

Reviewer's Comment

*It is noted that the vast majority of the patients was middle age, and ethnically classified as white. There was a predominance of females. The gender and ethnic distribution was equal between the two treatment arms.*

## 8.4.1.1.7.1.3 Patient Diagnoses

The most common diagnosis studied was abscess, followed by cellulitis, wound infection, and folliculitis. Less than 10% of the patients were diagnosed with impetigo, and only one patient in the entire study was diagnosed with erysipelas. The table below, reproduced from the applicant's Study Report (Table 8.4.2, p. 65), summarizes the number of patients with each diagnosis per treatment arm.

Infection Diagnosis, All Treated Patients

	Number of Patients (%)		
	Gatifloxacin N = 202	Levofloxacin N = 205	Total N = 407
Abscess	45 (22)	59 (29)	104 (26)
Cellulitis	53 (26)	50 (24)	103 (25)
Wound Infection	48 (24)	48 (23)	96 (24)
Folliculitis	44 (22)	34 (17)	78 (19)
Impetigo	12 (6)	13 (6)	25 (6)
Erysipelas	0	1 (<1)	1 (<1)

Reviewer's Comment

*The Points to Consider document indicates that in order for this general claim to be granted, there should be at least 20% each of the following: simple abscesses, impetiginous lesions, furuncles, and cellulitis. The applicant was able to study sufficient number of patients for three of the four types of infections. They were not able to study sufficient number of patients with impetiginous lesions. The wording of the label may need to reflect this information.*

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## 8.4.1.1.7.2 Patient Disposition

Thirty-seven patients discontinued therapy prior to the completion therapy. Twenty-one patients were in the gatifloxacin treatment arm, and 16 in the levofloxacin treatment arm. The following table, reproduced from the applicant's study report (Table 9.2, p. 74), indicates the reason for premature discontinuations.

**Reason for Discontinuation of Study Medication**

	Number (%) of Patients		
	Gatifloxacin N = 202	Levofloxacin N = 205	Total N = 407
Number Completed Therapy	181 (90)	189 (92)	370 (91)
Number that Discontinued Therapy	21 (10)	16 (8)	37 (9)
Adverse Event	6 (3)	10 (5)	16 (4)
Lost to Follow-Up	11 (5)	2 (<1)	13 (3)
Patient Decision/Request	3 (1)	0	3 (1)
Protocol Violation	0	2 (<1)	2 (<1)
Therapy Ineffective	1 (<1)	1 (<1)	2 (<1)
Other Antibiotic Administered	0	1 (<1)	1 (<1)

Reviewer's Comments

*Of the 13 patients lost to follow-up, 11 were in the gatifloxacin treatment group, and 2 were in the levofloxacin treatment group. The applicant did not have any explanation to account for the imbalance. Review of the case report forms by this reviewer did not reveal any obvious reason.*

*Of the 11 patients in the gatifloxacin treatment arm, 7 were lost after the initial visit, and 4 were lost to follow-up after the second visit. The lost to follow-up occurred across various centers. Although it is impossible to know, this reviewer believes that of the patients that were lost to follow-up after the first contact, there is only a low probability that the reason for loss of contact was due to a drug-related adverse event. This is based on the review of the patients' demographic data, histories and physicals found in the case report forms.*

*Both patients lost from the levofloxacin treatment group were lost to follow-up after the initial visit. Of the patients that were followed through to the second visit, none reported any adverse event of any significance.*

*Review of the case report forms revealed that of the patients on gatifloxacin that were discontinued due to an adverse event, one was classified as having a*

*“probable” relationship to study drug, and the rest were classified as “unrelated.” Of the patients on levofloxacin that were discontinued due to adverse events, five were classified as having a “certain” relationship to study drug.*

#### 8.4.1.3 Applicant Analyses

The applicant considered the clinically evaluable and microbiologically evaluable patient groups, as defined above (Section 8.4.1.1.6: Sample Size and Statistical Plan) as the primary efficacy data sets. Eligible and All Treated Patients were secondary efficacy sets. Clinical and bacteriological responses were determined at the Test of Cure visit, which was to be scheduled between 5 and 18 days after the cessation of therapy.

The following table, adapted from the applicant’s study report (Table 8.1.B, p. 60), summarizes the distribution of the different patient populations:

#### Distribution of Patients in Study Populations and Reasons for Exclusion

Study Population/Reason Excluded	Number (%) of Patients		
	Gatifloxacin	Levofloxacin	Total
All Treated	202 (100)	205 (100)	407 (100)
Eligible	193 (96)	199 (97)	392 (96)
Ineligible	9 (4)	6 (3)	15 (4)
Reason Ineligible			
Other reasons	7 (3)	4 (2)	11 (3)
Less than required signs/symptoms	2 (1)	2 (1)	4 (1)
Clinically Evaluable	161 (80)	172 (84)	333 (82)
Unevaluable	41 (20)	33 (16)	74 (18)
Reason Unevaluable			
Ineligible	9 (4)	6 (3)	15 (4)
Received <5 days of study drug treatment (excluding failure)	6 (3)	8 (4)	14 (3)
No post-treatment follow-up/follow-up outside window	12 (6)	5 (2)	17 (4)
Received systemic antibacterial prior to post-treatment follow-up	3 (1)	1 (<1)	4 (1)
No pre-treatment culture obtained	8 (4)	8 (4)	16 (4)
Other reasons	3 (1)	5 (2)	8 (2)
Microbiologically Evaluable	95 (47)	85 (42)	180 (44)
Microbiologically Unevaluable	107 (54)	120 (59)	227 (56)

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Study Population/Reason Excluded	Number (%) of Patients		
	Gatifloxacin	Levofloxacin	Total
<b>Reason Unevaluable</b>			
No pre-treatment pathogen isolated	85 (42)	101 (49)	186 (46)
Subject clinically unevaluable	14 (7)	10 (5)	24 (6)
Other reasons	8 (4)	8 (4)	16 (4)
Pathogen resistant	-	1 (<1)	1 (<1)

Reviewer's Comment:

*The number of patients that were in each patient efficacy subset was comparable between the two treatment groups. Review of the SAS datasets and the case report forms verified that above table.*

Safety data were collected in all patients who took a dose of study drug. Any adverse event experienced between Day 1 and Day +30 were evaluated.

8.4.1.3.1 Primary Analyses

Of the 370 patients who completed therapy, 333 were deemed clinically evaluable (161 in the gatifloxacin arm, 172 in the levofloxacin arm). The primary endpoint of clinical response at the Test of Cure visit in this patient subset revealed that gatifloxacin had comparable efficacy compared to levofloxacin. This information is demonstrated in the table below, adapted from a table in the applicant's study report (Table 10.1.1, p. 84):

**Clinical Response at Test of Cure Visit, Clinically Evaluable Patients**

Clinical Response	Number of Patients (%)		
	Gatifloxacin N = 161	Levofloxacin N = 172	Total N = 333
Cure	146 (91)	145 (84)	291 (87)
Failure	15 (9)	27 (16)	42 (13)

95% Confidence Interval for Difference in Cure Rate: (-2.0, 15.2)

Reviewer's Comment

*Dr. Silliman performed a conservative analysis of the data, using an imputation method for missing data. Missing gatifloxacin values were imputed to be failures, and missing levofloxacin values were imputed to be successes. Gatifloxacin's response rates, compared to levofloxacin, were still favorable. For additional details, please refer to Dr. Silliman's review.*

The applicant noted the following as the most frequent reason for failure of response was due to persistence, or worsening of primary signs and symptoms. The following table is adapted from the applicant's Study Report (Table 10.1.1.1, p. 85):

#### Reason Clinical Response is Failure, Clinically Evaluable Patients

Reason	Number of Patients (%)		
	Gatifloxacin N = 161	Levofloxacin N = 172	Total N = 333
Number of Failures	15 (100)	27 (100)	42 (100)
Persistence/Worsening of Primary Signs & Symptoms	12 (80)	21 (78)	33 (79)
New Clinical Signs & Symptoms	-	2 (7)	2 (5)
Surgery on Affected Area	3 (20)	4 (15)	7 (17)

#### Reviewer's Comment

*The reasons attributed for failure of clinical response were comparable between the two groups. Review of the case report forms verified the applicant's assessment of the reason for failure of the clinical response.*

#### 8.4.1.3.2 Additional Analyses

Additional analyses performed by the applicant included analyses of cure rates on infection diagnoses, and based on baseline pathogens. The following table, adapted from the applicant's Study Report (Table 10.1.1.2, p. 86) summarizes the response rate based on the entry diagnoses:

#### Clinical Cure Rates by Infection Diagnosis, Clinically Evaluable Patients

Diagnosis	Number Cured/Number of Patients (%)		
	Gatifloxacin N = 161	Levofloxacin N = 172	Total N = 333
Cellulitis	39/40 (98)	35/42 (83)	74/82 (90)
Abscess	28/35 (80)	37/47 (78)	65/82 (79)
Wound Infection	35/37 (95)	35/40 (88)	70/77 (91)
Folliculitis	34/39 (87)	26/31 (84)	60/70 (86)
Impetigo	10/10 (100)	11/11 (100)	21/21 (100)
Erysipelas	-	1/1 (100)	1/1 (100)

#### Reviewer's Comments

*Gatifloxacin had similar clinical cure rates as levofloxacin, except for cellulitis, where it appeared to do slightly better. There were not enough cases of erysipelas to be able to draw any conclusions.*

The following table, adapted from the adapted from the applicant's Study Report (Table 10.1.1.3, p. 87-88) summarizes the response rate based on the entry pathogen:

**Clinical Cure Rates by Pathogen, Clinically Evaluable Patients with Pathogens**

Pathogen	Number (%) of Patients		
	Gatifloxacin N = 161	Levofloxacin N = 172	Total N = 333
Total	93/103 (90)	80/94 (85)	173/197 (88)
<b>Aerobic Isolates (Gram-positive)</b>			
<i>S. aureus</i> (MS)	55/57 (96)	47/54 (87)	102/111 (92)
<i>S. aureus</i> (MR)	4/5 (80)	4/4 (100)	8/9 (89)
<i>S. aureus</i> (susceptibility unspecified)	7/7 (100)	3/4 (75)	10/11 (91)
<i>S. pyogenes</i>	4/6 (67)	4/5 (80)	8/11 (73)
<i>S. agalactiae</i>	1/2 (50)	8/9 (89)	9/11 (82)
<i>Bacillus</i> sp.	3/3 (100)	2/3 (67)	5/6 (83)
Other Gram-positive aerobes	1/2 (50)	2/2 (100)	3/4 (75)
<b>Aerobic Isolates (Gram-negative)</b>			
<i>A. lwoffii</i>	5/6 (83)	4/7 (57)	9/13 (69)
<i>P. aeruginosa</i>	0/1 (0)	5/6 (83)	5/7 (71)
<i>A. baumannii</i>	3/3 (100)	6/6 (100)	9/9 (100)
<i>E. coli</i>	2/2 (100)	3/4 (75)	5/6 (83)
<i>F. oryzihabitans</i>	2/3 (67)	1/1 (100)	3/4 (75)
<i>S. marcescens</i>	2/2 (100)	1/2 (50)	3/4 (75)
<i>K. pneumoniae</i>	1/2 (50)	2/2 (100)	3/4 (75)
<i>K. oxytoca</i>	2/2 (100)	1/1 (100)	3/3 (100)
<i>Pseudomonas</i> sp.	1/1 (100)	3/3 (100)	4/4 (100)
<i>P. mirabilis</i>	1/1 (100)	1/1 (100)	2/2 (100)
Other Gram-negative aerobes	13/14 (93)	14/14 (100)	27/28 (96)
<b>Anaerobic Isolates (Gram-positive)</b>			
<i>P. acnes</i>	1/1 (100)	2/2 (100)	3/3 (100)
<i>Peptostreptococcus</i> sp.		1/1 (100)	1/1 (100)
<i>P. magnus</i>	1/1 (100)	0/1 (0)	1/2 (50)
Unidentified Gram-positive anaerobes	1/3 (33)	2/2 (100)	3/5 (60)

Pathogen	Number (%) of Patients		
	Gatifloxacin N = 161	Levofloxacin N = 172	Total N = 333
<b>Anaerobic Isolates (Gram-negative)</b>			
<i>B. vulgatus</i>	1/1 (100)		1/1 (100)
<i>Prevotella</i> sp.	0/1 (0)	1/1 (100)	1/2 (50)
<i>B. caccae</i>	1/1 (100)		1/1 (100)
<i>Fusobacterium</i> sp.	0/1 (0)		0/1 (0)
Unidentified Gram-negatives anaerobes		1/1 (100)	1/1 (100)
<b>Unidentified Anaerobes</b>	<b>2/2 (100)</b>	<b>0/2 (0)</b>	<b>2/4 (50)</b>

In the microbiologically evaluable patients, the bacteriological eradication rates were as follows:

#### **Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients**

Pathogen	Number (%) of Patients <sup>a</sup>		
	Gatifloxacin N = 95	Levofloxacin N = 85	Total N = 180
<b>Total</b>	<b>107/116 (92)</b>	<b>113/123 (92)</b>	<b>220/239 (92)</b>
<b>Aerobic Isolates (Gram-positive)</b>			
<i>S. aureus</i> (MS)	53/57 (93)	49/54 (91)	102/111 (92)
<i>S. aureus</i> (MR)	4/5 (80)	4/4 (100)	8/9 (89)
<i>S. aureus</i> (susceptibility unspecified)	7/7 (100)	3/3 (100)	10/10 (100)
<i>S. pyogenes</i>	4/6 (67)	5/5 (100)	9/11 (82)
<i>S. agalactiae</i>	2/2 (100)	7/9 (78)	9/11 (82)
<i>Bacillus</i> sp.	3/3 (100)	1/1 (100)	4/4 (100)
Other Gram-positive aerobes	1/1 (100)	2/2 (100)	3/3 (100)
<b>Aerobic Isolates (Gram-negative)</b>			
<i>A. lwoffii</i>	6/6 (100)	7/7 (100)	13/13 (100)
<i>P. aeruginosa</i>	1/1 (100)	5/6 (83)	6/7 (86)
<i>A. baumannii</i>	3/3 (100)	6/6 (100)	9/9 (100)
<i>E. coli</i>	2/2 (100)	3/4 (75)	5/6 (83)
<i>F. oryziabittans</i>	2/3 (67)	1/1 (100)	3/4 (75)
<i>S. marcescens</i>	2/2 (100)	1/2 (50)	3/4 (75)
<i>K. pneumoniae</i>	2/2 (100)	2/2 (100)	4/4 (100)

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Pathogen	Number (%) of Patients <sup>a</sup>		
	Gatifloxacin N = 95	Levofloxacin N = 85	Total N = 180
<i>K. oxytoca</i>	2/2 (100)	1/1 (100)	3/3 (100)
<i>Pseudomonas</i> sp.	1/1 (100)	2/2 (100)	3/3 (100)
<i>P. mirabilis</i>	1/1 (100)	1/1 (100)	2/2 (100)
Other Gram-negative aerobes	11/12 (92)	13/13 (100)	24/25 (96)

<sup>a</sup> A patient may have more than one pathogen isolated pre-treatment.

#### Reviewer's Comments

The cure rates between the two patient subsets were comparable in both types of analyses. In Study AI420-005, the applicant only had adequate microbiologic data for methicillin-susceptible *S. aureus*. They do not have sufficient data to support their claim of efficacy against *S. pyogenes*, *S. agalactiae*, nor *Acinetobacter* spp.

The applicant was informed of this concern, and asked whether they had additional data on *S. pyogenes* from other skin infection studies. The applicant submitted a table (Amendment No. 228, submitted 12 August 1999) with patient information from studies performed by Kyorin Pharmaceuticals Co., Inc., in Tokyo, Japan. A total of 8 additional cases of *S. pyogenes* were reported.

In those trials, the diagnoses included:

Felons - 3	Impetigo contagiosa - 1	Cellulitis - 1
Wound infection - 1	Furunculosis - 1	Infected pierced ear - 1

Daily dosage of gatifloxacin ranged from 200 to 400 mg, duration of therapy was 4 to 8 days, and the clinical responses were reported as "good" (3) and "excellent" (5). The bacteriologic response was reported as "eliminated" for all patients. The actual case report forms were not available for review.

The overall package of the data submitted by the applicant, as presented for Study AI420-005, supports the scientific plausibility that gatifloxacin could be effective as treatment of uncomplicated skin infections caused by *Streptococcus pyogenes*. Therefore, although the actual case report forms for the patients in the overseas studies have not been submitted, it is believed that this information can support the assertion that gatifloxacin's efficacy against this organism.

#### 8.4.1.4 FDA Analyses

The focus of the FDA's interest was on the verification of the applicant's assertion of gatifloxacin's efficacy for this indication in this patient population. This included verification of data by reviewing the case report forms, including assessment of evaluability as proposed by the applicant, and statistical analyses which assessed the

robustness of the results. When there was a discrepancy in the interpretation of the data between the applicant and this reviewer, an assessment was made to determine if this discrepancy was significant enough to alter the results of the study.

The following table, reproduced from Dr. Silliman's review, summarizes the clinical cure rates based on the analysis population:

#### Clinical Cure Rates by Analysis Population

Analysis Population	Number Cured/Number of Patients (%)		95% Confidence Interval*
	Gatifloxacin N = 205	Levofloxacin N = 205	
All Treated Patients	162/202 (80)	161/205 (79)	(-6.9%, 10.9%)
Clinically Eligible Patients	159/193 (82)	159/199 (80)	(-6.1%, 11.6%)
Clinically Evaluable Patients	146/161 (91)	145/172 (84)	(-2.0%, 15.2%)
Microbiologically Evaluable Patients	88/95 (93)	75/85 (88)	(-6.5%, 16.8%)

\*For the difference in cure rates, gatifloxacin minus levofloxacin.

Dr. Silliman noted that the results were generally consistent across clinical sites.

#### 8.4.1.5 FDA Efficacy Summary

For full details of the statistical analysis results, please refer to Dr. Nancy Silliman's, the reviewing biometrician, review. It is believed that the efficacy results for Study AI420-005 are fairly robust, and that the applicant had shown that statistically, gatifloxacin is equivalent to levofloxacin in terms of efficacy. In addition, she believed that it is unlikely that the dynamic randomization used had a significant impact on the results of this study.

Based on the microbiologic data submitted, it is believed that the applicant has demonstrated that gatifloxacin is equivalent to levofloxacin in the treatment of uncomplicated skin and skin structure infections caused by methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pyogenes*.

### 8.4.2 Safety Assessment

#### 8.4.2.1 Integrated Safety Summary for this indication

The sponsor is utilizing data to from 36 studies to support the safety of gatifloxacin. These studies enrolled a total of 6,784 patients (4,495 patients receiving gatifloxacin and 2,389 patients receiving either placebo or an active comparator). Dr. Joyce Korvick, the Division's lead medical reviewer for this application, performed the integrated safety assessment. Please refer to Section 9.0 of the clinical review for complete details.

This section of this clinical review will address the safety data derived from the studies performed for this indication – uncomplicated skin and soft tissue infections.

#### 8.4.2.2 Extent of Drug Exposure in Pivotal Study

All treated patients were included in the safety analyses. Of the 205 patients randomized to the gatifloxacin arm, 202 took at least one dose. The following table, adapted from the

applicant's Study Report (Table 9.1, p. 72), summarizes the duration of study drug exposure for the study:

### Study Drug Exposure, All Treated Patients

	Number (%) of Patients		
	Gatifloxacin N = 202	Levofloxacin N = 205	Total N = 407
<u>Number of Doses</u>			
<5	7 (4)	11 (5)	18 (4)
5 - 6	3 (2)	2 (1)	5 (1)
7	43 (22)	30 (15)	73 (18)
8 - 9	6 (3)	11 (5)	17 (4)
10	131 (68)	149 (73)	280 (71)
20	2 (1)	1 (<1)	3 (1)
Not recorded	10	1	11

### Duration (days)

Mean (SD)	9 (1.81)	9 (1.96)	9 (1.89)
Median	10	10	10
Range			

### Reviewer's Comments

*Most patients took 10 days of therapy; the distribution of dose and duration was comparable between the two treatment groups.*

### 8.4.2.3 Adverse Events

#### 8.4.2.3.1 All Causalities

Of the 407 patients in the study, 207 (51%) reported at least one adverse event during the study period. The most common complaint for gatifloxacin was nausea, followed by headache, diarrhea, dizziness, pruritus, and vaginitis. This frequency was closely mirrored

by levofloxacin, except for pain, which had a higher incidence in the levofloxacin treatment arm than in the gatifloxacin treatment arm.

Appendix C contains a table adapted from the applicant's Study Report (Table 12.2.1 p. 98), providing additional information within each of the categories. The following table is a partial reproduction of that table, summarizing the frequency of the top ten adverse events:

#### Adverse Clinical Events of All Causes. All-Treated Patients (Top ten)

	Number of Patients							
	Gatifloxacin N = 202				Levofloxacin N = 205			
	Related	Not related	Unknown relationship	Total	Related	Not Related	Unknown relationship	Total
No. of patients with any AE	70 (35)	30 (15)	2 (1)	104 (51)	58 (28)	44 (21)	0	103 (50)
Nausea	16 (8)	1 (<1)	0	17 (8)	16 (8)	2 (<1)	0	18 (9)
Headache	6 (3)	8 (4)	0	14 (7)	10 (5)	8 (4)	0	18 (9)
Diarrhea	12 (6)	1 (<1)	0	13 (6)	12 (6)	1 (<1)	0	13 (6)
Dizziness	7 (3)	3 (1)	0	10 (5)	4 (2)	2 (<1)	0	6 (3)
Pruritus	5 (2)	4 (2)	1 (<1)	10 (5)	4 (2)	1 (<1)	0	6 (3)
Vaginitis	9 (8)	0	0	10 (9)*	4 (4)	0	0	4 (4)
Pain Abdomen	6 (3)	2 (<1)	1 (<1)	9 (4)	4 (2)	1 (<1)	0	5 (2)
Pain	2 (<1)	5 (2)	0	8 (4)	5 (2)	7 (3)	0	12 (6)
Rash	4 (2)	2 (<1)	0	6 (3)	3 (2)	2 (1)	0	5 (2)
Accidental Injury	0	5 (2)	0	5 (2)	0	3 (1)	0	3 (1)

\* percentage calculated based on women patients only

#### Reviewer's Comments

*The most common types of adverse events observed in the gatifloxacin treatment group were similar to what was observed in the comparator, levofloxacin.*

*Comparison of the data reported in the Integrated Safety Summary with the Safety Update indicated that there was no significant change in the overall impression of the safety profile for this indication.*

#### 8.4.2.3.2 Treatment Related

Of the 407 patients that reported adverse events, the applicant stated that the investigators felt that the adverse events were related to study drug treatment in 128 (31%) patients [70 (35%) in the gatifloxacin treatment group and 58 (28%) in the levofloxacin treatment group]. The following table is adapted from the applicant's Study Report (Table 12.2.2, p. 101):

**Drug Related Adverse Clinical Events, All Treated Patients**

Adverse Clinical Event <sup>a</sup>	Number of Patients (%)							
	Gatifloxacin N = 202				Levofloxacin N=205			
No. of patients with any Drug-Related AE	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
	38 (19)	23 (11)	8 (4)	70 (35)	27 (13)	26 (13)	5 (2)	58 (28)
Nausea	11 (5)	3 (1)	1 (<1)	16 (8)	10 (5)	5 (2)	1 (<1)	16 (8)
Diarrhea	6 (3)	5 (2)	1 (<1)	12 (6)	6 (3)	6 (3)	0	12 (6)
Vaginitis	7 (6)	1 (1)	1 (1)	9 <sup>b</sup> (8)	3 (3)	1 (1)	0	4 <sup>b</sup> (4)
Dizziness	3 (1)	2 (<1)	2 (<1)	7 (3)	4 (2)	0	0	4 (2)
Headache	2 (<1)	2 (<1)	2 (<1)	6 (3)	7 (3)	3 (1)	0	10 (5)
Pain Abdomen	3 (1)	3 (1)	0	6 (3)	2 (<1)	2 (<1)	0	4 (2)
Asthenia	1 (<1)	3 (1)	1 (<1)	5 (2)	0	0	0	0
Pruritus	4 (2)	1 (<1)	0	5 (2)	1 (<1)	3 (1)	0	4 (2)
Rash	1 (<1)	3 (1)	0	4 (2)	2 (<1)	1 (<1)	0	3 (1)
Nervousness	1 (<1)	1 (<1)	1 (<1)	3 (1)	1 (<1)	0	0	1 (<1)
Eructation	2 (<1)	0	0	2 (<1)	2 (<1)	3 (1)	0	5 (2)
Pain	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	2 (<1)	2 (<1)	5 (2)
Taste Perversion	1 (<1)	0	0	1 (<1)	2 (<1)	1 (<1)	0	3 (1)
Insomnia	0	1 (<1)	0	1 (<1)	3 (1)	1 (<1)	1 (<1)	5 (2)

<sup>a</sup> All adverse clinical events occurring in ≥1% or more of the patients in either treatment group.

<sup>b</sup> % calculated based on women only.

Reviewer's Comments

*The largest number of adverse events that were attributed to gatifloxacin therapy revolved around the gastrointestinal system. Most were graded as mild in severity. This was mirrored in the levofloxacin treatment arm. Notable exceptions were: vaginitis, which were more common in the gatifloxacin arm, and headaches, which were more common in the levofloxacin arm.*

## 8.4.2.3.3 Serious Adverse Events

There were ten serious adverse events reported for the study (9 in the gatifloxacin treatment arm, 1 in the levofloxacin treatment arm); 4 patients reported the events in the gatifloxacin arm. None of the events were attributed to the study therapy by the investigator, or the applicant.

The following table summarizes the serious adverse events that were reported by the applicant:

### Serious Adverse Clinical Events, All Treated Patients

Adverse Clinical Event	Number of Patients (%)	
	Gatifloxacin N = 202	Levofloxacin N=205
Fall, with subsequent fracture of hip		007-460
Confusion	015-337	-
Lower extremity weakness	015-337	
Difficulty walking	015-337	
Syncope	020-315	
Chest pain	021-055	
Fever	025-022	
Chills	025-022	
Loss of appetite	025-022	
Worsening pain associated with the presenting infection	025-022	
<b>Total Number of patients</b>	<b>4</b>	<b>1</b>

#### Reviewer's Comments

None of the serious adverse events reported in the gatifloxacin arm were attributed to study drug. Review of the case report forms did not reveal any additional information to contradict the applicant's assessment.

Patient #020-315 was a 20-year-old white male, enrolled with the diagnosis of an abscess on the left big toe. He completed 7 days of gatifloxacin therapy. Approximately eight days after completion of therapy, he had what was felt by the investigator to be a vasovagal syncopal episode. The patient was admitted to a hospital for 23 hours for observation, during which a CT scan of the head, and an electrocardiogram were performed and interpreted as normal. The patient had no significant past medical history, specifically for cardiac arrhythmias. The event was attributed to a combination of viral syndrome and dyspepsia.

Due to the patient's age, past medical history, and temporal relationship between the adverse event and study drug administration (occurred 8 days after completion of therapy), the syncopal episode can probably be excluded as being caused by a drug-related cardiac arrhythmia.

## 8.4.2.3.4 Severe and Life-threatening events

There were no severe and/or life-threatening adverse events reported by the applicant for this study.

## 8.4.2.3.5 Discontinuations from Studies

The following table is adapted from the applicant's Study Report (Table 12.4, p. 103), and summarizes the type of adverse events that resulted in discontinuation from the study drug:

### Discontinuation of Study Medication Due to Adverse Clinical Events, All Treated Patients

Number Discontinued	Number of Patients (# drug related)		
	Gatifloxacin N = 202	Levofloxacin N = 205	Total N = 407
	6	10	16
Nausea	1 (1)	5 (5)	6 (6)
Dizziness	1 (1)	1 (1)	2 (2)
Pain	1 (0)	1 (1)	2 (1)
Rash	1 (1)	1 (1)	2 (2)
Diarrhea	-	2 (2)	2 (2)
Accidental Injury	1 (0)	-	1 (0)
Anorexia	1 (0)	-	1 (0)
Chills	1 (0)	-	1 (0)
Disorder Tendon	1 (0)	-	1 (0)
Erythema	1 (0)	-	1 (0)
Fever	1 (0)	-	1 (0)
Induration Wound	1 (0)	-	1 (0)
Vasodilatation	1 (0)	-	1 (0)
Arthralgia	-	1 (1)	1 (1)
Cellulitis	-	1 (0)	1 (0)
Dry Mouth	-	1 (1)	1 (1)
Hallucination	-	1 (1)	1 (1)
Hyperventilation	-	1 (1)	1 (1)
Insomnia	-	1 (1)	1 (1)
Myalgia	-	1 (1)	1 (1)
Pain Abdomen	-	1 (1)	1 (1)
Pain Chest	-	1 (1)	1 (1)
Vomiting	-	1 (1)	1 (1)

<sup>a</sup> A patient may be included in more than one category.

Reviewer's Comments

The most common reason for discontinuation from the study was nausea (6 patients; 1 in the gatifloxacin treatment arm and 5 in the levofloxacin treatment arm. Causality was deemed as possibly related to study drug.

For gatifloxacin, the rash and dizziness were felt to be attributable to the drug, while the other adverse events reported were felt to be unrelated.

## 8.4.2.3.5.1 Discontinuations Due to Adverse Events

Review of the previous table indicates that there was no specific adverse event category that resulted in discontinuations from gatifloxacin. The most common adverse event that resulted in discontinuation from the levofloxacin treatment group was nausea.

## 8.4.2.3.5.2 Discontinuations Due to Laboratory Abnormalities

Laboratory abnormalities were assessed by utilization of published toxicity grades: CTC (Common Toxicity Criteria from the National Cancer Institute) and ACTG (from the AIDS Clinical Trials Group), or scales developed by the applicant's Anti-infective Clinical Department. The table of toxicity criteria is reproduced below:

**Toxicity Criteria**

Laboratory Test	Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<b>Hematologic Function†</b>						
Hemoglobin (g/dL)	Anemia	≥ 1nl	10.0- <1nl	8.0 - 9.9	6.5 - 7.9	<6.5
Platelet Count (x10 <sup>3</sup> cells/μL)	Thrombocytopenia	≥ 1nl	75 - <1nl	50 - 74	25 - 49	<25
Leukocyte Count (x10 <sup>3</sup> cells/μL)	Leukopenia	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
Neutrophil Count (cells/μL)	Neutropenia	≥ 2000	1500 - 1999	1000 - 1499	500 - 999	<500
<b>Kidney Function</b>						
Blood Urea Nitrogen (mg/dL) † (BUN)	Elevated BUN	≤ 1.25 x unl	1.26-2.5 x unl	2.6 - 5.0 x unl	5.1 - 10.0 x unl	>10.0 x unl
Urea (mmol/L) †	Elevated urea	≤ 1.25 x unl	1.26-2.5 x unl	2.6 - 5.0 x unl	5.1 - 10.0 x unl	>10.0 x unl
Creatinine (mg/dL) ‡	Elevated creatinine	≤ unl	1.1 - 1.5 x unl	1.6 - 3.0 x unl	3.1 - 6.0 x unl	>6.0 x unl
<b>Liver Function ‡</b>						
AST (SGOT), ALT (SGPT) and Alkaline Phosphatase (U/L)	Abnormal liver function	≤ unl	1.1 - 2.5 x unl	2.6 - 5.0 x unl	5.1 - 20.0 x unl	>20.0 x unl
Total Bilirubin (mg/dL)	Hyperbilirubinemia	≤ unl	---	1.1 - 1.4 x unl	1.5 - 3.0 x unl	>3.0 x unl
<b>Metabolic Function</b>						
Amylase (U/L) ‡	Hyperamylasemia	≤ unl	1.1 - 1.5 x unl	1.6 - 2.0 x unl	2.1 - 5.0 x unl	>5.0 x unl
Glucose (mg/dL) ‡ Grade to be attached to result of fasting	Hypoglycemia or Hyperglycemia	65 - 115	55 - 64 or 116 - 160	40 - 54 or 161 - 250	30 - 39 or 251 - 500	<30 or >500

Indication: Uncomplicated Skin/Skin Structure Infections

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Laboratory Test	Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
specimen only.						
Sodium (mEq/L) †	Hyponatremia or Hypernatremia	136 - 145	130 - 135 or 146 - 150	123 - 129 or 151 - 157	116 - 122 or 158 - 165	<116 or >165
Potassium (mEq/L) †	Hypokalemia or Hyperkalemia	3.5 - 5.5	3.0 - 3.4 or 5.6 - 6.0	2.5 - 2.9 or 6.1 - 6.5	2.0 - 2.4 or 6.6 - 7.0	<2.0 or >7.0
Chloride (mEq/L) §	Hypochloremia or Hyperchloremia	95 - 110	92 - 94 or 111 - 113	89 - 91 or 114 - 116	86 - 88 or 117 - 119	<86 or >119
Bicarbonate (mEq/L) §	Acidosis or Alkalosis	22.0 - 29.9	18.0 - 21.9 or 30.0 - 33.9	14.0 - 17.9 or 34.0 - 37.9	10.0 - 13.9 or 38.0 - 41.9	<10.0 or >41.9

\*Grades based on CTC ‡ or ACTG † Scales or established by BMS AI Clinical §

#### Reviewer's Comments

*There were no discontinuations due to abnormal laboratory values. Of the patients that had normal baseline laboratory parameters and then experienced laboratory abnormalities while on therapy, most of them were grade 1.*

#### 8.4.2.3.6 Assessment of Drug Relationship for Selected Adverse Events

##### 8.4.2.3.6.1 Hepatobiliary System Abnormalities

###### *Hepatic transaminases*

Twenty-seven patients had elevated serum aspartate transaminase (AST) values during treatment. Of these twenty-seven patients, 20 (75%) also had elevated serum alanine transaminase (ALT) – 9 in the gatifloxacin treatment arm, and 11 in the levofloxacin treatment arm. In addition, 14 of the twenty patients (9 on the gatifloxacin arm, and 5 on the levofloxacin arm) had elevated AST values at baseline.

###### *Serum total bilirubin*

In the group of patients that had normal pre-treatment total bilirubin values, thirteen patients manifested elevated total bilirubin during treatment during or after treatment. The mean day of onset was comparable between the two treatment arms. Of the thirteen, 7 (54%) had elevated total bilirubin with normal transaminases, three had elevated total bilirubin with an elevation in ALT alone, and three had elevated total bilirubin accompanied by elevation in both, ALT and AST. None of the patients had an elevation of their serum total bilirubin and AST alone.

#### Reviewer's Comments

*The incidences of hepatic enzyme abnormalities seen in the treatment arms were comparable. With respect to patients that had normal total bilirubin at baseline, who then manifested a rise in total bilirubin combined with a concurrent rise in their hepatic transaminases, the incidence was twice as high in the levofloxacin treatment group (4 to 2)*

*Review of the case report forms of the three patients that manifested concurrent elevations of their ALT and total bilirubin revealed the following:*

*Patient #018-00240 (Gatifloxacin)*

*Patient was a 20 year-old white male enrolled with a diagnosis of folliculitis on the left shoulder. He completed 7 days of gatifloxacin therapy without incident. His laboratory work revealed an elevation in total bilirubin on the 11<sup>th</sup> day post-therapy (1.4 mg/dL, from baseline value of 0.7 mg/dL). Although he also had an elevated ALT (55 U/L) post-therapy, the value was actually lower than what it was at baseline, 67 U/L. He had no significant past medical history, nor any concomitant medications listed in his case report form. Follow-up values were not available.*

*Patient #020-00313 (Levofloxacin)*

*Patient was a 22 year-old white male enrolled with a diagnosis of abscess on the left ankle. He completed 10 days of levofloxacin therapy without incident. His total bilirubin rose to 1.3 mg/dL from a baseline value of 0.8 mg/dL. He had an elevation in ALT (50 U/L, from a baseline value of 29 U/L) on Day 8 post-therapy. His past medical history was significant only for mitral valve prolapse; he was on no chronic medications. The only concomitant medication that he took while on study was acetaminophen for a headache on Day 5 post-therapy. Follow-up values were not available.*

*Patient #022-00142 (Levofloxacin)*

*Patient was a 21 year-old male enrolled with a diagnosis of folliculitis on the left upper back. He completed 10 days of therapy with levofloxacin without incident. His total bilirubin rose to 1.1 mg/dL on the 5<sup>th</sup> day of therapy, from a baseline value of 0.8 mg/dL. On the 8<sup>th</sup> day post-therapy, his ALT increased to 79 U/L, however this was from a baseline value of 67 U/L. It was noted that he also received doxycycline for pharyngitis on the 7<sup>th</sup> day post-therapy. His past medical history was insignificant. Follow-up values were not available.*

*Review of the case report forms of the three patients that manifested concurrent elevations of both, ALT and AST, and total bilirubin revealed the following:*

*Patient # 010-00589 (Levofloxacin)*

*Patient was a 39-year-old white female who was enrolled with cellulitis of the left elbow. She was assigned to the levofloxacin treatment arm, and completed the course of therapy without any incident. Her laboratory work revealed an elevation in total bilirubin on the 9<sup>th</sup> day post-therapy*

(1.1 mg/dL) with concomitant elevations in ALT (81 U/L) and AST (85 U/L). Although she had a normal total bilirubin at entry (0.7 mg/dL), she had elevated transaminases (ALT= 64 U/L, and AST= 51 U/L). Her past medical history was only significant for a history of recurrent cellulitis, and tobacco use. She was not on any chronic medications. Follow-up values were not available.

Patient # 021-00290 (Levofloxacin)

Patient was a 22 year-old Hispanic male enrolled with a diagnosis of cellulitis of the left gluteal fold. He completed 10 days of levofloxacin therapy without incident. His laboratory work showed an elevated total bilirubin on the 8<sup>th</sup> day post-treatment (1.1 mg/dL). The transaminases were concurrently elevated (ALT = 66 U/L, and AST = 50 U/L), however, pre-treatment values were not available for comparison. His past medical history was significant only for trauma to his left thigh, for which he was taking ibuprofen. Follow-up values were not available.

Patient # 027-00540 (Gatifloxacin)

Patient was a 52 year-old white female enrolled with a diagnosis of cellulitis of the left ear lobe. She completed 10 days of therapy with gatifloxacin without incident. On the 10<sup>th</sup> day post-therapy, she had an elevated total bilirubin (1.8 mg/dL from a baseline of 0.5 mg/dL). Her transaminases were also noted to be elevated (ALT 65 U/L; and AST 55 U/L) but these values actually represented a decrease from baseline values (ALT 86 U/L and AST 80 U/L). The case report form indicated that she had a history of cholelithiasis and a "fatty liver." She was s/p cholecystectomy, and s/p hysterectomy. She also had a history of diabetes, hypercholesterolemia, tobacco use, and bronchial asthma. The case report form did not list any chronic medications. No follow-up laboratory work was available.

In view of the above information, it is difficult to make any conclusions about the significance of the concurrent elevation of transaminases, either ALT alone, or in combination with AST, in these six patients with elevated total bilirubin. It should be noted that only one of these patients (#027-00540) had a bilirubin level > 1.5 mg/dL. In addition, the long-term post-marketing experience with levofloxacin currently does not suggest that hepatotoxicity is a problem. Therefore, in this study, gatifloxacin did not appear to behave worse than an active control that is not considered a problem with respect to this adverse event.

#### § 4.2.3.6.2 Pancreatic Enzyme Abnormalities

There were seven patients who had elevated serum amylase during or after treatment. Six patients were on the gatifloxacin treatment arm, and one on the levofloxacin arm. There were 4 males and 3 females, mean age of 55 (range: 20 – 82 years). One of these patients

(on the gatifloxacin arm) had an elevated serum amylase at baseline. The average elevation was to 122 U/L (range: 118 – 179 U/L) with the high normal value being 102 U/L.

#### Reviewer's Comments

*Review of the patients' case report forms revealed that only one patient had any past medical history that could place him at risk for pancreatitis. Patient #015-00339 was a 75 year-old male with a history of alcohol consumption that was noted as ">2 drinks/day." He was on the levofloxacin treatment arm. The case report form did not indicate the duration of this alcohol history. None of the case report forms indicated that any of the patients reported any symptoms consistent with clinical pancreatitis. There were no follow-up values reported to assess whether these lab values return to normal.*

*It is noted that the gatifloxacin treatment group had more cases than the levofloxacin treatment group. However, it is difficult to make any reliable conclusions about the findings of elevated serum amylase values in the absence of clinical symptoms.*

#### 8.4.2.3.7 Mortality Experience

There was one death in the study; it was in the gatifloxacin treatment group. Patient 021-055 committed suicide 33 days after the end of study therapy. The investigators did not attribute the death to the study drug.

#### Reviewer's Comments

*The patient narrative was reviewed. This reviewer concurs that the death was more than likely not due to study drug.*

#### 8.4.2.4 Safety Assessment Summary

The patient database submitted by the applicant in the NDA was sufficient to reasonably evaluate gatifloxacin's safety profile. In the patient population that was reviewed for this indication, the adverse events that were observed were generally consistent with what was reported in the other clinical trials. The only finding worth noting, but difficult to interpret with respect to its significance, is that there were more patients on the gatifloxacin treatment group had asymptomatic elevations in serum amylase values than in the comparator arm. Due to the nature of the study design, there is little data to assess the time to resolution of this abnormal laboratory finding.

### 8.4.3 Special Populations

#### 8.4.2.1 Gender, Age, and Ethnic group

##### *Efficacy*

Gatifloxacin's efficacy rates were similar to levofloxacin in the subset categories of gender, age, and ethnic group.

### *Safety*

Gatifloxacin adverse event rates were similar to levofloxacin in the subset categories of age and ethnic groups. As mentioned above, there were more serious adverse events reported in the gatifloxacin treatment group than in the levofloxacin treatment group. However, these were not significantly different with respect to age, gender, or ethnic group within the gatifloxacin treatment group.

It was noted that overall, more adverse events were reported for female patients than for male patients in the gatifloxacin treatment group (156 to 75). Although this trend was also observed in the levofloxacin treatment group (142 to 102 events), it was numerically higher in the gatifloxacin treatment group.

"Nausea" was the only adverse event that was reported in females more than in males – out of 17 patients, 14 were females. Most were graded as "Mild/Grade 1" in severity. This was similar to the levofloxacin treatment group with respect to severity, however the gender breakdown was slightly different in the levofloxacin treatment group – out of 17 patients, 11 were females. It is believed that these numbers are too small to be able to draw any significant conclusions about this finding, other than the fact that it was observed.

The incidences of abnormal laboratory values were similar within the subset categories of age, gender, and ethnic group.

#### **8.4.2.2 Pediatric Database**

There were no pediatric patients enrolled in the clinical study designed to support this indication. However, with the submission of the 4-month safety update (Amendment No. 12, Submission date 5 May 1999), the applicant indicated that they have begun clinical studies in the pediatric population. The first study is a pharmacokinetic assessment of an oral suspension in children under the age of 16 years.

#### **8.4.4 Regulatory Recommendations**

The Points to Consider document indicates that in order for this general claim to be granted, there should be at least 20% each of the following: simple abscesses, impetiginous lesions, furuncles, and cellulitis. The applicant was able to study sufficient number of patients for three of the four types of infections. They were not able to study sufficient number of patients with impetiginous lesions.

The medical officer recommendation for gatifloxacin regarding uncomplicated skin and skin structure infections :

1. Approval of the indication only for methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pyogenes*.
2. The label should reflect the type of uncomplicated skin infections that were studied in this clinical trial; a) simple abscesses, b) furuncles, c) folliculitis, d) wound infections and e) cellulitis.

3. The label should indicate that an insufficient number of patients with the diagnosis of impetiginous lesions were available for evaluation.

#### 8.4.4 Label Review

The portion of the label for this indication should be amended to read 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."

In addition, the applicant has included in the Clinical Studies section a table that lists clinical cure rates by diagnosis (reproduced from the applicant's proposed label):

Diagnosis	Clinical Cure at Test of Cure Visit	
	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)
Folliculitis	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 revised table would list the diagnoses as follows:

Diagnosis	Clinical Cure at Test of Cure Visit	
	Gatifloxacin	Levofloxacin
All Diagnoses	90% (136/151)	83% (133/160)
Abscess	80% (28/35)	79% (37/47)
Cellulitis	98% (39/40)	83% (35/42)
Folliculitis	87% (34/39)	84% (26/31)
Wound Infection	95% (35/37)	88% (35/40)

#### 8.4.5 Phase IV Commitments

There were no phase IV commitments for this indication.

**/S/**

Rigoberto Roca, M.D.  
Reviewing Medical Officer, DSPIDP

Concurrences:

/S/

11/5/99

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11/5/99

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Marc Cavaillé-Coll, M.D., Ph. D.  
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/S/

Mark Goldberger, M.D., M.P.H.  
Division Director  
Division of Special Pathogen and  
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cc:

Original NDA 21-061

HFD-590/Div. Dir/Goldberger

HFD-590/Dep. Div. Dir/Albrecht

HFD-590/TV/Cavallé-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

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## Appendix A – Approved Products for This Indication

The following agents have been approved in the United States for the treatment of skin and skin structure infections:

### Skin and Skin Structures

Amoxicillin/clavulanate potassium (Augmentin™)

caused by beta-lactamase-producing strains of *S. aureus*, *E. coli*, and *Klebsiella* spp.

Cefamandole: *S. aureus* (penicillinase- and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, *E. coli*, *Enterobacter* sp, and *P. mirabilis*.

Ceftazidime: *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Cefuroxime:

Zinacef™ *S. aureus* (penicillinase- and non-penicillinase-producing strains), *S. pyogenes*, *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

Kefurox™ *S. aureus* (penicillinase- and non-penicillinase-producing strains), *S. pyogenes*, *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

Cephalexin:

Keflex™ Staphylococci and/or streptococci.

Keftab™ *S. aureus* and/or beta-hemolytic streptococci.

Cefpodoxime: *S. aureus* (including penicillinase-producing strains) or *S. pyogenes*.

Imipenem

Intramuscular preparation: including abscesses, cellulitis, infected skin ulcers and wound infections caused by *Staphylococcus aureus* including penicillinase-producing strains; *Streptococcus pyogenes*\*; Group D streptococcus including *Enterococcus faecalis*; *Acinetobacter* species\* including *A. calcoaceticus*\*; *Citrobacter* species\*; *Escherichia coli*; *Enterobacter cloacae*; *Klebsiella pneumoniae*\*; *Pseudomonas aeruginosa*\* and *Bacteroides* species\* including *B. fragilis*\*.

\*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Intravenous preparation: *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella*

species, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*\*, *Pseudomonas aeruginosa*, *Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species\*.

\*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Piperacillin: It is approved for treatment of skin infections due to the following organisms (however, there is no specification as to whether the infections are to be complicated or uncomplicated): *E. coli*, *Klebsiella* sp, *Serratia* sp, *Acinetobacter* sp, *Enterobacter* sp, *Pseudomonas aeruginosa*, indole-positive *Proteus* sp, *Proteus mirabilis*, *Bacteroides* sp, including *B. fragilis*, anaerobic cocci, and enterococci.

The following agents have been approved in the United States specifically for the treatment of *uncomplicated* skin and skin structure infections:

Azithromycin: *S. aureus*, *S. pyogenes*, or *S. agalactiae*.

Clarithromycin: *S. aureus*, and *S. pyogenes*.

Dirithromycin: *S. aureus* (methicillin-susceptible strains).

Cefaclor: *S. aureus* (methicillin-susceptible strains).

Cefepime: *S. aureus* (methicillin-susceptible strains only) or *S. pyogenes*.

Cefprozil: *S. aureus* (including penicillinase-producing strains) and *S. pyogenes*.

Cefuroxime:

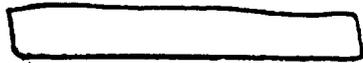
Ceftin™ *S. aureus* (including beta-lactamase-producing strains), and *S. pyogenes*.

Ciprofloxacin: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, (methicillin susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

(Note: Ciprofloxacin's label has a table listing dosages guidelines per indication and it has an entry under Skin and Skin Structure for "Severe/Complicated." It is believed that the use of the term "complicated" in this label is different than how it is presently intended in the Points to Consider document, as it precedes the existence of the document.)

Levofloxacin: *S. aureus* or *S. pyogenes*.

Loracarbef: *S. aureus* (including penicillinase-producing strains) or *S. pyogenes*.

 Piperacillin resistant, beta-lactamase producing strains of *S. aureus*.

Ofloxacin: *S. aureus*, *S. pyogenes*, and *P. mirabilis*.

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**Appendix B – List of Investigators**

Table 4 from Applicant Study Report (p. 22)

**List of Investigators**

Site #	Investigator	Affiliation	Location
001	Anthony Puopolo, M.D.	Milford Emergency Associates, Inc.	Milford, MA
002	Frank Maggiacomo, D.O.	Silver Lake Medical, Inc.	Providence, RI
003	Ian Baird, M.D.	Remington-Davis, Inc.	Columbus, OH
004	Frederick Bieberdorf, M.D.	HealthQuest Therapy and Research Institute	Austin, TX
005	Alicia Bucko, D.O.	Academic Dermatology Associates	Albuquerque, NM
006	Albert Cattell, M.D.	ClinSite	Ypsilanti, MI
007	John Champlin, M.D.	Clinical Research, Inc.	Carmichael, CA
008	George Day, M.D.	Family Medical Clinic of Harrogate, P.C.	Harrogate, TN
009	Meera Dewan, M.D.	N/A	Omaha, NE
010	John Ervin, M.D.	The Center for Pharmaceutical Research	Kansas City, MO
011	Donald Fraser, M.D.	N/A	Charlotte, NC
012	Lisa Gidday, M.D.	Arapahoe Internal Medicine	Littleton, CO
013	Robert Glenn, M.D.	Unifour Medical Research Associates	Hickory, NC
014	Bernard Goffe, M.D.	Novum, Inc.	Seattle, WA
015	Stephen Green, M.D.	Hampton Roads Medical Specialists, P.C.	Hampton, VA
016	Adelaide Hebert, M.D.	Dermatology Clinical Research Center	Houston, TX
017	Robert Holloway, M.D.	InSite Clinical Trials, L.L.C.	Atlanta, GA
018	Terry Jones, M.D.	J & S Studies, Inc.	Bryan, TX
019	Anne Lucky, M.D.	Dermatology Research Associates	Cincinnati, OH
020	Michael Faircloth, M.D.	Brookwood Leeds Clinic	Leeds, AL
021	Phillip McElvaine, M.D.	El Paso Emergency Physicians Group	El Paso, TX
022	Barry Miskin, M.D.	Palm Beach Research Center	West Palm Beach, FL
023	Gary Post, M.D.	Denver Drug Research Associates, Inc.	Englewood, CO
024	Robert Rhoades, M.D.	Medical Parameters	Martinez, GA
025	Jeffrey Rosen, M.D.	Clinical Research of South Florida	Coral Gables, FL
026	Joel Shavin, M.D.	Gwinnett Clinical Research Center, Inc.	Snellville, GA
027	Malcolm Sperling, M.D.	Edinger Medical Group, Inc.	Fountain Valley, CA

Indication: Uncomplicated Skin/Skin Structure Infections

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Site #	Investigator	Affiliation	Location
028	Gary Tarshis, M.D.	Express Care Plus	Colorado Springs, CO
029	Kevin Wingert, M.D.	Sierra Medical Research	Fresno, CA
030	Timothy Hodges, D.O.	Advanced Clinical Research	Boise, ID
031	John Richards, M.D.	Advanced Clinical Research	Salt Lake City, UT

---

Four sites (003, 006, 011, and 017) did not enroll any patients

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**Appendix C - Adverse Clinical Events, All-Causes**

Table 12.2.1 from Study Report

**Adverse Clinical Events<sup>a</sup> of All Causes, All Treated Patients (Protocol AI420-005)**

Adverse Clinical Event <sup>a</sup>	Number of Patients							
	Gatifloxacin N = 202				Levofloxacin N = 205			
	Related	Not Related	Unknown Relationship	Total	Related	Not Related	Unknown Relationship	Total
Any Adverse Event	70 (35)	30 (15)	2 (1)	104 <sup>b</sup> (51)	58 (28)	44 (21)	0	103 <sup>b</sup> (50)
Nausea	16 (8)	1 (<1)	0	17 (8)	16 (8)	2 (<1)	0	18 (9)
Headache	6 (3)	8 (4)	0	14 (7)	10 (5)	8 (4)	0	18 (9)
Diarrhea	12 (6)	1 (<1)	0	13 (6)	12 (6)	1 (<1)	0	13 (6)
Dizziness	7 (3)	3 (1)	0	10 (5)	4 (2)	2 (<1)	0	6 (3)
Pruritus	5 (2)	4 (2)	1 (<1)	10 (5)	4 (2)	1 (<1)	0	6 <sup>b</sup> (3)
Vaginitis	9 (8)	0	0	10 <sup>c</sup> (9)	4 (4)	0	0	4 (4)
Pain Abdomen	6 (3)	2 (<1)	1 (<1)	9 (4)	4 (2)	1 (<1)	0	5 (2)
Pain	2 (<1)	5 (2)	0	8 <sup>b</sup> (4)	5 (2)	7 (3)	0	12 (6)
Rash	4 (2)	2 (<1)	0	6 (3)	3 (2)	2 (1)	0	5 (2)
Accidental Injury	0	5 (2)	0	5 (2)	0	3 (1)	0	3 (1)
Asthenia	5 (2)	0	0	5 (2)	0	2 (<1)	0	2 (<1)
Drainage	2 (<1)	3 (1)	0	5 (2)	1 (<1)	9 (4)	0	10 (5)
Constipation	2 (<1)	1 (<1)	1 (<1)	4 (2)	1 (<1)	0	0	1 (<1)

Indication: Uncomplicated Skin/Skin Structure Infections

Revision date: 7-Nov-99

Adverse Clinical Event <sup>a</sup>	Number of Patients							
	Gatifloxacin N = 202				Levofloxacin N = 205			
	Related	Not Related	Unknown Relationship	Total	Related	Not Related	Unknown Relationship	Total
Vomiting	2 (<1)	2 (<1)	0	4 (2)	1 (<1)	0	0	1 (<1)
Nervousness	3 (1)	0	1 (<1)	4 (2)	1 (<1)	0	0	1 (<1)
Vasodilatation	2 (<1)	2 (<1)	0	4 (2)	0	3 (1)	0	3 (1)
Lesion	0	3 (1)	0	3 (1)	2 (<1)	5 (2)	0	7 (3)
Erythema	0	2 (<1)	0	2 (<1)	2 (<1)	5 (2)	0	gb (4)
Pharyngitis	0	5 (2)	0	5 (2)	0	5 (2)	0	5 (2)
Insomnia	1 (<1)	1 (<1)	0	2 (<1)	5 (2)	0	0	5 (2)
Myalgia	0	0	0	0	0	3 (1)	1 (<1)	4 (2)
Edema	0	0	0	0	1 (<1)	5 (2)	0	6 (3)
Induration Wound	0	2 (<1)	0	2 (<1)	0	5 (2)	0	5 (2)

<sup>a</sup> All adverse clinical events occurring in 2% or more of the patients in either treatment group.

<sup>b</sup> The discrepant total reflects missing information re: relationship to study drug.

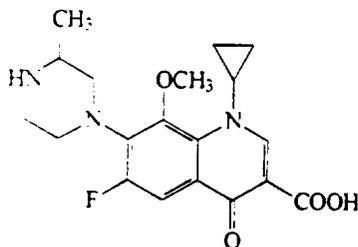
<sup>c</sup> % calculated based on women only.

## 8.5 Medical Officer Review of NDA 21-061: Gatifloxacin (Tequin™) for the treatment of uncomplicated urinary tract infection

Date Submitted: 28 December 1998  
Date Received: 29 December 1998  
Date Assigned: 29 December 1998  
Date Completed: 15 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<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> · 1.5 H<sub>2</sub>O  
Molecular weight - 402.42 (sesquihydrate)



Molecular structure -

1.5 H<sub>2</sub>O

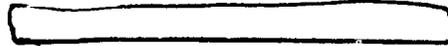
Drug Class: 8-methoxyfluoroquinolone antibacterial

Indication: Uncomplicated Urinary Tract Infections

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

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

Related NDA: 21-062



Indication: Uncomplicated Urinary Tract Infections

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## Executive Summary

Bristol-Myers Squibb has submitted NDA 21-061 for seven indications. Treatment of uncomplicated urinary tract infection (cystitis) is one of the indications and the subject of this review. 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. The "Indications and Usage" section of the proposed label states that gatifloxacin will be utilized for the treatment of:

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

Currently, the oral quinolone antimicrobials that are approved for the treatment of uncomplicated urinary tract infection include:

1. **Ciprofloxacin:** for acute, uncomplicated cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus*.
2. **Floxin:** for uncomplicated urinary tract infection caused by *Citrobacter diversus*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* or *Pseudomonas aeruginosa*.
3. **Maxaquin:** for uncomplicated urinary tract infection caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Staphylococcus saprophyticus*.
4. **Noroxin:** for uncomplicated urinary tract infection caused by *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Proteus vulgaris*, *Streptococcus agalactiae*.
5. **Penetrex :** for uncomplicated urinary tract infection caused by *Escherichia coli*, *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

**Reviewer's note: The aforementioned quinolones that have been approved for**

**Indication: Uncomplicated Urinary Tract Infections**

*the treatment of uncomplicated urinary tract infection have not been approved as single dose regimens. A single dose regimen, such as the single 400 mg dose of gatifloxacin used in this study, has inherent advantages with respect to compliance.*

*It is also important to note that gatifloxacin is excreted as unchanged drug primarily by the kidney with more than 70% of an administered gatifloxacin dose recovered as unchanged drug in the urine within 48 hours following oral administration. The mean elimination half-life of gatifloxacin ranges from 7.1 to 8.4 hours respectively after a single oral dose and in fact the urine levels of the drug at 72 hours are still well above the MIC for all uropathogens especially E.coli. The high urinary excretion rate of gatifloxacin, coupled with its long half-life, make this drug well suited to daily dosing and single-dose therapy.*

The clinical data in the applicant's-NDA submission for this indication were derived from one trial. It was a multi-center, randomized, double-blind, active-control trial. There were 57 outpatient centers recruited in the United States, 50 centers enrolled patients. A table listing of the study centers is provided in Appendix 1. The table below (Table 1) outlines the study design of the trial.

**Table 1: Study Design**

Study Number	Study Design	Start-Completion Dates	Number of Subjects	Age Range	Dose and Duration of Treatment
A1420-010	Randomized, double blind, multicenter, Phase II/III study	27 June 1997-4 June 1998	1334 enrolled, 1323 received at least one dose of therapy	18 years of age or older	Gatifloxacin 400 mg qd x 1 dose or Gatifloxacin 200 mg qd x 3 days or Ciprofloxacin 100 mg bid x 3 days

In the microbiologically evaluable population, the applicant reported the rates among patients for sustained eradication of all uropathogens in the three treatment groups

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were equivalent. Ten percent of patients overall had a recurrence of the original uropathogen. Clinical cure rates were similar between all three treatment groups for all analysis populations (see Table 2 below).

**Table 2: Eradication Rates by Analysis Population<sup>1</sup>**

Analysis Population	Number Eradicated		Number of Patients (%)		97.5% Confidence Interval (gati 1D - cipro)	97.5% Confidence Interval (gati 3D - cipro)
	Gatifloxacin 400 mg x 1D N = 436	Gatifloxacin 200 mg x 3D N = 443	Ciprofloxacin N = 444			
All Treated	186/223 (83%)	198/223 (89%)	188/227 (83%)			
Clin Eligible	183/218 (84%)	194/219 (89%)	183/221 (83%)			
Clin Evaluable	181/205 (88%)	190/207 (92%)	179/203 (88%)			
Micro Evaluable	181/202 (90%)	190/201 (95%)	179/201 (89%)			
Applicant Analysis						

The following table (Table 3) and comments are taken from Dr. Nancy Silliman's FDA statistical review of uncomplicated urinary tract infection. Table 3 summarizes the bacteriologic response results stratified by site for the various analysis populations. Confidence intervals are calculated using a Mantel-Haenszel stratified approach. Results are generally consistent with those from the unstratified confidence intervals.

**Table 3: Stratified 97.5% Confidence Intervals by Analysis Population<sup>1</sup>**

Analysis Population	97.5% Confidence Interval for the Difference in Eradication Rates Stratified by Site	
	Gatifloxacin 1D - Ciprofloxacin	Gatifloxacin 3D - Ciprofloxacin
All Treated Patients	(-7.3%, 9.6%)	(-2.7%, 13.5%)
Clinically Eligible Patients	----	----
Clinically Evaluable Patients	----	----
Microbiologically Evaluable Patients	(-6.9%, 9.4%)	(-1.6%, 14.0%)
FDA analysis.		

Table 4 summarizes eradication rates using a very conservative imputation method for missing values. Missing ("unable to determine") gatifloxacin values are imputed to be failures and missing ciprofloxacin values are imputed to be cures. Given how conservative the imputation rule is, results in Table 4 are impressively robust for the 3 day regimen and reasonable for the 1 day regimen. Both lower bounds remain above -10% for the

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gatifloxacin regimens. This is due, in part, to the fairly good follow-up rates in this study. Only approximately 6-7% of patients with a baseline pathogen  $10^5$  cfu/mL had responses of "unable to determine".

Note that the sponsor's imputation rule was to impute all missing values as failures. In an equivalence trial, it is not clear that the sponsor's imputation rule is actually as conservative as they state (e.g., a large amount of missing data could lead to a false conclusion of equivalence simply because missing values are treated the same in both arms).

**Table 4:**  
**Eradication Rates by Analysis Population - Conservative Imputation of Missing Values\*1**

Analysis Population	Gatifloxacin		Number Eradicated Number of Patients (%)		Confidence Interval**	
	400 mg x 1D N = 436	200 mg x 3D N = 443	Gatifloxacin 200 mg x 3D N = 444	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%)	204/227 (90%)	198/221 (90%)	(-14.1%, 1.1%)	(-8.0%, 5.9%)
Clinically Eligible	183/218 (84%)	194/219 (89%)	198/221 (90%)	198/221 (90%)	(-13.3%, 2.0%)	(-8.1%, 6.1%)

\*Assuming that missing gatifloxacin values are failures and missing ciprofloxacin values are cures.  
\*\*Calculated using the normal approximation to the binomial with the continuity correction.  
1FDA analysis

**FDA Statistical Reviewer's Conclusions:**

Efficacy results for this study are fairly robust and suggest that both gatifloxacin regimens are similar to ciprofloxacin in terms of efficacy. The results for the 3 day gatifloxacin regimen are somewhat more promising and robust than those for the 1 day gatifloxacin regimen. In this study, it is unlikely that conclusions would change for the 3 day gatifloxacin regimen if we could perform an analysis to account for the dynamic randomization used. Given that we are already using the conservative [redacted] adjustment, results also seem reasonable for the 1 day regimen.

**Safety:**

The overall incidence of adverse drug-related clinical events was low. Most of the drug-related adverse events were mild to moderate in severity. Symptoms were classified as severe in only 1-2% of all treated patients. There were eight serious adverse events in the study, but none were drug related. The 17 patients that were

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discontinued due to adverse clinical events were nearly equally distributed among the treatment groups. Nausea, vomiting and/or headache were the most common drug related reasons for discontinuation. There were no deaths in the study.

#### Special Populations

There were no differences observed in the efficacy rates or safety profile between the treatment groups with respect to gender, age or ethnic group.

#### Recommendation of the reviewing medical officer:

The 400 mg single dose regimen of gatifloxacin will enhance patient compliance. The 200 mg/day three day regimen of gatifloxacin may minimize potential risks associated with adverse effects seen at the C<sub>max</sub> for gatifloxacin. Safety, efficacy and relapse rates were similar for the two dose regimens.

Approval of both the single-dose and three day dosing regimens of gatifloxacin to treat uncomplicated urinary tract infection (cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. There was an insufficient number of uncomplicated urinary tract infections due to *Staphylococcus saprophyticus* to support the indication for treatment of this organism.

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### Review Team

Regulatory Project Management Officer:	Brenda Atkins, B.S. Dolores Bernato, R.N., M.N.
Chemistry Reviewer:	John Smith, Ph.D.
Microbiology Reviewer:	Sousan Altaie, Ph.D. Peter Dionne, Ph.D.
Pharmacokinetics/Biopharmaceutics Reviewer:	Kathleen Uhl, M.D. Philip Colangelo, Ph.D.
Pharmacotoxicologist Reviewer:	Amy Ellis, Ph.D.
Biometrics Reviewer:	Nancy Silliman, Ph.D.
Medical	
Medical Reviewer:	R. Tiernan, M.D.
Lead Medical Reviewer:	J. Korvick, M.D., M.P.H.
Medical Team Leader:	M. Cavallé-Coll, M.D., Ph. D.

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**8.5.1 A Randomized, Double-Blind, Multicenter, Phase II/III Comparison Of Two Dose Regimens Of Gatifloxacin To Ciprofloxacin In The Treatment Of Women With Acute, Uncomplicated Urinary Tract Infection (A1420-010)**

*Reviewer's note: Much of the following description of the study in this review, is taken directly from the Applicant's electronic submission. Reviewer comments will be highlighted in italics, and efficacy and safety analyses performed by FDA will be marked as such.*

**8.5.1.1 Efficacy Evaluation**

**INVESTIGATORS:** Fifty investigators.

**STUDY CENTERS:** Fifty study centers in the United States.

*Reviewer's note: Because of the nature of the indication, this study was conducted in outpatient clinics as opposed to a large university-based inpatient setting.*

**STUDY PERIOD:** First patient enrolled 27 June 1997. Last patient last visit was 04-June-1998.

**CLINICAL PHASE:** II/III

**8.5.1.1.1 Study Design and Objectives**

**OBJECTIVES:** 1) To compare the efficacy and safety of gatifloxacin at a dose of 200 mg once a day (QD) x 3 days to ciprofloxacin at a dose of 100 mg twice a day (BID) x 3 days; 2) To assess the efficacy and safety of a single 400 mg dose of gatifloxacin compared to ciprofloxacin at a dose of 100 mg BID x 3 days.

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**Reviewer's note:** *Ciprofloxacin is approved for the treatment of acute uncomplicated cystitis in females at the dosage of 100 mg po every 12 hrs. and consequently serves as an adequate control.*

**METHODOLOGY:** This was a double-blind comparative study.

**Reviewer's note:** *Please see the description of the dynamic randomization algorithm, the reference for this algorithm, and the statistical reviewer's comment concerning the use of dynamic randomization in an active-controlled equivalence trial given in the description of Study 420-005 (uncomplicated skin and soft tissue infections).*

#### **Protocol Amendment**

A medical history, physical exam, measurement of vital signs, clinical signs and symptoms, urine cultures, assessment of pyuria, and laboratory profiles were obtained within 48 hours prior to treatment. The Test of Cure Visit was made at Day +4 to +11 post-treatment and an extended follow-up was planned at Day +25 to +50 post-treatment for those patients who had a bacteriologic response of eradication at the Test of Cure Visit.

**Reviewer's comment:** *The original test of cure was to be at day +5 to +9 and the extended follow-up visit at day +29 to +42. The study visit windows were changed by the Applicant prior to unblinding the study. These changes in study visit dates were agreed to by the Division.*

#### 8.5.1.1.2 Eligibility Criteria

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Only female patients 18 years of age or older with clinical evidence (i.e., dysuria, urgency and frequency of urination, suprapubic pain, pyuria) of acute, uncomplicated urinary tract infection (UTI) with no presumptive evidence of upper urinary tract infection were eligible for enrollment.

Documentation of pyuria was defined by either a dipstick test positive for leukocyte esterase or 10 WBC/mm<sup>3</sup> in an unspun urine specimen or 5 WBC/HPF of resuspended, unstained urine sediment.

**Indication: Uncomplicated Urinary Tract Infections**

***Reviewer's note:*** In order to be considered microbiologically evaluable, patients had to satisfy both the clinical criteria (dysuria, urgency, frequency and/or suprapubic pain without evidence for a complicated UTI) and microbiologic criteria consisting of both pyuria as defined above and urine culture with  $\geq 10^5$  organisms. Patients had to have both a pre- and post-treatment/test of cure visit (Day 4+ to +11). The culture post-treatment had to demonstrate at least a one log decrease in growth from  $\geq 10^5$  to  $< 10^4$  of the original bacterial pathogen.

For women of childbearing potential:

- A documented negative serum or urine pregnancy test (minimum sensitivity 25 IU/L of -HCG) within 48 hours prior to the start of study medication;
- A signed agreement to use an effective method of contraception from initiation of study medication until the end of participation in the study.

Patients were to be excluded if they met any of the following criteria at the time of randomization:

- Three or more episodes of urinary tract infection in the previous 12 months;
- Presence of overt pyelonephritis;
- Underlying structural or functional defect of the urinary system, including obstructive uropathy, chronic interstitial nephritis, chronic urethritis, reflux, recent (previous 10 days) instrumentation, urinary retention or incontinence;
- Presence of an indwelling catheter;
- Receipt of any systemic antibiotic therapy (with documented [i.e., in the package insert] activity against the pathogen) within the 14-day period prior to randomization, or likelihood of receiving other presumably effective systemic antibiotics during randomization in the study;
- Current clinically significant hepatic disease (i.e., ALT and/or AST and/or total bilirubin 3 times the upper limit of normal);
- Known renal insufficiency (e.g., serum creatinine 1.5 mg/dL or requiring renal

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- dialysis);
- Previously diagnosed disease(s) of immune function (e.g., AIDS or history of clinical manifestations of HIV infection, neutrophil count  $<1000/\text{mm}^3$ );
  - Serious gynecological problems;
  - Previously received treatment in any gatifloxacin clinical trial;
  - History of a serious hypersensitivity reaction to any fluoroquinolone compound;
  - Malabsorption syndromes or other gastrointestinal disturbances affecting drug absorption;
  - Diseases which, in the opinion of the investigator, might have a bearing on the outcome of the study;
  - Pregnancy and/or lactation.

-The rationale for these exclusions included:

- UTI in women with serious gynecological problems, patients with structural abnormalities, and compromised hosts are considered "complicated";
- Pyelonephritis treatment should be longer than 3 days;
- Significant laboratory abnormalities may compromise patient safety;
- Patients in previous gatifloxacin trials might harbor resistant organisms;
- The effect of gatifloxacin on developing children is unknown.

*Reviewer's note: Fluoroquinolones are currently not recommended for use in children because of concern over the potential for arthropathy and osteochondrodystrophy demonstrated in preclinical studies in juvenile animals.*

8.5.1.1.3 Description of Patients Enrolled in the Study

8.5.1.1.3.1 Number of Patients Enrolled

**NUMBER OF PATIENTS:** The target enrollment was 1,300 patients. Most sites contributed between 10 and 40 patients. There were 10 sites that contributed more

**Indication: Uncomplicated Urinary Tract Infections**

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than 50 patients, and 15 sites that contributed less than 10 patients.

**Reviewer's note:** All study sites were in the United States. When study results were evaluated by site there was no overall change in the results of the analysis. (See APPENDIX 1 for a list of the study sites).

#### 8.5.1.1.3.2 Patient Demographic Data

##### Demography and Patient Characteristics

Of the 1323 treated patients, the distribution of all demographic characteristics were comparable (Table 5) across all groups. All of the patients were female and most of the patients were white. The mean age overall was 39 years.

**Table 5: Demography, All Treated Patients<sup>1</sup>**

Characteristic	Gatifloxacin 400 mg QD single dose N = 436	Gatifloxacin 200 mg QD x 3 days N = 443	Ciprofloxacin 100 mg BID x 3 days N = 444	Total N = 1323
<u>Race [(%)]</u>				
White	326 (75)	330 (74)	330 (74)	986 (75)
Black	47 (11)	47 (11)	58 (13)	152 (11)
Oriental	7 (2)	10 (2)	3 (<1)	20 (2)
Hispanic/Latino	56 (13)	54 (12)	51 (11)	161 (12)
Other	0	2 (<1)	2 (<1)	4 (<1)
<u>Age (years)</u>				
Mean	40	38	39	39
Median	37	35	36	36
Minimum/maximum	18 - 88	18 - 88	18 - 86	18 - 88
<u>Weight (kg)</u>				
Mean	72.1	71.5	70.2	71.3

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Median	68.0	67.1	66.2	67.6
Minimum/maximum	44 - 146	36 - 172	40 - 146	36 - 172
Not Recorded	2	4	1	7

## 1. Applicant Analysis

**Reviewer's note:** *The treatment arms in this study were similarly balanced by age, ethnicity and weight.*

## 8.5.1.1.3.3 Distribution of Patients

## Definitions:

There were four study populations of interest:

1. **All Treated Patients:** All patients known to have received at least one dose of study drug.
2. **Clinically Eligible Patients:** All treated patients who had at least one of the following signs/symptoms at the pre-treatment visit: dysuria, urgency, frequency, suprapubic pain documentation of pyuria; no evidence of upper urinary tract infection.
3. **Clinically Evaluable Patients:** All eligible patients who had the following:
  - a. received at least one full day of treatment with study drug (i.e., 2 doses);
  - b. pre-treatment urine culture positive (i.e.,  $10^5$  cfu/mL) for a uropathogen that was susceptible to both study drugs at test of Cure Visit;
  - c. no other presumably effective systemic antimicrobial agent between pre-treatment and the test of cure visit.
4. **Microbiologically Evaluable Patients:** All clinically evaluable patients who had a quantitative urine culture performed at the test of cure visit. In addition, a secondary analysis was performed on patients in this group who had a pre-treatment uropathogen at  $10^3$  cfu/ml.

**Table 6: Distribution of Patients in Study Populations and Reasons for Exclusion<sup>1</sup>**

Study Population	Reason Excluded	Number of Patients			Total
		Gatifloxacin 400 mg QD single dose	Gatifloxacin 200 mg QD x 3 days	Ciprofloxacin 100 mg BID x 3 days	
All Treated		436	443	444	1323
Eligible		424	433	435	1292

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Ineligible	12	10	9	31
Complicating Factors for UTI	6	5	4	15
Did not have any of required signs/symptoms	3	1	1	5
>3 UTI past 12 months	1	2	2	5
No documentation of pyuria	2	1	1	4
Vaginitis mimicing UTI	0	1	1	2
Clinically Evaluable	207	208	203	618
Clinically Unevaluable	229	235	241	705
Colony Count <105 cfu/mL	200	203	207	610
No Test of Cure Visit or Visit Outside Study Windows	12	18	19	49
Patient Ineligible	12	10	10	32
Less than one full day of therapy	3	2	2	7
Other Systemic Antimicrobial Administered before TOC visit	2	1	2	5
Pathogen Resistant Pre-treatment	0	1	1	2
Microbiologically Evaluable	202	201	201	604
Microbiologically Unevaluable	234	242	243	719
Clinically Unevaluable	229	235	241	705
No Test of Cure Visit Culture	5	6	2	13
Pathogen Resistant Pre-treatment	0	1	0	1
Applicant Analysis				

The majority (75%) of patients were white. The median age was 39 years (range: 18 - 88). Most of the patients (72%) had a history of previous urinary tract infections, and 40% had between 1-3 episodes of UTI's in the past 12 months. The general medical history of All Treated Patients was comparable between treatment groups. There was a diversity of clinical symptoms at the time of presentation of the urinary tract infection; the most common symptoms were urinary frequency, urgency, and dysuria. All but four All Treated Patients in the study met the qualifications for pyuria. No patient in any group received pre-treatment antibiotic therapy.

There were 711 pathogens isolated pre-treatment from All Treated Patients with colony counts of 105 cfu/mL. The most common isolate present was *E. coli* (535 isolates). The next most frequent uropathogen was *K. pneumoniae* (35 isolates).

This was a blinded study. All patients were evaluated in clinic, satisfied the signs and symptoms for uncomplicated UTI, demonstrated pyuria, cultures were obtained and they were treated with study drug. However, on subsequent review of the pre-treatment cultures,

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610 patients were considered clinically unevaluable because they did not satisfy the criteria for pre-treatment isolation of a pathogen at  $>10^5$  cfu/ml. (See Table 6 above)

Over 90% of patients in each treatment arm took study drug (and/or placebo) for exactly three days. Another 6-7% of patients in each arm received 4 days of study therapy.

There were five patients in the All Treated Population that received antibacterial therapy with presumptive efficacy against the pre-treatment pathogen before the Test of Cure Visit. They were considered clinically/microbiologically unevaluable ( see Table 6 above)

Table 2, in the Executive Summary, shows the bacteriologic response rates for the four analysis populations. Eradication rates are slightly lower in the clinically eligible and all treated patients as missing values were imputed to be failures. In all populations, both gatifloxacin regimens were considered to be equivalent to ciprofloxacin.

The "All Treated" population was utilized for the safety evaluation.

***Reviewer's note: I concur with the applicant's analysis of patient distribution presented in Table 6.***

#### 8.5.1.1.4 Discontinuation and Clinical Follow-up

There was no provision for dose modifications reductions or temporary discontinuations of medication in this protocol.

***Reviewer's note: Duration of antimicrobial therapy in this trial was "short course" i.e. 3 days. Consequently, if adverse events occurred, the medication was just discontinued. Laboratory abnormalities would not have been detected until after the course of therapy was complete (see Table 7 which outlines study procedures).***

Table 7: Study Procedures

Procedure	Pre-treatment (within 48 hours prior to dosing)	End of Treatment Contacta (Day 3)	Post-treatment Visit (Days +4 to +11)	Extended Follow-up (Days +25 to +50)
Informed Consent	X			
Inclusion/Exclusion	X			

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Medical History	X	-	-	-
Physical Exam	X	Xc	X	X
Vital Signs <sup>b</sup>	X	Xc	X	X
Clinical Signs and Symptoms	X	X	X	X
Cultures/Subculture (Urine)	X	Xc	X	X
Assessment for Pyuria	X	Xc	X	X
Laboratory Tests	X	Xc,d	Xd	Xc,d
Assess Adverse Events	-	X	X	X
Assess Medication Use	-	X	X	-
Pregnancy Test	X	-	X	-

a Telephone contact. If not clinically improved, the patient was to be scheduled for an immediate office visit, at which time all of the procedures listed for the initial post-treatment visit (Day -5 to Day +9) were to be performed.

b Blood pressure, pulse, respiratory rate, temperature.

c If clinically indicated.

d Abnormal test results were to be repeated until they returned to pre-treatment levels or were deemed to be unrelated to study drug treatment by the investigator.  
(Reference vol 15, p 37 NDA Applicant NDA submission)

#### Removal of Patients from Therapy or Assessment

A patient could be discontinued from the study at any time for any of the following reasons:

- An adverse clinical event;
- Persistence or worsening of signs and symptoms of the acute infection after three days of study drug therapy;
- An intercurrent illness;
- Patient's decision not to participate any further;
- Investigator's decision that discontinuation was in the patient's best interest;

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- A female patient with a positive pregnancy test during study drug therapy (immediate discontinuation);
- Decision by the Sponsor to terminate the study (at some or all sites).

Patients who had a poor clinical response were to be removed from the study and to have the clinical and laboratory procedures specified for the Test of Cure Visit performed before the start of alternative antibiotic therapy. Patients with early symptoms of relapse or new UTI were to have the clinical and laboratory procedures specified for the late assessment visit.

Patients who discontinued study drug because of an adverse clinical event were examined as often as necessary to document that the reaction had subsided and that no sequelae persisted.

Concomitant medications:

Patients were allowed to receive [redacted] up to 48 hours as needed. Patients were not allowed to receive any other presumably effective systemic antibiotic therapy within the time period extending 14 days prior to randomization to the completion of post-treatment procedures.

Twenty-nine patients were administered a concomitant antimicrobial—half received systemic and the other half non-systemic medication. Seven patients received systemic antibacterial agents (4 single dose gatifloxacin, 2 multi-dose gatifloxacin and 1 ciprofloxacin patient) and six of the seven received the antibiotics at 24 hours post-completion of study drug. All patients were considered microbiologically unevaluable and actually five of these seven patients had insufficient colony counts of microorganisms on entry culture that would have disqualified them from being microbiologically evaluable.

#### 8.5.1.1.5 Study Drugs and Randomization Methods

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: 200 mg film-coated tablets of gatifloxacin (Lot No. N96153,

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1319520C) administered QD for 3 days; 400 mg gatifloxacin (Lot Nos. N97004, N97070, N97078) administered as a single dose; Placebo tablets were matched in weight and appearance to gatifloxacin (Lot Nos. N96162, N97116); all study treatment was given orally (PO).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: 100 mg ciprofloxacin hydrochloride tablets (Lot Nos. C97101, C97338, N98013) were administered BID. Placebo tablets were matched in weight and appearance to ciprofloxacin (Lot No. N96129).

#### 1.1.1.1.6 Study Endpoints

#### **CRITERIA FOR EVALUATION:**

**Efficacy analysis:** Clinical and bacteriologic responses were determined from the Test of Cure Visit and included data obtained from Day +4 to Day +11 post-treatment. A **clinical response** of cure included all patients whose signs and symptoms had subsided or improved and did not require additional antibiotic treatment. A clinical response of failure indicated no apparent response to therapy with a continuation or worsening of most/all signs and symptoms. **Bacteriologic response** was determined from the urine cultures obtained at the Test of Cure Visit with the following definitions: eradication- reduction of original infecting pathogen to  $<10^4$  cfu/mL; persistence-  $10^4$  cfu/mL of original pathogen; new infection-  $10^5$  cfu/mL of a pathogen other than baseline pathogen detected after treatment stopped; and unable to determine. The clinical and bacteriologic responses were repeated at an extended follow-up (Day +25 to +50 post-treatment) for those patients who had a bacteriologic response of eradication at the Test of Cure Visit.

#### **OUTCOME EVALUATION:**

##### **Clinical Evaluation:**

Each patient was assigned a clinical response to therapy based upon symptoms at the Test of Cure Visit and at the extended follow-up visit. Clinical response was classified according to the following criteria defined in the approved analytical plan (revised from the original protocol):

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