CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-061 and 21-062

MEDICAL REVIEW

Medical Officer Review of NDA 21-061 and 21-062: Gatifloxacin (Tequin ™)

Date Submitted:	28 December 1998
Date Received :	29 December 1998
Date Assigned:	29 December 1998
Date Completed:	21 December 1999

Applicant: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, Connecticut 06492
203-677-6883
Contact person: Douglas Kriesel, Ph.D.

Drug:

Proprietary name - Tequin ™

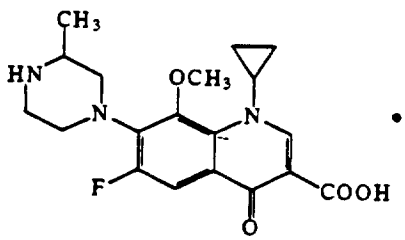
Generic name - Gatifloxacin

Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate

Molecular formula - $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$

Molecular weight - 402.42 (sesquihydrate)

Molecular structure -



• 1.5 H_2O

Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets

Related NDA: 21-062, 21-061 [redacted]

REVIEW TEAM:

Primary Reviewers:	Team Leaders:
Consumer Safety Officer: Brenda Atkins, BS Deloris Bernato, RN, MN	Ellen Frank, RPh
Chemistry: John Smith, PhD	Norman Schmuff, PhD
Pharmacological Toxicology: Amy Ellis, PhD (HFD-520)	Robert Osterberg, PhD Kenneth Hastings, Dr.PH
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Microbiology: Sousan Altaie, PhD (HFD520) Peter Dionne, MS (HFD-590)	Albert Sheldon, PhD (HFD-520) Sherry Lard, PhD (HFD-590)
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FDA EXECUTIVE SUMMARY: MEDICAL REVIEW

1.0 INTRODUCTION

Editorial Note: The medical review of gatifloxacin is organized into several sections, and this description should aid the reader. Sections 1.0 through 7.0 provide the reader with an integrated overview of the FDA reviews of efficacy and safety for this NDA, including recommendations and phase IV commitments. Specific review of each efficacy claim is reported in section 8.0. Each subsection within section 8.0 contains medical officer reviews of the clinical trials submitted in support of that specific indication. Each of these subsections contains an overall summary of all of the trials reviewed within that indication, and a more detailed table of contents for that section. The indication summary is located at the beginning of each indication subsection. Finally, the integrated summary of safety can be found in section 9.0.

Gatifloxacin or Tequin™ ((±-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid sesquihydrate)) is a fluoroquinolone antibiotic developed by Kyorin Pharmaceutical Co., Ltd. (Tokyo, Japan). Bristol-Meyers Squibb Company then developed gatifloxacin for the treatment of a wide range of infections. [redacted] performed additional clinical studies that are not included in this application, but will form the basis for the company's submission to the European Agency for approval. At the present time gatifloxacin is not approved in the U.S. or any other country in the world.

Structure-activity relationships have been noted within the fluoroquinolone class. It is believed that substitutions at position 8 of the ring are important determinants of activity of these compounds. Gatifloxacin is an 8-methoxy derivative; this substitution has been associated with enhanced Gram-positive activity. It is further believed that halogen atoms at position 8 have been associated with phototoxicity reported to occur in some of the fluoroquinolones. Again, gatifloxacin is an 8-methoxy derivative and does not have a halogen atom in this position.

The registrational dossier includes a total patient exposure of more than 14,000 patients worldwide. Studies were supported by three companies; Bristol-Meyers Squibb, [redacted] and Kyorin Pharmaceuticals (Tokyo, Japan).

The primary data supporting the efficacy and safety of gatifloxacin are derived from 36 studies conducted by Bristol-Meyers Squibb. These studies enrolled a total of 6,784 patients, with 4,395 receiving gatifloxacin and 2,389 receiving a comparator agent, or placebo (clinical pharmacology studies). As of June 30, 1998, the cut-off date for analysis of foreign data, all studies conducted by [redacted] and most of those supported by Kyorin were reported by the applicant to be still blinded. The safety data from these two companies was provided as a summary report in the Integrated Summary of Safety and the Periodic Report of Safety.

1.1 Chemistry

Gatifloxacin is available as 200 mg and 400 mg tablets (NDA 21-061) and 20 mL (200 mg) and 40 mL (400 mg) single use vials and in ready-to-use 100-mL (200 mg) and 200 mL (400 mg) flexible bags (NDA 21-062). Gatifloxacin exists as a racemate. For further details regarding the chemistry review, please refer to Dr. John Smith's review.

1.2 Microbiology

Gatifloxacin appears to be active against Gram-negative and Gram-positive aerobic micro-organisms. Based upon extensive review of the pharmacokinetics and MIC90 values from populations of organisms studied by the applicant, the MIC breakpoint was generally set at 2 mg/ml by the FDA with some exceptions (see labeling recommendations). FDA recommendations lower than 2 mg/ml were based upon the data presented by the applicant were populations of organisms were close to breakpoint of 2 mg/ml. (For additional detail please see microbiology review by Dr. Sousan Altaie and supplemental review by Dr. Dionne).

For specific recommendations regarding inclusion of organisms in the in vitro listing, please see Dr. Altaie's review. In general organisms which were excluded from the list by the FDA had insufficient numbers of isolates to warrant inclusion.

1.3 Pharmacological Toxicology

Standard pre-clinical toxicology studies were carried out by the applicant and referred to in this submission. For specific details and FDA review of these studies, please refer to the pharmacological toxicology section reviewed by Dr. A. L. Ellis.

Several areas were of particular interest to the clinical review of gatifloxacin and include the phototoxicity studies, articulator cartilage studies and cardiovascular toxicity studies.

Multiple dose studies in animals found that the currently recommended dose of 400 mg per day for 10-14 days was substantially lower than the exposure found to cause significant adverse events in rats, monkeys and dogs. Gatifloxacin produced reversible changes in glucose tolerance, serum insulin levels and morphology of pancreatic beta-cells when given orally to rats for 7 days at a dose of 810 mg/kg/day, but not at 270 mg/kg/day. Similar changes in beta-cells were seen in dogs (6 months at 24 mg/kg/day) and monkeys (5 months at 60 mg/kg/day) given orally. In the beagle dogs the microscopic findings were described as vacuolation of pancreatic beta-cells with dilation of rough endoplasmic reticulum. In monkey study, electron microscopy revealed vesiculation of rough endoplasmic reticulum and decreased secretory granules in pancreatic bets-cells, and these effects were determined to be reversible. Pancreatic beta-cell findings required the use of an electron microscope to be clearly identified and this technology is not used on a routine basis in studies conducted in the U. S. and Europe. However, these findings in the animal models lead the medical review team to further scrutinize the clinical database for potential, drug-induced cases of hyper- or hypoglycemia.

Phototoxicity studies did not show evidence of phototoxicity and/or sensitization in mice and guinea pigs. In juvenile rats and dogs, gatifloxacin produced arthrotoxic and osteotoxic effects similar to those seen with other quinolone antibiotics.

The electrocardiographic (ECG) profile of gatifloxacin has been evaluated in a number of animal studies. These include 1- and 6-month oral and 1-month intravenous studies in dogs, a 5 month study in monkeys, and safety pharmacology studies in dogs. The one-month dog study administered gatifloxacin at doses of 7, 20 and 60 mg/kg (lowered to 40 mg/kg on day 14). ECG changes were limited to the high dose group and included lower heart rates (week 2 only) and ventricular extrasystole in one of 12 animals (week 4 only). All changes returned to control values by the end of a 1-month post-dose period. In the 6-month oral toxicity study in dogs at doses of 6,12, and 24 mg/kg, the 1-month intravenous toxicity study in dogs at doses of 7, 15, and 30 mg/kg, and the 5-mongh oral toxicity study in monkeys at doses of 15, 30 and 60 mg/kg, no notable changes in heart rates of ECG were noted at any dose. In a battery of safety studies conducted in anesthetized dogs, decreases in blood pressure and heart rate, and reductions in QRS- and T-wave amplitude on ECGs were observed after a single 10-mg/kg IV bolus dose. When administered as a continuous 10-mg/kg iv infusion, these changes were not observed. No changes were noted after a 3/mg/kg iv dose. ECGs were performed continuously throughout the infusion of gatifloxacin. The maximum dose used in this study was approximately 4 times that anticipated to be given to humans (400 mg/day). It would have been preferable to continue the dose escalation to a higher dose to insure a wider margin of safety. Given these studies, the applicant concluded there was little potential for cardiovascular effects to occur with gatifloxacin treatment. However, additional studies were undertaken in Phase II human studies (see below). *In vitro* studies of the inward rectifier potassium channel pump (Ikr) were not performed originally. The applicant supplied the FDA with the results (in draft form only) of this enzyme assay in November, 1999. Details are provided in section 9.4.2. This model reported preliminary data that gatifloxacin was similar in activity to that of ciprofloxacin for its effect on the Ikr. The applicant will send the FDA a final report of this study for additional varification.

In vitro studies, to evaluate the inhibitory activity of gatifloxacin on cytochrome P450 isozymes 3A4, 1A2, and 2C9, revealed that gatifloxacin is not an inhibitor of these enzymes and thus is unlikely to significantly alter the metabolic clearance of drugs metabolized by the cytochrome P450 isozymes evaluated.

The results of the nonclinical pharmacokinetic studies showed that the pharmacokinetics of gatifloxacin and its individually administered R- and S-enantiomers were essentially identical following intravenous and oral administration. In addition there was no *in vivo* interconversion of the R- and S-enantiomers detected when serum samples, obtained after intravenous infusion of each pure enantiomer to rats, dogs, or monkeys, were analyzed using an analytical method specific for the individual enantiomers.

1.4 Clinical Pharmacology

Gatifloxacin is highly water soluble. The applicant states that with the addition of a methyl substituted piperazinyl group metabolic stability is provided (as evidenced by unchanged drug elimination primarily by the kidney), and may minimize interaction with drug metabolizing enzymes with corresponding decrease in risk of metabolically-based drug-drug interactions.

The single and multiple dose oral and intravenous administration of gatifloxacin have been studied in approximately 750 volunteers and patients.

The following tables reflect the primary phramacokinetic parameters which the FDA has reviewed with the sponsor and which appear in the gatifloxacin label.

"**Pharmacokinetics**

The mean (SD) pharmacokinetic parameters of gatifloxacin after single 200-mg oral doses, single and multiple 400-mg oral doses, and single and multiple one-hour intravenous infusions of 200 mg and 400 mg are listed in Tables 1 and 2.

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Table 1
Gatifloxacin Pharmacokinetic Parameters – Oral Administration

	C_{max} (µg/mL)	T_{max}[a] (h)	AUC[b] (µg•h/mL)	$T_{½}$ (h)	Cl/F (mL/min)	Cl_R (mL/min)	UR (%)
200 mg - Healthy Volunteers							
Single Dose (n=12)	2.0±0.4	1.00 (0.50, 2.50)	14.2±0.4	-	241±40	-	73.8±10.9
400 mg - Healthy Volunteers							
Single Dose (n=202)[c]	3.8±1.0	1.00 (0.50, 6.00)	33.0±6.2	7.8 ±1.3	210±44	151±46	72.4±18.1
Multiple dose (n=18)	4.2±1.3	1.00 (0.50, 4.00)	34.4±5.7	7.1 ±0.6	199±31	159±34	80.2±12.1
400 mg - Patients with Infection							
Multiple dose (n=140)[d]	4.2 ±1.9	-	51.3 ± 20.4	-	147±48	-	-
400-mg Single Dose - Subjects with Renal Insufficiency							
CL_{cr} 50-89 mL/min (n=8)	4.4 ± 1.1	1.13(0.75,2.00)	48.0 ± 12.7	11.2 ± 2.8	148 ± 41	124 ± 38	83.7 ± 7.8
CL_{cr} 30-49 mL/min (n=8)	5.1 ± 1.8	0.75 (0.50,6.00)	74.9 ± 12.6	17.2 ± 8.5	92 ± 17	67 ± 24	71.1 ± 7.4
CL_{cr} < 30 mL/min (n=8)	4.5 ± 1.2	1.50 (0.50,6.00)	149.3 ± 35.6	30.7 ± 8.4	48 ± 16	23 ± 13	44.7 ±13.0
Hemodialysis (n=8)	4.7 ± 1.0	1.50 (1.00,3.00)	180.3 ± 34.4	35.7 ± 7.0	38 ± 8	-	-
CAPD (n=8)	4.7 ± 1.3	1.75 (0.50,3.00)	227.0 ± 60.0	40.3 ± 8.3	31 ± 8	-	-

[a] Median (Minimum, Maximum)
[b] Single dose: AUC(0-∞), Multiple dose: AUC(0-24)
[c] n=184 for Cl/F, n=134 for Cl_R, and n=132 for UR;
[d] Based on the patient population pharmacokinetic modeling, n=103 for C_{max}
C_{max}: Maximum serum concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Cl/F: Apparent total clearance; Cl_R: Renal clearance; UR: Urinary recovery; CAPD: Continuous ambulatory peritoneal dialysis.

Table 2
Gatifloxacin Pharmacokinetic Parameters – Intravenous Administration

	C_{max} (µg/mL)	T_{max}[a] (h)	AUC[b] (µg•h/mL)	$T_{½}$ (h)	Vd_{ss} (L/kg)	Cl (mL/min)	Cl_R (mL/min)	UR (%)
200 mg - Healthy Volunteers								
Single dose (n=12)	2.2±0.3	1.00 (0.67, 1.50)	15.9 ± 2.6	11.1 ± 4.1	1.9 ± 0.1	214 ± 36	155 ± 32	71.7 ± 6.8
Multiple dose (n =8)[c]	2.4±0.4	1.00 (0.67, 1.00)	16.8 ± 3.6	12.3 ± 4.6	2.0 ± 0.3	207 ± 44	155 ± 55	72.4 ± 16.4
400 mg - Healthy Volunteers								
Single dose (n=30)	5.5±1.0	1.00 (0.50, 1.00)	35.1 ± 6.7	7.4 ± 1.6	1.5 ± 0.2	196 ± 33	124 ± 41	62.3 ± 16.7
Multiple dose (n=5)	4.6±0.6	1.00 (1.00, 1.00)	35.4 ± 4.6	13.9 ± 3.9	1.6 ± 0.5	190 ± 24	161 ± 43	83.5 ± 13.8

[a] Median (Minimum; Maximum)
[b] Single dose: AUC(0-∞), Multiple dose: AUC(0-24)
[c] n=7 for Cl_R and UR
C_{max}: Maximum serum concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Vd_{ss}: Volume of distribution; Cl: Total clearance; Cl_R: Renal clearance; UR: Urinary recovery.

Gatifloxacin pharmacokinetics are linear and time-independent at doses ranging from 200 to 800 mg administered over a period of up to 14 days. Steady-state concentrations are achieved by the third daily oral or intravenous dose of gatifloxacin. The mean steady-state peak and trough plasma concentrations attained following a dosing regimen of 400 mg once daily are approximately 4.2 • g/mL and 0.4 • g/mL,

respectively, for oral administration and 4.6 • g/mL and 0.4 • g/mL, respectively, for intravenous administration."

The volume of distribution at Steady-State of gatifloxacin ranges from 1.5 to 2.1 L/kg, exceeds total body water, suggesting that gatifloxacin accumulates intracellularly and/or binds to tissue constituents. This larger volume of distribution is consistent with approximately 20% protein binding of the drug.

Gatifloxacin does not undergo appreciable metabolic biotransformation. Based on assays of urine from subjects receiving 400 mg oral doses of gatifloxacin, two minor (oxidative) metabolites, each accounting or 0.03% of the dose when urine was collected over 72 hours, were found. No glucuronide metabolites appear to be formed in humans.

In human, drug interaction studies, gatifloxacin does not alter the pharmacokinetics of theophylline, warfarin, midazolam, or glyburide. Digoxin dose adjustments are warranted for concomitant gatifloxacin and digoxin administration, this is due the potential for gatifloxacin to eradicate E.lentum form the gastrointestinal tract, an organism that may be responsible for the presystemic elimination of digoxin.

Food does not have an effect on the pharmacokinetics of gatifloxacin. However, cations delay gatifloxacin absorption. For further information regarding this issue, please see Dr. Uhl's review and the label recommendations.

Dose adjustment was recommended for moderate renal failure. Child-Pugh B (moderate) class of cirrhosis was studied, and it appears that no dose adjustment is required for these classes. Severe hepatic impairment was not studied at the time of this submission.

A phototoxicity study was conducted which further supports the lack of phototoxic potential of gatifloxacin.

Additional phase I/II studies of the effect of gatifloxacin on glucose metabolism and ECGs were undertaken. Discussion of the results of these studies is listed in sections 9.4.8 and 9.4.2., and in Dr. Uhl's review.

1.4 Statistical Considerations

A global statistical issue was raised by the applicant's use of a dynamic randomization process. It was important for FDA to understand the effect such a process would have on the outcome analysis. At this time there is no statistical analysis that would take this randomization process into account. The analyses conducted by the FDA assumed simple randomization. At the request of the FDA the applicant undertook simulations in an attempt to address this issue. Though only a fixed number of possible scenarios could be simulated, the results showed that results based on data randomized using the Pocock-Simon randomization technique were not less conservative than results based on data randomized using simple randomization, or permutated block randomization. Since the conclusions could not be proven theoretically the true affect of dynamic randomization on the results in unknown. However, based on these simulations the FDA statistical reviewers feel that the results in this applicant could be expected to be similar to the

results that would have been obtained had simple randomization been used. Hence, the outcomes would be no worse than those reported by the applicant. Dr. Silliman's review further details the effect of the dynamic randomization on the efficacy analyses.

The statistical review of efficacy was performed in concert with the medical review. For the most part the clinical reviewers were in agreement with the applicant's assessment of cases. Thus, the statistical reviewers were able to verify the applicant's analyses and perform sensitivity analyses. For further information regarding statistical review, please refer to FDA reviews by Dr. Silliman and Dr. Higgins.

1.5 Other : Electronic NDA Submission

The medical review was based upon the submission of an electronic database. The applicant supplied efficacy and safety data for each of the pivotal studies reviewed in this application in the form of a SAS transport file. These files were utilized by the medical reviewers using the JMP data program. PDF files were provided for the CRFs and patient profiles. The CRFs were adequately book-marked for relative ease of use. Electronic study reports were provided in Microsoft Word format.

In general, the FDA review and verification of the analyses provided by the applicant were in agreement. There were relatively few mistakes in the translation of the data from the CRFs to the data tables, and these were of a minor nature and did not effect the overall analysis. This was the first review for the medical officers utilizing the JMP statistical program. In general, it took some time to understand the functionality of the program and the database provided by the applicant. It was felt by most of the reviewers to be relatively easy to access the data that was to be reviewed. There were some minor recommendations regarding the formatting of certain variables. For example, it was difficult to perform an independent review of the patients who discontinued due to an adverse event. Information regarding this variable was spread across several columns and was not easily manipulated. Finally, JMP as a review tool is very useful in sub-setting the data; however, it does not provide an audit trail so that it is clear how the resulting data table was obtained. Short of taking notes or trying to re-run the analysis it is difficult to document these tables. The PDF files for the CRFs were useful and fairly well book-marked. No primary data form was provided to verify the microbiology data.

2.0 SUMMARY OF EFFICACY

(Note all of the 95% Confidence Intervals are for the difference in success rate (Gatifloxacin minus Comparator, unless otherwise specified).

2.1 Community Acquired Pneumonia: (for complete review of this indication please see Dr. Korvick's review in Section 8.1)

The NDA submission included data from 5 clinical studies; 3 controlled (Study 002, 037, 038), 2 open label (003,006). Gatifloxacin was given at a dose of 400 mg daily in each of the studies. Study 037 and 038 included an iv to oral switch, the other studies administered Gatifloxacin orally (Study 002, 003, 006).

Study Number	Study Design	Start-Completion Dates	Number of Subjects	Age (yrs)	Comparator
- 002	Randomized, double-blind, multi-center, Phase III	23Jun97-24Jun98	431	18-97	Clarithromycin 500 mg PO 7-14 days
- 037	Randomized, double-blind, multi-center, Phase III	16Nov97 - 26Jun98	283	18-92	Ceftriaxone 1-2g QD IV ± Erythromycin 0.5-1.0g QID IV with step down to Clarithromycin 500 mg PO BID 7-14 days
- 038	Randomized, double-blind, multi-center, Phase III	6Nov97-11Jun98	417	19-91	Levofloxacin 500 mg QD either PO or IV → PO 7-14 days
- 003	Open-label, Non-controlled, Phase II	18Feb97 - 30Apr98	150	18-92	NONE
- 006	Open-label, Non-controlled, Phase II	12Apr97 - 15Jan98	45	18-76	NONE

FDA review of the applicant's studies was in general agreement. There were very few outcome assignments that the medical officer did not agree with, and these did not result in significant differences in the calculated efficacy rates represented below.

It should be noted that the patients enrolled into study -037 were hospitalized and noted to have more severe pneumonia than the other study populations.

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APPLICANT'S CLINICAL EFFICACY RESULTS BY SUBGROUP*

Analysis Population	Gatifloxacin	Comparator	95% Confidence Interval
STUDY 002			
		Clarithromycin	
All Treated Patients (N=431)	82% (177/217)	85% (203/214)	-12.8%, 3.2%
Eligible Patients (N=412)	84% (173/207)	87% (178/205)	-11.7%, 4.4%
Evaluable Patients (N=381)	88% (169/191)	91% (172/190)	-10.1%, 5.1%
STUDY 037			
		Ceftriaxone	
All Treated Patients (N=287)	73% (102/141)	70% (103/142)	-8.4%, 14.8%
Eligible Patients (N=276)	74% (100/136)	71% (99/140)	-8.5%, 15.0%
Evaluable Patients (N=212)	88% (92/104)	85% (92/108)	-7.6%, 15.3%
STUDY 038			
		Levofloxacin	
All Treated Patients (N=417)	83% (173/209)	88% (183/208)	-13.1%, 2.7%
Eligible Patients (N=400)	89% (168/203)	95% (175/197)	-14.5%, 1.7%
Evaluable Patients (N=350)	90% (154/172)	93% (166/178)	-11.5%, 3.6%
STUDY 003			
All Treated Patients	84% (126/150)	----------	77.1%, 89.5%
Clinically Eligible	84% (113/134)	----------	----------
Clinically Evaluable	89% (109/122)	----------	82.5%, 94.2%
STUDY 006			
All Treated Patients	62% (28/45)	----------	46.5%, 76.2%
Eligible Patients	68% (28/41)	----------	----------
Evaluable Patients	90% (27/30)	----------	73.5%, 97.9%

* Cure Rates

The clinical cure rates for gatifloxacin in the Evaluable Patient population ranged from 88% to 90% compared to the control group cure rates of 85% to 93%. The FDA performed several sensitivity analyses controlling for enrollment site, global failure rates (failures and relapses), severity of illness, and a conservative loss to follow-up analysis. In general the cure rates in the levofloxacin and clarithromycin treatment groups tended to be higher than those for gatifloxacin. The comparison of gatifloxacin to levofloxacin for the evaluable patient analysis demonstrated a 90% vs. 93% clinical cure rate, respectively. The lower bound of the confidence interval for this comparison (gatifloxacin - levofloxacin) was -11.5%. The applicant had assumed, for purposes of analysis, that the efficacy rates would be in the 80% range when defining the confidence interval for equivalence. In this case, the applicant stated that equivalence would be defined if lower limit of the confidence interval did not exceed -15%. Regarding this bound, where the efficacy rates were in the 90% range, the applicant made no comment. In the past the FDA had recommended the lower bound for the confidence interval of the

difference to be no greater than -10%; however, this recommendation is under reconsideration by the FDA. The overall conclusion regarding the comparison of gatifloxacin to levofloxacin shows that the clinical cure rates are lower than those of levofloxacin, and that a weak equivalence relationship was shown in this study. Gatifloxacin had a somewhat higher cure rate than ceftriaxone.

Overall, the lower limits of the confidence intervals did not exceed -15% in these analyses (where the outcomes were in the 809% range or lower), except for the very conservative loss to follow-up analysis. These analyses reported in the table above supported the overall assessment that gatifloxacin is efficacious for the treatment of community acquired pneumonia. Further, because of the activity to treat pneumonia, these studies are felt to be supportive of the acute exacerbation of chronic bronchitis indication.

Because of the difficulty in assessing cases of atypical pneumonia according to serology, and effort was made by the FDA to more stringently classify cases of definite atypical pathogens. For a complete description of this analysis please refer to details in Section 8.1. The results are listed below.

FDA Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin (Studies 002,037,038)

	M. pneumoniae	*C. pneumoniae*	*L. pneumophila*
Culture positive or PCR	14*	2	0
Definitive (4X rise in IgG or IgM)	1	4	5
Presumptive (single high titer)	16	14	14
Urinary Antigen	NA	NA	0
TOTAL	31	20	19

*culture proven

All of these patients were clinical cures except for one which was diagnosed with *M. pneumoniae*. In addition, M. pneumoniae was the only pathogen in which cultures were positive. When the "10% rule" (See appendix accompanying Community Acquired Pneumonia review: Section 8.1) is applied to the microbiologically evaluable patient population then 40 cases would be required. However, from an epidemiological point of view, these pathogens may cause from 2-5% of the community acquired pneumonia encountered in the population at large. Taking this in to consideration would allow for between 8-20 cases to be studied in order for these organisms to be included in the label. Based upon the FDA analysis each of these pathogens may be included. Finally, regulatory history shows that for *C. pneumoniae* and *L. pneumophila*, inclusion of these pathogens was based solely upon serologic criteria. The approval of Levofloxacin was based upon161 cases of *C. pneumoniae* and 10 cases of *L.pneumophila*, Azithromycin IV was based upon 21 cases of *C. pneumoniae* and 16 cases of *L. pneumonphila*, Grepafloxacin was not granted the indication for *L. pneumophila* due to fewer than 10 cases being studied.

The FDA reviewer recommended gatifloxacin for this indication due to the following organisms: *S. pneumoniae* (penicillin-susceptible only), *H. influenzae, H. parainfluenzae, M. catarrhalis* and *S. aureus.* There were not enough cases of *Klebsiella pneumoniae* or *S. pneumoniae* (penicillin-resistant) studied to warrant the inclusion of either pathogen in this clinical indication.

The FDA further recommended that it should not be stated that there was Microbiologic Eradication of these atypical pathogens, even though the definition in the protocol states that this could be based on clinical cure as a presumptive eradication. This study supports the inclusion of these pathogens in the proposed label; however, it is highly recommended that a statement be made regarding the low numbers treated and the method of detecting the pathogen (serology).

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2.2 Acute Exacerbation of Chronic Bronchitis: (for complete review of this indication please see Dr. Akl's review in Section 8.2)

Three studies were submitted by the applicant in support of this indication. They are listed below.

Overview of Studies

Protocol/Phase	Study Type	Dose/Duration	Number of Patients
AI420-004 (study 4) Phase II	Multicenter, open-label non-comparative trial	Gatifloxacin 400 mg PO qd for 10 days	210 enrolled, 162 evaluable
AI420-001 (study 1) Phase III	Multicenter, randomized, double-blind controlled trial	Gatifloxacin 400 mg PO qd vs. Levofloxacin 500 mg PO qd for 7-10 days	360 enrolled, 296 evaluable
AI420-020 (study 20) Phase III	Multicenter, randomized, double-blind controlled trial	Gatifloxacin 400 mg PO qd vs. cefuroxime axetil 250 mg PO BID for 7-10 days	340 enrolled, 284 evaluable

The FDA reviewer performed several sensitivity analyses regarding the following issues:

- The applicant's definition of cure in studies 1 and 20 included those patients whose symptoms improved as well as those whose symptoms returned to baseline. Therefore a separate analysis was done that considered as cured only those patients whose 3 cardinal symptoms of cough, dyspnea and sputum production either returned to baseline at the TOC visit, or were only improved at the TOC visit but returned to baseline at the extended follow-up visit. This is referred to below as "reviewer's analysis #1".

- The applicant included in the analysis those patients who had >10 epithelial cells/LPF in their sputum. Another separate analysis was done that considered ineligible those patients whose sputum contained >10 epithelial cells/LPF. This was referred to as "reviewer's analysis #2".

- A third analysis was done that took into account both above issues. This was referred to as "reviewer's analysis #3".

The results of these analyses are compared to the applicant's analysis in the following tables.

Clinical Efficacy of Gatifloxacin and Comparator (Applicant' Analysis)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.*	Eligible Patients Efficacy Rate	95% C.I.*
Study 4	Gatifloxacin	88% (143/162)	(82%, 93%)	80% (143/178)	(74%, 86%)
Study 1	Gatifloxacin	88% (127/145)	(-14.6%, 6.2%)	77% (129/167)	(-17.6%, 4.5%)
	Levofloxacin	92% (139/151)		83% (141/169)	
Study 20	Gatifloxacin	86% (124/145)	(-4.8%, 11.4%)	81% (126/156)	(-6.9%, 10.6%)
	Cefuroxime	83% (115/139)		79% (121/153)	

* 95% Confidence Interval for the cure rate for study 4, and around the difference in cure rates for studies 1 and 20.

Clinical Efficacy of Gatifloxacin and Comparator (Reviewer's Analysis #1)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.	Eligible Patients Efficacy Rate	95% C.I.*
Study 1	Gatifloxacin	70% (102/145)	(-13.8%, 5.6%)	62% (103/167)	(-15.9%, 4.3%)
	Levofloxacin	75% (113/151)		68% (114/169)	
Study 20	Gatifloxacin	61% (88/145)	(-19.24%, 23.28%)	58% (90/156)	(-18.89%, 19.54%)
	Cefuroxime	59% (82/139)		58% (88/153)	

*95% Confidence Interval around the difference in cure rates.

Clinical Efficacy of Gatifloxacin and Comparator (Reviewer's Analysis #2)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.	Eligible Patients Efficacy Rate	95% C.I.*
Study 1	Gatifloxacin	87% (115/132)	(-16.3%, 9.1%)	77% (117/152)	(-19.8%, 8.8%)
	Levofloxacin	91% (120/132)		82% (122/149)	
Study 20	Gatifloxacin	85% (112/132)	(-5.61%, 11.75%)	81% (114/140)	(-5.54%, 12.87%)
	Cefuroxime	82% (104/127)		78% (109/140)	

*95% Confidence Interval around the difference in cure rates.

Table 6 **Clinical Efficacy of Gatifloxacin and Comparator (Reviewer's Analysis #3)**

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.	Eligible Patients Efficacy Rate	95% C.I.*
Study 1	Gatifloxacin	71% (94/132)	(-15.7%, 8.4%)	63% (95/152)	(-18.1%, 8.2%)
	Levofloxacin	75% (99/132)		67% (100/149)	
Study 20	Gatifloxacin	58% (76/132)	(-24.91%, 24.87%)	55% (78/140)	(-23.4%, 23.21%)
	Cefuroxime	58% (73/127)		55% (78/140)	

*95% Confidence Interval around the difference in cure rates.

In line with the recent July 1998 Anti-infective Advisory Committee meeting, the limit of equivalence will be considered independent of the observed response. Since 15% was discussed and agreed upon by the FDA in reference to all recently submitted gatifloxacin protocols, 15% will be used in determining equivalence in studies 1 and 20. For study 1, cure rates were slightly higher for levofloxacin across all analyses. The lower limit of the 95% CI for the 4 analyses is within or slightly beyond the designated limit of –15%. For study 20, cure rates were equal or slightly higher for gatifloxacin. The 95% CI for the difference in cure rates were narrow, but widened when patients who were only improved (but not cured) were considered as failures, and the lower limit exceeded –15%. These results are supportive of this indication and are further supported by the studies on community acquired pneumonia.

Additional analyses were performed by the stratification variable "smoking status". It should be noted that the study was stratified by smoking status. Results of studies 1 and 20 show that patients who were current smokers at study entry had a higher cure rate than those who were not, both in the gatifloxacin arm and the comparator arm (a patient was considered a current smoker if he or she was a smoker at the time of enrollment or had stopped smoking within the two months before enrollment). To find out if other variables accounted for this difference in response rates, logistic regression analyses were performed for current smoking status and history of smoking on the clinical response using the following covariates: age, race, gender, history of asthma, use of other drugs concomitantly and the presence of one of the 5 major pathogens isolated. The analyses did not identify any significant imbalance between the various treatment groups that would explain the observed effect of current smoking status on the overall outcome. Its value as a prognostic variable in these studies remains uncertian, perhaps due to the particular definition assigned in the protocol for smoking status.

The FDA reviewer recommended approval of gatifloxacin for the treatment of acute exacerbation of chronic bronchitis. In addition, regarding microbiologic efficacy were supportive of effectiveness against the major pathogens involved in AECB, *namely H. influenzae, S. pneumoniae* and *M. catarrhalis*, but also against *S. aureus and H. parainfluenzae.*

2.3 Acute Sinusitis (for complete review of this indication please see Dr. Mann's review in Section 8.3)

The sponsor submitted three clinical studies in support of the acute bacterial sinusitis indication for gatifloxacin:

Protocol	Study Type	Dose/Frequency/Duration	Number of Patients
AI420-008	Multicenter, randomized, double-blind, controlled trial	Gatifloxacin 400 mg qd for 10 days Clarithromycin 500 mg bid for 14 days	Gatifloxacin 211 enrolled, 146 evaluable Clarithromycin 214 enrolled, 157 evaluable
AI420-007	Multicenter, open-label, uncontrolled trial	Gatifloxacin 400 mg qd for 10 days	Gatifloxacin 445 enrolled, 339 evaluable
AI420-066*	Multicenter, randomized, double-blind, controlled Trial	Gatifloxacin 400 mg qd for 10 days Trovafloxacin 200 mg qd for 10 days	Gatifloxacin 124 enrolled, 113 evaluable Trovafloxacin 131 enrolled, 115 evaluable

*Study No. AI420-066 was submitted to the NDA as a major amendment on June 11, 1999.

The following efficacy tables represent the applicant's analyses and the FDA analyses. The differences resulting from changing classification of cures and inclusion or exclusion from specific analysis populations. It should be noted that in only one study antral puncture of the maxillary sinus was performed and microbiologic cultures obtained.

Clinical Efficacy of Gatifloxacin and Comparators in Acute Sinusitis (per Sponsor)

Study	Drug	Clinically Evaluable Patients		All-Treated Patients	
		Efficacy Rate	95% C.I.*	Efficacy Rate	95% C.I.*
AI420-008	Gatifloxacin	72% (105/146)	(-15.2, 6.7)	62% (131/210)	(-10, 9.6)
	Clarithromycin	76% (119/157)		63% (132/211)	
AI420-007	Gatifloxacin	79% (276/339)	(76.9%,85.4%)	78% (329/424)**	(73.3%,81.5%)
AI420-066	Gatifloxacin	88% (99/113)	(-9.6, 12.2)	80% (99/123)	(-7.2, 16.1)
	Trovafloxacin	87% (100/116)		76% (100/131)	

*95% confidence interval (C.I.) refers to point estimate for gatifloxacin efficacy rate in Study AI420-007 and refers to the difference in efficacy rates for the remaining studies
**Eligible patient population

Clinical Efficacy of Gatifloxacin and Comparators in Acute Sinusitis (per Medical Officer)

Study	Drug	Clinically Evaluable Patients		All-Treated Patients	
		Efficacy Rate	95% C.I.*	Efficacy Rate	95% C.I.*
AI420-008	Gatifloxacin	61% (89/146)	(-16.5, 6.6)	54% (113/210)	(-9.0, 11.0)
	Clarithromycin	66%(103/157)		53% (112/211)	
AI420-007	Gatifloxacin	79% (276/339)	(76.9%,85.4%)	78% (329/424)**	(73.3%,81.5%)
AI420-066	Gatifloxacin	88%(94/107)	(-7.0, 15.8)	80% (99/123)	(-5.8, 17.7)
	Trovafloxacin	84%(94/112)		75% (98/131)	

*95% confidence interval (C.I.) refers to point estimate for gatifloxacin efficacy rate in Study AI420-007 and refers to the difference in efficacy rates for the remaining studies
**Eligible patient population

The reviewer recommended approval of the acute sinusitis indication for *Streptococcus pneumoniae* and *Haemophilus influenzae*, but not *Moraxella catarrhalis* based upon the supporting microbiological efficacy data from study 007. Simply, there were not enough documented cases of *Moraxella catarrhalis*.

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2.4 Uncomplicated Skin and Skin Structure: (for complete review of this indication please see Dr. Roca's review in Section 8.4)

The applicant submitted one study in support of the requested indication. The study was a randomized, double-blind, multicenter study. Twenty-seven centers were recruited, and 410 patients were enrolled. Patients were randomized to gatifloxacin, 400 mg daily, or levofloxacin, 500 mg daily. Duration of treatment was 7 to 10 days.

In general the FDA review was in agreement with the applicant results. The following is a summary of the applicant by type of infection which was reproduced from the original proposed label.

BMS Analysis

	Clinical Cure at Test of Cure Visit	
Diagnosis	Gatifloxacin	Levofloxacin
All Diagnoses	91% (146/161)	84% (145/172)
Abscess	80% (28/35)	79% (37/47)
Cellulitis/Erysipelas	98% (39/40)	84% (36/43)
Folliculitus	87% (34/39)	84% (26/31)
Impetigo	100% (10/10)	100% (11/11)
Wound Infection	95% (35/37)	88% (35/40)

Since Study AI420-005 did not enroll enough patients with erysipelas or impetigo to be able to draw any conclusions, these two diagnoses must be removed from the table.

The FDA reviewer did recommend gatifloxacin for approval as follows:

> Gatifloxacin is indicated for the treatment of "...simple abscesses, furuncles, folliculitis, wound infections, and cellulitis caused by to methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pyogenes*. Insufficient number of patients with the diagnosis of impetiginous lesions were studied to be able to draw any conclusions."

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2.5 Uncomplicated Urinary Tract Infection: (for complete review of this indication please see Dr. Tiernan's review in Section 8.5)

The applicant submitted one study in support of the requested indication: treatment of uncomplicated urinary tract infection (cystitis). The proposed dosage for the treatment of cystitis is either a single, oral 400 mg dose or the 200 mg oral dose once daily for 3 days.

Study A1420-010 was a Randomized, double blind, multicenter, Phase II/III study. There were 57 outpatient centers recruiting patients in the United States; 50 centers enrolled patients.

Study Design	Start-Completion Dates	Number of Subjects	Age	Dose / Duration of Treatment
Randomized, double blind, multicenter, Phase II/III	27 June 1997-4 June 1998	1334 enrolled, 1323 received at least one dose of study drug	≥ 18 years	Gatifloxacin 400 mg qd x 1 dose; OR Gatifloxacin 200 mg qd x 3 days; OR Ciprofloxacin 100 mg bid x 3 days

Table 12 is the Applicant's summary of the bacteriologic response rates for the four analysis populations (verified by FDA). Eradication rates are slightly lower in the clinically eligible (83-89%) and all treated patients (83-89%) because missing values were imputed to be failures. In all populations, both gatifloxacin regimens were considered to be equivalent to ciprofloxacin.

Table 12: Eradication Rates by Analysis Population[1]

	Number Eradicated/Number of Patients (%)							
Analysis Population	Gatifloxacin 400 mg x 1D N = 436		Gatifloxacin 200 mg x 3D N = 443		Ciprofloxacin N = 444		97.5% Confidence Interval (gati 1D - cipro)	97.5% Confidence Interval (gati 3D - cipro)
All Treated	186/223	(83%)	198/223	(89%)	188/227	(83%)	(-8.1%, 9.9%)	(-2.2%, 14.8%)
Clin Eligible	183/218	(84%)	194/219	(89%)	183/221	(83%)	(-7.3%, 9.6%)	(-2.1%, 13.7%)
Clin Evaluable	181/205	(88%)	190/207	(92%)	179/203	(88%)	(-7.5%, 7.8%)	(-3.5%, 10.7%)
Micro Evaluable	181/202	(90%)	190/201	(95%)	179/201	(89%)	(-7.8%, 8.9%)	(-2.1%, 13.2%)

1. Applicant analysis.

In addition, it should be noted that in the microbiologically evaluable population, the rates among patients for sustained eradication of all uropathogens in the three treatment groups were equivalent. Approximately, ten percent of patients overall had a "recurrence" of the original uropathogen (only one patient had a resistant isolate, and they were in the ciprofloxacin group). Similarly, 2% of patients overall had the growth of other uropathogens in significant numbers. At the extended follow-up visit, the three groups had comparable rates of sustained cure with an overall rate of 83%.

The medical reviewer recommended approval of gatifloxacin for the utilized for the treatment of Gatifloxacin 200 mg daily for three days or Gatifloxacin 400 mg one dose for:

"Uncomplicated urinary tract infection (cystitis) caused by *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

An insufficient number of clinical cases of uncomplicated urinary tract infection due to *Staphylococcus saprophyticus*, therefore, it was not recommended for the final label.

Both doses of gatifloxacin were shown to be effective in the treatment of uncomplicated urinary tract infection. Each has a slightly different side effect profile. The one time 400-mg dose of gatifloxacin was noted to have a somewhat greater frequency of discontinuation due to nausea and vomiting. The 200-mg dose X 3 days was noted to cause a more frequent occurrence of vaginitis than the single 400-mg dose of gatifloxacin. From the risk/benefit standpoint, it was felt that the duration of exposure was low with both the single dose and the 3 day (half the single dose) dose that concerns about the effect of gatifloxacin on the QTc interval would be expected to be very rare.

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2.6 Complicated Urinary Tract Infection: (for complete review of this indication please see Dr. Roca's review in Section 8.7)

The clinical data in the applicant's NDA submission for this indication were derived from two clinical trials. They were multicenter, randomized, double-blind active control trials. There were a total of 70 centers recruited, of which 59 were able to enroll patients. Study AI420-031 was conducted entirely in the United States; Study AI420-011 was predominantly conducted in the United States, however it did contain 5 Canadian sites. The table below outlines the clinical trials:

Study Number	Study Design	Start - Completion Dates	Number of Subjects	Age Range	Dose	Duration of Treatment
AI420-031	Randomized, double-blind, multi-center, Phase III study	20 August 1997 – 9 July 1998	376 enrolled; 372 received at least one dose of therapy	18-90 years	Daily doses of either 400 mg of gatifloxacin, or 500 mg of ciprofloxacin twice a day	7 to 10 days
AI420-011	Randomized, double-blind, multi-center, Phase III study	27 July 1997 – 3 June 1998	354 enrolled; 350 received at least one dose of therapy	18-90 years	Daily doses of either 400 mg of gatifloxacin, or 500 mg of ciprofloxacin twice a day	7 to 10 days

In the microbiologically evaluable population, the applicant reported a response rate that was equivalent to the comparator.

	Response/Number of patients (%)		
	Gatifloxacin	Ciprofloxacin	95% Confidence Interval*
Clinically eligible patients	172/260 (68)	173/264 (66)	-6.1, +10.1
Complicated UTI	147/221 (67)	149/222 (66)	
Pyelonephritis	29/39 (74)	27/42 (64)	
Microbiologically evaluable	155/177 (88)	157/189 (83)	-4.5, +14.2
Complicated UTI	128/147 (87)	132/161 (82)	
Pyelonephritis	27/30 (90)	25/28 (89)	
Sustained Eradication	102/132 (77)	93/129 (72)	-5.5, +15.5
Complicated UTI	82/106 (77)	75/106 (71)	
Pyelonephritis	20/26 (77)	18/23 (78)	

Adapted from Table 7.10 (ISSE, p. 340)
*Confidence interval of the difference in response rate (Gatifloxacin - comparator)

Additional analyses by Dr. Silliman to assess the strength of the data included evaluation of the response rates based on the patient populations, site and diagnoses. The analyses helped to confirm that the data submitted appeared to be robust, and support the applicant's claim of comparable efficacy to ciprofloxacin in this indication.

The microbiological data submitted by the applicant however, was not sufficient to support their claim of efficacy for all of the pathogens that were listed in the proposed label.

The medical officer recommendations for gatifloxacin regarding complicated the indications of urinary tract infection and pyelonephritis are:

1. Approval of gatifloxacin for the indication of treatment of complicated urinary tract infections (UTI) and pyelonephritis.
2. The label should indicate the pathogens for which the applicant was able to provide sufficient data to support their claims of efficacy.

The portion of the label for this indication should be amended as follows:

Gatifloxacin is indicated for the treatment of "...**complicated urinary tract** infections caused by Escherichia coli, Klebsiella pneumonia, or Proteus mirabilis.

Pyelonephritis caused by Escherichia coli."

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2.7 Uncomplicated Gonococcal Urethritis/Cervicitis: (for complete review of this indication please see Dr. Albrecht's review in Section 8.7)

One study was submitted in support of this indication. This study was a comparison of two doses of gatifloxacin (400mg, 600 mg) orally, compared to ofloxacin 400 mg orally, in the treatment of uncomplicated gonorrhea in male and female patients.

The eradication rates for *Neisseria gonorrhoeae* in bacteriologically evaluable patients from each of the studies is summarized in the table below.

Bacteriological Eradication Rates in Evaluable **MALES**:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Urethra	116/117 (99%)	122/122 (100%)	55/55 (100%)
Pharynx	3/3	5/5	1/1
Rectum	0	0	0

The one patient who had persistence of gonorrhea after treatment with 400 mg gatifloxacin reported reexposure to an infected partner on day 4. While this may therefore represent a reinfection, in the worst case scenario it is included as a persistence.

Bacteriological Eradication Rates in Evaluable **FEMALES**:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Cervix	100/101 (99%)	103/104 (100%)	55/55 (100%)
Rectum	21/21 (100%)	16/16	8/8
Pharynx	7/7	15/15	3/3

The bacteriological results presented above indicate that gatifloxacin is 99% effective at each dose in eradicating gonorrhea from the urethra in men and cervix in women. The size of the study meets the recommended number for both men and women.

In addition, the data are adequate to support approval of treatment of rectal gonorrhea in women. However, there are no data on the treatment of rectal gonorrhea in males.

The information on pharyngeal gonorrhea treated with 400 mg PO (the proposed dosing regimen) is marginal for both males and females and therefore should not be approved.

These results support approval of gatifloxacin for the treatment of uncomplicated gonorrhea -- cervical and urethral, as well as rectal gonorrhea in females -- at a dose of 400 mg, as requested by the applicant. Data on the effectiveness of the 400 mg dose for pharyngeal gonorrhea was inadequate (see tables above).

The applicant has provided information on the rate of beta-lactamase producing *N. gonorrhoeae* isolates from the trial, but, in keeping with the regulatory policy on this subject, has not requested any labeling statements about that group of isolates, because this mechanism of resistance is not linked to resistance to quinolones. None of the quinolones approved for the treatment of gonorrhea have included any comments relative to beta-lactamase production.

The medical reviewer recommended that the INDICATIONS AND USAGE section of the proposed package insert, relative to the indication of gonorrhea, should be revised to read:

"Uncomplicated urethral and cervical gonorrhea due to Neisseria gonorrhoeae. Acute, uncomplicated rectal infections in women due to Neisseria gonorrhoeae."

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3.0 SUMMARY OF SAFETY

The safety evaluation in BMS-sponsored trials includes 586 patients from clinical pharmacology studies and 6198 patients from 15 efficacy trials. Two clinical pharmacology studies had active controls, study AI420-015 used ciprofloxacin and AI420-032 used both lomefloxacin and ciprofloxacin. Six other clinical pharmacology trials were placebo-controlled. Overall, 475 patients received gatifloxacin, 307 as a single dose and 168 as multiple doses. IV gatifloxacin was administered to 28 patients. The cut off for this safety analysis was 30-Sep-98.

In the efficacy trials, the largest experience was with a dose of 400 mg once a day given either orally (PO) (3021 patients) or intravenously (IV) followed by PO (165 patients). The duration of treatment was usually 7 to 14 days, with shorter courses of therapy given in two studies (AI420-010 and –012). The 200 and 600 mg PO doses were administered to 443 and 291 patients, respectively.

The total numbers of patients exposed to gatifloxacin in the Bristol-Myers SquibbPharmaceutical Research Institute, efficacy trials is as follows:
Gatifloxacin 200 mg PO: 443 patients,
Gatifloxacin 400 mg PO: 3,021 patients,
Gatifloxacin 600 mg PO: 291 patients,
Gatifloxacin 400 mg IV-PO switch: 165 patients.
Total exposed to Gatifloxacin at any dose in the clinical efficacy trials = 3, 920 patients compared to 2,278 patients exposed to comparator treatments.

In addition, the applicant supplied limited safety data from its' partner organizations Kyron. Japan and [redacted] The database from Kyron, Japan was analyzed earlier this year and information on 2,782 patients exposed to gatifloxacin is presented. The information from the [redacted] group was still under analysis at the time of the safety update, the experience there was based upon 7 phase III, double blind, efficacy trials trials which accrued 3,894 patients.

It will be noted here that the 4 month safety data included an update of the Kyorin and [redacted] data. The [redacted] studies were still blinded. The update did not reveal any additional unexpected adverse events increase in frequency of serious events. No significant cardiac or liver events were reported from either database.

Adverse Clinical Events:

Adverse Events most frequently see among patients treated with gatifloxacin include headache, nausea, vaginitis, and dizziness. There was slightly more nausea and dizziness in the gatifloxacin group; however, when event rates were compared to those seen with other quinolones, specifically levofloxacin, these events occurred at a similar rate. The applicant reported integrated adverse clinical events according to gatifloxacin dose administered, where the 400 mg PO dose was the most frequently admininstered. Types of events were similar across dosage groups, and comparable frequencies were demonstrated across dosage groups. A table of Adverse Clinical Events of All Cause is

presented below for the reader's information and is considered to be representative of the adverse event profile of gatifloxacin.

Selected Frequent Adverse Clinical Events All Cause: Gatifloxacin 400 mg PO				
	No. (%) Patients			
Adverse Event	Non-Comparative Trials Gatifloxacin N=769	Comparative Trials Gatifloxacin N=2252	Comparator N=2111	TOTAL GATIFLOXACIN N=3021
Headache	76 (10)	186 (8)	204 (10)	262 (9)
Nausea	61 (8)	241 (11)	171 (8)	302 (10)
Dizziness	32 (4)	93 (4)	63 (3)	125 (4)
Diarrhea	32 (4)	118 (5)	143 (7)	150 (5)
Vaginitis	40 (9)•	91 (7)	54 (4)	131 (7)
Insomnia	11 (1)	39 (2)	47 (2)	50 (2)
Rash	11 (2)	34 (2)	30 (1)	48 (2)

Most of the adverse clinical events in the 400 mg group, were reported to be of mild to moderate severity. Of the eight percent of patients reported to have severe events, they were scattered throughout the adverse event classifications with all categories being reported at less than 1% in frequency.

Discontinuation of therapy, in the gatifloxacin 400 mg PO studies, was due to an adverse event in 128/3021 (4%) gatifloxacin-treated patients and 86/2111 (4%) patients treated with the comparator agents. Treatment discontinuation was associated with drug-related adverse events in 169 (3%) patients, equally distributed between the treated groups. The most common reasons for discontinuation of therapy were diarrhea and vomiting. Diarrhea was reported in 11% of patients discontinuing either study drug. Vomiting was reported in 21% of patients discontinuing gatifloxacin as compared to 15% of patients discontinuing comparator.

It is of interest to view this population of events across studies as some of the events are specific to the underlying disease in which gatifloxacin is being studied (see table below). The following table displays this information for selected events in the gatifloxacin 400 mg (oral) treatment group. Overall, the events were similar in character between the North American Countries and Other Countries. The symptoms related to upper respiratory tract infections were more commonly seen in the pneumonia, brochitis and sinusitis studies. Nausea and Dizziness were more frequently seen in the complicated urinary tract infection study. Independent review of these events in Dr. Roca's review did not reveal any specific underlying cause for these events other than the infection being treated. It is not uncommon to see nausea in complicated urinary tract infections. Vaginitis was highest in the sinusitis and gonorrhea studies. Insomnia was seen at a low frequency across all studies and occurred more frequently in the CAP studies where it might be expected if the patient were having difficulty breathing.

Adverse Events of All Cause by Diagnosis, Gatifloxacin 400 mg PO										
No. (%) Patients										
	North America							Other Countries		
	Pneumonia N=461	AECB N=494	Sinusitis N=468	SSTI N=202	CUTI N=359	UUTI N=436	Gonorrhea N=295	Pneumonia N=136	Bronchitis N=64	Sinusitis N=106
Abnormal Breath Sounds	75 (16)	29 (6)	3 (<1)	--	1 (<1)	1 (<1)	1 (<1)	15 (11)	10 (16)	1 (<1)
Nausea	52 (11)	46 (9)	52 (11)	17 (8)	54 (15)	33 (8)	25 (8)	12 (9)	5 (8)	5 (5)
Coughing	47 (10)	39 (8)	39 (8)	--	3 (<1)	--	1 (<1)	11 (8)	9 (14)	8 (8)
Increased Sputum	47 (10)	34 (7)	--	--	--	--	--	10 (7)	8 (13)	--
Headache	44 (10)	35 (7)	51 (11)	14 (7)	22 (6)	53 (12)	17 (6)	15 (11)	3 (5)	8 (8)
Chest Pain	32 (7)	31 (6)	1 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)	5 (4)	6 (9)	--
Diarrhea	31 (7)	31 (6)	29 (6)	13 (6)	18 (5)	13 (3)	6 (2)	7 (5)	1 (2)	1 (<1)
Pharyngitis	28 (6)	20 (4)	29 (6)	5 (2)	16 (4)	10 (2)	2 (<1)	2 (1)	4 (6)	6 (6)
Vomiting	28 (6)	17 (3)	7 (1)	4 (2)	14 (4)	7 (2)	2 (<1)	6 (4)	--	--
Pain	21 (5)	8 (2)	48 (10)	8 (4)	11 (3)	15 (3)	1 (<1)	8 (6)	--	4 (4)
Insomnia	19 (4)	8 (2)	7 (1)	2 (<1)	7 (2)	--	1 (<1)	4 (3)	1 (2)	1 (<1)
Dizziness	17 (4)	23 (5)	17 (4)	10 (5)	28 (8)	12 (3)	6 (2)	3 (2)	5 (8)	4 (4)
Vaginitis	16 (7)	14 (6)	35 (12)	10 (9)	12 (6)	11 (3)	24 (16)	5 (7)	3 (14)	1 (2)
Abdomen Pain	16 (3)	10 (2)	17 (4)	9 (4)	14 (4)	17 (4)	2 (<1)	9 (7)	--	1 (<1)
Rash	16 (3)	3 (<1)	8 (2)	6 (3)	5 (1)	4 (<1)	1 (<1)	5 (4)	--	--
Dry Mouth	9 (2)	9 (2)	7 (1)	--	11 (3)	1 (<1)	--	6 (4)	2 (3)	2 (2)

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In summary, review of the adverse event reports reveals that the most common adverse events that are related to gatifloxacin include headache and nausea. Dizziness and diarrhea were seen at a lower level (2-4%) and occurred at a rate similar to the comparator. Overall, the events were mild or moderate, with few being reported as severe.

Deaths:

There were 29 deaths, 16 among gatifloxacin-treated patients and 13 in the comparator groups which occurred at any time (see section 9.2). More than half of the deaths occurred in patients treated for pneumonia. In the 12 gatifloxacin cases which occurred less than 30 days after therapy was initiated the causes of death included cardiovascular events (acute myocardial infarction, congestive heart failure or cardiac arrest) in 5 patients, underlying respiratory condition (4 patients), cerebrovascular accident (1 patients), underlying carcinoma (2 patients). The causes of death were similar between both groups. The timing of the deaths was somewhat earlier in the gatifloxacin group where 9 patients died within 10 days of initiating therapy. Review of these deaths revealed the cause of death was probably unrelated to gatifloxacin, and more likely due to the serious nature of the underlying disease of these patients (descriptions of these patients follow-up in section 9.2). Most patients were more than 60 years of age. The average age in the gatifloxacin group was 76.2 years and 71.8 years for the comparator group. Only one patient in the gatifloxacin group who died was under 60 years of age; a 43 year old female with a history of psychotic problems who committed suicide 43 days after therapy.

Laboratory Abnromalities:

(Note: additional discussion of liver function abnormalities, glucose, hemoglobin and creatinine appear in section 9.2 within class effects)

Laboratory Abnormalities in Patients with Normal Baseline Values

The development of laboratory abnormalities in patients with normal baseline values was an infrequent occurrence (see table below). Among the more frequently developing abnormalities were: decreased bicarbonate (13% of all patients treated with the 400 mg strength gatifloxacin), anemia (8%), hyperglycemia (8%), neutropenia (6%), hyponatremia (5%), and elevated AST (5%) and ALT (also 5%). The aforementioned abnormalities in serum sodium and liver transaminases were somewhat more frequent in the non-comparative studies. In the comparative studies, there were no striking differences in the gatifloxacin and pooled comparator arms with respect to the occurrence of laboratory abnormalities. When laboratory abnormalities occurred, they were generally minimal (Grade 1). They should be interpreted in the context of contributing factors such as the patient's general medical history, underlying infection, and use of concomitant medications. Keeping in mind that the number of patients treated in countries outside North America is small. it is interesting to note that, with two exceptions, the development of laboratory abnormalities tended to be more common in other countries.

Laboratory Abnormalities in Patients with Normal Baseline Values, Gatifloxacin 400 mg PO

No. Patients with Abnormal Value/Assessed (%)				
	Non-comparative trials	Comparative Trials		TOTAL
	Gatifloxacin	Gatifloxacin	Comparator	Gatifloxacin
Leukopenia	19/702 (3)	92/1899 (5)	63/1808 (3)	111/2601 (4)
Neutropenia	33/694 (5)	125/1890 (7)	79/1793 (4)	158/2584 (6)
Anemia	51/624 (8)	132/1696 (8)	134 /1591 (8)	183/2320 (8)
Thrombocytopenia	17/685 (2)	44/1884 (2)	35/1761 (2)	61/2569 (2)
BUN/Blood Urea	12/708 (2)	63/1960 (3)	53/1847 (3)	75/2668 (3)
Creatinine	25/708 (4)	42/1979 (2)	33/1857 (2)	67/2687 (2)
AST/SGOT	44/625 (7)	82/1889 (4)	87/1786 (5)	126/2514 (5)
ALT/SGPT	51/638 (8)	82/1887 (4)	86/1773 (5)	133/2525 (5)
Bilirubin	17/692 (2)	58/1932 (3)	44/1810 (2)	75/2624 (3)
Hypoglycemia*	2/87 (2)	0/79 (0)	1/67 (1)	2/166 (1)
Hyperglycemia*	6/87 (7)	8/79 (10)	5/67 (7)	14/166 (8)
Amylase	32/618 (5)	66/1901 (3)	39/1780 (2)	98/2519 (4)
Hyponatremia	44/635 (7)	80/1878 (4)	70/1749 (4)	124/2513 (5)

*This represents fasting values only, additional discussion regarding glucose homeostasis can be found in section 9.4.8.

An analysis of laboratory abnormalities by infection under study was discussed by the applicant. Hematologic abnormalities such as anemia and neutropenia developed more frequently in the pneumonia studies; as previously noted, these patients were among the sickest enrolled in the gatifloxacin program. The complicated UTI studies also had a higher incidence of anemia (15%). Not surprisingly, elevations in BUN and creatinine were more frequent in the complicated UTI studies; by definition, many of these patients had underlying structural abnormalities of their urinary tracts which may have contributed to increases in BUN and/or creatinine.

There was a slight trend toward more laboratory abnormalities the longer the course of gatifloxacin therapy. This trend was not seen for neutropenia, suggesting that myelosuppression was not related to gatifloxacin exposure.

The development of clinically relevant laboratory abnormalities (i.e., Grade 3 or 4 in severity) was infrequent (<1%) and comparable between treatment groups. Elevations in bilirubin were the most common such abnormality (10 gatifloxacin-treated patients and 8 for the comparator); they were noted more typically in the comparative studies and in these randomized studies, the incidence was comparable for gatifloxacin and the pooled comparator agents. All clinically relevant laboratory abnormalities occurred in ≤1 percent of patients in either geographic area . (See discussion of liver function abnormalities in section 9.4.4).

In an analysis by infection under study, the lowest incidence of clinically relevant laboratory tests was noted among patients in the uncomplicated skin and skin structure study (3 tests), the uncomplicated UTI study (1 test), and the gonorrhea study (3 tests); the latter two studies employed single dose gatifloxacin therapy. Even among sicker

patients (e.g. those with pneumonia or complicated UTI), clinically relevant laboratory abnormalities were an unusual occurrence.

Clinically relevant laboratory abnormalities were most frequent among patients treated with between 7 and 10 days of gatifloxacin therapy; this category accounted for the greatest percentage of patients enrolled. There were no striking differences noted across geographic regions.

Laboratory Abnormalities in Patients with Abnormal Baseline Values

Among patients with abnormal baseline laboratory values, worsening results were not distinctly common. In the comparative studies, a worsening of baseline neutropenia was more frequently noted in the pooled comparator arm (27% vs. 13% gatifloxacin).

The worsening of abnormal baseline laboratory tests rarely resulted in clinically relevant values. Among all gatifloxacin-treated patients, a clinically relevant elevation in bilirubin was the most common such abnormality. In the comparative studies, gatifloxacin was comparable to the pooled comparator arm.

Quinolone Class Effects:
Potential class effects for the quinolones include phototoxicity, cardiac toxicity, central nervous system toxicity, hepatotoxicity, hemolytic uremic syndrome, tendon rupture, hypoglycemia, anaphylaxis. Each of these effects was reviewed within the study population as a whole. Additional phase II studies were conducted to further elucidate the potential for phototoxicity and cardiac toxicity. A detailed review of these can be found in section 9.4 of this review of the integrated summary of safety. The results will be briefly described here for the reader.

Phototoxicity:
Studies conducted in animals did not show evidence of phototoxicity. A phase II human trial was conducted in 48 healthy volunteers assigned to receive either gatifloxacin 400 mg QD, ciprofloxacin 500 mg BID, lomefloxacin 400 mg QD or placebo for 7 consecutive days. In this study the phototoxicity potential of gatifloxacin was found to be comparable to that of placebo at all wavelengths tested. Gatifloxacin did not appear to have any phototoxic potential as defined by the percent change in minimal erythema dose or the phototoxic factor whereas ciprofloxacin could have been considered to have a mild photosensitizing effect and lomefloxacin to have a moderated photosensitizing effect. There was no demonstrable relationship between drug exposure and phototoxic effect.

In the applicant's clinical database of almost 4,000 patients treated with gatifloxacin, there were no reports by Investigators of phototoxicity. A more complex analysis of events associated with phototoxicity (COSTART TERMS: erythema, photosensitivity, eye photosensitivity, rash, and vesiculobullus rash) failed to identify any difference between gatifloxacin-treated patients and those who received either other quinolones (ciprofloxacin or levofloxacin [ofloxacin])or other antibiotics (cephalosporins or macrolides).

Cardiovascular Effects:

An extensive post-hoc review of potential cardiac toxicity was undertaken in the original application as well as during the review (see section 9.4.2). Of the animal studies conducted, the most informative was that conducted in dogs with continuous ECG (electrocardiographic) monitoring. This study administered a 10 mg/kg bolus to the dogs (4x the intended dose in humans). There were no demonstrable QT interval changes. The applicant did not provide *in vitro* studies of the cardiac potassium rectifer channel enzymes (Ikr) in the original NDA. However, at the request of the FDA following the October 1999 FDA Advisory Committee Meeting, the applicant performed and supplied information to the FDA regarding the human ether a-go-go related gene (HERG) model (draft report form). From this model it appeared that gatifloxacin was mildly inhibitory and less so than [redacted] sparfloxacin and grepafloxacin. A final report is to be submitted to the NDA following approval for further verification of results by the FDA.

At this time there is much debate within the field as to which *in vitro* model may most accurately predict risk of QT prolongation. It has been noted that results among various models can vary widely. In phase II studies of healthy volunteers, specifically a dose escalation study (30 patients), where paired ECGs were evaluated and plasma concentrations were measured (at steady-state), gatifloxacin appeared to have a weak effect in prolongation of the QTc (slope for the line of the change in QTc interval versus serum concentration was estimated between 2.7 (-1.26, 6.66; 95% CI.) and 3.4 (-1.58. 8.26; 95% C.I.). Categorical analysis of the changes among these patients paired ECGs revealed that no changes in QTc interval were greater than 40 msec, and that none of the patients tested had an individual QTc interval greater than 450 msec.

The phase II information, provided by the applicant, on change in QTc from baseline represents a small patient population (mostly healthy males). At the time these studies were completed the applicant felt there appeared to be no cardiac risk to patients and further paired ECG measurements were not undertaken in the larger phase III trials. The FDA was in agreement at that time. However, it was felt that further analysis of the potential cardiac toxicity of gatifloxacin should be undertaken after the October 1999 FDA Anti-infectives Advisory Committee Meeting. Recommendations from the committee regarding additional studies of cardiac safety among the quinolones [redacted] were made. These recommendations lead to further analysis of the clinical trial database regarding potential cardiac toxicity. Adverse event terms related to cardiac toxicity in the phase III studied were reviewed.

Phase III studies did not contain paired ECG measurements nor did they exclude patients on concomitant cardiac medication or conditions that may increase the QTc. In this regard, the applicant had the ability to report only adverse clinical events relative to the cardiovascular system. Although gatifloxacin is not metabolized extensively in the liver and does not interfere with the cytochrome P450 system, the potential for additive interaction with other cardiovascular drugs was reviewed by the applicant as a result of consultation with the FDA after the October 1999 FDA Advisory Committee on [redacted].

The applicant carried out a post-hoc analysis of the phase III safety database on order to assess the potential for adverse cardiac consequences arising in patients who received concomitant drugs associated with QTc prolongation. A total of 118 patients treated with gatifloxacin 400 mg and 89 patients treated with various comparators were identified. The most common potentially cardiotoxic agents were amitriptyline, cisapride and nortriptyline (see table below). These drugs were relatively evenly distributed between the two treatment groups. Overall, no difference was detected between the four subsets (gatifloxacin 400 mg with/without concomitant drugs prolonging QTc and comparators with/without concomitant drugs). This is a relatively small group of patients on numerous agents, thus the true effect or lack thereof can only be hypothesized at this time. Additional studies were recommended to the sponsor in the phase IV commitment section of the approval letter.

Bristol-Myer Squibb Analysis of Cardiovascular Adverse Events- All Causes- Patients With/Without Concomitant Cardiac Drugs

	Gatifloxacin 400 mg and Concomitant drugs N = 115	Gatifloxacin 400 mg and NO Concomitant drugs N=3088	Comparator and Concomitant drugs N=89	Comparator and NO Concomitant drugs N=2189
Hypertension	1	8	1	14
Palpitation	--	12 (0.39%)	1	9 (0.41%)
Tachycardia	1	6	--	9
CHF	2	6	--	6
Hypotension	1	5	1	6
Migraine	--	11	--	2
Myocardial Infarction	2	7	--	1
Syncope	--	6 (0.2%)	--	2 (0.1%)
Arrhythmia	--	3	1	4
Extrasystoles	--	1	--	6
Atrial fibrillation	--	4	--	4
Cardiac Arrest	--	3	--	1
Bradycardia	--	2	--	1

Of the patients in the gatifloxacin treatment group, only 6 tachycardia patients in each group were considered to be related to study medication, and for tachycardia it was noted by the investigator to be related to study drug in only 3 comparator patients.

In summary, no striking effect on QT could be detected in the review of the pre-clinical animal data. However, the applicant could have extended the dose of gatifloxacin to higher levels in the beagle model. The Phase II/III data, on a small number of patients, provided a small positive association between concentration and delta QTc; eg. a shallow rise in the slope of the delta QTc measurement associated with increase in plasma concentration of gatifloxacin. The evaluation of the Phase III clinical adverse event

database related to the cardiovascular system in over 8,500 patients treated with gatifloxacin did not reveal any striking differences between gatifloxacin and comparator, although paired ECGs were not performed in a prospective manner within this study population. Given the data at hand, it would appear that gatifloxacin may have a weak effect on the QTc and thus potential to cause cardiac arrhythmia; however, at this time the clinical relevance of the small change in QTc is unknown. A more precise evaluation of the effect of gatifloxacin on the cardiovascular conduction system could be described by studying additional patients at higher doses (800 mg, 600mg) where the ECG would be taken during the expected peak serum concentration. (see phase IV commitments)

Central Nervous System (CNS) Effects:
CNS side effects were uncommon. In particular, dizziness occurred in about 3% of all patients exposed to gatifloxacin. There was no evidence that dizziness was dose-related, and there was no evidence that dizziness occurred more frequently in females and in younger patients, as has been described with other quinolones. In general, dizziness was minimal and led to treatment discontinuation in very few patients. Other CNS side effects were rare, and were reported in one or two patients.

There were five patients reported to have had convulsions in the data base. One patient was treated with ciprofloxacin and 4 patients were treated with gatifloxacin (400mg PO). None of these cases were felt to be related to study drug by the site investigators. The cases are reviewed in detail in the review of clinical trials section (section 8.0).

Hepatotoxicity:

Of the patients with normal baseline laboratory values reviewed in the study database, 3,043 were treated with gatifloxacin and 1731 comparator drug. Of these patients, 25 (1%) gatifloxacin treated patients and 29 (2%) comparator treated patients were exposed to more than 15 days of therapy. An abnormal ALT of any level occurred in 118 (3.9%) patients in the gatifloxacin group and 89 (5.1%) patients in the comparator group. However, abnormal ALT and/or AST plus Total Bilirubin were seen in 9 (0.2985%) patients treated with gatifloxacin and 2 (0.1155%) treated with comparator (ofloxacin and ceftriaxone). These liver function abnormalities were grade 1 or grade 2 in severity (mild to moderate). None of the patients had liver failure, liver transplant or death due to possible hepatic etiology. The sponsor also states that none of the patients were discontinued from study drug due to concerns about liver toxicity.

Review of the CRFs reveals that the peak total bilirubin in the gatifloxacin group was 1.5 times the upper limit of normal (1 mg/dl bilirubin = ULN in most studies) (detailed table appears in section 9.4.4). Of those 9 patients treated with gatifloxacin, none of the patients had the pattern of elevated ALT and Total Bilirubin only. Of the 9 gatifloxacin cases reported, only 4 patients had elevated ALTs (0.1325%). Only the patient receiving the ceftriaxone had an isolated elevated ALT. Of these 4 gatifloxacin patients all of the AST elevations were mild, grade 1 elevations (1.4-1.6x ULN). Two patients were from the gonorrhea study, and one admitted to drinking heavily prior to the follow-up visit, the other admitted to smoking marijuana daily. Neither had symptoms of hepatitis. The third

patient was treated for acute exacerbation of chronic bronchitis, was 76 years old and had a history of hypertension and heart disease. He complained of moderated nausea and was discontinued due to nausea. The final patient was a 26 year old male treated for community acquired pneumonia, diagnosed with severe pneumonia and was hospitalized. He did well and was discharged.

From the above analysis it appears that there is no serious or significant hepatotoxicity in the gatifloxacin treated patient group reported (3,043 patients). In addition, liver test abnormalities were seen at a rate and level comparable to the "comparator" drugs. These abnormal values may be in part a result of the infection under treatment, or the underlying disease. When compared to drugs with no known potential for sever hepatotoxicity, based on substantial post-marketing experience, gatifloxacin did not demonstrate any significant increase in liver abnormalities.

Hemolytic Uremic Syndrome:
The applicant stated that there were no reports of a [redacted]-like syndrome in the entire database. They searched the safety database for the association of fever and other signs of hemolytic anemia, thrombocytopenia or renal failure. No such cases were identified. FDA requested an additional analysis of the laboratory abnormality database to search for this syndrome. The applicant reported that they searched the safety database for any patients with all three of the following laboratory findings: a total bilirubin of > Grade III toxicity, an increase in serum creatinine of one toxicity grade, and a drop in serum hemoglobin of one toxicity grade. No such patients were found.

Tendon Rupture:
Only one case of "torn tendon" was reported, and this occurred in a patient in the comparator group (ciprofloxacin).

The applicant reported that there was no report in the entire database of any rupture of any tendon, in particular the Achilles tendon. To further investigate the potential for gatifloxacin-induced tendonitis, we looked at four specific adverse events: contraction tendon, disorder joint, disorder tendon, and tenosynovitis. Overall, the incidence of these events was lower among gatifloxacin-treated patients (<0.1%) compared to those treated with quinolones or non-quinolones antibiotics (0.3% in each) . The most common of these abnormalities was an unspecified disorder tendon, which occurred in 8 patients total. Only 3 of these events were considered drug-related; these were one disorder joint and two disorder tendon, all three occurring in patients treated with quinolones other than gatifloxacin.

Anaphylaxis:
There were 13 cases of "allergic reaction" which were further classified as urticaria, hives or drug reaction. Nine of these were in the gatifloxacin group and 4 were in the comparator group (1 patient given clarithromycin; 3 patients given ciprofloxacin). Only one of the patients were reported to have a severe allergic reaction (#06-04-00001). This 30 year old, white male was given a dose of gatifloxacin orally and after 15-20 minutes, left the emergency room where he was enrolled. As he was waiting for a bus his throat tightened up and he became short of breath. He returned to the emergency room where

he was treated with benedryl and epinephrine. He was admitted to the ICU for observation and was discharged the next day without further problems. He was discontinued from study drug. The rate of allergic reactions was very low (<1%).

Glucose Homeostasis:
As a result of the animal toxicology study findings, the applicant performed several studies in patients in order to understand the potential clinical effect of gatifloxacin regarding glucose homeostasis. Two studies were conducted in volunteers: one in patients with Type II diabetes controlled with diet and exercise; one in Type II diabetes treated with glyburide. In addition, glucose homeostasis was assessed in another ultiple dose trial.

Results:

- In the first study, the results showed a lack of effect of gatifloxacin on glucose tolerance and pancreatic β-cell function. Of note, there was a slight increase in fasting insulin levels on Day 1 with a decrease in fasting glucose which was not found on subsequent days. This effect was not clinically significant. An acute effect of gatifloxacin on insulin release could not be ruled out.
- The second study revealed that gatifloxacin had no effect on the steady-state pharmacokinetics of glyburide. There was also no effect on glucose tolerance or insulin homeostasis, although a modest decrease in insulin production with multiple dose administration could not be ruled out.
- The third study, a randomized, double-blind, placebo-controlled study in healthy volunteers, assessed the effect of intravenous gatifloxacin, at doses of 200 to 800 mg, and placebo on oral glucose tolerance, glucose and insulin homeostasis, and fasting predose serum glucose, insulin and C-peptide in healthy volunteers. Each subject received a single-dose of study drug on Day 1, followed by repeated, once daily dosing on Days 4 through 17. There was no change apparent in serum insulin or C-peptide and the effect on serum glucose was less on Day 10. Changes in pre-dose, fasting serum glucose insulin and C-peptide levels over a 20-day period were similar in all treatment groups, including placebo. There was no effect of gatifloxacin on oral glucose tolerance. Fasting serum glucose, insulin and C-peptide concentrations were also measured over a 6 hour period following the start of the one hour infusion of gatifloxacin on Days 1 and 10. There was a transient decrease in serum glucose at all dose levels at the one hour time point on Day 1 with a prompt recovery by the end of the second hour.

Safety Database in Phase III Trials

There were seven episodes of hypoglycemia reported as an adverse event by Investigators, six in patients treated with gatifloxacin 400 mg and one in a clarithromycin-treated patient. One gatifloxacin patient did not have a history of diabetes. On Day 2, the glucose level was 33 mg/dL. The reason for this symptomatic hypoglycemic episode is unknown. The five other gatifloxacin patients had a history of diabetes; three were treated with glyburide, one with insulin and one with both glyburide

and insulin. In all five of these patients, the glucose value at the time of hypoglycemia was not available, and hyperglycemia was consistently reported in non-fasting glucose tests pre- and/or post- the "hypoglycemia" episode.

To further assess the potential hypoglycemic effect of gatifloxacin, the applicant searched their database which included a total 4,733 patients for whom glucose levels were available both pre- and either during- or post-treatment. Potential hypoglycemia was defined as a serum glucose (fasting or non-fasting) below 60 mg/dL. Seventy-nine patients were identified, translating to an incidence of 1.7% in the gatifloxacin-treated group, 1.4% in patients treated with other quinolones, and 1.8% in patients treated with other antibiotics. In most cases, the glucose levels ranged from 50 to 60 mg/dL. Among gatifloxacin-treated patients, there were 4/3000 patients with a value <40 mg/dL, the lowest being 31 mg/dL, 0/1183 in the other quinolone group and 1/550 in the non-quinolone group, this value being 27 mg/dL in a patient treated with ceftriaxone.

Patient 04-08-00003: A 35 year old, black, female treated with gatifloxacin was reported to have a glucose value of 34 mg/dL which was considered a laboratory error; inorganic phosphorus was high as well. Repeat labs were normal. The patient did not suffer symptoms of hypoglycemia. The patient's medical history was only positive for COPD.

Patient 04-08-00005: A 39 year old, black, female treated with gatifloxacin was noted to have a glucose of 34 mg/dL. This value was considered a laboratory error by the investigator. A repeat value was within normal limits. The patient did not suffer symptoms of hypoglycemia. The patient's medical history included chronic bronchitis, lumbar strain, insomnia.

Patient 031-05-00046: A 75 year old white, male treated with gatifloxacin was noted to have a glucose of 31 mg/dL. This patient had a medical history of NIDDM, gout, generalized osteoarthritis, Alzheimer's disease, and coronary artery disease. The patient was on concomitant medication including glipizide, amitriptyline, prozac, and allopurinol. The patient completed 10 days of therapy without further hypoglycemia. Additional blood tests were slightly elevated, as would be expected in a diabetic patient.

Patient 02-62-00430: An 83 year old white, male treated with gatifloxacin was noted to have a glucose of 33 mg/dL. The medical history was negative except for a cholecystectomy in 1995. The patient was given a dose of diabeta on the same day as the hypoglycemia was reported. This patient was reported to have been confused and aggitated. He was hospitalized with pneumonia. The patient's gatifloxacin was discontinued on the second treatment day. It is unclear what role the gatifloxacin played in this patient's hypoglycemia.

Among the gatifloxacin patients, the low serum glucose was seen at equal frequency in patients treated with the 200 or 400 mg doses; hypoglycemia (glucose <60 mg/dL) was not seen in patients treated with 600 mg single dose. Seventy-five percent (39/53 patients) of these episodes of hypoglycemia occurred in patients who were less than 65 years of age, 15.4% (8/52 patients) in patients 65 - 74 years of age and 9.6% (5/52 patients) in patients greater than 75 years of age. There was no clear evidence that hypoglycemia was related to duration of therapy; the highest incidence occurred in patients who received between 6 and 10 days of treatment. The episodes occurred mainly among Caucasian patients. There was a greater number of female patients than male patients in this group; however, many of the female patients came from the urinary tract infection study which enrolled only female patients.

Summary

The three studies conducted in volunteers demonstrated a lack of gatifloxacin effect on glucose homeostasis. There was no evidence of hypoglycemia, significant changes in insulin production, or interaction with glyburide in patients with Type II diabetes. In the safety database, the incidence of hypoglycemia (serum glucose below 60 mg/dL) was similar in gatifloxacin-treated patients and in those treated with other antibiotics. There were six episodes of "hypoglycemia" in gatifloxacin-treated patients but low serum glucose was documented in only one of them. In the remaining four patients who had a history of diabetes and treatment with glyburide and/or insulin, hypoglycemia was possibly related to other factors (e.g., poor nutrition) rather than to a direct toxicity/interaction of gatifloxacin.

In conclusion, based on data in volunteers and from the phase III, clinical safety database, hypoglycemia appears to be a rare event not clearly associated with the administration of gatifloxacin. No special precautions need to be taken by the general population treated with gatifloxacin, or by diabetic patients on oral hypoglycemic agents.

3.1 Risk Benefit Assessment:

Given the concern regarding potential cardiac toxicity among the quinolone class, and the uncertainty of the potential due to the demonstrated weak effect of gatifloxacin on the QT interval, the approval of uncomplicated skin and soft tissue infections is dependant upon and understanding of the risk-benefit for such a patient. Since there are other potentially, less toxic treatment modalities available for such infections, it was felt that the risk of adverse event in an otherwise healthy individual was not acceptable at this time. Further delineation of the clinical effect on cardiac events must be understood prior to approval of this indication (see phase IV commitments).

The applicant has requested several indications for which other antibiotic therapies (penicillins and cephalosporins) exist. The quinolones as a class have a separate mechanism of action, hence different site of resistance, than the beta-lactam antibiotics. In the past several years the innovator companies have been able to produce quinolones with not only cover the Gram negative organisms, but include some of the important Gram-positive organisms. This makes the newer quinolones attractive alternative therapies to clinicians. Currently the most commonly utilized approved newer, agent is Levofloxacin.

The applicant has studied community acquired pneumonia, including severe cases, and has demonstrated efficacy with the oral as well as the intravenous-to-oral switch therapies. The daily dose schedule should enhance compliance with completion the full treatment regimen. In the case of pneumonia it was felt that the seriousness of this illness balanced the risk of the potential for prolonging the QTc interval. Similar rationale was applied to acute exacerbation of chronic bronchitis and sinusitis. Complicated urinary tract infections is a significant infection with serious medical outcomes if not adequately treated. It was felt that seriousness of this illness was balanced against the potential for prolonged QTc. Each of these indications is approved and clearly labeled with a warning

regarding the potential cardiac effect. It is up to clinicians and patients to make the final decision as to the correct therapy for that individual patient. (See WARNINGS section of the final product label)

Given the fact that uncomplicated gonorrhea was treated with a single dose, which provided a substantial benefit to compliance, it was felt the risk of QTc prolongation was very low given this exposure to gatifloxacin. This indication was therefore recommended for approval. Finally, a similar rationale was applied to the approval of gatifloxacin for uncomplicated urinary tract infection. Both doses provide a low exposure to the patient (400 mg one time; 200 mg daily for 3 days). Both courses of treatment for uncomplicated urinary tract offer the potential for increased compliance.

Consideration by the FDA for approval of the various indications requested by the applicant was based upon demonstrated efficacy balanced by the potential for adverse events, particularly prolongation of the QTc interval. Serious infections were felt to offer a balance in risk benefit, such as, community acquired pneumonia, acute exacerbation of chronic bronchitis and some cases of acute sinusitis. With regard to less serious diseases, the limited extent of exposure was felt to balance the potential cardiac risk, for example, single dose treatment for gonorrhea an uncomplicated urinary tract infection or a three day exposure to a lower dose of gatifloxacin for uncomplicated urinary tract infection.

4.0 SPECIAL POPULATIONS (Age, Race, Gender):

Again this analysis reflects the applicant's strategy for reviewing the dose regimens separately in order to determine if any dose related events could be detected. The following include review of the adverse events by age, race and gender.

Safety In Health Volunteers (Phase II):

With respect to the analysis by age, nausea and headache appeared to be somewhat more frequent in patients less than 65 years of age, but the results should be interpreted with caution due to the small number of elderly patients.

Gatifloxacin Selected Adverse Events of All Causes by Age, Studies in Healthy Volunteers			
	No. (%) Patients		
Adverse Event	Age <65 yrs N=424	Age 65-74 yrs. N=42	Age ≥ 75 yrs. N=9
Headache	62 (15)	3 (7)	--
Nausea	43 (10)	2 (5)	--
Dizziness	29 (7)	4 (9)	1 (11)
Pruritus	22 (5)	--	--

Analysis of gatifloxacin adverse clinical events by race did not identify substantial differences between White, Black, and Hispanic volunteers. There was a somewhat higher rate of puritus among Blacks and Hispanics than for Whites; however, the numbers are too small to draw specific conclusions regarding this event.

Gatifloxacin Selected Adverse Events of All Causes by Race, Studies in Healthy Volunteers					
	No. (%) Patients				
Adverse Events	White N=392	Black N=58	Hispanic N=21	Asian N=2	Other N=2
Headache	56 (14)	5 (9)	3 (14)	--	1 (50)
Nausea	36 (9)	5 (9)	4 (19)	--	--
Dizziness	28 (7)	5 (9)	1 (5)	--	--
Puritus	11 (3)	7 (12)	4 (19)	--	--

There were essentially no differences in the analysis by gender. It should be noted, however, that dizziness was somewhat more frequent in females than males. This was mild to moderate in severity.

Gatifloxacin Selected Adverse Events of All Causes by Gender, Studies in Healthy Volunteers		
	No. (%) Patients	
Adverse Events	Male N=379	Female N=96
Headache	49 (13)	16 (7)
Nausea	29 (8)	16 (7)
Dizziness	21 (5)	13 (14)
Puritus	20 (5)	2 (2)
Pain Abdomen	11 (3)	7 (7)

Gatifloxacin 400 mg PO (all Phase III studies):

The majority of patients treated with the 400 mg PO dose of gatifloxacin were less than sixty-five years of age; just over half of these patients experienced at least one adverse clinical event. The incidence of adverse clinical events in the elderly population was somewhat higher: sixty percent among patients aged 65 to 74 years, and 65% among patients greater than 75 years of age. These data did not differ by geographic region. When considering individual events, nausea, vomiting, and dizziness each occurred with greater frequency among those ≥75 years; this was true in both North America and other countries. Headache was seen in a lower frequency in those ≥ 75 years. (mostly mild to moderate)

Selected Adverse Events by Age All Cause: Gatifloxacin 400 mg PO			
Adverse Event	<65 years N=2463	65-74 years N=321	≥ 75 years N=237
Nausea	233 (9)	27 (8)	42 (18)
Headache	232 (9)	22 (7)	8 (3)
Diarrhea	121 (5)	17 (5)	12 (5)
Vaginitis	119 (8)	9 (6)	3 (3)
Dizziness	89 (4)	18 (6)	18 (8)
Pain Abdomen	74 (3)	13 (4)	8 (3)
Vomiting	63 (3)	6 (2)	16 (7)
Insomnia	39 (2)	6 (2)	5 (2)
Rash	39 (2)	3 (<1)	6 (3)

The incidence of adverse clinical events by race is presented in the table below; the overall incidence data are remarkably consistent across geographic regions. With the caveat that there were very few Asian patients enrolled, there were no adverse clinical events that occurred with greater frequency in a particular race.

Selected Adverse Events of All Cause by Severity by Race, Gatifloxacin 400 mg PO				
	No. (%) Patients			
Adverse Event	White N=2095	Black N=570	Hispanic N=306	Asian N=31
Nausea	233 (11)	44 (8)	20 (7)	3 (10)
Headache	207 (10)	32 (6)	18 (6)	3 (10)
Diarrhea	117 (6)	21 (4)	11 (4)	1 (3)
Vaginitis	94 (7)	30 (11)	7 (3)	--
Dizziness	89 (4)	16 (3)	14 (5)	4 (13)
Pain Abdomen	75 (4)	7 (1)	9 (3)	2 (6)
Vomiting	71 (3)	6 (1)	7 (2)	--
Insomnia	41 (2)	5 (<1)	3 (<1)	1 (3)
Rash	40 (2)	2 (<1)	5 (2)	--

Fifty-seven percent of females and forty-nine percent of males experienced adverse clinical events; this difference in incidence is largely accounted for by the cases of vaginitis occurring in females. The two most frequent adverse clinical events, nausea and headache, were somewhat more common in females than in males. In most instances, the occurrence of adverse events by gender was very consistent across geographic regions.

Gatifloxacin Selected Adverse Events of All Causes by Gender, Gatifloxacin 400 mg PO		
	No. (%) Patients	
Adverse Events	Male N=1221	Female N=1800
Headache	84 (7)	178 (10)
Nausea	74 (6)	228 (13)
Dizziness	55 (5)	70 (4)
Rash	15 (1)	33 (2)
Vaginitis	---	131 (7)
Diarrhea	70 (6)	80 (4)
Vomiting	17 (1)	68 (4)
Pain Abdomen	26 (2)	69 (4)

400 mg IV-PO Dose Regimen in Efficacy Trials:

The overall incidence of adverse clinical events was somewhat higher among patients ≥75 years of age. Coughing (7 patients:15%), constipation (8 patients; 17%), agitation (4 patients; 9%), confusion (5 patients;11%), and anxiety (patients: 9%) were among the events occurring more frequently in this age group.

An analysis of adverse clinical events by race did not highlight any notable differences; the overwhelming majority of patients treated with this dose and formulation were white, making comparisons difficult.

The incidence of adverse clinical events was higher in females (92%) than males (82%). Constipation, chest pain, and headache were among the events more common in women, while dyspnea, vomiting, and anxiety were noted more often in men.

200 mg PO dose in Efficacy Trials:
This study was conducted in women alone. Analysis by age and race did not reveal any substantial differences.

600 mg PO dose in Efficacy Trials:
All patients enrolled were less than 65 years of age.

In contrast to the demography of other dosage groups, the majority of patients treated with the 600 mg dose of gatifloxacin were Black. There was no difference in the overall incidence of adverse clinical events in Black and White patients. Data from Hispanics and Asians were insufficient to make any conclusions.

The incidence of adverse clinical events was slightly higher in females (38% vs. 31% in males); this difference is accounted for by the cases of vaginitis, dizziness and vomiting.

APPEARS THIS WAY
ON ORIGINAL

5.0 RECOMMENDATIONS:

According to the FDA analysis of the above efficacy data, we have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling submitted December 17, 1999, for:

INDICATIONS AND USAGE

TEQUIN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

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

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

Community-acquired pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Legionella pneumophila.*

Uncomplicated urinary tract infections (cystitis) due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

Pyelonephritis due to *Escherichia coli.*

Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae.* **Acute, uncomplicated rectal infections in women** due to *Neisseria gonorrhoeae.*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to gatifloxacin. Therapy with TEQUIN may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

In addition, we have concluded that the indication of uncomplicated skin and skin structure infections is approvable pending submission of post-marketing data confirming the safety of gatifloxacin and therefore demonstrating an acceptable risk/benefit profile. This especially relates to the potential QTc interval prolongation.

6.0 PROPOSED LABELING CHANGES:

The following issues were addressed during the labeling negotiations:

1. Safety: potential class effects, especially potential cardiac toxicity (see Warnings Section of the Label). Especially important was the inclusion of the following paragraph in the warning section (see below), until further phase 4 studies are analyzed providing additional information on clinical impact of potential QTc prolongation issue.

GATIFLOXACIN MAY HAVE THE POTENTIAL TO PROLONG THE QTc INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. DUE TO THE LACK OF CLINICAL EXPERIENCE, GATIFLOXACIN SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA, AND PATIENTS RECEIVING CLASS IA (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS.

In addition, it was felt that a patient information portion of the label would provide easily accessible information to the patient regarding gatifloxacin's safety and activity. This portion of the label was reviewed with advice from DDMAC. This section is a portion of the label and is not to be confused with patient package inserts.

2. Efficacy: approval of specific indications (see above); recommendation of specific organisms included in the microbiology section of the label.

3. Clinical Pharmacology: deletion of tissue levels for unapproved indications, recommendations regarding administration of gatifloxacin with regard to antacids and cationic minerals (see label). For additional changes please see Dr. Uhl's review and the final label dated December 17, 1999.

7.0 PHASE IV COMITTMENTS:

The Phase 4 commitments to which Bristol-Myers Squibb Company agreed in its submission dated December 16, 1999, along with any completion dates agreed upon, are listed below:

1. To better understand the risk/benefit profile of oral gatifloxacin, Bristol-Myers Squibb will review post-marketing adverse event data following at least one million patient exposures worldwide. A substantial proportion of these exposures will be from the United States. The results of this evaluation will be submitted to the Division by December 31, 2000.

2. Bristol-Myers Squibb will conduct and submit the results of an active surveillance program. The results of this program will provide information on the incidence of adverse events for at least 15,000 patients using gatifloxacin tablets and/or gatifloxacin injection. Please submit protocols and methods for this study to the

Division within ninety days of receipt of this letter. A report on this experience will be submitted to the Division by December 31, 2000.

3. Bristol-Myers Squibb will conduct a study of the effect of gatifloxacin on the QTc interval by studying its effect in patients receiving gatifloxacin in currently ongoing studies. Pre-dose and post-dose valid electrocardiograms and concurrent gatifloxacin serum concentrations should be performed. The results of this study should be submitted to the Division by December 31, 2000.

4. Bristol-Myers Squibb will conduct a gatifloxacin single oral dose escalation study of the effects on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.

5. Bristol-Myers Squibb will conduct a study to compare the effects of gatifloxacin, ciprofloxacin, clarithromycin and sparfloxacin on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.

6. The pharmacokinetic studies described in items 3, 4 and 5 will include equal number of men and women over a broad range of ages (≥18 years; including geriatric patients).

7. Bristol-Myers Squibb will repeat the rat oral and intravenous teratology studies using adequately high dose levels. The results of these studies will be submitted to the Division by December 31, 2000.

In addition to the above Phase 4 commitments, we suggest that Bristol Myers Squibb consider conducting the following studies:

1. Bristol-Myers Squibb should consider extending the understanding of the effect of gatifloxacin on the rapidly-activating delayed-rectifier current compared to additional members of the quinolone class by adding them to your *in vitro* HERG model (e.g., levofloxacin). Bristol Myers Squibb may also wish to consider testing gatifloxacin in the AT-1 model.

2. Bristol-Myers Squibb should consider performing another study in the anesthetized beagle model with higher intravenous doses of gatifloxacin and concurrent measurements of gatifloxacin plasma concentration with cardiac monitoring so that the rhythm/concentration relationship could be studied at the higher, potentially toxic levels.

3. Bristol-Myers Squibb should consider conducting a gatifloxacin single dose drug interaction study with aluminum/magnesium antacids to determine the appropriate time for dosing gatifloxacin AFTER antacids are taken.

4. Bristol-Myers Squibb should consider approaches to evaluating potential pharmacodynamic interactions effecting QTc length between gatifloxacin and class IA and III antiarrhythmics.

Concurrences:

/S/ 12/28/99

Joyce Korvick, M.D., M.P.H.
Lead Medical Officer
Division of Special Pathogen and Immunologic Drug Products

/S/ 1/4/00

Marc Cavaillé-Coll, M.D., Ph. D.
Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products

/S/

Mark Goldberger, M.D., M.P.H.
Division Director
Division of Special Pathogen and Immunologic Drug Products

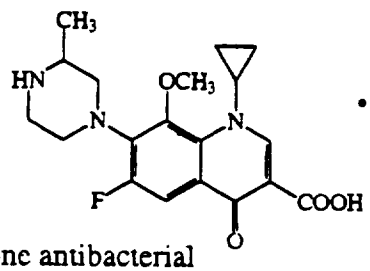
cc:
Original NDA 21-061
HFD-590/Div. Dir/Goldberger
HFD-590/Dep. Div. Dir/Albrecht
HFD-590/TL/Cavaillé-Coll
HFD-590/MO/Korvick
HFD-590/MO/Roca
HFD-590/Chem/Smith
HFD-520/Micro/Altaie
HFD-880/BioPharm/Uhl
HFD-520/Pharmtox/Ellis
HFD-725/Biometrics/Silliman
HFD-590/RPM/Atkins
HFD-590/RPM/Bernato

8.1 Medical Officer Review of NDA 21-061, 21-062: Gatifloxacin (Tequin ™) for the treatment of community acquired pneumonia

Date Submitted:	28 December 1998
Date Received :	29 December 1998
Date Assigned:	29 December 1998
Date Completed:	03 November 1999

Applicant: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, Connecticut 06492
203-677-6883
Contact person: Douglas Kriesel, Ph.D.

Drug: Proprietary name - Tequin ™
Generic name - Gatifloxacin
Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate
Molecular formula - $C_{19}H_{22}FN_3O_4 \bullet 1.5\ H_2O$
Molecular weight - 402.42 (sesquihydrate)
Molecular structure -



• 1.5 H_2O

Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets (21-061)
Intravenous; 400 mg suspension (21-062)

Related NDA: 21-061, 21-062 [redacted]

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