i> (PEN-S)	37	37 (100)	0 (0.0)	0 (0.0)	35 (94.6)	0 (0.0)	2 (5.4)	35 (94.6)	0 (0.0)	2 (5.4)
<i>S. pneumoniae</i> (PEN-I)	10	10 (100)	0 (0.0)	0 (0.0)	5 (50.0)	0 (0.0)	5 (50.0)	6 (60.0)	1 (10.0)	3 (30.0)
<i>S. pneumoniae</i> (PEN-R)	2	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	2 (100)
<i>H. influenzae</i> (BLA-)	38	38 (100)	0 (0.0)	0 (0.0)	38 (100)	0 (0.0)	0 (0.0)	36 (94.7)	2 (5.3)	0 (0.0)
<i>H. influenzae</i> (BLA+)	20	20 (100)	0 (0.0)	0 (0.0)	20 (100)	0 (0.0)	0 (0.0)	16 (80.0)	4 (20.0)	0 (0.0)
<i>H. parainfluenzae</i> (BLA-)	56	56 (100)	0 (0.0)	0 (0.0)	52* (92.9)	0 (0.0)	0 (0.0)	36 (64.3)	14 (25.0)	6 (10.7)
<i>H. parainfluenzae</i> (BLA+)	5	5 (100)	0 (0.0)	0 (0.0)	5 (100)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	3 (60.0)
<i>M. catarrhalis</i> (BLA-)	2	2 (100)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)
<i>M. catarrhalis</i> (BLA+)	69	69 (100)	0 (0.0)	0 (0.0)	69 (100)	0 (0.0)	0 (0.0)	69 (100)	0 (0.0)	0 (0.0)
<i>S. aureus</i> (Meth-S)	86	86 (100)	0 (0.0)	0 (0.0)	69 (80.2)	1 (1.2)	16 (18.6)	69 (80.2)	0 (0.0)	17 (19.8)
<i>S. aureus</i> (Meth-R)	6	4 (66.6)	2 (33.3)	0 (0.0)	1 (16.6)	0 (0.0)	5 (83.4)	1 (16.6)	0 (0.0)	5 (83.4)
Other Gram-Positive	13	13 (100)	0 (0.0)	0 (0.0)	9 (69.2)	0 (0.0)	4 (30.8)	9 (69.2)	0 (0.0)	4 (30.8)
Other Gram-Negative	113	112 (99.1)	1 (0.9)	0 (0.0)	4 (3.5)	0 (0.0)	109 (96.5)	3 (2.7)	0 (0.0)	110(97.3)

*Four isolates were non-susceptible (only a susceptible breakpoint is defined)

PEN-S = Penicillin susceptible
 PEN-I = Penicillin Intermediate
 PEN-R = Penicillin Resistant
 BLA- = β -lactamase negative
 BLA+ = β -lactamase positive
 Meth-S = Methicillin-susceptible
 Meth-R = Methicillin-resistant

Only three isolates were not susceptible to gatifloxacin (two methicillin-resistant *S. aureus* and one isolate of *Pseudomonas putida* had intermediate susceptibility). Against *Haemophilus* species the activity of clarithromycin was less compared to the other two drugs. Against *Streptococcus pneumoniae* gatifloxacin's activity was not affected by the penicillin susceptibility of the isolate. The activity of both macrolides against *S. pneumoniae* was affected by penicillin susceptibility. Against *Staphylococcus aureus* both macrolides exhibited less activity than gatifloxacin. Methicillin-resistant *S. aureus* were less susceptible to all three drugs. Both macrolides had very little activity against the "other" Gram-Negative species.

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

No new information is included in this submission. It is well known that fluoroquinolone MICs are not significantly affected by changes in culture media, human serum or a CO₂ atmosphere. Use of very heavy inocula (100 x normal) may cause a slight (usually only two-fold) increase in MIC value. The only factors that normally result in significant decreases in activity are a reduction in pH of the culture medium from 7.0 to 6.0 or lower and excessively high concentrations of magnesium (9mM) and calcium (50mM) ions. The factors that alter the activity of gatifloxacin are similar to those that effect the activity of other fluoroquinolones.

BACTERICIDAL ACTIVITY

No new information is included in this submission. All of the fluoroquinolones show bactericidal activity.

MECHANISMS OF RESISTANCE STUDIES

No new information is included in this submission.

The frequency of spontaneous mutations *in vitro* for staphylococcal strains ranged from 10⁻⁷ to \leq 10⁻⁸ at a gatifloxacin concentration of 2 x MIC. This frequency was 100-fold lower than that seen with ciprofloxacin and 10-fold lower than that seen with ofloxacin. At 4 x MIC no mutants were selected with gatifloxacin but mutants were selected with ciprofloxacin and ofloxacin at a frequency of 10⁻⁸. In gram-negative bacteria selection rates ranged from 10⁻⁷ to 10⁻⁹ in *Escherichia coli* to 10⁻⁷ in *Pseudomonas aeruginosa* at gatifloxacin concentrations equal to 2 x MIC. These rates are comparable to those seen with ciprofloxacin and ofloxacin.

Serial passages of staphylococci in the presence of gatifloxacin lead 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.

Studies have shown that quinolones inhibit DNA gyrase and DNA topoisomerase IV. Both enzymes act by a double strand DNA break mechanism and are essential for bacterial growth. These enzymes cooperate in DNA replication to facilitate DNA unlinking and chromosome segregation. Gyrase, an A₂B₂ tetramer encoded by the *gyrA* and *gyrB* genes, catalyses negative DNA supercoiling and is thought to act ahead of the replication fork neutralizing positive supercoils arising from DNA unwinding. Topoisomerase IV is a C₂D₂ complex specified by *parC* and *parE* genes that functions to allow segregation of daughter chromosomes during cell division. Point mutations in the quinolone resistance-determining regions (QRDRs) of the gyrase and topoisomerase IV genes are responsible for the development of resistance. For most fluoroquinolones resistance in gram-positive organisms arises through mutation of the *parC* or *parE* genes which precedes changes in gyrase genes. In gram-negative bacteria, gyrase is usually the prime target. Single-point mutations in the *gyrA* gene resulted in a 2-fold increase in gatifloxacin MICs in pneumococci. In comparison the *gyrA* 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 that is the primary target for the other fluoroquinolones. Against *Escherichia coli* single point mutations in the *gyrA* gene lead 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* (*gyrA* equivalent) led to a 4-fold increase in gatifloxacin MIC and an 8-fold increase in the MICs of ciprofloxacin and ofloxacin. It appears that single step mutations do not increase gatifloxacin MICs as much as those of older quinolones. As with the other fluoroquinolones, DNA gyrase appears to be the primary target in gram-negative bacteria for gatifloxacin.

Some fluoroquinolones are substrates for efflux pumps, such as NorA in *Staphylococcus aureus*. These pumps can cause bacteria to become resistant to certain fluoroquinolones by pumping the drug out of the cell. Over expression of the staphylococcal NorA efflux pump results in MIC increases of 2- to 8-fold to gatifloxacin. This increase is less than the 15- to 60-fold increases in MICs observed with ciprofloxacin, norfloxacin, and ofloxacin. Sparfloxacin MICs increased 3-fold. The decreased effect of the NorA system on gatifloxacin may be due to its higher hydrophobicity. Efflux systems in *Pseudomonas aeruginosa* increase gatifloxacin MIC 4- to 8-fold for gatifloxacin and 8- to 16-fold for ciprofloxacin, norfloxacin, and ofloxacin.

Some gram-negative bacteria may become resistant to fluoroquinolones and many other types of antimicrobials by changes in porins that alter the uptake of drugs. In *Escherichia coli* the absence of the OmpF porin had essentially no effect on gatifloxacin MICs but resulted in 2- to 5-fold increases in ciprofloxacin, norfloxacin, and ofloxacin MICs.

Mutations that cause one fluoroquinolone to have higher MICs will also confer higher MICs to other fluoroquinolones. Some fluoroquinolones may have much lower MICs against the parent strain than others so that a mutant that is resistant to one fluoroquinolone may still be susceptible to another although both drugs will have higher MIC values. The MIC value may increase more for one fluoroquinolone than for another against the same species.

RESISTANCE DEVELOPMENT DURING THERAPY

During the two clinical trials (A1420-064 and A1420-065) susceptibility tests were performed on pathogens isolated at pre-treatment and post-treatment evaluations. Four hundred and fifty-seven (457) pathogens were isolated at the pre-treatment visit (excluding the 7-day gatifloxacin arm in study A1420-064). There were 49 *Streptococcus pneumoniae* isolates, 58 *Haemophilus influenzae* isolates, 71 *Moraxella catarrhalis* isolates, 61 *Haemophilus parainfluenzae* isolates, 92 *Staphylococcus aureus* isolates, 13 other gram-positive isolates, and 113 other gram-negative isolates. All isolates except for 2 methicillin-resistant *S. aureus* and one *Pseudomonas putida* isolates were susceptible to gatifloxacin.

In the groups treated with gatifloxacin for five days there were eight isolates that persisted at the post-treatment visit. TABLE 3 shows these isolates and their MICs pre-treatment and at the post-treatment visits. MICs for the comparator drug (azithromycin unless indicated) are given in parenthesis.

TABLE 3
 MICs of Isolates Persisting Post-treatment (5-day Gatifloxacin Treatment)
 All Treated Subjects

Isolate	Pre-treatment MIC (µg/mL)	Post-Treatment MIC (µg/mL)	Change
<i>Pseudomonas aeruginosa</i>	0.5 (>32-Clarithromycin)	1.0 (>32)	+2x
<i>Staphylococcus aureus</i> (MS)	0.06 (1.0)	0.12 (1.0)	+2x
<i>Staphylococcus aureus</i> (MS)	0.12 (1.0)	0.12 (1.0)	----
<i>Staphylococcus aureus</i> (MR)	4.0 (>16)	4.0 (>16)	----
<i>S. pneumoniae</i> (Pen-S)	0.25 (0.06)	0.25 (0.06)	----
<i>Klebsiella pneumoniae</i>	0.03 (8.0)	0.015 (4.0)	-2x
<i>Escherichia coli</i>	0.06 (2.0)	0.015 (2.0)	-4x
<i>H. parainfluenzae</i> (BLA-)	0.03 (1.0)	0.015 (1.0)	-2x

Almost all of the MICs were the same or within one-dilution of what they were pre-treatment. It appears that treatment does not cause increases in MIC values.

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In the group treated with clarithromycin there were three isolates that persisted at the post-treatment visit. TABLE 4 shows these isolates and their MICs pre-treatment and at the post-treatment visits. MICs of the comparator drug (gatifloxacin) are given in parenthesis.

TABLE 4
MICs of Isolates Persisting Post-treatment (Clarithromycin Treatment)
All treated Subjects

Isolate	Pre-treatment MIC (µg/mL)	Post-Treatment MIC (µg/mL)	Change
<i>Proteus mirabilis</i>	>32 (0.12)	>32 (0.12)	----
<i>Staphylococcus aureus</i> (MS)	>32 (0.03)	>32 (0.06)	----
<i>Pseudomonas aeruginosa</i>	32 (2.0)	>32 (1.0)	+2x

Clarithromycin treatment did not cause an increase in clarithromycin MICs. The gatifloxacin MIC values for these isolates were also the same or within one dilution of each other.

In the group treated with azithromycin there were eight isolates that persisted at the post-treatment visit. TABLE 5 shows the species and MICs of these isolates at the pre-treatment and post-treatment visits. MICs of the comparator drug (gatifloxacin) are given in parenthesis.

TABLE 5
MICs of Isolates Persisting Post-treatment (Azithromycin Treatment)
All treated Subjects

Isolate	Pre-treatment MIC (µg/mL)	Post-Treatment MIC (µg/mL)	Change
<i>Citrobacter diversus</i>	2.0 (0.15)	4.0 (0.03)	+2x
<i>Staphylococcus aureus</i> (MR)	>16 (0.12)	>16 (0.06)	----
<i>Klebsiella pneumoniae</i>	8.0 (0.12)	16.0 (0.12)	+2x
<i>Staphylococcus aureus</i> (MS)	1.0 (0.12)	1.0 (0.06)	----
<i>H. parainfluenzae</i> (BLA+)	2.0 (0.03)	2.0 (0.03)	----
<i>Staphylococcus aureus</i> (MS)	2.0 (0.06)	1.0 (0.06)	-2x
<i>Serratia marcescens</i>	>16 (0.12)	>16 (0.12)	----
<i>H. parainfluenzae</i> (BLA-)	2.0 (0.03)	2.0 (0.03)	----

Azithromycin treatment did not cause an increase in azithromycin MICs. The gatifloxacin MIC values for these isolates were also the same or within one dilution of each other.

PRECLINICAL EFFICACY (IN VIVO)

PHARMACOKINETICS/BIOAVAILABILITY

No new information is included in this submission. Gatifloxacin is rapidly absorbed following oral administration. The absolute bioavailability of gatifloxacin is 96%.

Single-dose and steady-state pharmacokinetic parameters following administration of 200-mg and 400-mg doses to healthy volunteers are shown in TABLE 6 for oral administration and TABLE 7 for intravenous administration.

TABLE 6
 Pharmacokinetic Parameters in Healthy Volunteers (Oral Administration)

Parameter	Single-Dose Pharmacokinetic Parameters		Steady-State Pharmacokinetic Parameters	
	200 mg (n = 12)	400 mg (n = 202)	400 mg Infected (n = 140)	400 mg (n = 18)
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	14.2 \pm 0.4	33.0 \pm 6.2	51.3 \pm 20.4	34.4 \pm 5.7
C _{max} ($\mu\text{g}/\text{mL}$)	2.0 \pm 0.4	3.8 \pm 1.0	4.2 \pm 1.9	4.2 \pm 1.3
Trough ($\mu\text{g}/\text{mL}$)	Not applicable	Not applicable	----	0.4 $\mu\text{g}/\text{mL}$

AUC = AUC_(0- ∞) for single dose; AUC₍₀₋₂₄₎ for steady state

TABLE 7
 Pharmacokinetic Parameters in Healthy Volunteers (Intravenous Administration)

Parameter	Single-Dose Pharmacokinetic Parameters		Steady-State Pharmacokinetic Parameters	
	200 mg (n = 12)	400 mg (n = 30)	200 mg (n = 8)	400 mg (n = 5)
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	15.9 \pm 2.6	35.1 \pm 6.7	16.8 \pm 3.6	35.4 \pm 4.6
C _{max} ($\mu\text{g}/\text{mL}$)	2.2 \pm 0.3	5.5 \pm 1.0	2.4 \pm 0.4	4.6 \pm 0.6
Trough ($\mu\text{g}/\text{mL}$)	Not applicable	Not applicable	----	0.4 $\mu\text{g}/\text{mL}$

AUC = AUC_(0- ∞) for single dose; AUC₍₀₋₂₄₎ for steady state

The peak plasma concentration is achieved 1 to 2 hours after dosing. Steady-state concentrations are achieved by the third daily dose. Dosing with meals has no effect on gatifloxacin pharmacokinetic parameters. Binding of gatifloxacin to serum protein is approximately 20% and is concentration independent.

The mean elimination half-life of gatifloxacin ranges from 7 to 14 hours and is independent of dose or route of administration. More than 70% of an administered dose was recovered as unchanged drug in the urine within 48 hours and 5% was recovered in the feces. Less than 1% of the dose is excreted in the urine as ethylenediamine and methylethylenediamine.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

The sponsor had conducted two clinical studies. Study AI420-064 compared the efficacy and safety of treating acute bacterial exacerbations of chronic bronchitis (ABECB) with a 5-day course of gatifloxacin at 400 mg once daily with clarithromycin given at 400 mg twice a day for ten days. A 7-day gatifloxacin treatment arm was also included in this study. Study AI420-065 compared a 5-day gatifloxacin course of treatment with a 5-day course of azithromycin administered as a 500 mg dose on Day 1 followed by a 250 mg dose on Days 2-5. At the present time gatifloxacin is approved for ABECB at a dose of 400 mg once a day for 7-14 days. Clinical signs and symptoms were evaluated at pre-treatment (≤ 2 days before treatment), during treatment (Day 3-5 during treatment—Study AI420-064 only), end of treatment (Day 1 to 3 after treatment), post-treatment (Day 7 to 14 after treatment), and at extended follow-up (Day 21 to 28 after treatment). Clinical and bacteriological responses were determined from data at the Test of Cure Visit which could occur from Day 5 to Day 18 post-treatment. Treatment failures could be assessed earlier. Relapses were assessed at the final follow-up visit (Day 21 to Day 28).

All purulent sputum specimens were plated semi-quantitatively for aerobic growth. All potential pathogens were tested for susceptibility to gatifloxacin and the comparator agent by the disk diffusion and minimum inhibitory concentration (MIC) methods described by NCCLS. *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis* were tested for β -lactamase production. *H. influenzae* and *H. parainfluenzae* were tested for susceptibility to ampicillin. *Streptococcus pneumoniae* isolates were tested for susceptibility to penicillin and *Staphylococcus aureus* isolates were tested for methicillin susceptibility.

In the two studies combined a total of 629 patients were enrolled and 624 were treated. Three hundred and sixty-nine (369) patients received gatifloxacin; two hundred and fifty-six (256) received a 5-day course and 113 received a 7-day course. Two hundred and fifty-five patients received a comparator agent (108 clarithromycin, 147 azithromycin). Approximately half of all patients were Microbiologically Evaluable (45% gatifloxacin, 45% comparator). Of the 450 Clinically Evaluable patients, 299 had a pathogen isolated pre-treatment. A total of fifty-seven (37 gatifloxacin, 20 comparator) were considered microbiologically unevaluable solely because of resistant pathogens. Other patients were unevaluable because of resistant pathogens and other reasons. In all cases, the pathogens in question were resistant to clarithromycin or azithromycin, not gatifloxacin. Most of the isolated Gram-negative pathogens were not evaluable since they were resistant to the comparators. TABLE 8 gives a summary of the reasons that pathogens were not included in the microbiological evaluable population.

TABLE 8
 Summary of Unevaluable Pathogens

	5-day Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
Total No. of Pathogens	87	152	239	78	140	218
No. Evaluable	52	88	140	44	87	131
No. Unevaluable	35	64	99	34	53	87
<u>Reason Pathogens Were Microbiologically Unevaluable</u>						
Pathogen Resistant						
<i>S. pneumoniae</i>						
Penicillin-Susceptible	1	--	1	1	--	1
Penicillin-Intermediate	--	3	3	1	1	2
Penicillin-Resistant	--	2	2	--	--	--
<i>S. aureus</i>						
Methicillin-Susceptible	4	8	12	4	1	5
Methicillin-Resistant	1	2	3	--	2	2
<i>H. parainfluenzae</i> (BLA-)	1	--	1	2	1	3
<i>H. parainfluenzae</i> (BLA+)	1	--	1	--	--	--
Other Gram-Negative	23	33	56	23	28	51
Other Gram-Positive	--	1	1	1	2	3
Patient Clinically Unevaluable:						
<i>H. influenzae</i> (BLA-)	1	1	2	--	3	3
<i>H. influenzae</i> (BLA+)	--	3	3	--	--	--
<i>H. parainfluenzae</i> (BLA-)	1	1	2	--	3	3
<i>H. parainfluenzae</i> (BLA+)	--	--	--	1	1	2
<i>M. catarrhalis</i> (BLA+)	1	2	3	1	3	4
<i>S. aureus</i> (Meth-S)	1	3	4	--	2	2
<i>S. pneumoniae</i> (PEN-S)	--	3	3	--	1	1
<i>S. pneumoniae</i> (PEN-I)	--	1	1	--	--	--
Other Gram-Negative	--	1	1	--	5	5
Other Gram-Positive	--	--	--	--	--	--

Over 60% of patients had a pre-treatment pathogen identified (see TABLE 9). Overall pathogen recovery rates were higher in study AI420-065. Of the three key respiratory pathogens, *Moraxella catarrhalis* was the most frequently identified, 71 isolates, all but two of which produced β -lactamase. One third of the 58 *H. influenzae* isolates were β -lactamase positive. *Streptococcus pneumoniae* was recovered in about 10% of the patients (49 or 511). Of the 49 strains, 10 were penicillin-intermediate and only two were fully penicillin-resistant. *Staphylococcus aureus* (92 isolates) and *H. parainfluenzae* (61 isolates) were also commonly recovered.

TABLE 9
Pathogens Recovered from Patients

	5-day Gatifloxacin			Comparator		
	064 N=109	065 N=147	Total N=256	064 N= 108	065 N=147	Total N=255
No. of Patients with Pathogens: (%)	66(61)	104 (71)	170 (66)	61 (56)	102 (69)	163 (64)
Single	49 (45)	65 (44)	114 (45)	48 (44)	70 (48)	118 (46)
Multiple	17 (16)	39 (27)	56 (22)	13 (12)	32 (22)	45 (18)
Pathogens^a						
<i>S. pneumoniae</i>	14	16	30	8	11	19
Pen-Susceptible	12	8	20	7	10	17
Pen-Intermediate	2	6	8	1	1	2
Pen-Resistant	---	2	2	---	---	---
<i>S. aureus</i>	16	32	48	17	27	44
Methicillin-Susceptible	15	30	45	17	24	41
Methicillin-Resistant	1	2	3	--	3	3
<i>H. influenzae</i>	13	16	29	8	21	29
β -lactamase -	8	10	18	6	14	20
β -lactamase +	5	6	11	2	7	9
<i>M. catarrhalis</i>	12	28	40	12	19	31
β -lactamase -	---	1	1	---	1	1
β -lactamase +	12	27	39	12	18	30
<i>H. parainfluenzae</i>	8	23	31	7	23	30
β -lactamase -	7	21	28	6	22	28
β -lactamase +	1	2	3	1	1	2
Other Gram-Positive ^b	1	3	4	2	7	9
Other Gram-Negative ^c	23	34	57	24	32	56

^a Patients may have more than one pathogen

^b Includes *S. pyogenes*, *S. canis*, Strep Group C, *S. agalactiae*, and *S. constellatus*

^c Includes 24 different organisms

BACTERIAL RESPONSE BY PATHOGEN

The bacteriological response achieved at the Test-of-Cure Visit for patients who were clinically and microbiologically evaluable in each treatment group is shown by pathogen in TABLE 10.

TABLE 10
Summary of Bacteriological Response (Eradicated/Total (%))

	Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
All pathogens	50/52 (96)	77/88 (88)	127/140 (91)	42/44 (95)	73/87 (84)	115/131 (88)
<i>S. pneumoniae</i>	12/13 (92)	6/7 (86)	18/20 (90)	6/6 (100)	8/9 (89)	14/15 (93)
PEN-S	10/11 (91)	4/5 (80)	14/16 (88)	6/6 (100)	8/9 (89)	14/15 (93)
PEN-I	2/2 (100)	2/2 (100)	4/4 (100)	—	—	—
<i>S. aureus</i>	9/10 (90)	16/19 (84)	25/29 (86)	13/13 (100)	19/22 (86)	32/35 (91)
Meth-S	9/10 (90)	16/19 (84)	25/29 (86)	13/13 (100)	18/21 (86)	31/34 (91)
Meth-R	—	—	—	—	1/1 (100)	1/1 (100)
<i>H. influenzae</i>	12/12 (100)	11/12 (92)	23/24 (96)	8/8 (100)	15/18 (83)	23/26 (88)
BLA +	5/5 (100)	2/3 (67)	7/8 (88)	2/2 (100)	6/7 (86)	8/9 (89)
BLA -	7/7 (100)	9/9 (100)	16/16 (100)	6/6 (100)	9/11 (82)	15/17 (88)
<i>M. catarrhalis</i>	11/11 (100)	24/26 (92)	35/37 (95)	11/11 (100)	14/16 (88)	25/27 (93)
BLA +	11/11 (100)	23/25 (92)	34/36 (94)	11/11 (100)	13/15 (87)	24/26 (92)
BLA -	—	1/1 (100)	1/1 (100)	—	1/1 (100)	1/1 (100)
<i>H. parainfluenzae</i>	5/5 (100)	18/22 (82)	23/27 (85)	2/4 (50)	13/18 (72)	15/22 (68)
BLA+	—	2/2 (100)	2/2 (100)	—	—	—
BLA -	5/5 (100)	16/20 (80)	21/25 (84)	2/4 (50)	13/18 (72)	15/22 (68)
Other Gram-Pos ^a	1/1 (100)	2/2 (100)	3/3 (100)	1/1 (100)	3/3 (100)	4/4 (100)
Other Gram-Neg ^b	—	—	—	1/1 (100)	1/1 (100)	2/2 (100)

^a Includes *S. pyogenes*, *S. canis*, Strep C, *S. agalactiae*, *S. caris*, and *S. constellatus*

^b Includes *C. indologenes* and *A. radiobacteri*

Bacteriological response by pathogen was generally similar between gatifloxacin and the comparator groups. It appears that comparator group may be slightly better against *S. pneumoniae* and that gatifloxacin does better against *Haemophilus* species.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir _____ Signature _____ Date _____
HFD-590/TLMicro _____ Signature _____ Date _____

CC:
HFD-590/Original NDA # 21-061/SE2-007
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/Johanaliang
HFD-520/Pharm/SHundley
HFD-590/Chem/JSmith
HFD-590/CSO/DWillard

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

NDA #: 21-061/SE2-007 **REVIEWER:** Peter A. Dionne
CORRESPONDENCE DATE: 21-DEC-00
CDER DATE: 21-DEC-00
REVIEW ASSIGN DATE: 05-JAN-01
REVIEW COMPLETE DATE: 31-JAN-01

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SUBMISSION REVIEWED: Supplement with information to support an alternative duration of treatment (i.e. 5 days) for patients with acute bacterial exacerbations of chronic bronchitis (ABECB).

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

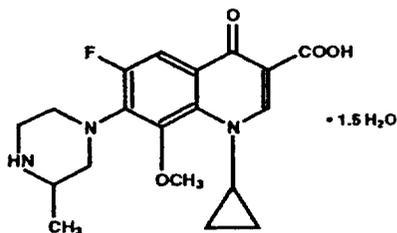
INDICATIONS: ABECB, Acute Sinusitis, Community Acquired Pneumonia, Urinary Tract Infections and Gonorrhea.

DOSAGE FORM: 200 mg and 400 mg Tablets

DRUG PRODUCT NAME

PROPRIETARY: TEQUIN®
NONPROPRIETARY/USAN: Gatifloxacin
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: C₁₉H₂₂FN₃O₄ • 1½ H₂O
Molecular Weight: 402.42

SUPPORTING DOCUMENTS: NDA 21-062—Gatifloxacin IV solution

BACKGROUND:

This supplement requests an alternative duration of treatment for acute bacterial exacerbations of chronic bronchitis (ABECB). Gatifloxacin was approved for the treatment of ACECB due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus* on December 17, 1999. The approved treatment was 400 mg once daily for 7-10 days. In this submission the sponsor seeks approval of a 400 mg once daily for 5 days dosage.

Data from two clinical trials are submitted for this new treatment duration. The combined accrual in these two studies was 828 patients. Four hundred and ninety-six (496) patients received gatifloxacin; three hundred and twenty-two (322) received a 5-day course and 175 received a 7-day course. Three hundred and twenty-five patients received a comparator agent (178 clarithromycin, 147 azithromycin). Study AI420-064 compared the safety and efficacy of gatifloxacin, given orally at a dose of 400 mg once daily, to a standard regimen of clarithromycin, 500 mg BID for 10 days. Gatifloxacin was dosed for 5 or 7 days in this study. Study AI420-065 compared gatifloxacin, given orally at a dose of 400 mg once daily for 5 days to azithromycin, 500 mg on Day 1, followed by 250 mg QD for 4 days.

CONCLUSIONS & RECOMMENDATIONS:

This NDA supplemental application requests approval of an alternative duration of treatment (i.e. 5 days) for acute bacterial exacerbations of chronic bronchitis. Data from two clinical trials were submitted.

Over 60% of patients had a pre-treatment pathogen identified. Of the three key respiratory pathogens *Moraxella catarrhalis* was the most frequently identified pathogen (82 isolates, all but two of which produced β -lactamase). There were 76 isolates of *Haemophilus influenzae* (one-third produced a β -lactamase), 63 *Streptococcus pneumoniae* isolates of which 15 were penicillin-intermediate and only two were penicillin-resistant. There were also 123 *Staphylococcus aureus* isolates and 75 *Haemophilus parainfluenzae* isolates recovered pre-treatment.

Streptococcus pneumoniae had the highest gatifloxacin MIC₉₀ value of the three key respiratory pathogens. Gatifloxacin eradicated 20 of 22 *S. pneumoniae* isolates.

No new microbiological pre-clinical information is provided in the supplement. The supplement may be approved from the microbiological viewpoint. There are no microbiological points to convey to the sponsor. No changes are needed in the Microbiology subsection of the label.

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**APPEARS THIS WAY
ON ORIGINAL**

EXECUTIVE SUMMARY

This supplemental application contains information in support of a request for an alternative duration of treatment (i.e. 5 days) for adult patients with acute bacterial exacerbations of chronic bronchitis (ABECB). No new preclinical microbiological information has been included with this application.

Two randomized, double-blind, multicenter studies were performed to compare the safety and efficacy of gatifloxacin, given orally at a dose of 400 mg once daily, to a standard regimen of either clarithromycin, 500 mg BID for 10 days (Study AI420-064), or azithromycin, 500 mg on Day 1, followed by 250 mg QD for 4 days (AI420-065). Gatifloxacin was dosed for 5 days; study AI420-064 also had a 7-day gatifloxacin arm.

The overall microbiological eradication rates in the pooled arms were comparable (93% gatifloxacin, 91% comparators). For *Streptococcus pneumoniae*, the comparators eradicated 24 of 25 isolates, while gatifloxacin eradicated 20 of 22. Eradication rates for *Haemophilus influenzae* and *Moraxella catarrhalis* were favorable in both treatment groups. Only three organisms (two isolates of methicillin-resistant *S. aureus* and one of *Pseudomonas putida*) were not susceptible to gatifloxacin. Only 63% and 68% of the isolated pathogens were susceptible to clarithromycin and azithromycin, respectively. Eighty-four percent of *S. pneumoniae* isolates were susceptible to the macrolides. Clarithromycin was not as active as the other two drugs against β -lactamase positive *Haemophilus* isolates.

PRECLINICAL EFFICACY (IN VITRO)

MECHANISM OF ACTION

No new information has been submitted. Like other quinolones, gatifloxacin inhibits the activity of the 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.

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ON ORIGINAL

ANTIMICROBIAL SPECTRUM OF ACTIVITY

(FIVE PATHOGENS INVOLVED IN THIS INDICATION)

No new pre-clinical information has been presented. Susceptibility data presented in the original NDA 21-061 are shown in TABLE 1 for the pathogens that are approved for ABECB. The data in TABLE 1 demonstrate that *Streptococcus pneumoniae* will probably be the pathogen that will be the most affected by a shorter duration of treatment. The MIC₉₀ value (0.5 µg/mL) for this pathogen is close to the susceptible breakpoint of 1 µg/mL. The MIC₉₀ values for the other pathogens are well below the susceptible breakpoints. *Staphylococcus aureus* has the second highest MIC₉₀ at 0.1-0.25 µg/mL. Methicillin-resistant *S. aureus* isolates usually have a much higher MIC value and are usually resistant to gatifloxacin.

TABLE 1
 Activity of Gatifloxacin Against ABECB Organisms (Summary data from Original NDA)

Organism	No. of Isolates in NDA	Country	Geometric Mean MIC ₉₀ (µg/mL)	
<i>Streptococcus pneumoniae</i>	2039	USA	0.5	
	524	ex-USA	0.7	
	PEN-S	101	USA	0.5
	64	ex-USA	0.7	
	PEN-I	91	USA	0.5
	70	ex-USA	0.5	
	PEN-R	65	USA	0.5
	33	ex-USA	0.5	
<i>Staphylococcus aureus</i>	Meth-S	368	USA	0.11
		1389	ex-USA	0.25
	Meth-R	2744	USA	>4
		1642	ex-USA	6.2
<i>Haemophilus influenzae</i>	1422	USA	<0.03	
	410	ex-USA	0.01	
<i>H. parainfluenzae</i>	54	USA	0.09	
<i>Moraxella catarrhalis</i>	679	USA	<0.03	
	245	ex-USA	0.06	

Susceptibility data generated for pre-treatment isolates in the two clinical studies submitted with this supplement are presented in TABLE 2.

TABLE 2
 Susceptibility Results for Causative Pathogens (excluding 7-day Gatifloxacin Treated)

Pathogen	Total Isolated	Gatifloxacin			Azithromycin			Clarithromycin		
		S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
<i>S. pneumoniae</i> (PEN-S)	46	46 (100)	0 (0.0)	0 (0.0)	43 (93.5)	0 (0.0)	3 (6.5)	43 (93.5)	0 (0.0)	3 (6.5)
<i>S. pneumoniae</i> (PEN-I)	15	15 (100)	0 (0.0)	0 (0.0)	10 (66.7)	0 (0.0)	5 (33.3)	10 (66.7)	1 (6.7)	4 (26.7)
<i>S. pneumoniae</i> (PEN-R)	2	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	2 (100)
<i>H. influenzae</i> (BLA-)	51	51 (100)	0 (0.0)	0 (0.0)	51 (100)	0 (0.0)	0 (0.0)	49 (96.1)	2 (3.9)	0 (0.0)
<i>H. influenzae</i> (BLA+)	25	25 (100)	0 (0.0)	0 (0.0)	25 (100)	0 (0.0)	0 (0.0)	21 (84.0)	4 (16.0)	0 (0.0)
<i>H. parainfluenzae</i> (BLA-)	67	67 (100)	0 (0.0)	0 (0.0)	62* (92.5)	0 (0.0)	0 (0.0)	44 (65.7)	15 (22.4)	8 (11.9)
<i>H. parainfluenzae</i> (BLA+)	8	8 (100)	0 (0.0)	0 (0.0)	8 (100)	0 (0.0)	0 (0.0)	5 (62.5)	0 (0.0)	3 (37.5)
<i>M. catarrhalis</i> (BLA-)	2	2 (100)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)
<i>M. catarrhalis</i> (BLA+)	80	80 (100)	0 (0.0)	0 (0.0)	80 (100)	0 (0.0)	0 (0.0)	77 (96.3)	2 (2.5)	1 (1.3)
<i>S. aureus</i> (Meth-S)	112	112 (100)	0 (0.0)	0 (0.0)	91 (81.3)	1 (0.9)	20 (17.9)	92 (82.1)	0 (0.0)	20 (17.9)
<i>S. aureus</i> (Meth-R)	11	9 (81.8)	2 (18.2)	0 (0.0)	2 (18.2)	0 (0.0)	9 (81.8)	2 (18.2)	0 (0.0)	9 (81.8)
Other Gram-Positive	27	27 (100)	0 (0.0)	0 (0.0)	22 (81.5)	1 (3.7)	4 (14.8)	21 (77.8)	2 (7.4)	4 (14.8)
Other Gram-Negative	139	138 (99.3)	1 (0.7)	0 (0.0)	4 (2.9)	0 (0.0)	135 (97.1)	3 (2.2)	0 (0.0)	136(97.8)

*Five isolates were non-susceptible (only a susceptible breakpoint is defined)

PEN-S = Penicillin susceptible

PEN-I = Penicillin Intermediate

PEN-R = Penicillin Resistant

BLA- = β -lactamase negative

BLA+ = β -lactamase positive

Meth-S = Methicillin-susceptible

Meth-R = Methicillin-resistant

Only three isolates were not susceptible to gatifloxacin (two methicillin-resistant *S. aureus* and one isolate of *Pseudomonas putida* had intermediate susceptibility). Against *Haemophilus* species the activity of clarithromycin was less compared to the other two drugs. Against *Streptococcus pneumoniae* gatifloxacin's activity was not affected by the penicillin susceptibility of the isolate. The activity of both macrolides against *S. pneumoniae* was affected by penicillin susceptibility. Against *Staphylococcus aureus* both macrolides exhibited less activity than gatifloxacin. Methicillin-resistant *S. aureus* were less susceptible to all three drugs. Both macrolides had very little activity against the "other" Gram-Negative species.

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

No new information is included in this submission. It is well known that fluoroquinolone MICs are not significantly affected by changes in culture media, human serum or a CO₂ atmosphere. Use of very heavy inocula (100 x normal) may cause a slight (usually only two-fold) increase in MIC value. The only factors that normally result in significant decreases in activity are a reduction in pH of the culture medium from 7.0 to 6.0 or lower and excessively high concentrations of magnesium (9mM) and calcium (50mM) ions. The factors that alter the activity of gatifloxacin are similar to those that effect the activity of other fluoroquinolones.

BACTERICIDAL ACTIVITY

No new information is included in this submission. All of the fluoroquinolones show bactericidal activity.

MECHANISMS OF RESISTANCE STUDIES

No new information is included in this submission.

The frequency of spontaneous mutations *in vitro* for staphylococcal strains ranged from 10⁻⁷ to \leq 10⁻⁸ at a gatifloxacin concentration of 2 x MIC. This frequency was 100-fold lower than that seen with ciprofloxacin and 10-fold lower than that seen with ofloxacin. At 4 x MIC no mutants were selected with gatifloxacin but mutants were selected with ciprofloxacin and ofloxacin at a frequency of 10⁻⁸. In gram-negative bacteria selection rates ranged from 10⁻⁷ to 10⁻⁹ in *Escherichia coli* to 10⁻⁷ in *Pseudomonas aeruginosa* at gatifloxacin concentrations equal to 2 x MIC. These rates are comparable to those seen with ciprofloxacin and ofloxacin.

Serial passages of staphylococci in the presence of gatifloxacin lead 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.

Studies have shown that quinolones inhibit DNA gyrase and DNA topoisomerase IV. Both enzymes act by a double strand DNA break mechanism and are essential for bacterial growth. These enzymes cooperate in DNA replication to facilitate DNA unlinking and chromosome segregation. Gyrase, an A₂B₂ tetramer encoded by the *gyrA* and *gyrB* genes, catalyses negative DNA supercoiling and is thought to act ahead of the replication fork neutralizing positive supercoils arising from DNA unwinding. Topoisomerase IV is a C₂D₂ complex specified by *parC* and *parE* genes that functions to allow segregation of daughter chromosomes during cell division. Point mutations in the quinolone resistance-determining regions (QRDRs) of the gyrase and topoisomerase IV genes are responsible for the development of resistance. For most fluoroquinolones resistance in gram-positive organisms arises through mutation of the *parC* or *parE* genes which precedes changes in gyrase genes. In gram-negative bacteria, gyrase is usually the prime target. Single-point mutations in the *gyrA* gene resulted in a 2-fold increase in gatifloxacin MICs in pneumococci. In comparison the *gyrA* 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 that is the primary target for the other fluoroquinolones. Against *Escherichia coli* single point mutations in the *gyrA* gene lead 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* (*gyrA* equivalent) led to a 4-fold increase in gatifloxacin MIC and an 8-fold increase in the MICs of ciprofloxacin and ofloxacin. It appears that single step mutations do not increase gatifloxacin MICs as much as those of older quinolones. As with the other fluoroquinolones, DNA gyrase appears to be the primary target in gram-negative bacteria for gatifloxacin.

Some fluoroquinolones are substrates for efflux pumps, such as NorA in *Staphylococcus aureus*. These pumps can cause bacteria to become resistant to certain fluoroquinolones by pumping the drug out of the cell. Over expression of the staphylococcal NorA efflux pump results in MIC increases of 2- to 8-fold to gatifloxacin. This increase is less than the 15- to 60-fold increases in MICs observed with ciprofloxacin, norfloxacin, and ofloxacin. Sparfloxacin MICs increased 3-fold. The decreased effect of the NorA system on gatifloxacin may be due to its higher hydrophobicity. Efflux systems in *Pseudomonas aeruginosa* increase gatifloxacin MIC 4- to 8-fold for gatifloxacin and 8- to 16-fold for ciprofloxacin, norfloxacin, and ofloxacin.

Some gram-negative bacteria may become resistant to fluoroquinolones and many other types of antimicrobials by changes in porins that alter the uptake of drugs. In *Escherichia coli* the absence of the OmpF porin had essentially no effect on gatifloxacin MICs but resulted in 2- to 5-fold increases in ciprofloxacin, norfloxacin, and ofloxacin MICs.

Mutations that cause one fluoroquinolone to have higher MICs will also confer higher MICs to other fluoroquinolones. Some fluoroquinolones may have much lower MICs against the parent strain than others so that a mutant that is resistant to one fluoroquinolone may still be susceptible to another although both drugs will have higher MIC values. The MIC value may increase more for one fluoroquinolone than for another against the same species.

RESISTANCE DEVELOPMENT DURING THERAPY

During the two clinical trials (A1420-064 and A1420-065) susceptibility tests were performed on pathogens isolated at pre-treatment and post-treatment evaluations. Five hundred and eighty-five pathogens were isolated at the pre-treatment visit. There were 63 *Streptococcus pneumoniae* isolates, 76 *Haemophilus influenzae* isolates, 82 *Moraxella catarrhalis* isolates, 75 *Haemophilus parainfluenzae* isolates, 123 *Staphylococcus aureus* isolates, 27 other gram-positive isolates, and 139 other gram-negative isolates. All isolates except for 2 methicillin-resistant *S. aureus* and one *Pseudomonas putida* isolates were susceptible to gatifloxacin.

In the groups treated with gatifloxacin for five days there were eight isolates that persisted at the post-treatment visit. TABLE 3 shows these isolates and their MICs pre-treatment and at the post-treatment visits. MICs for the comparator drug (azithromycin unless indicated) are given in parenthesis.

TABLE 3
MICs of Isolates Persisting Post-treatment (5-day Gatifloxacin Treatment)
All Treated Subjects

Isolate	Pre-treatment MIC (µg/mL)	Post-Treatment MIC (µg/mL)	Change
<i>Pseudomonas aeruginosa</i>	0.5 (>32-Clarithromycin)	1.0 (>32)	+2x
<i>Staphylococcus aureus</i> (MS)	0.06 (1.0)	0.12 (1.0)	+2x
<i>Staphylococcus aureus</i> (MS)	0.12 (1.0)	0.12 (1.0)	----
<i>Staphylococcus aureus</i> (MR)	4.0 (>16)	4.0 (>16)	----
<i>S. pneumoniae</i> (Pen-S)	0.25 (0.06)	0.25 (0.06)	----
<i>Klebsiella pneumoniae</i>	0.03 (8.0)	0.015 (4.0)	-2x
<i>Escherichia coli</i>	0.06 (2.0)	0.015 (2.0)	-4x
<i>H. parainfluenzae</i> (BLA-)	0.03 (1.0)	0.015 (1.0)	-2x

Almost all of the MICs were the same or within one-dilution of what they were pre-treatment. It appears that treatment does not cause increases in MIC values.

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In the group treated with clarithromycin there were five isolates that persisted at the post-treatment visit. TABLE 4 shows these isolates and their MICs pre-treatment and at the post-treatment visits. MICs of the comparator drug (gatifloxacin) are given in parenthesis.

TABLE 4
MICs of Isolates Persisting Post-treatment (Clarithromycin Treatment)
All treated Subjects

Isolate	Pre-treatment MIC (µg/mL)	Post-Treatment MIC (µg/mL)	Change
<i>Proteus mirabilis</i>	>32 (0.12)	>32 (0.12)	----
<i>Klebsiella pneumoniae</i>	>32 (0.06)	>32 (0.12)	----
<i>Serratia marcescens</i>	32 (0.12)	>32 (0.12)	+2x
<i>Staphylococcus aureus</i> (MS)	>32 (0.03)	>32 (0.06)	----
<i>Pseudomonas aeruginosa</i>	32 (2.0)	>32 (1.0)	+2x

Clarithromycin treatment did not cause an increase in clarithromycin MICs. The gatifloxacin MIC values for these isolates were also the same or within one dilution of each other.

In the group treated with azithromycin there were eight isolates that persisted at the post-treatment visit. TABLE 5 shows the species and MICs of these isolates at the pre-treatment and post-treatment visits. MICs of the comparator drug (gatifloxacin) are given in parenthesis.

TABLE 5
MICs of Isolates Persisting Post-treatment (Azithromycin Treatment)
All treated Subjects

Isolate	Pre-treatment MIC (µg/mL)	Post-Treatment MIC (µg/mL)	Change
<i>Citrobacter diversus</i>	2.0 (0.15)	4.0 (0.03)	+2x
<i>Staphylococcus aureus</i> (MR)	>16 (0.12)	>16 (0.06)	----
<i>Klebsiella pneumoniae</i>	8.0 (0.12)	16.0 (0.12)	+2x
<i>Staphylococcus aureus</i> (MS)	1.0 (0.12)	1.0 (0.06)	----
<i>H. parainfluenzae</i> (BLA+)	2.0 (0.03)	2.0 (0.03)	----
<i>Staphylococcus aureus</i> (MS)	2.0 (0.06)	1.0 (0.06)	-2x
<i>Serratia marcescens</i>	>16 (0.12)	>16 (0.12)	----
<i>H. parainfluenzae</i> (BLA-)	2.0 (0.03)	2.0 (0.03)	----

Azithromycin treatment did not cause an increase in azithromycin MICs. The gatifloxacin MIC values for these isolates were also the same or within one dilution of each other.

PRECLINICAL EFFICACY (IN VIVO)

PHARMACOKINETICS/BIOAVAILABILITY

No new information is included in this submission. Gatifloxacin is rapidly absorbed following oral administration. The absolute bioavailability of gatifloxacin is 96%.

Single-dose and steady-state pharmacokinetic parameters following administration of 200-mg and 400-mg doses to healthy volunteers are shown in TABLE 6 for oral administration and TABLE 7 for intravenous administration.

TABLE 6
 Pharmacokinetic Parameters in Healthy Volunteers (Oral Administration)

Parameter	Single-Dose Pharmacokinetic Parameters		Steady-State Pharmacokinetic Parameters	
	200 mg (n = 12)	400 mg (n = 202)	400 mg Infected (n = 140)	400 mg (n = 18)
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	14.2 \pm 0.4	33.0 \pm 6.2	51.3 \pm 20.4	34.4 \pm 5.7
C _{max} ($\mu\text{g}/\text{mL}$)	2.0 \pm 0.4	3.8 \pm 1.0	4.2 \pm 1.9	4.2 \pm 1.3
Trough ($\mu\text{g}/\text{mL}$)	Not applicable	Not applicable	-----	0.4 $\mu\text{g}/\text{mL}$

AUC = AUC_(0-∞) for single dose; AUC₍₀₋₂₄₎ for steady state

TABLE 7
 Pharmacokinetic Parameters in Healthy Volunteers (Intravenous Administration)

Parameter	Single-Dose Pharmacokinetic Parameters		Steady-State Pharmacokinetic Parameters	
	200 mg (n = 12)	400 mg (n = 30)	200 mg (n = 8)	400 mg (n = 5)
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	15.9 \pm 2.6	35.1 \pm 6.7	16.8 \pm 3.6	35.4 \pm 4.6
C _{max} ($\mu\text{g}/\text{mL}$)	2.2 \pm 0.3	5.5 \pm 1.0	2.4 \pm 0.4	4.6 \pm 0.6
Trough ($\mu\text{g}/\text{mL}$)	Not applicable	Not applicable	-----	0.4 $\mu\text{g}/\text{mL}$

AUC = AUC_(0-∞) for single dose; AUC₍₀₋₂₄₎ for steady state

The peak plasma concentration is achieved 1 to 2 hours after dosing. Steady-state concentrations are achieved by the third daily dose. Dosing with meals has no effect on gatifloxacin pharmacokinetic parameters. Binding of gatifloxacin to serum protein is approximately 20% and is concentration independent.

The mean elimination half-life of gatifloxacin ranges from 7 to 14 hours and is independent of dose or route of administration. More than 70% of an administered dose was recovered as unchanged drug in the urine within 48 hours and 5% was recovered in the feces. Less than 1% of the dose is excreted in the urine as ethylenediamine and methylethylenediamine.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

The sponsor had conducted two clinical studies. Study AI420-064 compared the efficacy and safety of treating acute bacterial exacerbations of chronic bronchitis (ABECB) with a 5-day course of gatifloxacin at 400 mg once daily with clarithromycin given at 400 mg twice a day for ten days. A 7-day gatifloxacin treatment arm was also included in this study. Study AI420-065 compared a 5-day gatifloxacin course of treatment with a 5-day course of azithromycin administered as a 500 mg dose on Day 1 followed by a 250 mg dose on Days 2-5. At the present time gatifloxacin is approved for ABECB at a dose of 400 mg once a day for 7-14 days. Clinical signs and symptoms were evaluated at pre-treatment (≤ 2 days before treatment), during treatment (Day 3-5 during treatment—Study AI420-064 only), end of treatment (Day 1 to 3 after treatment), post-treatment (Day 7 to 14 after treatment), and at extended follow-up (Day 21 to 28 after treatment). Clinical and bacteriological responses were determined from data at the Test of Cure Visit which could occur from Day 5 to Day 18 post-treatment. Treatment failures could be assessed earlier. Relapses were assessed at the final follow-up visit (Day 21 to Day 28).

All purulent sputum specimens were plated semi-quantitatively for aerobic growth. All potential pathogens were tested for susceptibility to gatifloxacin and the comparator agent by the disk diffusion and minimum inhibitory concentration (MIC) methods described by NCCLS. *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis* were tested for β -lactamase production. *H. influenzae* and *H. parainfluenzae* were tested for susceptibility to ampicillin. *Streptococcus pneumoniae* isolates were tested for susceptibility to penicillin and *Staphylococcus aureus* isolates were tested for methicillin susceptibility.

In the two studies combined a total of 828 patients were enrolled and 821 were treated. Four hundred and ninety-two (492) patients received gatifloxacin; three hundred and twenty-one (321) received a 5-day course and 175 received a 7-day course. Three hundred and twenty-five patients received a comparator agent (178 clarithromycin, 147 azithromycin). Approximately half of all patients were Microbiologically Evaluable (45% gatifloxacin, 46% comparator). Of the 566 Clinically Evaluable patients, 370 had a pathogen isolated pre-treatment. A total of seventy-seven (41 gatifloxacin, 36 comparator) were considered microbiologically unevaluable solely because of resistant pathogens. Other patients were unevaluable because of resistant pathogens and other reasons. In all cases, the pathogens in question were resistant to clarithromycin or azithromycin, not gatifloxacin. Most of the isolated Gram-negative pathogens were not evaluable since they were resistant to the comparators. TABLE 8 gives a summary of the reasons that pathogens were not included in the microbiological evaluable population.

TABLE 8
 Summary of Unevaluable Pathogens

	5-day Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
Total No. of Pathogens	147	152	299	146	140	286
No. Evaluable	87	88	175	89	87	176
No. Unevaluable	60	64	124	57	53	110
<u>Reason Pathogens</u>						
<u>Microbiologically</u>						
<u>Unevaluable</u>						
Pathogen Resistant						
<i>S. pneumoniae</i>						
Penicillin-Susceptible	2	--	2	1	--	1
Penicillin-Intermediate	--	3	3	1	1	2
Penicillin-Resistant	--	2	2	--	--	--
<i>S. aureus</i>						
Methicillin-Susceptible	4	8	12	7	1	8
Methicillin-Resistant	3	2	5	2	2	4
<i>H. parainfluenzae</i> (BLA-)	2	--	2	2	1	3
<i>H. parainfluenzae</i> (BLA+)	1	--	1	--	--	--
Other Gram-Negative	34	33	67	38	28	66
Other Gram-Positive	--	1	1	1	2	3
Patient Clinically Unevaluable:						
<i>H. influenzae</i> (BLA-)	5	1	6	1	3	4
<i>H. influenzae</i> (BLA+)	--	3	3	--	--	--
<i>H. parainfluenzae</i> (BLA-)	1	1	2	1	3	4
<i>H. parainfluenzae</i> (BLA+)	--	--	--	1	1	2
<i>M. catarrhalis</i> (BLA+)	4	2	6	1	3	4
<i>S. aureus</i> (Meth-S)	3	3	6	--	2	2
<i>S. pneumoniae</i> (PEN-S)	--	3	3	1	1	2
<i>S. pneumoniae</i> (PEN-I)	--	1	1	--	--	--
Other Gram-Negative	--	1	1	--	5	5
Other Gram-Positive	1	--	1	--	--	--

Over 60% of patients had a pre-treatment pathogen identified (see TABLE 9). Overall pathogen recovery rates were higher in study AI420-065. Of the three key respiratory pathogens, *Moraxella catarrhalis* was the most frequently identified, 82 isolates, all but two of which produced β -lactamase. One third of the 76 *H. influenzae* isolates were β -lactamase positive. *Streptococcus pneumoniae* was recovered in about 10% of the patients (63 or 646). Of the 63 strains, 17 were penicillin-intermediate and only two were fully penicillin-resistant. *Staphylococcus aureus* (123 isolates) and *H. parainfluenzae* (75 isolates) were also commonly recovered.

TABLE 9
Pathogens Recovered from Patients

	5-day Gatifloxacin			Comparator		
	064 N=174	065 N=147	Total N=321	064 N= 178	065 N=147	Total N=325
No. of Patients with Pathogens: (%)	106(61)	104 (71)	210 (65)	105 (59)	102 (69)	207 (64)
Single	73 (42)	65 (44)	138 (43)	73 (41)	70 (48)	143(44)
Multiple	33 (19)	39 (27)	72 (22)	32 (18)	32 (22)	64 (20)
Pathogens^a						
<i>S. pneumoniae</i>	17	16	33	19	11	30
Pen-Susceptible	14	8	22	14	10	24
Pen-Intermediate	3	6	9	5	1	6
Pen-Resistant	---	2	2	---	---	---
<i>S. aureus</i>	32	32	64	32	27	59
Methicillin-Susceptible	28	30	58	30	24	54
Methicillin-Resistant	4	2	6	2	3	5
<i>H. influenzae</i>	20	16	36	19	21	40
β -lactamase -	14	10	24	13	14	27
β -lactamase +	6	6	12	6	7	13
<i>M. catarrhalis</i>	17	28	45	18	19	37
β -lactamase -	---	1	1	---	1	1
β -lactamase +	17	27	44	18	18	36
<i>H. parainfluenzae</i>	17	23	40	12	23	35
β -lactamase -	14	21	35	10	22	32
β -lactamase +	3	2	5	2	1	3
Other Gram-Positive ^b	10	3	13	7	7	14
Other Gram-Negative ^c	34	34	68	39	32	71

^a Patients may have more than one pathogen

^b Includes *S. pyogenes*, *S. canis*, Strep Group C, *S. agalactiae*, and *S. constellatus*

^c Includes 28 different organisms

BACTERIAL RESPONSE BY PATHOGEN

The bacteriological response achieved at the Test-of-Cure Visit for patients who were clinically and microbiologically evaluable in each treatment group is shown by pathogen in TABLE 10.

TABLE 10
 Summary of Bacteriological Response (Eradicated/Total (%))

	Gatifloxacin			Comparator		
	064	065	Total	064	065	Total
All pathogens	85/87 (98)	77/88 (88)	162/175 (93)	87/89 (98)	73/87 (84)	160/174 (91)
<i>S. pneumoniae</i>	14/15 (93)	6/7 (86)	20/22 (91)	16/16 (100)	8/9 (89)	24/25 (96)
PEN-S	11/12 (92)	4/5 (80)	15/17 (88)	12/12 (100)	8/9 (89)	20/21 (95)
PEN-I	3/3 (100)	2/2 (100)	5/5 (100)	4/4 (100)	—	4/4 (100)
<i>S. aureus</i>	21/22 (95)	16/19 (84)	37/41 (90)	23/23 (100)	19/22 (86)	42/45 (93)
Meth-S	20/21 (95)	16/19 (84)	36/40 (90)	23/23 (100)	18/21 (86)	41/44 (93)
Meth-R	1/1 (100)	—	1/1 (100)	—	1/1 (100)	1/1 (100)
<i>H. influenzae</i>	15/15 (100)	11/12 (92)	26/27 (96)	18/18 (100)	15/18 (83)	33/36 (92)
BLA +	6/6 (100)	2/3 (67)	8/9 (89)	6/6 (100)	6/7 (86)	12/13 (92)
BLA -	9/9 (100)	9/9 (100)	18/18 (100)	12/12 (100)	9/11 (82)	21/23 (91)
<i>M. catarrhalis</i>	13/13 (100)	24/26 (92)	37/39 (95)	17/17 (100)	14/16 (88)	31/33 (94)
BLA +	13/13 (100)	23/25 (92)	36/38 (95)	17/17 (100)	13/15 (87)	30/32 (94)
BLA -	—	1/1 (100)	1/1 (100)	—	1/1 (100)	1/1 (100)
<i>H. parainfluenzae</i>	13/13 (100)	18/22 (82)	31/35 (89)	6/8 (75)	13/18 (72)	19/26 (73)
BLA+	2/2 (100)	2/2 (100)	4/4 (100)	1/1 (100)	—	1/1 (100)
BLA -	11/11 (100)	16/20 (80)	27/31 (87)	5/7 (71)	13/18 (72)	18/25 (72)
Other Gram-Pos ^a	9/9 (100)	2/2 (100)	11/11 (100)	6/6 (100)	3/3 (100)	9/9 (100)
Other Gram-Neg ^b	—	—	—	1/1 (100)	1/1 (100)	2/2 (100)

^a Includes *S. pyogenes*, *S. canis*, Strep C, *S. agalactiae*, *S. caris*, and *S. constellatus*

^b Includes *C. indologenes* and *A. radiobacteri*

Bacteriological response by pathogen was generally similar between gatifloxacin and the comparator groups. It appears that comparator group may be slightly better against *S. pneumoniae* and that gatifloxacin does better against *Haemophilus* species.

NDA #21-061...SE2-007
Bristol-Myers Squibb
Gatifloxacin Tablets

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