

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-404**

**21-405**

**21-061/s010, s016**

**21-062/s011, s017**

**MEDICAL REVIEW**

**Division of Special Pathogens and Immunologic  
Drug products HFD-590  
Medical Officer Review of NDA 21-404, NDA 21-405, NDA 21-061/S-010,  
NDA 21-061/S-016, NDA 21-062/S-011, and NDA 21-062/S-017**

**Initial Date of Submission:** February 6, 2002

**Date Assigned:** February 12, 2002

**Date Completed:** June 28, 2002

**1 General Information**

**Sponsor:** Bristol Myers-Squibb Company

**Drug Name:** Tequin® (Gatifloxacin HCl)

**2 Background:** Gatifloxacin is an 8-methoxy fluoroquinolone approved for marketing in the United States on December 17, 1999. In the original new drug application (NDA) for gatifloxacin, the sponsor also sought approval for the indication of uncomplicated skin and skin structure infections (USSSI). However, given its relatively non-serious nature, the indication was considered approvable and the sponsor was required to provide additional data in the phase 4 commitment demonstrating acceptable benefit-risk profile for gatifloxacin.

One of the safety issues raised in the phase 4 commitments was the need to provide additional data regarding the effect of gatifloxacin on the QT interval. In fulfillment of the stipulated phase 4 commitments, the sponsor provided data in the submission of February 6, 2001, resubmitted on July 29, 2001. In the course of the review of the July 2001 resubmission, the Agency received several reports of disturbances of glucose homeostasis in patients on treatment with gatifloxacin. Consequently, the Agency engaged the sponsor in negotiations to revise product labeling to adequately reflect the reports of disturbances of glucose homeostasis. The Agency also proposed revisions to the Clinical Pharmacology section of the labeling to reflect electrocardiographic (ECG) data submitted by the sponsor in fulfillment of the phase 4 commitments. An approvable letter was again issued to the sponsor for the indication of USSSI on December 21, 2001. Approval for this indication was dependent on conclusion of negotiations of the proposed labeling.

The current resubmission contains sponsor's responses to the labeling revisions proposed by the Agency in December 2001. The current resubmission also contains the report of the ECG sub-study from the PROVE IT study.

It should be pointed out that on April 4, 2002, during the course of this review, the sponsor submitted proposed labeling revisions pertaining to glucose homeostasis. Data for this proposed labeling revisions were based on the executive summary of results of Study AI420-105 titled "Open-label Study of the Reversibility of the Effect of Gatifloxacin on Insulin Secretion Following Oral Glucose Challenge in Type 2 Diabetics." In a teleconference held with the sponsor on April 16, 2002, the Agency

informed the sponsor that executive summary could not allow a substantive review that a full study report would, and therefore, could not be used to support labeling revisions. At the same teleconference, the applicant was advised to submit a 'Changes Being Effected' (CBE) supplement that addresses new information on the effect of gatifloxacin on glucose homeostasis. The CBE supplement was eventually submitted on May 10, 2002. The CBE submission also contained the full report from Study AI420-105.

This written review specifically addresses the ECG sub-study of the PROVE-IT study and briefly comments on the CBE supplement together with Study AI420-105. Besides data on the effect of gatifloxacin on QTc interval, the PROVE-IT study contains no safety or efficacy data. For an assessment of the benefits versus risks of gatifloxacin in actual use, the reader should see the medical officer review of the resubmission for the indication of USSSI (attached).

### 3 Protocol CV123-229

#### 3.1 Title

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT): ECG Substudy of Gatifloxacin Effects on the QTc Interval

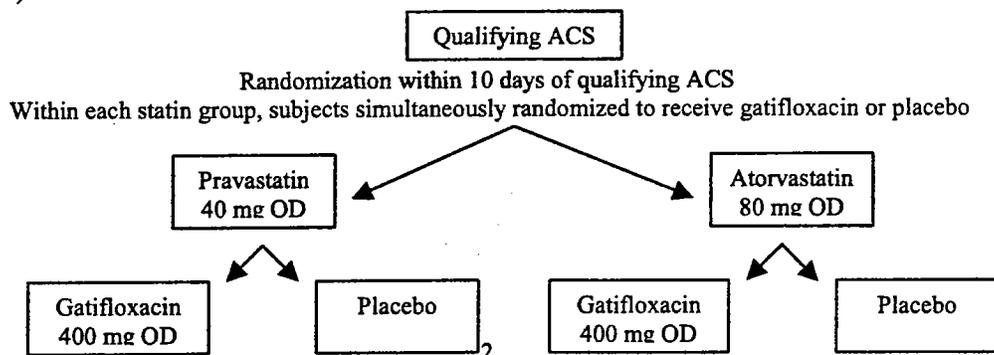
#### 3.2 Objectives

**Primary Objective:** To demonstrate the clinical equivalence of the acute effect of gatifloxacin or placebo on the corrected QT interval (QTc) on Day 15 (the first day of dosing of gatifloxacin or placebo).

**Secondary Objective:** To assess the steady-state effect, in the first 100 subjects, of gatifloxacin on the QTc on Day 20 (the 6<sup>th</sup> day of once-daily dosing of gatifloxacin or placebo).

Additional objectives, not pre-specified in the protocol, were to assess the acute-on-chronic effect, in the 1<sup>st</sup> 100 subjects, of gatifloxacin on the QTc on Day 20 compared with baseline on Day 20 and to assess the relationship between the change from baseline in QTc and gatifloxacin plasma concentration in the gatifloxacin treatment group on Day 15 and Day 20.

**3.3 Study Design:** The PROVE IT study is an ongoing multicenter, multinational randomized, double blind, 2X2 factorial, parallel group design trial comparing pravastatin and atorvastatin, and also comparing gatifloxacin and placebo in subjects with a total cholesterol of  $\leq 240$  mg/dL (6.21 mmol/L) following an acute coronary syndrome (ACS).



The first dose of gatifloxacin (or placebo) was administered at the Day 15 visit. The timing of the antibiotic therapy was selected to allow patients to be more stable since gatifloxacin may have the potential to prolong the QTc in this patient population at increased risk for arrhythmia. Subjects received an initial 14-day course of gatifloxacin (or placebo) during the first 30 days followed by a 10-day course of gatifloxacin (or placebo) every month for the period they are on the PROVE IT trial, which is expected to be 18 months.

*Medical officer's comment: The exact content of the placebo is not clear from the submission. However, one can assume that it is the same as the active drug formulation minus the active drug.*

For the ECG substudy, the first 500 subjects in the PROVE IT study were targeted. Enrollment criteria were identical to those for the PROVE IT study. However, exclusion criteria pertinent to the ECG substudy were the following:

- QTc (LeadII) > 0.45 seconds (or QTc > 0.50 seconds for subjects with intraventricular conduction delay such as Left Bundle Branch Block LBBB) using Bazett's formula for heart rate correction [ $QTc = QT \text{ (actual)} / \sqrt{RR \text{ interval (seconds)}}$ ];
- History of prolonged QT interval;
- Current or anticipated need for treatment with class IA or III antiarrhythmic agents (e.g., quinidine, procainamide, sotalol, amiodarone) or history of prior episode of torsade de pointes;
- Uncorrected hypokalemia;
- Renal insufficiency (defined as calculated creatinine clearance < 40 ml/min);
- Treatment with any of the following agents (some of which are known to prolong the QTc interval) within the last month, or likelihood of requiring such treatment during the study period:
  - Oral or parenteral corticosteroids
  - Immunosuppressive agents (e.g., cyclosporine)
  - Estrogens, progestogens and androgens (except hormone replacement therapy)
  - Erythromycin or clarithromycin
  - Probenecid
  - Orlistat
  - Terfenadine
  - Cisapride
  - Antipsychotics
  - Tricyclic antidepressants
  - Protease inhibitors
- Atrial fibrillation (were allowed in the PROVE IT study)

*Medical Officer's Comments: The population for this study comprises those at risk for abnormalities of cardiac rhythm. However, subjects more prone to malignant rhythm disturbances are excluded.*

Subjects in the ECG substudy had baseline 12-lead ECG obtained on Day 15. Two hours post gatifloxacin (or placebo) blood sample (for gatifloxacin plasma concentration) and a repeat ECG were obtained. The study planned for the first 100 of these subjects to also have baseline ECG and a repeat ECG together with blood sample (for gatifloxacin plasma concentration) 2-hour post gatifloxacin (or placebo) obtained on Day 20 of treatment. ECG collection across sites was standardized. A central ECG laboratory measured the QTc intervals and compared with those measured by individual sites.

### 3.4 Data analysis

Selected baseline demographics and clinical characteristics of the gatifloxacin and placebo groups were tabulated and compared. QTc changes from baseline were analyzed using analysis of covariance (ANCOVA) model to compare gatifloxacin and placebo at 2 hours post-dose. A 90% two-sided confidence interval was constructed for the estimated mean difference between gatifloxacin and placebo from the ANCOVA model. For clinical equivalence between the two groups, the upper bound of the confidence interval of the estimated mean difference adjusted for baseline was pre-specified in the protocol to be less than 6 milliseconds. In the cross-tabulations of demographic and clinical characteristics, the only risk factor that appeared to be unbalanced between gatifloxacin and placebo arms was a higher proportion of diabetes mellitus on the gatifloxacin arm compared to the placebo arm. Since diabetes mellitus is a known risk factor for prolonged QTc, this factor was included in the ANCOVA model.

*Medical officer's comment: Gender is a factor in assessing QTc. Generally, women have longer QTc than men. There were more females on the placebo arm than on the gatifloxacin arm. Gender was not included in the ANCOVA model; however, the review statistician considers that inclusion of gender in the model is unlikely to affect results of the analysis as there are only small differences in proportions of males and females between the two groups.*

Further, the cross-tabulations of baseline and 2 hour post-dose QTc intervals for each of the two treatment groups was classified into four categories of < 450 msec, 450-480 msec, > 480-500 msec and > 500 msec and absolute change from baseline QTc (< 30 msec, 30-60 msec, and > 60 msec).

Change from baseline in QTc at 2 hour post-dose was also summarized for the following subgroups: elderly ( $\geq 65$  years), non-elderly (< 65 years) and gender (male, female). Differences in treatment effects within these subgroups were summarized and 90% two-sided CIs were also given.

To assess the relationship between the change from baseline QTc and gatifloxacin plasma concentrations, the change from baseline QTc was regressed on the gatifloxacin plasma concentration and the baseline QTc.

The potential interaction of investigative site was not examined in any analysis as all sites were pooled for each of the analysis. As per the objectives, analyses were performed for each of the three types of change from baseline:

- Day 15 post-dose – Day 15 baseline
- Day 20 post-dose – Day 15 baseline
- Day 20 post-dose – Day 20 baseline

*Medical Officer's Comment: It should be noted that only 73 subjects (36 on the gatifloxacin arm and 37 on the placebo arm) were included in the comparison of Day 20 post-dose and Day 15 baseline ECGs, and 77 subjects (38 gatifloxacin, 39 placebo) were included in the comparison of Day 20 post-dose and Day 20 baseline ECGs. Further, given that only 4 subjects had paired ECGs on Day 20, it is assumed that subjects with baseline ECG on Day 20 are different from those with 2 hours post-dose ECG on the same day.*

### 3.5 Interim Analysis

In July 2001, the Data and Safety Monitoring Board (DSMB) reviewed a summary of ECG data from 488 subjects on Day 15 and 34 subjects on Day 20 and recommended continuing the study since no harm was demonstrated. The interim summary is only in the purview of unblinded personnel and is yet to be released. As a result, no adjustments were made to levels of significance based on multiple looks at the data.

### 3.6 Results

#### 3.6.1 Baseline Characteristics

**Table 1: Baseline and clinical Characteristics**  
(Adapted from Table 5.2 Page 39 of Applicant's Submission)

Characteristics	Gatifloxacin N=374	Placebo N=386
Age (years)		
Mean (sd)	58 (11.3)	58 (11.1)
(min, max)	(33, 84)	(30, 89)
Age group, n (%)		
Elderly (≥ 65 years)	107 (28.6)	112 (29.0)
Non-elderly (< 65 years)	267 (71.4)	274 (71.0)
Gender <sup>a</sup> , n (%)		
Male	295 (78.9)	288 (74.6)
Female	79 (21.1)	97 (25.1)
Diabetes Mellitus, n (%)	85 (22.7)	57 (14.8)
Qualifying event, n (%)		
Unstable angina pectoris (UAP)	140 (37.4)	121 (31.3)
Acute myocardial infarction (AMI)	233 (62.3)	264 (68.4)
Antiarrhythmics <sup>b</sup> , n (%)	14 (3.7)	11 (2.8)
Antihistamines, n (%)	93 (24.9)	97 (25.1)
Antibiotics <sup>c</sup> , n (%)	17 (4.5)	13 (3.4)
Central Nervous System Agents <sup>d</sup> , n (%)	27 (7.2)	30 (7.8)

- a. Reflects Missing gender data in one subject
- b. Class Ia and Class III antiarrhythmics taken during the 2 weeks prior to the qualifying event
- c. Fluoroquinolone and macrolide antibiotics taken during the 2 weeks prior to the qualifying event
- d. Selective serotonin re-uptake inhibitor (SSRI) and tricyclic antidepressants taken during the 2 weeks prior to the qualifying event

### 3.6.2 Subject Disposition

Subject disposition is shown on Table 2.

**Table 2: Subject Disposition**  
(Reproduced from Appendix 5.1 Page 170 of Applicant's Submission)

	<b>Gatifloxacin</b>	<b>Placebo</b>	<b>Total</b>
Number of subjects entered in Day 15	614	618	1232
Number of subjects Included in Day15 Analysis	372	384	756
Excluded from Day 15 Analysis	242	234	476
<b>Reason for Exclusion</b>			
Baseline Measurement Date > Medication Date	3	2	5
2-Hour Measurement Date Differs from Medication Date	4	2	6
No Baseline and 2-Hour Time Recorded	1	0	1
Baseline Time Greater than 2-Hour Time	24	25	49
2-Hour ECG Measurement < 1.5 Hours	11	19	30
2-Hour ECG Measurement > 3 Hours	11	6	17
No Baseline ECG Measurement	20	26	46
No 2-Hour ECG Measurement	213	194	407

A subject could have more than one reason for exclusion

As shown on Table 2, the bulk of subjects excluded from day 15 analysis did not have 2-hour ECG measurements.

### 3.6.3 Changes in QTc Interval on Day 15

Table 3 presents summary of changes in QTc from baseline on Day 15 to 2 hours post-dose on Day 15.

**Table 3: Summary of Changes in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 15**  
(Reproduced from Table 6.1.1A Page 44 of Applicant's Submission)

<b>QTc Intervals (msec)</b>	<b>Gatifloxacin N=372</b>	<b>Placebo N=384</b>
<b>Baseline</b>		
Mean (sd)	395.2 (25.9)	393.2 (26.2)
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	393.0 (377.0, 412.5)	393.0 (377.5, 410.5)
<b>2 Hours Post-Dose</b>		
Mean (sd)	401.4 (26.3)	395.8 (6.8)
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	401.0 (384.0, 418.5)	394.0 (376.5, 411.0)
<b>Change from baseline at 2 Hours Post-Dose</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	8 (-6.0, 19.0)	2.0 (-8.0, 14.0)
Adjusted Mean (se)	6.5 (0.94)	2.4 (0.92)
Adjusted Mean Difference from Placebo (90% 2-sided CI)	4.2 (2.00, 6.34)	

Subset analyses showed no differences between gatifloxacin and placebo among the male or female subjects and also among the elderly ( $\geq 65$  years), non-elderly ( $< 65$  years) patients. The only imbalance in baseline characteristics was the presence of diabetes mellitus. There were proportionately more diabetic patients on the gatifloxacin arm than on the placebo arm. Adjustment for this imbalance in the ANCOVA model made no difference to the overall result.

Further analysis showed no significant relationship between the actual baseline QTc and the 2-hour post dose QTc on Day 15 among the subjects. In addition, None of the patients had an absolute increase of QTc > 500 msec post dose compared with baseline QTc on Day 15.

### 3.6.4 Changes in QTc Interval on Day 20

**Table 4: Summary of Day 20 Post-Dose QTc Compared with Day 15 Post-Dose QTc**  
(Reproduced from Table 6.2.1A Page 56 of Applicant's Submission)

QTc Intervals (msec)	Gatifloxacin N=36	Placebo N=37
<b>Baseline on Day 15</b>		
Mean (sd)	398.2 (25.7)	399.6 (22.3)
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	396.5 (381.5, 409.0)	398.0 (386.0, 414.0)
<b>2 Hours Post-Dose on Day 20</b>		
Mean (sd)	404.8 (32.8)	393.4 (25.2)
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	400.0 (384.0, 420.5)	392.0 (378.0, 405.0)
<b>Change from Day 15 baseline</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	4.5 (-8.0, 20.0)	-1.0 (-15.0, 5.0)
Adjusted Mean (se)	6.5 (3.51)	-6.0 (3.46)
Adjusted Mean Difference from Placebo (90% 2-sided CI)	12.5 (4.31, 20.73)	

Placebo-adjusted mean increase in QTc on Day 20 compared to baseline on Day 20 was 12.5 msec, suggesting a potential QTc-prolonging effect of gatifloxacin following steady state dosing. Indeed, one of the 36 subjects on the gatifloxacin arm developed a QTc > 500 msec and absolute increase of QTc of >60 msec compared to none of the subjects on the placebo arm. It is unclear if this subject was symptomatic. However, she was discontinued from Treatment B part of the study per protocol, even though the investigator felt the event was unrelated to Treatment B.

**Table 5: Summary of Day 20 Post-Dose QTc Compared with Day 20 Baseline QTc**  
(Reproduced from Table 6.2.2A Page 62 of Applicant's Submission)

QTc Intervals (msec)	Gatifloxacin N=38	Placebo N=39
<b>Baseline</b>		
Mean (sd)	400.1 (25.2)	400.7 (24.1)
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	394.5 (385.0, 413.0)	396.0 (385.0, 416.0)
<b>2 Hours Post-Dose</b>		
Mean (sd)	404.4 (32.1)	394.0 (24.7)
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	400.0 (384.0, 420.0)	394.0 (378.0, 408.0)
<b>Change from baseline at 2 Hours Post-Dose</b>		
Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	4.0 (-13.0, 17.0)	-4.0 (-18.0, 3.0)
Adjusted Mean (se)	4.3 (3.41)	-6.7 (3.37)
Adjusted Mean Difference from Placebo (90% 2-sided CI)	11.0 (3.02, 18.98)	

Gatifloxacin potentially caused a placebo-adjusted increase in QTc at 2-hour post dose on Day 20 of 11 msec compared to baseline QTc on Day 20. The findings from the single

subject from the gatifloxacin arm that had QTc > 500 msec and an increase in QTc of > 60 msec are also captured in this analysis.

As required by the protocol, additional ECGs were obtained from 24 subjects on follow-up visits after Day 20, including paired ECGs collected on Day 45. QTc was increased by > 60 msec in one gatifloxacin-treated subject on the pre-dose ECG on Day 52 compared to Day 1 of antibiotic study drug dosing. However, that subject's increase in QTc on the post-dose ECG on the same Day 52 was 56 msec compared to baseline on Day 1 of antibiotic dosing. The sponsor is awaiting further details on this subject.

### 3.6.6 Plasma Concentration of Gatifloxacin and QTc on Day 15 and on Day 20

A total of 226 (61%) of the 372 subjects on the gatifloxacin arm had paired ECGs and a blood sample collected for gatifloxacin levels on Day 15. Among gatifloxacin patients, a scatterplot showed no significant relationship between plasma levels and change in QTc on Day 15 compared to baseline on the same day. However, there was a significant inverse relationship between baseline QTc and change in QTc on Day 15 that the sponsor suggests might be due to regression to the mean or a decreased drug effect in those with higher baseline QTc.

In addition, scatterplots of the changes in QTc interval from baseline on Days 15 and 20 to 2 hours post-dose on Day 20 showed no significant correlation with plasma concentration of gatifloxacin on Day 20. However, only 24 of 36 gatifloxacin subjects had paired ECGs (baseline on Day 15 and 2 hours post-dose on Day 20) and gatifloxacin plasma concentration measurement on Day 20. Similarly, only 26 of 38 gatifloxacin-treated subjects with paired ECGs (baseline on Day 20 and 2 hours post-dose on Day 20) had gatifloxacin plasma levels measured.

Table 6 summarizes gatifloxacin plasma concentrations obtained on Days 15 and 20.

**Table 6: Gatifloxacin Concentrations on Days 15 and 20**

Timing of Gatifloxacin Plasma Concentration Measurement	No. of Subjects	Plasma Gatifloxacin Concentration (µg/mL)		
		Mean (SD)	Median	Range
Day 15: 2 hours Post-dose	226	3.00 (1.03)	2.98	0.0 – 6.5
Day 20: Baseline	24	3.43 (1.27)	3.47	0.7 – 6.5
Day 20: 2 hour Post-dose	26	3.33 (1.28)	3.34	0.7 – 6.5

## 4 Protocol AI420105

Study AI420105 was an unblinded study of stable type 2 diabetics controlled with oral antidiabetic agents. Specifically, the study enrolled two groups of patients: those on glyburide-containing regimen and those on non-glyburide-containing regimen. Enrollment was stratified for other antidiabetic agents. The primary objective of Study

was to examine the reversibility of any effects of 14 days of once-daily gatifloxacin on insulin secretion following oral glucose challenge in Type 2 diabetics controlled with oral antidiabetic agents. The secondary objectives of the study were 1) to compare the effects of gatifloxacin on insulin secretion and glucose tolerance following oral glucose tolerance test (OGTT) in Type 2 diabetics controlled with glyburide containing to those controlled with non-glyburide containing oral antidiabetic regimens. 2) To examine the effects of gatifloxacin on glucose tolerance and c-peptide secretion in Type 2 diabetics controlled with glyburide containing to those controlled with non-glyburide containing oral antidiabetic regimens and to assess the reversibility of any noted effects. 3) To examine the effects of gatifloxacin on glucose homeostasis in Type 2 diabetics controlled with glyburide containing to those controlled with non-glyburide containing oral antidiabetic regimens. 4) To examine the safety and tolerability of gatifloxacin administered for 14 days in Type 2 diabetics controlled with oral antidiabetic agents.

Seventy eligible patients (male or female  $\geq 18$  years) were enrolled (35 per arm) at two sites in the U.S. The patients were admitted to the study center 4 days prior to dosing. Gatifloxacin 400 mg was administered once daily at about 8 am along with the patient's antidiabetic medication on Days 1 through 14. Oral glucose tolerance test (OGTT) was performed. Measurements of blood glucose, insulin, and c-peptide prior to and for up to 5 hours after each OGTT were obtained. In addition, glucose and insulin homeostasis were monitored by measuring fasting serum glucose, insulin, and c-peptide on Study Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 26-28, and 40-42, each following an overnight fast for at least 8 hours. Further serum samples were obtained on Days -2, 1, 2, and 3 for detailed monitoring of glucose, insulin, and c-peptide. In addition, markers of glucose control, fructosamine and glycosylated hemoglobin (HbA1c) were measured at specified intervals. Finally, physical examination, vital signs, electrocardiogram (ECGs) and clinical laboratory tests were done at screening, prior to dosing, and at selected intervals while also monitoring for adverse events throughout the study.

Appropriate statistical methods were employed. Reversibility of the effect of gatifloxacin on insulin secretion following an OGTT was concluded if the 90% confidence interval for the ratio of the Day 28 over Day -1 geometric mean fell entirely within 0.80, 1.25 for AUC of insulin and within 0.70, 1.43 for Cmax of insulin. Similarly, reversibility of the effects of gatifloxacin on glucose tolerance and c-peptide secretion was based on the glucose and c-peptide AUC and Cmax parameters. Most other measures were summarized by treatment group and study day.

#### Summary of Results and Conclusions from Study AI420105

- In this population of well-controlled Type 2 diabetics without infection, the effects of gatifloxacin on glucose metabolism, as measured by glucose, insulin, and c-peptide levels at a dose of 400 mg once daily for 14 days, were modest and reversible.
- Gatifloxacin 400 mg administered orally once daily for 14 days was generally safe and well tolerated. Although transient hypoglycemia or hyperglycemia was noted in some subjects, these events were tolerated and subjects were able to continue on gatifloxacin therapy.

- Following an OGTT, the no effect criteria were met for all comparisons of C<sub>max</sub> and AUC of glucose, insulin, and c-peptide relative to baseline, except for the AUC of insulin in the non-glyburide treated subjects on Day 15; however, this effect was not accompanied by clinical symptoms and was reversible by Day 28.
- Transient increases in insulin and decreases in glucose were noted during the first 2 days of dosing with gatifloxacin. The magnitude of changes were larger in glyburide treated subjects compared to the non-glyburide treated subjects.
- In the glyburide treated subjects, decreases in serum glucose levels in the first 2 days of gatifloxacin administration were associated with symptomatic events in some patients.
- Increases in fasting glucose of about 40 mg/dL were noted after Day 3 in both glyburide and non-glyburide treated groups, which returned towards baseline by Day 28.
- Glucose homeostasis should be monitored in Type II diabetics following the initiation of gatifloxacin therapy. Signs and symptoms of hypoglycemia (particularly early in gatifloxacin therapy) and of hyperglycemia (particularly late in gatifloxacin therapy) should be monitored and supportive care administered when necessary.

## **5 Medical Officer's Overall Assessment of the Submission**

### **5.1 PROVE-IT ECG Substudy**

The ECG substudy of the PROVE-IT study is the only placebo-controlled multiple dose study to assess the effect of gatifloxacin on the QTc interval. Previous studies either assessed the effect on QTc interval following a single dose of gatifloxacin or lacked a control group. Further, the population studied is at risk for disturbances of cardiac rhythm. The study thus provides robust data to address this issue. In this relatively higher risk population, at 2 hours post-dose, gatifloxacin increased QTc interval by a mean of 4.2 msec on Day 15 of the study (Day 1 of gatifloxacin dosing) compared to baseline QTc interval on the same day. In subset analyses, the upper bound of the 90% confidence interval of the increase in QTc exceeded the protocol-specified limits in male and female subjects and in the elderly ( $\geq 65$  years). At steady-state on Day 20 (Day 6 of gatifloxacin dosing), the effect of gatifloxacin on the QTc interval is comparable to the effect following the first dose on Day 15. A larger increase in QTc was recorded following acute-on-chronic dosing of gatifloxacin (2 hours post-dose relative to baseline on Day 20). This may indeed reflect variability in QTc, given the small number of subjects studied on Day 20. The reader should refer to the review by the Biopharmaceutical reviewer, Philip Colangelo, Pharm. D., Ph.D., which provides a detailed review of the effect of gatifloxacin on QTc interval across studies and in comparison with other products.

### **5.2 Changes Being Effected Supplement of May 10, 2002**

As noted earlier, this supplement addresses reports of disturbances in glucose homeostasis following marketing approval of gatifloxacin and also contains full report from Study AI420105. In addition, the supplement provides a synopsis of a program that

the sponsor plans to employ in educating providers about the effect of gatifloxacin on glucose homeostasis.

In Study AI420105, sixty-six of the 70 subjects took either glyburide plus methformin or glyburide alone, therefore, the protocol-specified stratification for other antidiabetic drugs was not included in the ANOVA model. The impact of gatifloxacin used concomitantly with glyburide and antidiabetic drugs other than methformin is unknown. Pre-marketing studies showed that concomitant administration of gatifloxacin with glyburide had no significant pharmacokinetic effect on both drugs. Therefore, the findings of symptomatic pharmacodynamic effects following co-administration of gatifloxacin with glyburide cannot be explained on pharmacokinetic basis. Indeed, preclinical animal studies showed changes in the pancreatic  $\beta$ -cells. However, such changes may not fully explain the findings from Study AI420105. Although not designed to assess the potential impact of age on the findings of Study AI420105, the small size of the study limits post-hoc analysis during this review to assess the impact of age. On a separate note, Study AI420105 does not address the potential impact of underlying infection and other co-morbid conditions in the etiology of abnormal glucose homeostasis reported with gatifloxacin. The reader should refer to the review by the Biopharmaceutical reviewer, Philip Colangelo, Pharm. D., Ph.D. for a detailed review of Study AI420105.

The Division of Drug Risk Evaluation (DDRE), Office of Drug Safety (ODS) of the Agency has extensively reviewed reported cases of disturbances of glucose homeostasis associated with gatifloxacin use. For more details the reader should refer to the reviews of this topic by Sarah J. Singer, R.Ph., Safety Evaluator, DDRE. In addition, ODS provides a detailed comment to the Changes Being Effectuated supplement submitted by the sponsor on May 10, 2002 (attached). The medical officer shares the views of ODS and, in particular, agrees that the labeling and educational program must reflect the fact that the risk may be higher for elderly patients "who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems, and/or taking concomitant medications associated with hyperglycemia."

## **6 Conclusion and Recommendation**

From the submissions reviewed, it is reassuring that the effect of gatifloxacin on QTc interval in subjects with acute coronary events is minimal. However, gatifloxacin causes symptomatic disturbances in glucose homeostasis. The Agency and the applicant continue to work closely on labeling revisions that will adequately and effectively communicate this risk to patients and their providers. In the absence of other concerns, the medical officer recommends that the submissions be approved.

On August 2, 2002, the applicant was issued an approvable letter for these applications. Approval of these applications was dependent on the applicant providing certification that all the safety information on Tequin® submitted in Europe had previously been submitted to the Agency pending, as was discussed with and agreed to by Dr. Nicaise of Bristol-Myers Squibb during a teleconference with the Division on June 11, 2002.

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Ekopimo Ibia M.D., M.P.H.  
Medical Officer, DSPIDP

Concurrences:

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Marc Cavaille Coll, M.D., Ph.D.  
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Acting Division Director, DSPIDP

cc:

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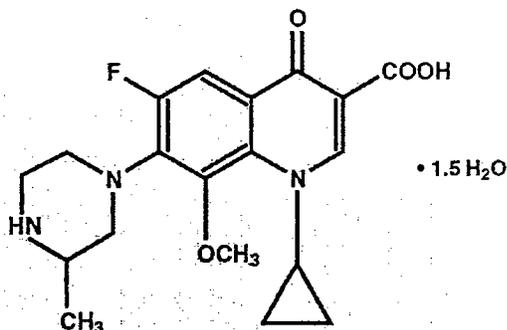
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**DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC  
DRUG PRODUCTS HFD-590  
MEDICAL OFFICER'S REVIEW OF NDAs 21-404 AND 21-405 GATIFLOXACIN FOR  
UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS**

Date Submitted: June 29, 2001  
Date Received: July 2, 2001  
Date Assigned: July 27, 2001  
Date Completed: November 10, 2001  
Date Revised: December 4, 2001

Sponsor: Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, CT 06492  
Telephone 203 677 6163  
Facsimile 203 677 7279

Product: Generic name: Gatifloxacin  
Trade name: Tequin®  
Chemical name: -1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate  
Chemical structure:



Drug class: Fluoroquinolone antimicrobial  
Routes of administration: Oral and intravenous  
Proposed indication: Uncomplicated skin and skin structure infections

Related INDs: IND 52,081  
IND 57,672  
IND 53,521  
Related NDAs: NDA 21-061  
NDA 21-062

Reviewer: Ekopimo Ibia, MD, MPH

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## Executive Summary

### I. Recommendations

#### A. Recommendation on Approvability

In submissions to NDAs 21-404 and 21-405, the applicant has provided data that satisfy all the remaining phase IV commitments entered into by the applicant on December 17, 1999 following the approval of the original NDAs for gatifloxacin (NDAs 21-061 and 21-062). Data provided in these submissions have contributed to further understanding the safety of gatifloxacin. The data expand gatifloxacin exposure population and in that regard show that gatifloxacin has a satisfactory risk-benefit profile for the relatively non-serious indication of treatment of simple abscesses, furuncles, folliculitis, wound infections, and cellulitis caused by *Streptococcus pyogenes* and methicillin sensitive *Staphylococcus aureus*. However, NDAs 21-404 and 21-405 are approvable pending labeling revisions to adequately reflect postmarketing safety updates, including cases of disturbances in glucose homeostasis reported mostly among diabetic and/or elderly patients being treated with gatifloxacin.

#### B. Recommendation on Phase 4 Studies and Risk Management Steps

There are no further recommendations on phase 4 studies and no new risk management steps are indicated beyond ongoing pharmacovigilance for the marketed product.

### II. Summary of Clinical Findings

#### A. Brief Overview of Clinical Program

Gatifloxacin received marketing approval in the US on December 17, 1999. At that time, the indication of uncomplicated skin and skin structure infections (USSSI) was considered approvable pending the demonstration of a satisfactory risk-benefit profile in the post-marketing period. Such risk-benefit assessment was to be determined from a series of six studies detailed in the phase IV commitment entered into by the applicant at the time of approval. Three of the studies were aimed at further understanding the effect of gatifloxacin on corrected QT interval. One study was to assess the safety of gatifloxacin in actual patient population while one study was to present the safety profile of gatifloxacin in the first one million patients worldwide treated with this medication. The sixth study in the phase IV commitments was a teratology study in rats using high doses of gatifloxacin. This last study had been completed and results submitted to the Agency. The current submissions contain data to fulfill the remaining phase IV commitments and to seek approval for the indication of USSSI.

#### B. Efficacy

The clinical response rates obtained in the treatment of community acquired respiratory tract infections (Protocol AI420-088) is consistent with the response rates in the pivotal trials in the original NDA submissions. It should be noted that no new data on gatifloxacin in the treatment of USSSI was presented in these submissions. Nevertheless, in an earlier review of this indication in the original NDA, the medical

officer was satisfied that gatifloxacin demonstrated sufficient efficacy in adequate numbers of subjects diagnosed with simple abscesses, furuncles, folliculitis, wound infections, and cellulitis. However, inadequate number of subjects diagnosed with \_\_\_\_\_ were studied to support efficacy in these particular indications.

C. Safety

Review of these submissions has not revealed any new safety concerns. Currently, labeling for gatifloxacin is being revised to reflect adverse events reported in the post-marketing period, including disturbances of glucose homeostasis, hepatitis, torsades de pointes, and thrombocytopenia.

D. Dosing

The approved dose of gatifloxacin is 400 mg once daily by oral and/or intravenous route. For the indication of uncomplicated skin and skin structure infections the proposed dose is 400 mg once daily for 7-10 days orally and/or intravenously.

E. Special Populations

Gatifloxacin is approved for use in patients aged 18 years or older. \_\_\_\_\_

\_\_\_\_\_ The data contained in these submissions show that women and subjects aged 65 years or older are adequately represented. In Study AI420-088, approximately 32% of females reported at least one adverse event compared to about 21% of the males. On the other hand, similar proportions of subjects reported adverse events among those 65 years or older compared to those younger than 65 years (31% and 27%, respectively). In the One Million Patient spontaneous adverse event report, gender was not defined for 123 (30.8%) of the 399 patients who reported adverse events, 178 (44.6%) were females while 98 (24.6%) were males. The reason for the higher numbers of adverse events among females is unclear but is apparently consistent with observations in published literature.

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## Clinical Review

### I. Introduction and Background

Gatifloxacin, a synthetic fluoroquinolone antimicrobial drug product, received marketing approval in the US on December 17, 1999. Gatifloxacin is currently approved for community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, uncomplicated and complicated urinary tract infection, pyelonephritis, and uncomplicated gonorrhea. Although the applicant sought approval for uncomplicated skin and skin structure infections (USSSI) in the original NDA submissions, gatifloxacin was granted an approvable status for the treatment of simple abscesses, furuncles, folliculitis, wound infections, and cellulitis caused by *Streptococcus pyogenes* and methicillin sensitive *Staphylococcus aureus*. Treatment of impetiginous lesions was not included in that list because insufficient numbers of patients with that diagnosis were enrolled. Approval of gatifloxacin for these uncomplicated skin and skin structure infections was dependent upon submission of further data to enable determination of an acceptable risk-benefit profile. Studies listed in the approval letter to be undertaken by the applicant as phase IV commitments included:

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 were to 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. *Protocols and methods for this study were to be submitted to the Division within ninety days of receipt of the approval letter. A report on this experience was to 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 have been 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 were to 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 were to 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 ( $\geq 18$  years; including geriatric patients).
7. Bristol-Myers Squibb will repeat the rat oral and intravenous teratology studies using adequately high dose levels.

In addition, in the approval letter the Agency suggested that BMS should consider the following:

1. Extending the understanding of the effect of gatifloxacin on the rapid component of the delayed-rectifier potassium channel ( $IK_R$ ) compared to additional members of the quinolone class by adding them to your *in vitro* human-ether-a-go-go gene (HERG) model (e.g., levofloxacin). Bristol-Myers Squibb may also wish to consider testing gatifloxacin in the AT-1 model.
2. 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. 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. Evaluating potential pharmacodynamic interactions effecting QTc length between gatifloxacin and class IA and III antiarrhythmics.

#### **Applicant's Response to Phase IV Commitments**

Commitment number seven that required repeat rat oral and intravenous teratology studies using high dose levels was fulfilled as per letter to the applicant dated October 19, 2000. Current data were submitted on February 7, 2001 to IND 52,081 to seek the Agency's opinion prior to submitting the data for the uncomplicated skin and skin structure infections (USSSI) indication. In a letter dated June 29, 2001, the applicant made reference to the February 7, 2001 data to initiate resubmission to effect the approval of the indication for the treatment of uncomplicated SSSI. For administrative purposes, the February 7, 2001 data were assigned new NDA numbers, NDA 21-404 and 21-405.

The February 7, 2001 submission contained the following reports designed to fulfill commitments one through six as contained in the approval letter. Specifically, the current submissions contain results of studies designed to address the Phase IV commitments as follows:

- Commitment 1: TEQUIN: A review of Adverse Event Reports after Marketed Use by One Million Patients.
- Commitment 2: An Open-Label, Multicenter Non-comparative Study of Oral Gatifloxacin in the Treatment of Community-Acquired Respiratory Tract Infections

(Acute Bacterial Exacerbation of Chronic Bronchitis, Acute Uncomplicated Maxillary Sinusitis, and Pneumonia).

- Commitment 3: An Open-Label, Multicenter Non-comparative Study of Oral Gatifloxacin in the Treatment of Community-Acquired Respiratory Tract Infections: Analysis of effects on QT Interval of the ECG.
- Commitment 4: Randomized, Double-Blind, Placebo Controlled, Single-Dose, Four-Way Crossover Study of the Effects of Gatifloxacin on QTc Interval in Healthy Adult Volunteers.
- Commitment 5: Randomized, Open-Label, Placebo Controlled, Single-Dose, Four-Way Crossover Study of the Effects of Gatifloxacin, Ciprofloxacin, Sparfloxacin, and Clarithromycin on QTc Interval in Adult Volunteers.
- Commitment 6: Required equal numbers of men and women over a broad range of ages ( $\geq 18$  years including geriatric patients) in the studies for commitments 3, 4, and 5. The final study reports documented the distributions obtained and are summarized in the Integrated Summary of Phase IV commitments: QTc Prolongation During Gatifloxacin Therapy.

This medical officer review focuses on data submitted to fulfill Phase IV commitments one and two. The reader should please refer to the review by the Biopharmaceutical reviewer for details on the Phase IV commitments three through six.

Uncomplicated skin and skin structure infections are frequently encountered in the US medical practice. However, there are several approved products to treat these infections (see Appendix). Nevertheless, availability of additional products offers practitioners wider therapeutic options.

## II. Clinically Relevant Non-Clinical Findings

These submissions do not present any new issues relevant to chemistry, manufacturing, and control, or animal pharmacology and toxicology. The reader may wish to refer to the respective reviews of the non-clinical sections in the original NDA approval package. Further, although there are no new microbiologic data in this submission, microorganisms responsible for USSSI and were studied in the original NDA will be added to the label. These microorganisms are *Staphylococcus aureus* and *Streptococcus pyogenes*. For additional information the reader should refer to the Microbiology reviews for these submissions and in the original NDA approval package dated December 17, 1999.

## III. Human Pharmacokinetics and Pharmacodynamics

There are no new human pharmacokinetic (PK) data in these submissions. Interested readers may refer to the PK review in the original NDA. However, pharmacodynamic data on the effects of

gatifloxacin on QTc interval is included in the submissions. Gatifloxacin is an inhibitor of the rapid component of the delayed rectifier potassium channel (IK<sub>R</sub>). In 76 paired ECGs from 55 subjects enrolled in three adult volunteer studies, the mean ± SD change in QTc interval was 2.9 ± 16.5 msec, with no subject having QTc interval > 450 msec. However, prior to the current submissions limited data were available on arrhythmia potential of gatifloxacin using paired ECG obtained from actual patients. These submissions contain results of four clinical studies to assess the effect of gatifloxacin on QTc. These studies were designed with input from the Agency. Two of the studies (AI420-092 and AI420-093) are in healthy volunteers while the other two (AI420-095 and AI520-088) were conducted on actual patients. Table 1 summarizes salient details of those four studies.

**Table 1: Salient Features of Studies of Gatifloxacin on QTc in Sponsor's Submission<sup>a</sup>**

	AI420-092	AI420-093	AI420-095	AI520-088
Design	Randomized, double blind single-dose, 4-way crossover	Randomized, double blind single-dose, 4-way crossover	Open-label non-comparative	Open-label non-comparative
Primary objectives	Safety, PK, QTc measure	Safety, PK, QTc measure	Safety, efficacy, QTc measure	Safety and efficacy
# of subjects	40	40	264	15,754
Population	Healthy volunteers	Healthy volunteers	Community acquired respiratory tract infection	Community acquired respiratory tract infection
Elderly %	13	7.5	9	18
Females %	50	50	65	60
Gatifloxacin dose	400, 800, 1200 mg	800 mg	400 mg QD	400 mg QD
Comparators	Placebo	Sparfloxacin 400 mg, ciprofloxacin 1000 mg, clarithromycin 1000 mg	None	None

<sup>a</sup> Adapted from the applicant's submission (Volume 1 of 10, Page 0000014, Table 2.1)

In Studies AI420-092 and AI420-093, time-averaged QTc assessments were used. Time-averaged QTc was defined as the area under the QTc curve from 0 (predose) to 6 hours after dosing on Day 1, divided by six hours [ΔQTc Avg (0-6)]. The primary outcome measure was change from baseline of QTc Avg (0-6). The longest QTc (QTc Max) recorded after dosing on Day 1 was also documented. In Study AI420-092, QTc Avg (0-6) was linearly regressed on average concentration of gatifloxacin over the first six hours following dosing, Cav (0-6). In Study AI420-093, the applicant performed an analysis of covariance to assess the effects of the treatments on certain QTc variables while a secondary analysis examined the effect of concentrations of the four drugs (gatifloxacin, sparfloxacin, ciprofloxacin, and clarithromycin) on QTc.

In Study AI420-095, ECG assessment was based on a single pair of ECG for each patient, one ECG was taken within 30 minutes prior to the first dose of gatifloxacin and the second ECG was taken two hours following the first dose. In contrast, there was no systematic assessment of ECG in Study AI420-088. ECG were performed only as relevant for routine clinical case management. Study AI420-088 is reviewed in more detail below.

For Studies AI420-092, AI420-093, and AI420-095, the applicant employed criteria established by the European Agency for the Evaluation of Medicinal Products (EMA) and The Commission for Proprietary Medicines (CPMP) Points to Consider document titled "The Assessment of the Potential for QT Prolongation by Non-Cardiovascular Medicinal products." Tables 2 and 3 summarize the EMA criteria for males and females and the CPMP guidance.

**Table 2: EMA Criteria for Prolongation of QTc Interval**

	QTc interval (msec)	
	Male	Female
Normal	<430	<450
Borderline	430-450	450-470
Prolonged	>450	>470

**Table 3: CPMP Guidance for Prolongation of QTc Interval**

	Absolute Change in QTc from Baseline (msec)
Unlikely to raise significant concern	<30
More likely to represent drug effect	30-60
Clear concerns for potential cardiac arrhythmia	>60

Table 4 summarizes the effects of gatifloxacin on QTc from studies AI420-092 and AI420-093.

**Table 4: Effects of Gatifloxacin on QTc Interval (Protocol AI420-092 and AI420-093)<sup>a</sup>**

	Placebo	400 mg	800 <sup>b</sup> mg	800 <sup>c</sup> mg	1200 mg
$\Delta$ QTc Avg (0-6) (mean, msec) <sup>d</sup>	-2.3	4.0	10.8	12.4	16.9
$\Delta$ QTc max (mean, msec)	18.1	22.6	27.5	34.4	38.0
Outliers n (%)					
Male					
30-60 msec	1 (6)	1 (6)	5 (26)	9 (45)	10 (53)
>60 msec	0	0	0	0	1 (5)
Female					
30-60 msec	3 (23)	5 (31)	6 (32)	15 (75)	9 (64)
>60 msec	0	0	0	0	2 (14)

a Adapted from applicant's submission (Volume 1 of 10, Page 0000020, Table 3.1).

b Study AI420-092

c Study AI420-093

d values for Study AI420-093 are adjusted mean values

As seen in Table 4, Studies AI420-092 and AI420-093 show a dose-response increase in QTc. At recommended dose of 400 mg, no subject had an increase in QTc greater than 60 msec while only one male and five females had an increase of QTc between 30 and 60 msec. Similarly, no subject given gatifloxacin at doses up to 1200 mg had a post-dose prolonged QTc over 450msec (males) or 470 msec (females). However, at the 800 mg and 1200 mg doses, a total of nine and seven subjects, respectively had borderline prolonged QTc (430-450 msec for males and 450-470 msec for females).

For Study AI420-095, the mean increase of QTc interval was 9.1 msec (95% confidence interval: 6.9msec, 11.4 msec) with a range of -47 to +63 msec. There was an apparent increase in the mean change in QTc with increasing gatifloxacin plasma concentration. After adjusting for the pre-dose QTc, the mean change in QTc estimated from linear regression analysis was 2.6 msec per every µg/ml increase in gatifloxacin plasma concentration.

**Table 5: Prolonged Absolute Post-Dose QTc Interval (Study AI420-095)<sup>a</sup>**

	N	Number (%) of Subjects		
		Normal	Borderline	Prolonged
Total	262	244 (93)	15 (6)	3 (1)
Gender				
Male	91	82 (90)	6 (7)	3 (3)
Female	171	162 (95)	9 (5)	0
Age (yrs)				
≤ 65	241	229 (95)	11 (5)	1 (<1)
> 65	21	15 (71)	4 (19)	2 (10)
Risk*				
Low	252	234 (93)	15 (6)	3 (1)
High	10	10 (100)	0	0

\* High risk = hypokalemic, or receiving concomitant medications known to prolong QTc interval

<sup>a</sup> Taken from applicant's submission (Volume 1 of 10, Page 0000025, Table 3.2A)

As shown on Table 5, in Study AI420-095, three patients (all males) developed absolute post-dose QTc values that were prolonged. Fifteen additional patients had absolute post-dose QTc values that were in the borderline range.

Only one patient (female) had a change in QTc over baseline that exceeded 60 msec. She had no cardiac related adverse events as a consequence of the prolonged QTc. Further, 25 (10%) patients had changes in QTc from baseline that met the criteria for borderline prolonged.

For details on these studies the reader should please read the review by the Biopharmaceutical reviewer.

#### IV. Description of Clinical Data and Sources

The clinical data for this review are obtained directly from the NDA submissions. These clinical data include:

- Protocol AI420-088 titled “An Open-label, Multicenter Non-comparative Study of Oral Gatifloxacin in the Treatment of Community-acquired Respiratory Tract Infections (Pneumonia, Acute Bacterial Exacerbation of Chronic Bronchitis, and Acute Uncomplicated Maxillary Sinusitis).”
- Electronic documents containing case report forms for Protocol AI420-088 and case report tabulations for Protocols AI420-088 and AI420-095.
- “Tequin® a Review of Adverse Event Reports After Marketed Use by One Million Patients.”

Other materials reviewed include:

- Additional information requested by the medical officer as a follow up or for clarification of data in the submission.
- Medical Officer review of original NDA 21-061 and 21-062 for gatifloxacin tablets and injection, respectively.
- Medical Officer review of supplemental NDA 21-334 for moxifloxacin for uncomplicated skin and skin structure infections.
- Postmarketing safety review by Office of Postmarketing Drug Risk Assessment (OPDRA). This safety review by Sarah J. Singer, R.Ph., Safety Evaluator, Division of Drug Risk Evaluation II, HFD-440, provides a comparative analysis of selected postmarketing adverse events reported for moxifloxacin and gatifloxacin.

#### V. Clinical Review Methods

The key focus of these submissions is to allow the Agency to assess the risk of gatifloxacin against its benefit within a sufficiently large exposure population. A favorable risk-benefit assessment should facilitate the decision to authorize marketing of gatifloxacin for a relatively less serious indication, uncomplicated skin and skin structure infections. Given that safety is the main issue in this risk-benefit assessment, this review will dwell largely on safety. However, the review will also present relevant details on efficacy, where appropriate.

#### VI. Integrated Review of Efficacy

The primary efficacy endpoint was clinical response to gatifloxacin as assessed by the investigator at post-treatment telephone contact or office visit. The primary efficacy analyses were performed on the clinically evaluable population. This population was defined by the applicant as all subjects who satisfied all entry criteria and met the criteria for clinical diagnosis of community-acquired respiratory tract infections (CARTI). In addition, subjects must have received at least five days of treatment with gatifloxacin (at least three days for failures) and also must have had a post-treatment assessment.

Clinical responses were classified into cured (all symptoms related to the acute infection have improved or are back to patient's baseline with no new symptoms or requirement for additional antibiotic treatment), failure, or unable to determine (subjects lost to follow-up).

Further, microbiologic responses were assessed and were categorized into eradication (documented and presumed), persistence (documented and presumed), or unable to determine.

### Clinical Response

The clinical response of subjects in Study AI420-088 is summarized on Table 6

**Table 6: Summary of Clinical Response in Study AI420-088<sup>a</sup>**

	Clinically Evaluable with any TOC Assessment (%)	Clinically Evaluable with 5-18 Day TOC Assessment (%)
CAP	95.2	96.7
ABECB	91.9	94.4
Acute Sinusitis	91.6	93.5
All Indications	92.0	94.0

<sup>a</sup> Summarized from applicant's submission (Volume 9 of 10, Pages 0000176-0000177, Section 10.1.1.1)

Of 9166 clinically evaluable subjects across all indications for whom a pre-treatment sputum or sinus specimen was submitted, at least one pathogen was isolated from samples of 3187 (34.8%). Table 7 summarizes clinical responses for all indications across pathogens for clinically evaluable subjects with any TOC and at 5-18 Day TOC assessment.

**Table 7: Clinical Responses for all Indications Across Pathogens (Study AI420-088)<sup>a</sup>**

	Clinically Evaluable with any TOC Assessment, n/N (%)	Clinically Evaluable with 5-18 Day TOC Assessment (%)
<i>H influenzae</i>	848/891 (95.2)	579/602 (96.2)
β-Lactamse -	628/658 (95.4)	427/445 (96.0)
β-Lactamse +	219/232 (94.4)	152/157 (96.8)
β-Lactamse Unknown	1/1 (100)	-
<i>M. catarrhalis</i>	819/863 (94.9)	562/591 (95.1)
β-Lactamse -	70/77 (90.9)	47/51 (92.2)
β-Lactamse +	749/786 (95.3)	515/540 (95.4)
<i>S. pneumoniae</i>	577/615 (93.8)	400/424 (94.3)
Penicillin sensitive	386/413 (93.5)	275/291 (94.5)
Penicillin Intermediate	120/125 (96.0)	80/84 (95.2)
Penicillin Resistant	65/71 (91.6)	41/45 (91.1)
Penicillin Unknown	6/6 (100)	4/4 (100)
<i>S. aureus</i>	351/394 (89.1)	235/256 (91.8)
<i>E. aerogenes</i>	88/94 (93.6)	66/67 (98.5)

<sup>a</sup> From applicant's submission (Volume 9 of 10, Pages 0000182, Table 10.2.2A)

**MO's Comment:** The results for clinical responses in Study AI420-088 are consistent with responses obtained for these indications in the original NDA submission.

## VII. Integrated Review of Safety

Overall, gatifloxacin shows a satisfactory safety profile as presented in these submissions with a total population of over a million patients. The safety data presented in this submission are consistent with details in the approved labeling for gatifloxacin. In addition, there are ongoing reviews of labeling revisions to capture cases of disorders of glucose homeostasis, hepatitis, thrombocytopenia, and torsades de pointes reported in the postmarketing period.

### Protocol AI420-088

An Open-label, Multicenter Non-comparative Study of Oral Gatifloxacin in the Treatment of Community-acquired Respiratory Tract Infections (Pneumonia, Acute Bacterial Exacerbation of Chronic Bronchitis, and Acute Uncomplicated Maxillary Sinusitis).

### Objective

The primary objective of this study was to evaluate the clinical safety and efficacy of gatifloxacin, 400 mg once daily, when used in to treat adults with community-acquired pneumonia (CAP), acute bacterial exacerbation of chronic bronchitis (ABECB), and acute uncomplicated maxillary sinusitis.

### Secondary objectives of this study were to:

- Evaluate the impact of the treatment of community-acquired respiratory tract infections with gatifloxacin in a broad-based community setting.
- Assess the microbiology of community-acquired respiratory tract infections, including pathogen frequency and antimicrobial susceptibility, in a typical clinical setting.
- Assess the clinical and bacteriologic response rate of CAP subjects in whom *Streptococcus pneumoniae* is the causative pathogen.

### Design

This was an open-label, non-comparative, multicenter study to assess the clinical safety and efficacy of gatifloxacin (400 mg PO once daily) for the treatment of CAP, ABECB, or acute uncomplicated maxillary sinusitis. The study was limited to outpatients only. Approximately 74% of subjects had acute uncomplicated maxillary sinusitis.

### Patient exposure

Study AI420-088 was conducted from January 14, 2000 to July 10, 2001. A total of 15,754 patients were enrolled from 2795 sites (all US). Of those enrolled, 15625 were treated and 14,781 were clinically evaluable. The safety dataset consisted of all treated subjects. The mean age of subjects was 49.2 years with subjects 65 years or older comprising 18.4%. Overall, approximately 60% of the patients were females and 85.5% were Caucasians. African American, Hispanic, and Asian subjects constituted 6.4%, 4.2%, and 1.6%, respectively while 0.6% of the subjects were classified as Other.

**MO's comment:** *From the entry criteria, this study enrolled fairly healthy subjects.*

Safety evaluation was based on vital signs, physical examinations, and adverse events reported by patients during telephone contact or office visit. There were no laboratory and/or electrocardiograph (ECG) evaluations except as necessary for routine patient care.

Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) preferred terms were used for coding adverse events, which the applicant categorized by body system. Descriptive analyses of adverse events in all treated subjects were presented as number of occurrences and percentages.

Of the 15625 treated subjects, the most common reported drug-related adverse events were nausea (4%), dizziness (1.7%), diarrhea (1.4%), and headache (0.9%). Most of these adverse events were non-serious. Indeed, there were only 27 subjects reporting serious drug-related adverse events. These adverse events are already captured in the labeling.

Safety concerns at the time of initial NDA approval and in the post-approval period include potential for adverse cardiovascular toxicity and disturbances of glucose homeostasis. As a consequence, two subgroup analyses were carried out in the safety evaluation of Study AI420-088. The first subgroup analysis comprised patients potentially at increased risk for arrhythmia. The applicant defined these as "subjects with a history of cardiovascular disease and/or subjects on cardiovascular medication." The second subgroup analysis involved subjects potentially at increased risk for abnormalities in glucose homeostasis defined by the sponsor as "subjects with a history of diabetes and/or subjects on diabetic medication."

**Patients Potentially at Increased Risk for Arrhythmia**

Cardiovascular adverse events in these subjects were tabulated alongside similar adverse events in those without such history. Overall, there were more adverse events and serious adverse events reported among the 4875 subjects with a history of cardiovascular disease and/or subjects on cardiovascular medication compared to the 10750 subjects with no such history. However, drug-related adverse events were balanced between the two groups as shown on Table 8.

**Table 8: All Drug-Related Cardiovascular Adverse Events (All Indications)<sup>a</sup>**

	<b>All Treated Subjects with a History of Cardiovascular Disease and/or Subjects on Cardiovascular Medication n=4875</b>	<b>All Treated Subjects with No History of Cardiovascular Disease and/or Subjects Not on Cardiovascular Medication n=10750</b>
<b>Drug-related Cardiovascular AEs</b>	n (%)	n (%)
<b>Body System Preferred Term</b>		
<b>Body as a whole</b>		
Chest pain	7 (0.1)	10 (<0.1)
<b>Cardiovascular</b>		

Arrhythmia	0 (0.0)	1 (<0.1)
Bradycardia	1 (<0.1)	0 (0.0)
Hemorrhage	0 (0.0)	1 (<0.1)
Migraine	0 (0.0)	4 (<0.1)
Palpitation	17 (0.3)	16 (0.1)
Postural Hypotension	1 (<0.1)	0 (0.0)
Syncope	3 (<0.1)	3 (<0.1)
Tachycardia	3 (<0.1)	8 (<0.1)

<sup>a</sup> Taken from Applicant's submission (Volume 9 of 10, Page 0000198, Table 11.1.4B)

**Patients Potentially at Increased Risk for Disruptions in Glucose Homeostasis**

Of the 15625 treated subjects, 1096 (7.0%) reported a history of diabetes mellitus. Of the 1096 subjects with a history of diabetes mellitus, 636 (58%) were medication-controlled while 460 (42%) were diet-controlled. Table 9 summarizes all adverse events related to disturbances of glucose homeostasis reported in all subjects with and without a history of diabetes mellitus.

**Table 9: Disruption of Glucose Homeostasis (All Indications)<sup>a</sup>**

AE	All with a History of Diabetes Mellitus N=1096	Subjects with Diet-Controlled Diabetes mellitus N=460	Subjects with Medication-controlled Diabetes Mellitus N=636	Subjects without Diabetes Mellitus N=14529
	n (%)	n (%)	n (%)	n (%)
Hyperglycemia	24 (2.2)	4 (0.9)	20 (3.1)	3 (<0.1)
Hypoglycemia	8 (0.7)	1 (0.2)	7 (1.1)	5 (<0.1)

<sup>a</sup> Taken from Applicant's submission (Volume 9 of 10, Page 0000202, Table 11.1.5)

*MO's comment: One subject with medication-controlled diabetes mellitus is included under hypoglycemia in the Table 9 above. This subject was listed in a separate category of hypoglycemic reaction in the sponsor's analysis.*

As shown on Table 9, disturbances of glucose homeostasis occurred more commonly in subjects with a history of diabetes mellitus and particularly in those on medication to control diabetes mellitus.

*MO comment: It is difficult to make conclusive remarks about these findings. Hyperglycemia in infected diabetic patients is not an unexpected finding. Subjects with a history of diabetes mellitus who were on medication might be considered to have more severe or more difficult to control diabetes mellitus compared to those with diet-controlled diabetes mellitus. In that regard, medication-controlled diabetes mellitus subjects would be expected to report more abnormalities of blood glucose homeostasis. In addition, infections in such subjects would be expected to be more serious compared to infection in subjects with diet-controlled diabetes mellitus. Such potential differences in severity of infections could further affect the frequency of reported abnormalities of blood glucose control.*

*Further, given the post-marketing reports of disturbances of glucose homeostasis with gatifloxacin especially in diabetics on oral hypoglycemic medications, it is reassuring that only about 7% of subjects in this study had a history of diabetes mellitus (with less than 5% of subjects having medication-controlled diabetes mellitus).*

**Discontinuations due to Adverse Events**

A total of 1019 (6.5%) of the 15625 subjects who received at least one dose of gatifloxacin in Protocol AI420-088 prematurely discontinued study therapy due to adverse clinical events. Discontinuation due to drug-related adverse events occurred in 857 (5.5%) of the treated subjects. The commonest drug-related adverse events resulting in premature discontinuation of therapy is summarized in Table 10.

**Table 10: Most Frequent Adverse Events Resulting in Discontinuation of Therapy (All Indications) <sup>a</sup>**

Reason for Premature Discontinuation of Therapy	Number of subjects (N=15625) n (%)
Nausea	254 (1.6)
Dizziness	133 (0.9)
Diarrhea	86 (0.6)
Vomiting	85 (0.5)
Headache	66 (0.4)
Abdominal pain	63 (0.4)
Rash	57 (0.4)
Asthenia	43 (0.3)
Nausea and vomiting	40 (0.3)
Insomnia	31 (0.2)
Palpitation	27 (0.2)

<sup>a</sup> Adapted from Applicant's submission (Volume 9 of 10, Page 0000214, Table 11.4)

*MO's comment: Most of the drug-related adverse events that led to study drug discontinuation were due to relatively minor gastrointestinal symptoms. In clinical trials data submitted to original NDA, drug-related adverse events resulted in study drug discontinuation in 2.7% of subjects. This number contrasts with 5.5% in Protocol AI420-088. The observed differences might potentially be due to differences in study design and study population.*

**Deaths**

Seven deaths were reported among subjects in Study AI420-088. All the deaths occurred in elderly subjects. Indeed, the mean age of those who died in this study, 76.4 years, was much more than the mean age of all the enrolled subjects, 49.2 years. Case narratives document that all the subjects who died had multiple comorbid conditions and that these deaths are unrelated to gatifloxacin. However, on review of the case report form (CRF), the medical officer notes two deaths with unclear relationship to gatifloxacin.

Subject 510-7 was a previous smoker with no other documented underlying medical history/risk factor at baseline. Subject 510-7 was later reported to have had a serious adverse event of "end-stage aortic stenosis." The dates of onset and resolution of this SAE on the CRF are given as \_\_\_\_\_ respectively. This subject was enrolled on 03/29/00 and died on \_\_\_\_\_. Autopsy was not done. The exact cause of the respiratory deterioration and death of this subject and the relationship to gatifloxacin are unclear.

Subject 2367-2 was an 86 year old Caucasian male, previous smoker with diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary artery disease, and a recent hospitalization for myocardial infarction and congestive heart failure. He was enrolled with suspected community acquired pneumonia and received a 14-day course of gatifloxacin starting on \_\_\_\_\_. On the day gatifloxacin was started, he sought care in the emergency department for a blood sugar of 491 which on recheck was 454. His physical examination was unrevealing. His blood sugar decreased to 300 with 5 units of regular Humulin and he was discharged. It is unclear if he was readmitted, but the CRF documents that he was discharged "home on hospice care on \_\_\_\_\_ as terminal." He died on \_\_\_\_\_ of unknown cause. Again, the exact relationship of to gatifloxacin is uncertain.

These and other reported deaths in Study AI420-088 are summarized in the appendix together with the ten deaths listed in the Spontaneous Adverse Events Report for the first one million patients reviewed below.

#### **A Review of Adverse Event Reports After Marketed Use by One Million Patients Worldwide**

In putting together this section of the submission, the applicant reasoned that between the international launch of this product in Mexico on June 21, 1999 and the cutoff date for the Adverse Event Reports Review (September 18, 2000), approximately one million patients should have been treated with gatifloxacin (assuming one prescription per patient). A total of 399 spontaneous adverse event reports were received during the review period with 91 (22.8%) of these being serious adverse events. These adverse event reports exclude reports from clinical trials.

*MO's comment:* The exact proportion of patients from the US included in this One Million Patient exposure population is unclear from the submissions. However, a review of the line listing of the reported adverse events reveals that 360 (90.2%) of the 399 events were reported from the US.

Further, the demographic characteristics of the One Million Patient exposure population is also not given in the submissions. In reviewing the line listing of the 399 patients who reported adverse events, age was not stated for 175 (43.9%) of the patients, 89 (22.3%) were 65 years or older, while 5 (1.2%) were younger than 18 years.

Similarly, gender was not defined for 123 (30.8%) of the 399 patients who reported adverse events, 98 (24.6%) were males while 178 (44.6%) were females.

During the period under review there were no gatifloxacin-related adverse events reported in the medical literature. The adverse event topics chosen for discussion in the submission were generally described under the applicable MedDRA Preferred Terms (PTs) within each System Organ Class (SOC). The top serious and non-serious adverse events by SOC are summarized in Table 11.

*MO's Comment: Lack of published adverse event reports in the medical literature needs to be interpreted with caution, given the relatively short marketing history of gatifloxacin and the expected time lag from occurrence of an event to appearance of report of that event in the medical literature.*

**Table 11: Most Frequent Serious and Non-Serious Adverse Events by System Organ Class<sup>a\*</sup>**

	Non-Serious	Serious	Total
Nervous system disorders	98	32	130
Gastrointestinal disorders	88	22	110
Skin and subcutaneous tissue disorders	78	12	90
General Disorders and Administration Site Conditions	66	21	87
Cardiac disorders	40	13	53
Metabolism and Nutrition Disorders	32	20	52
Psychiatric disorders	32	15	47
Investigations	30	10	40
Musculoskeletal, connective tissue, and bone disorders	30	3	33
Respiratory, thoracic, and mediastinal disorders	16	11	27
Immune system disorders	9	10	19

<sup>a</sup> Adapted from applicant's submission (Volume 10 of 10, Pages 0000202-0000319)

\* Multiple occurrence of a particular event in one subject is counted once

On the whole, the reported adverse events in these submissions were consistent with adverse events captured in the approved labeling. However, given the need for adequate risk-benefit assessment for the indication sought by the applicant in these submissions, an attempt is made to highlight serious adverse events that are relevant to the overall evaluation for the indication of USSSI. These serious adverse events are summarized in Table 12.

**Table 12: Frequency of SAE Considered by the MO to be Particularly Relevant to this Product<sup>a</sup>**

	SAE n
Nervous system disorders	
Convulsions NOS	8
Dizziness (excluding vertigo)	4
Grand mal convulsion	2
Headache NOS	3
Syncope	4
Gastrointestinal disorders	
Diarrhea	2

Nausea	2
Vomiting	7
Skin and subcutaneous tissue disorders	
Angioneurotic edema	1
Face edema	2
Pruritus NOS	2
Urticaria	2
General Disorders and Administration Site Conditions	
Chest pain	1
Death NOS	9
Sudden unexplained death	1
Cardiac disorders	
Atrial fibrillation	1
Cardiac arrest	2
Cardiac failure NOS	1
Myocardial infarction	2
Palpitations	1
Supraventricular arrhythmia NOS	1
Torsade de pointes	2
Ventricular extrasystoles	1
Ventricular tachycardia	1
Metabolism and Nutrition Disorders	
Hyperglycemia NOS	3
Hyperosmolar non-ketotic hyperglycemic coma	2
Hypoglycemia	10
Psychiatric disorders	
Confusion	5
Hallucinations NOS	5
Musculoskeletal, connective tissue, and bone disorders	
Rhabdomyolysis	1
Tendonitis	1
Tendon rupture#	1
Investigations	
Neutropenia+	1
Thrombocytopenia+	1
Blood creatinine increased	2
Electrocardiogram QT prolonged	3
Immune system disorders	
Anaphylactic reaction	8
Anaphylactic shock	1
Hypersensitivity NOS	1

<sup>a</sup> Adapted from applicant's submission (Volume 10 of 10, Page 0000202-0000319).

# Listed under Injury and Poisoning Tendon Rupture in the applicant's submission.

+ Listed under Blood and Lymphatic System Disorders in the applicant's submission.

NOS Not otherwise specified

### **Cardiac Disorders**

There were three reports of prolonged QT, two of which resulted in torsade de pointes. These events occurred in elderly patients with multiple co-morbid conditions and/or concomitant medications. In all three patients, QTc intervals returned to baseline with clinical intervention. Other cardiac disorders reported in the spontaneous adverse event database included one case of ventricular tachycardia, three cases of ventricular extrasystoles, two cases of myocardial infarctions, 14 reports of palpitations, 10 reports of tachycardia (not otherwise specified), two reports of sinus tachycardia, two reports of atrial fibrillation and one report of supraventricular tachycardia. Generally, information was often insufficient to reliably assess relatedness to gatifloxacin. However, where information was available alternative factors more readily explained the adverse events.

### **Metabolism and Nutritional**

Five reports of serious adverse events and 17 non-serious reports of hyperglycemia are listed in the submissions. Two of the five cases of hyperglycemia also had non-ketotic hyperosmolar coma. In addition, 10 serious and 24 non-serious reports of hypoglycemia were listed.

### **Musculoskeletal, Connective Tissue, and Bone Disorders**

One serious (left Achilles tendon rupture with right Achilles tendinitis in the same patient) and four non-serious reports of that included the terms tendon rupture, tendon disorder not otherwise specified, tendonitis, or tenosynovitis.

### **Deaths**

Reports of ten deaths were listed in the review of the Spontaneous Adverse Events Reports. The mean age of the nine dead subjects with known age in the One Million Patient Use study was 58.4 years. Most of the deaths occurred in elderly subjects with multiple comorbid conditions or the deaths were clearly unrelated to study drug. These together with the deaths reported in Study A1420-088 are summarized in Table 13.

### **Postmarketing safety review by OPDRA**

This safety review was conducted by the Division of Drug Risk Evaluation II, HFD-440, Office of Postmarketing Drug Risk Assessment (OPDRA). The safety review provides a comparative analysis of selected postmarketing adverse events reported for fluoroquinolone class of antimicrobials, including moxifloxacin, levofloxacin, and gatifloxacin. The OPDRA reviewer queried the FDA Adverse Events Reporting System (AERS) database on April 13, 2001 to obtain all adverse events reported for gatifloxacin. Further, on May 1, 2001, the OPDRA reviewer conducted a PubMed search for citations reporting adverse events with gatifloxacin. Finally, the OPDRA reviewer, in an updated query of the AERS database on November 28, 2001, provided additional data regarding reported cases of hypoglycemia, hyperglycemia, and torsades de pointes.

From the AERS database, eight unduplicated cases of torsade de pointes and a case of "polymorphic ventricular tachycardia with marked QT prolongation" were reported for gatifloxacin compared to three for moxifloxacin and 22 for levofloxacin. Prior to the November

28, 2001 updated query of the AERS database, the OPDRA reviewer noted that the following cases were reported for gatifloxacin:

- Hepatotoxicity, 23 (3 fatal)
- Hypoglycemia, 46
- Hyperglycemia, 45 (with 3 hyperosmolar nonketotic hyperglycemic coma)
- Renal failure, 15

The findings of the OPDRA reviewer appear to be consistent with data in the current supplemental new drug application. However, the November 28, 2001 update reveals that a total of 136 reports of hypoglycemia or hypoglycemia were received for gatifloxacin compared to 19 for moxifloxacin and 45 for levofloxacin as summarized in the tables below.

**Table 13: AERS CASES of GLUCOSE ABNORMALITIES With GATIFLOXACIN, MOXIFLOXACIN, or LEVOFLOXACIN As a SUSPECT DRUG (Searches performed 11/28/01)**

<b>HYPOGLYCEMIA</b>		
<b>DRUG</b>	<b>ALL AERS CASES OF HYPO-GLYCEMIA<sup>i</sup></b>	<b>U.S. CASES OF SERIOUS<sup>iii</sup> HYPOGLYCEMIA</b>
Gatifloxacin	77	40
Moxifloxacin	10	0
Levofloxacin	26	14

<b>HYPERGLYCEMIA</b>		
<b>DRUG</b>	<b>ALL AERS CASES OF HYPERGLYCEMIA<sup>iv,v</sup></b>	<b>U.S. CASES OF SERIOUS<sup>vi</sup> HYPERGLYCEMIA</b>
Gatifloxacin	59	23
Moxifloxacin	9	4
Levofloxacin	19	8

**Table 14: NEW-ONSET DIABETES and PROFOUND HYPERGLYCEMIC EVENTS REPORTED FOR GATIFLOXACIN, MOXIFLOXACIN, and LEVOFLOXACIN<sup>vii</sup>**

<b>DRUG</b>	<b>EVENT</b>	<b>UNDULICATED CASES IN AERS</b>
Gatifloxacin	Nonketotic hyperglycaemic-hyperosmolar coma	3*
	Diabetic hyperosmolar non ketoacidosis	1
	New-onset diabetes	6*
	Diabetic ketoacidosis	1
Moxifloxacin		0
Levofloxacin	Diabetic ketoacidosis	1
	New-onset diabetes	2

\*One case was coded with both terms; there were 10 total cases for gatifloxacin.

<sup>i</sup> AERS was searched for all cases coded either HYPOGLYCAEMIA NOS or BLOOD GLUCOSE DECREASED. The numbers are raw counts and probably include duplicates; in addition, there has been no attempt to evaluate the cases.

<sup>ii</sup> Bristol-Myers Squibb has a waiver allowing nonreporting of nonserious labeled events for gatifloxacin; neither of the two other sponsors have such waivers for moxifloxacin or levofloxacin, so the gatifloxacin numbers are underreported in relation to the two other drugs.

<sup>iii</sup> Involving death, hospitalization, or disability, or considered life-threatening by the reporter. Negates differences caused by Bristol-Myers Squibb's waiver (see footnote ii).

<sup>iv</sup> AERS was searched for all cases coded either HYPERGLYCAEMIA NOS or BLOOD GLUCOSE INCREASED. The numbers are raw counts and probably include duplicates; in addition, there has been no attempt to evaluate the cases.

<sup>v</sup> Bristol-Myers Squibb has a waiver allowing nonreporting of nonserious labeled events for gatifloxacin; neither of the two other sponsors have such waivers for moxifloxacin or levofloxacin, so the gatifloxacin numbers are underreported in relation to the two other drugs.

<sup>vi</sup> Involving death, hospitalization, or disability, or considered life-threatening by the reporter. Negates differences caused by Bristol-Myers Squibb's waiver (see footnote v).

<sup>vii</sup> AERS was searched on 11/27/01 for cases coded with any of the following terms: DIABETES MELLITUS NOS, DIABETIC COMA NOS, DIABETIC HYPEROSMOLAR NON KETOACIDOSIS, DIABETIC KETOACIDOSIS, or NONKETOTIC HYPERGLYCAEMIC-HYPEROSMOLAR COMA. All cases were obtained for hands-on review so the numbers above represent unique cases.

Spontaneous adverse events reporting database are fraught with limitations such as underreporting, undetected duplications, incomplete information in many reports, and lack of ability to assess causality. Nevertheless, these findings were shared with the applicant and appropriate revisions to the labeling are being negotiated. For further details, the reader should please read the OPDRA review.

Potential sources of bias are to be expected in Study AI420-088, given its size as well as non-randomized and open-label design. Similarly, the Review of Adverse Event Reports After Marketed Use by One Million Patients Worldwide shares known limitations of spontaneous adverse events reports as noted above.

*MO's Comment: In reviewing the data submitted by the applicant, the MO noted areas that additional information was needed and requested more information from the applicant. The applicant, in turn, made good faith effort to provide clarifications and information that became available.*

**Appears This Way  
On Original**

Table 15: Summary of Deaths Reported in Protocol AI420-088 and the One Million Patient Use

Subject ID#	Age/Sex	Medical History	Concomitant Medicines	Indication for Study Drug	Event(s)	Time to Event (days)	Relatedness	
							Investigator	MO
<b>Protocol AI420-088: An Open-label, Non-comparative Study of Oral Gatifloxacin in the Treatment of Community-acquired Respiratory Tract Infections</b>								
0315-4	65/F	COPD, pneumonia, nephrolithiasis, kidney infections	Not stated	ABECB	Respiratory failure, anoxic brain damage	4	Unrelated	Unrelated
0510-7	87/F	COPD, end-stage aortic stenosis	Not stated	ABECB	Atrial fibrillation	12*	Unrelated	Uncertain
1088-3	73/F	IDDM, HTN, Hypercholesterolemia, chronic renal insufficiency	Not stated	Bronchitis	Hypoxia, worsening DM, acute renal failure. Suspected pulmonary embolus	2	Unrelated	Unrelated
2234-1	87/F	IDDM, congestive heart failure, atrial fibrillation, pacemaker placement, coronary artery disease, hypertension and recent acute cholecystitis	Not stated	CAP	Sigmoid volvulus, Post-operative sepsis	Deterioration 2 days after start of study drug. Died on day 16 of hospitalization	Unrelated	Unrelated
2367-2	86/M	Congestive cardiac failure, COPD, uncontrolled DM, recent MI	Not stated	CAP	Hyperglycemia (glucose 454). Exact cause unknown.	Died 8 days after completing study therapy	Not stated	Uncertain
4062-1	66/M	COPD, coronary artery disease, peripheral vascular disease	Not stated	ABECB	Respiratory failure, hypotension, dysrhythmia, and MI	3	Unrelated	Possibly unrelated
4705-2	71/F	COPD (oxygen-dependent)	Not stated	Bronchitis	V-tach	2	Unrelated	Uncertain
<b>A Review of Adverse Event Reports After Marketed Use by One Million Patients Worldwide</b>								
10283745/US	62/M	DM, renal insufficiency, cardiomyopathy with cardiac failure (EF 20%)	Lasix, Digoxin	Foot ulcers	Worsened renal and cardiac failure	4	Unrelated	Possibly unrelated
10301273/US	68/M	CAD, angioplasty, MI, V-tach, HTN, cardiac failure, myocarditis, hemochromatosis, gout, and hyperlipidemia	Robitussin, Corgard, Paxil, Lipitor, Allopurinol, Diovan, Aspirin, Diazepam	Bronchitis	Sudden cardiac death, no autopsy	Not stated	Not stated	Uncertain

10341682/US	69/M	DM, HTN, CAD, cardiac failure sleep apnea syndrome, pernicious anemia	Lopressor, KCl, Lasix, Zestril, Cardura, Norvasc	Pneumonia	Exacerbation of heart failure	Same day	Not stated	Uncertain
10375517/MX	86/F	DM, alcoholism, tobacco use	Ampicillin, Garamycin, metformin, Acetaminophen, Naproxen	ABECB	Sudden death. Autopsy showed MI	5 hours	Unrelated	Unrelated
10384857/US	39/F	Ascites, edema, HTN. <i>MO's Comment: Baseline renal and LFT were normal</i>	Acetaminophen, metazolol, furosemide, spironolactone, NSAIDs, K-tab, Restoril, Clonopin, Zaroxolyn, Spectazol	CAP	Hepato-renal syndrome, septic shock	Not stated	Not stated	Uncertain
10463859/US	44/F	Not stated	Prednisone, ibuprofen, celecoxib, Reglan, Lorabid, Claritin, Triamterine, Hydrochloroquine, Prochlorperazine, Effexor	UTI	Gastric hemorrhage	Not stated	Unrelated	Unrelated
1048033/TH	37/F	Not stated	Zoloft, Rocoephin, Flumucil, Tryptanol, Domperidone, Xanax	UTI	Septic shock and acute tubular necrosis post-op for intestinal obstruction	Not stated	Unrelated	Unrelated
10305183/US	53/M	HTN and smoking	None documented	Bronchitis	Unknown	Two weeks after completion of gati therapy	Not stated	Uncertain
10520997/US	Not stated/M	Not stated	None documented	Not stated	Unknown	Not stated	Not stated	Uncertain
10483399/US	68/F	Asthma, osteoporosis, COPD, chronic bronchitis, HTN, hyperlipidemia, irritable bowel syndrome	Paxil, Ditropan, Prilosec, Maxair, Darvocet, Flonase, Monopril, Zocor, Fosamax, Benyl	CAP	Unknown but had Electrolyte imbalance with leukocytosis and C. difficile in stool	Not stated	Not stated	Uncertain

\*Study drug received for a total of 5 days. Event occurred an unspecified time following discontinuation of study drug

ABECB Acute bacterial exacerbation of chronic bronchitis; CAD Coronary artery disease; CAP Community-acquired pneumonia; COPD Chronic obstructive pulmonary disease; DM Diabetes mellitus; EF Ejection fraction; HTN Hypertension; IDDM Insulin-dependent diabetes mellitus; KCl Potassium chloride; LFT liver function tests; MI Myocardial infarction; UTI Urinary tract infection.

### VIII. Dosing, Regimen, and Administration Issues

Gatifloxacin is approved for oral and intravenous administration. Approved dosing regimen is 400 mg once daily for all approved indications other than cytitis for which the dosage is 200 mg once daily. Approved duration of therapy varies according to indication and ranges from single dose for uncomplicated urinary tract infection and uncomplicated gonorrhea to 7-14 days for community acquired respiratory tract infections (community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis).

### IX. Use in Special Population

Gatifloxacin is approved for use in patients aged 18 years or older.

The data contained in these submissions show that women and subjects aged 65 years or older are adequately represented. In Study AI420-088, approximately 32% of females reported at least one adverse event compared to about 21% of the males. On the other hand, similar proportions of subjects reported adverse events among those 65 years or older compared to those younger than 65 years (31% and 27%, respectively). In the One Million Patient spontaneous adverse event report, gender was not defined for 123 (30.8%) of the 399 patients who reported adverse events, 178 (44.6%) were females while 98 (24.6%) were males. The reason for the higher numbers of adverse events among females is unclear but appears consistent with observations in published literature.

### X. Conclusions and Recommendations

These limitations notwithstanding, the data submitted by the applicant satisfies all the phase IV commitments entered into by the applicant in the original NDA approval letter dated December 17, 1999. The data also demonstrate overall acceptable risk-benefit profile of gatifloxacin in a relatively large exposure population. In addition, the data provided show that gatifloxacin has a satisfactory risk-benefit profile specifically for the relatively non-serious indication of treatment of simple abscesses, furuncles, folliculitis, wound infections, and cellulitis caused by *Streptococcus pyogenes* and methicillin sensitive *Staphylococcus aureus*. However, the medical officer recommends that NDAs 21-404 and 21-405 are approvable pending labeling revisions to adequately reflect postmarketing safety updates, including cases of disturbances in glucose homeostasis reported mostly among diabetic and/or elderly patients being treated with gatifloxacin.

#### Proposed Labeling

The applicant proposes revisions to the INDICATIONS AND USAGE section of the labeling to add the following to the list of indications:

“Uncomplicated skin and skin structure infections (i.e., simple abscesses, furuncles, folliculitis, wound infections, and cellulitis) due to methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*.”

NOTE: An insufficient number of patients with the diagnosis of impetiginous lesions were available for evaluation.”

The medical officer accepts the proposed labeling revisions, including the addition of *Streptococcus pyogenes* to the clinical efficacy listing in the Microbiology section; the addition of dose for uncomplicated skin and skin structure infections to the table of dosage guidelines in the DOSAGE AND ADMINISTRATION section; and revisions to the patient package insert. For consistency with labeling for related products in this class and also for conciseness, the medical officer recommends that the phrase \_\_\_\_\_ be deleted from the applicant's proposed labeling that will then read:

“Uncomplicated skin and skin structure infections (i.e., simple abscesses, furuncles, folliculitis, wound infections, and cellulitis) due to *Staphylococcus aureus* or *Streptococcus pyogenes*.

NOTE: An insufficient number of patients with the diagnosis of impetiginous lesions were available for evaluation.”

The applicant should also revise the labeling in line with the recommendations of the microbiology reviewer. Finally, the applicant should effect revisions to the labeling proposed by the review team. These revisions, as proposed by the review team, seek to reflect postmarketing safety updates, including cases of disturbances in glucose homeostasis reported mostly among diabetic and/or elderly patients being treated with gatifloxacin.

**Appendix**

**Selected Approved Drug Products for Uncomplicated Skin and Skin Structure Infection**

<b>β-Lactams</b>	<b>Macrolides</b>
Penicillin	Erythromycin
Amoxicillin	Clarithromycin
Amoxicillin-clavulanate	Azithromycin
Cefazolin	Dirithromycin
Cephalexin	<b>Fluoroquinolones</b>
Cefaclor	Ciprofloxacin
Cefprozil	Ofloxacin
Cefpodoxime	Levofloxacin
Cefuroxime	Moxifloxacin
Loracarbef	<b>Tetracyclines</b>
Cefdinir	Doxycycline
Cefadroxil	Minocycline
<b>Lincosamine</b>	<b>Oxazolidinone</b>
Clindamycin	Linezolid

\_\_\_\_\_  
Ekopimo Ibia M.D., M.P.H.  
Medical Officer, DSPIDP

Concurrences: \_\_\_\_\_  
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cc:

HFD-590/Divisional File, IND 52,081

HFD-590/Ag.Div.Dir./Albrecht

HFD-590/MedTL/CavailleColl

HFD-590/MO/Ibia

HFD-590/Chem/Holbert

HFD-590/Micro/Dionne

HFD-590/Biopharm/Colangelo

HFD-590/Pharmtox/Hundley

HFD-590/Stats/Higgins

HFD-590/RPM/Willard

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Ekopimo Ibia  
12/21/01 03:20:39 PM  
MEDICAL OFFICER

Marc Cavaille Coll  
1/3/02 02:19:52 PM  
MEDICAL OFFICER

Renata Albrecht  
2/7/02 11:15:55 AM  
MEDICAL OFFICER