

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-678

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW

NDA: 21-678	Submission Date(s): October 27, 2003
Brand Name	Tequin® for Oral Suspension
Generic Name	Gatifloxacin
Reviewer	Seong H. Jang, Ph.D.
Team Leader	Phil M. Colangelo, Pharm.D., Ph.D.
Clinical Review Division	DSPIDP (HFD-590)
Sponsor	Bristol-Myers-Squibb
Submission Type; Code	Original NDA
Formulation; Strength(s)	Powder for Oral suspension; 1g/25 mL, 2g/50 mL, 3g/75mL and 4g/100mL
Proposed Indications	All approved indications for Tequin® tablets

I. Executive Summary

On October 27, 2003, the applicant submitted an original NDA for Tequin (gatifloxacin) for Oral Suspension as an alternative to Tequin Tablets which have been marketed under NDA 21-061 since 1999, for the use in adults

Thus, the NDA is to support the use of Tequin for Oral Suspension to treat indications that are currently approved for Tequin Tablets and Injection in adults and, accordingly, the approval of the NDA is mainly dependent upon the bioequivalence of the oral suspension to the tablets.

Two Biopharmaceutics studies were reviewed to evaluate the NDA.

The major findings of the Biopharmaceutics studies are as follows;

- 1. The 90% confidence intervals for the ratio of adjusted geometric means for the primary endpoints AUC_{0-inf} and C_{max} for gatifloxacin were completely contained within the equivalence range of 0.80 to 1.25, indicating that Tequin for Oral Suspension is**

bioequivalent to the currently marketed Tequin Tablets. This data supports the use of Tequin for Oral Suspension to treat indications approved for Tequin Tablets.

2. When compared to administration of the oral suspension under fasted conditions, the extent of oral bioavailability of gatifloxacin, i.e., AUC, was not significantly changed by a high fat meal. However, a high fat meal decreased the rate of oral bioavailability from Tequin Oral Suspension by an average of 25%; mean C_{max} was decreased from 3.12 $\mu\text{g/mL}$ to 2.34 $\mu\text{g/mL}$ and T_{max} was prolonged from 1.25 hr to 4 hr when gatifloxacin POS was administered with a high fat meal compared with when administered under fasted condition. Because AUC_{inf} is considered to be a major determinant for the antibacterial efficacy of fluoroquinolones, it seems appropriate to recommend that gatifloxacin oral suspension can be given without regard to food.

3. Co-administration of gatifloxacin oral suspension with omeprazole did not change the extent of oral bioavailability of gatifloxacin, i.e., AUC, but resulted in a modest decrease (18%) in the rate of oral bioavailability of gatifloxacin, i.e., lower C_{max} (2.57 $\mu\text{g/mL}$ vs. 3.12 $\mu\text{g/mL}$) and prolonged T_{max} (2.25 hr vs. 1.25 hr), compared with gatifloxacin POS alone under fasted condition. Since AUC is a major determinant for antimicrobial efficacy of fluoroquinolones, gatifloxacin POS can be coadministered with omeprazole.

I-1. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation-III (OCPB/DPE-III) reviewed NDA 21-678 submitted on October 27, 2003. The reviewer finds the clinical pharmacology/biopharmaceutics information provided in this NDA to be acceptable.

II. Labeling Comments

Labeling comments from the OCPB reviewer are incorporated into the final label (version 08/03/04) in Appendix 1.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Concurrence

Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Summary of Clinical Pharmacology and Biopharmaceutics Review

Detailed reviews of individual studies are incorporated in Appendix 2.

1. Bioequivalence of Gatifloxacin Powder for Oral Suspension (POS) to Tequin® Tablets (Study AI420098)

_____ a conventional oral suspension formulation of gatifloxacin (20 mg/mL strength) was initially developed (Early POS). Due to _____, it was considered necessary to develop an alternative formulation. Therefore, gatifloxacin/stearic acid _____ was formulated as a powder for oral suspension at a strength of 40 mg/mL (Clinical POS). _____

_____ The study AI420098 was designed to evaluate (a) the relative bioavailability of gatifloxacin/stearic acid 400-mg _____ powder for oral suspension (Clinical POS) to the conventional 400-mg oral suspension (Early POS), and (b) to evaluate the relative bioavailability of both gatifloxacin Clinical POS and Early POS to the marketed gatifloxacin tablet (Tablet). **The results showed that gatifloxacin Early POS, Clinical POS and Tablet satisfied the criteria for bioequivalence to one another (See Table 1).**

Table 1. Statistical analysis results for gatifloxacin C_{max} and AUC_{inf}

Pharmacokinetic Parameter (n = 16)	Adjusted Geometric Mean ^a		Ratio of Adjusted Geometric Means	
	Treatment	Point Estimate	Ratio	Point Estimate (90% C.I.)
C_{max} ($\mu\text{g/mL}$)	A: Tablet			
	B: Early POS	4.14	B : A	0.98 (0.91, 1.05)
	C: Clinical POS	4.05	C : A	0.90 (0.84, 0.97)
		3.74	C : B	0.92 (0.86, 0.99)
AUC_{inf} ($\mu\text{g}\cdot\text{h/mL}$)	A: Tablet			
	B: Early POS	35.7	B : A	1.05 (1.02, 1.08)
	C: Clinical POS	37.6	C : A	0.99 (0.96, 1.02)
		35.3	C : B	0.94 (0.91, 0.97)

^a Adjusted geometric means based on an ANOVA model.

The Clinical POS formulation had a _____ sucrose _____ sucrose-containing formulation of the gatifloxacin/stearic acid _____ was developed (Trade POS; 40 mg/mL) which replaced the Clinical POS formulation in Phase III studies. Based on the Biopharmaceutics Classification System (BCS), FDA granted a biowaiver for conducting bioequivalence studies for the Trade POS versus the Clinical POS and the commercial Tablet (See 3. Dissolution and Biowaiver).

2. Effect of food or omeprazole on pharmacokinetics of gatifloxacin suspension (Study AI420106)

The effect of food or omeprazole on the pharmacokinetics of gatifloxacin, 400 mg, following administration of gatifloxacin/stearic acid — powder for oral suspension (Trade POS) in healthy subjects was assessed. During Period 1, 14 subjects were randomized to receive a single oral dose of Trade POS, 400 mg, under fasted conditions or within 5 minutes of consuming a standard high fat breakfast (945 kcal). The alternate treatment was administered during Period 2. In Period 3, all 14 subjects received omeprazole 40 mg once daily for 6 days and Trade POS, 400 mg, was co-administered on Day 5 under fasted conditions. The results are summarized in Table 2. A high fat meal decreased the rate of oral bioavailability from Tequin Oral Suspension by an average of 25%; mean C_{max} was decreased from 3.12 $\mu\text{g}/\text{mL}$ to 2.34 $\mu\text{g}/\text{mL}$) and T_{max} was prolonged from 1.25 hr to 4 hr when gatifloxacin POS was administered with a high fat meal compared with when administered under fasted condition. However, the extent of oral bioavailability (AUC) was not affected by food, i.e., 26.05 $\mu\text{g}\cdot\text{hr}/\text{mL}$ vs. 29.08 $\mu\text{g}\cdot\text{hr}/\text{mL}$ with 90% confidence interval of (0.82 to 0.98). **Considering that AUC_{inf} is a major determinant for the antibacterial efficacy of fluoroquinolones, it is recommended that gatifloxacin POS can be given without regard to food.**

Co-administration of gatifloxacin oral suspension with omeprazole did not change the extent of oral bioavailability (AUC) of gatifloxacin, i.e., 28.68 $\mu\text{g}\cdot\text{hr}/\text{mL}$ vs. 29.08 $\mu\text{g}\cdot\text{hr}/\text{mL}$ with 90% confidence interval of (0.90 to 1.08), but resulted in a modest decrease in the rate of oral bioavailability of gatifloxacin, i.e., lower C_{max} (2.57 $\mu\text{g}/\text{mL}$ vs. 3.12 $\mu\text{g}/\text{mL}$) and greater T_{max} (2.25 hr vs. 1.25 hr), compared with gatifloxacin Trade POS alone under fasted condition. Since AUC is a major determinant for antimicrobial efficacy of fluoroquinolones, **gatifloxacin POS can be co-administered with omeprazole.**

Table 2. Statistical analysis results for gatifloxacin C_{max} and AUC_{inf}

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Reference (Fasted)	Test Treatment	Point Estimate	90% Confidence Limits
C_{max} ($\mu\text{g}/\text{mL}$)	3.12	High fat meal	2.34	0.75 (0.65, 0.87)
		Omeprazole	2.57	0.82 (0.71, 0.96)
AUC_{inf} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	29.08	High fat meal	26.05	0.90 (0.82, 0.98)
		Omeprazole	28.68	0.99 (0.90, 1.08)

3. Dissolution Specification and Biowaiver

The in vitro dissolution of gatifloxacin for oral suspension, 40 mg/mL is determined by the current USP dissolution procedure using Apparatus 2 (Paddle method). The dissolution medium is 1,000 mL of 0.1 N HCl at 37°C, and a paddle rotation speed of 50 rpm. The specification is — (Q) dissolved in 20 minute.

The biopharmaceutic properties (solubility, permeability, and dissolution) of gatifloxacin were assessed to classify the drug based on the Biopharmaceutics Classification System (BCS). The solubility of gatifloxacin, is pH dependent over the pH range of 1-8, and its minimum solubility is 4.2 mg/mL at pH 7.6 (equals 1050 mg in 250 mL). The approved dose of gatifloxacin is 400 mg in adults; since, the minimum solubility is 1050 mg in 250 mL, gatifloxacin is considered a "highly soluble" drug. The absolute bioavailability of gatifloxacin in healthy adults is 96%, which qualifies it as a "highly permeable" drug, since the absolute bioavailability is greater than 90%. The Trade POS was rapidly dissolved in 1000 mL of aqueous media at pH 1.2 (100% dissolution in 10 minutes) and pH 4.0 (90% dissolution in 20 minutes). Since dissolution was greater than 85% at 30 minutes, the Trade POS was considered to be "rapidly dissolving". Thus, gatifloxacin was determined to be a BCS "Class I" drug.

The Trade POS differs from the Clinical POS only in the sugar content: — for the Trade POS versus ← for the Clinical POS), and hence, the two are anticipated to be bioequivalent. Per the official FDA Meeting Minutes, dated March 14, 2002 (Submission No. 058 to IND No 57,672), FDA granted a biowaiver for conducting bioequivalence studies for the Trade POS versus the Clinical POS and the commercial Tablet.

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 1

Proposed Labeling with OCPB Reviewer Revision

NDA-21-678: Tequin®

(Gatifloxacin; BMS-206584, AM-1155, CG-5501)

Version: August 05, 2004

44 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Appendix 2

Individual Study Reviews

NDA-21-678: Tequin®

(Gatifloxacin; BMS-206584, AM-1155, CG-5501)

1. Randomized, open-label, three-way crossover, relative bioavailability study of gatifloxacin tablet and two gatifloxacin suspension formulations [AI420098]

Ai420098.pdf, pp 1-624

Gatifloxacin (Tequin®) is available for oral and intravenous administration. A conventional oral suspension formulation of gatifloxacin (20 mg/mL strength) was initially developed (Early POS).

, it was considered necessary to develop an alternative formulation. Therefore, gatifloxacin/stearic acid was formulated as a powder for oral suspension at a strength of 40 mg/mL (Clinical POS). This formulation exhibits pH-dependent dissolution, with both the rate and extent of dissolution impaired at pH > 5.2, and hence has minimal dissolution in the mouth but maintains rapid dissolution properties in the acidic pH environment of the stomach.

The present study was designed to evaluate (a) the relative bioavailability of gatifloxacin/stearic acid 400-mg powder for oral suspension (Clinical POS) to the conventional 400-mg oral suspension (Early POS), and (b) to evaluate the relative bioavailability of both gatifloxacin Clinical POS and Early POS to the marketed gatifloxacin tablet (Tablet). The results showed that gatifloxacin Early POS, Clinical POS and Tablet satisfied the criteria for bioequivalence to one another.

Study period: Date first subject enrolled: 21 February 2001

Date last subject completed: 11 March 2001.

Objectives:

The primary objective of this study was to assess the bioavailability of gatifloxacin/stearic acid powder for oral suspension (Clinical POS) relative to the gatifloxacin conventional oral suspension (Early POS).

The secondary objectives of this study were:

- To assess the bioavailability of gatifloxacin Clinical POS relative to the marketed gatifloxacin tablet (Tablet).
- To assess the bioavailability of gatifloxacin Early POS relative to the Tablet.
- To assess the safety and tolerability of gatifloxacin.

Methodology:

This was a randomized, open-label, three-period, three-treatment, crossover study balanced for carryover effects. Healthy volunteers underwent screening evaluations to determine eligibility within 21 days before study enrollment. Subjects were admitted to the clinical facility the evening before dosing (Day -1) for each period. Subjects were randomized to receive one of the three formulations of gatifloxacin according to one of six randomly assigned treatment sequences. During Period 1, subjects received a single oral 400-mg dose of gatifloxacin Tablet (Treatment A), Early POS (Treatment B), or Clinical POS (Treatment C). The alternate treatments were administered during Periods 2 and 3. The washout period

between treatments was at least 7 days. For each treatment period, subjects were confined to the study site until 48 hours post-dose. Blood samples were collected for pharmacokinetic analysis up to 48 hours post-dose. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations were performed at selected times. Subjects were monitored closely for adverse events (AEs) throughout the study.

Study Population and Demographic Data:

A total of 18 subjects who met the eligibility criteria were enrolled in the study. One subject (AI420098-1-3) withdrew consent after randomization; this subject did not receive study drug, and no data were recorded for this subject. Of the 17 subjects who received study drug, 16 (94.1%) completed the study and 1 (5.9%) (Subject AI420098-1-9) discontinued from the study early due to personal reasons.

Eight subjects were male, and 9 were female. There were 15 caucasian and 2 black subjects. Their ages ranged from 20 to 44 years, with an average of 36 years. The weight ranged from 49.5 to 95.9 kg, with an average of 77.9 kg. The height ranged from 158.8 to 185.4 cm, with an average of 173.2 cm. The body mass index (BMI) ranged from 19.5 to 29.0 kg/m², with an average of 26.1 kg/m²

Test Product, Dose and Mode of Administration, Batch Numbers:

Table 1 summarizes study drug information.

Table 1.

Drug	Strength	Formulation	Route	Batch #	Description
Gatifloxacin	400 mg	Tablet	Oral	1319520C1	White, film-coated tablet
Gatifloxacin	20 mg/mL	Early POS	Oral	C99215	White to off-white powder (constitution with water produces a white to off-white suspension)
Gatifloxacin	40 mg/mL	Clinical POS	Oral	C00372	White to off-white powder (constitution with water produces a white to off-white suspension)

Safety Parameters:

Adverse event (AE) information was monitored from the time of study specific informed consent until discharge from the study (AEs reported to the investigator up to 30 days after discharge were also included). AE data were obtained by volunteering of information by the subjects, frequent monitoring, and daily questioning of the subjects by the study staff. **Vital signs** (body temperature, respiratory rate, seated blood pressure, and heart rate), **12-lead electrocardiogram (ECG)**, and **physical examinations** were recorded at screening, before dosing on Day 1 for each treatment period, and at discharge on day 3 of period 3. Blood and urine samples for **hematology, clinical chemistry and urinalysis** were obtained from fasting subjects at screening, before the dosing on Day 1 for each treatment period, and before discharge from the clinical facility on Day 3 of Period 3.

Pharmacokinetic Parameters:

Blood samples (5 ml each) were collected at 0 time (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, 24, 36 and 48 hour after dosing for each treatment. Plasma samples were assayed for gatifloxacin by a validated HPLC/fluorescence method. The lower limit of quantification (LLQ) for this method was 0.01 µg/ml. Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}), area under the concentration-time curve from time zero to the time of the last measurable plasma concentration (AUC_{0-t}) and the apparent terminal half-life ($T_{1/2}$).

Statistical Methods:

Log-transformed AUC and C_{max} of gatifloxacin were analyzed by ANOVA. Point estimates and 90% confidence intervals for treatment differences were derived. The criteria for bioequivalence between two formulations were met if the 90% confidence interval for the ratio of the geometric means of C_{max} and AUC_{0-inf} was contained entirely within the 0.80 to 1.25 interval.

Pharmacokinetic Results:

Mean plasma concentration of gatifloxacin and its relevant pharmacokinetic parameters after administration of 400 mg oral tablet, Early POS, and Clinical POS to healthy subjects were described in Figure 1 and Table 2, respectively.

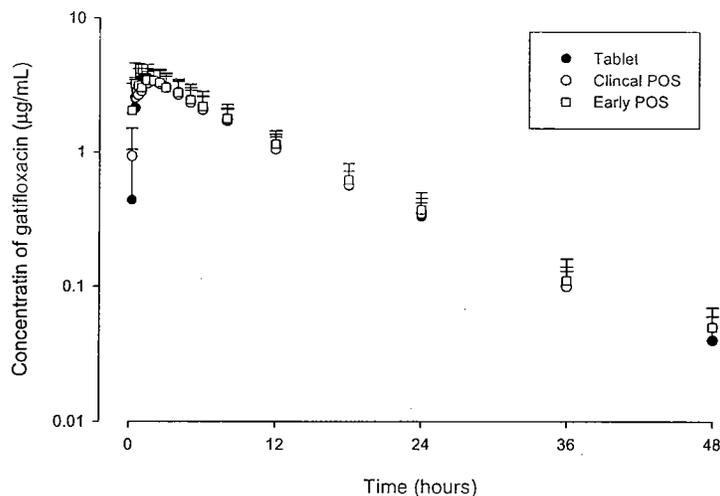


Figure 1. Plasma concentration of gatifloxacin after oral administration of 400 mg tablet, Early POS, and clinical POS to healthy subjects (n=17). Bars represent standard deviation.

Table 2. Pharmacokinetic parameters of gatifloxacin after administration of 400 mg oral tablet, Early POS, and Clinical POS in normal healthy subjects.

Pharmacokinetic Parameter (n = 16)	Treatment A: Tablet	Treatment B: Early POS	Treatment C: Clinical POS
C _{max} (µg/mL) Geometric mean (C.V.%)	4.13 (22)	4.04 (19)	3.70 (19)
AUC(INF) (µg·h/mL) Geometric mean (C.V.%)	36.04 (19)	37.95 (21)	35.57 (20)
AUC(0-T) (µg·h/mL) Geometric mean (C.V.%)	35.60 (19)	37.40 (21)	35.10 (20)
T _{max} (h) Median (Min, Max)	1.3 (0.5, 2.5)	1.0 (0.5, 3.0)	1.5 (0.5, 3.0)
T-HALF (h) Mean (S.D.)	7.5 (0.9)	7.6 (0.9)	7.5 (1.1)

Table 3 summarized statistical analysis results for gatifloxacin C_{max} and AUC_{0-inf}. The relative bioavailability of Clinical POS with respect to Early POS was 94%, of Clinical POS with respect to Tablet was 99%, and of Early POS with respect to Tablet was 105%. The Clinical POS satisfied the criteria for bioequivalence to the Early POS with respect to C_{max} and AUC_{0-INF} (Table 3). The Early POS and Clinical POS formulations also satisfied the criteria for bioequivalence to the Tablet with respect to C_{max} and AUC_{0-INF} (Table 3). The median T_{max} of gatifloxacin Clinical POS was 1.5 hours compared to 1.0 hour and 1.3 hours for Early POS and Tablet, respectively. Mean T_{1/2} was substantially identical (7.5 or 7.6 hours) for all three formulations.

Table 3. Statistical analysis results for gatifloxacin C_{max} and AUC_{0-inf}

Pharmacokinetic Parameter (n = 16)	Adjusted Geometric Mean ^a		Ratio of Adjusted Geometric Means	
	Treatment	Point Estimate	Ratio	Point Estimate (90% C.I.)
C _{max} (µg/mL)	A: Tablet			
	B: Early POS	4.14	B : A	0.98 (0.91, 1.05)
	C: Clinical POS	4.05	C : A	0.90 (0.84, 0.97)
		3.74	C : B	0.92 (0.86, 0.99)
AUC(INF) (µg·h/mL)	A: Tablet			
	B: Early POS	35.7	B : A	1.05 (1.02, 1.08)
	C: Clinical POS	37.6	C : A	0.99 (0.96, 1.02)
		35.3	C : B	0.94 (0.91, 0.97)

^a Adjusted geometric means based on an ANOVA model.

Safety and Tolerability Results:

There were no deaths, other serious adverse events (SAEs), or withdrawals due to AEs related to gatifloxacin. Overall, 23 treatment-emergent clinical AEs that counted (including follow-up) were reported for 11 (64.7%) subjects. Treatment-emergent AEs were reported in 6 of 17 (35.3%) subjects while receiving the Tablet formulation (total of 7 events), in 4 of 17 (23.5%) subjects while receiving the Early POS formulation (total of 6 events), and in 8 of 17 (47.1%) subjects who received the Clinical POS formulation (total of 10 events). All events were mild (14/23, 60.9%) or moderate (9/23, 39.1%) in intensity. Most frequently reported

AEs were nausea, pruritus, flatulence, and headache. All AEs were resolved prior to discharge.

Overall, 45 marked laboratory abnormalities (MAs) were reported; 15, 16, and 14 marked laboratory abnormalities for 10 subjects receiving the Tablet, 12 subjects while receiving the Early POS, and 11 subjects receiving the Clinical POS, respectively. Decreased hemoglobin was the most common hematology marked abnormality, occurring in 4 subjects (23.5%) receiving the Tablet and Early POS, and 5 subjects (29.4%) receiving the Clinical POS. All decreased hemoglobin MAs were Grade I and not clinically significant according to the Investigator. No other laboratory MA was considered to be clinically significant by the Investigator. The distribution of marked abnormalities was generally similar between treatment groups.

No clinically meaningful changes were apparent in physical examinations, vital signs, and ECGs.

Reviewer's Conclusions:

1. The gatifloxacin/stearic acid — suspension formulation (Clinical POS) satisfied the criteria for bioequivalence to the gatifloxacin conventional suspension (Early POS) with respect to C_{max} and AUC_{0-inf} .
2. Early POS and Clinical POS satisfied the criteria for bioequivalence to gatifloxacin Tablet with respect to C_{max} and AUC_{0-inf} .
3. A single oral dose of 400 mg gatifloxacin administered as the Tablet, Early POS, and Clinical POS was generally safe and well tolerated.

Reviewer's comment: Overall, the study design and the interpretation of data are acceptable from the perspective of Clinical Pharmacology and Biopharmaceutics.

**APPEARS THIS WAY
ON ORIGINAL**

2. Effect of high fat meal or omeprazole on the pharmacokinetics of gatifloxacin suspension in healthy subjects [AI420106]

Ai420106.pdf, pp 1-674

The effect of food or omeprazole on the pharmacokinetics of gatifloxacin, 400 mg, following administration of gatifloxacin/stearic acid — powder for oral suspension (intended for commercialization) in healthy subjects was assessed. During Period 1, 14 subjects were randomized to receive a single oral dose of Trade POS, 400 mg, under fasted conditions or within 5 minutes of consuming a standard high fat breakfast (945 kcal). The alternate treatment was administered during Period 2. In Period 3, all 14 subjects received omeprazole 40 mg once daily for 6 days and Trade POS, 400 mg, was co-administered on Day 5 under fasted conditions. A high fat meal decreased the rate of oral bioavailability from Tequin Oral Suspension by an average of 25%; mean C_{max} was decreased from 3.12 $\mu\text{g/mL}$ to 2.34 $\mu\text{g/mL}$ and T_{max} was prolonged from 1.25 hr to 4 hr when gatifloxacin POS was administered with a high fat meal compared with when administered under fasted condition. However, the extent of oral bioavailability (AUC) was not affected by food, i.e., 26.05 $\mu\text{g}\cdot\text{hr/mL}$ vs. 29.085 $\mu\text{g}\cdot\text{hr/mL}$ with 90% confidence interval of (0.82 to 0.98). Considering that AUC_{inf} is a major determinant for the antibacterial efficacy of fluoroquinolones, it is recommended that gatifloxacin POS can be given without regard to food. Co-administration of gatifloxacin oral suspension with omeprazole did not change the extent of oral bioavailability (AUC) of gatifloxacin, i.e., 28.68 $\mu\text{g}\cdot\text{hr/mL}$ vs. 29.08 $\mu\text{g}\cdot\text{hr/mL}$ with 90% confidence interval of (0.90 to 1.08), but resulted in a modest decrease in the rate of oral bioavailability of gatifloxacin, i.e., lower C_{max} (2.57 $\mu\text{g/mL}$ vs. 3.12 $\mu\text{g/mL}$) and greater T_{max} (2.25 hr vs. 1.25 hr), compared with gatifloxacin Trade POS alone under fasted condition. Since AUC is a major determinant for antimicrobial efficacy of fluoroquinolones, gatifloxacin POS can be co-administered with omeprazole.

Study period: Date first subject enrolled: 12 September 2001

Date last subject completed: 11 October 2001.

Objectives:

To assess the effect of food or omeprazole on the pharmacokinetics of gatifloxacin, 400 mg, following administration of gatifloxacin/stearic acid — powder for oral suspension (POS; intended for commercialization) in healthy subjects.

To assess the single dose safety of gatifloxacin, 400 mg, administered as the POS.

Methodology:

This was an open-label, randomized, two-period, two-treatment, crossover study followed by a third treatment period in healthy subjects. The formulation used in this study was gatifloxacin/stearic acid — powder for oral suspension (POS; intended for commercialization), 40 mg/mL. During Period 1, 14 subjects were randomized to receive a single oral dose of Trade POS, 400 mg, under fasted conditions (Treatment A) or within 5 minutes of consuming a standard high fat breakfast (945 kcal) (Treatment B). The alternate

treatment was administered during Period 2. In Period 3, all 14 subjects received omeprazole 40 mg once daily for 6 days and Trade POS, 400 mg, was co-administered on Day 5 (Treatment C) under fasted conditions. The washout period between treatments was at least 7 days. For each treatment period, subjects were admitted to the clinical facility the evening prior to dosing (Day -1) and remained in the facility until 48 hours after dosing. Blood samples were collected for pharmacokinetic analysis up to 48 hours after gatifloxacin administration. Subjects were monitored closely for adverse events throughout the study.

Study Population and Demographic Data:

A total of 14 subjects (9 male, 5 female) were enrolled. All enrolled subjects completed the protocol as designed. The age of the subjects ranged from 25 to 45 years with an average of 34 years. The average height of the subjects was 173.1 cm with a range from 155.2 to 186.0 cm. The weight of the subjects ranged from 57.9 to 90.5 kg with an average of 78.1 kg. The average BMI was 25.9 kg/m² with a range of 20.7 to 28.2 kg/m². There were 5 Black, 4 White, and 4 Hispanic/Latino subjects and 1 Indian subject enrolled in this study.

Test Product, Dose and Mode of Administration, Batch Numbers:

POS containing 40 mg/mL of gatifloxacin was administered orally under fasted conditions, with a high fat meal, or with omeprazole; the batch number for POS was 8MGM140-25. Omeprazole (Prilosec[®] delayed-release capsule, 40 mg, lot number 9362700, AstraZeneca, Wilmington, DE) was obtained from commercial sources.

Safety Parameters:

Safety assessment was based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms, physical examinations, and clinical laboratory tests.

Pharmacokinetic Parameters:

Blood samples (5 ml each) were collected at 0 time (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, 24, 36 and 48 hour after dosing for each treatment. Plasma samples were assayed for gatifloxacin by a validated HPLC/fluorescence method. The lower limit of quantification (LLQ) for this method was 0.01 µg/ml. Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), area under the concentration-time curve from time zero to the time of the last measurable plasma concentration (AUC_{0-t}) and the apparent terminal half-life ($T_{1/2}$).

Statistical Methods:

Log-transformed AUC and C_{max} of gatifloxacin were analyzed by ANOVA. Point estimates and 90% confidence intervals for treatment differences were derived.

Pharmacokinetic Results:

Mean plasma concentration of gatifloxacin and its relevant pharmacokinetic parameters after administration of 400 mg POS to healthy subjects (a) under fasted condition, (b) with high fat meal, and (c) with omeprazole (40 mg QD for 6 days) were described in Figure 1 and Table 1, respectively.

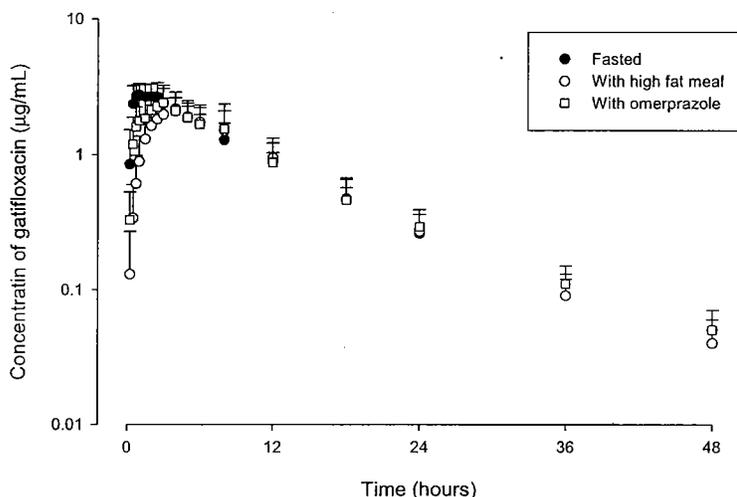


Figure 1. Plasma concentration of gatifloxacin after oral administration of 400 mg Trade POS to healthy subjects (n=14) (a) under fasted condition, (b) with high fat meal, and (c) with omeprazole (40 mg QD for 6 days). Bars represent standard deviation.

Table 1. Pharmacokinetic parameters of gatifloxacin after administration of 400 mg Trade POS to healthy subjects (a) under fasted condition, (b) with high fat meal, and (c) with omeprazole (40 mg QD for 6 days).

Treatment Group	C _{max} (µg/mL) Geometric Mean (CV%)	AUC(0-∞) (µg•h/mL) Geometric Mean (CV%)	AUC(0-T) (µg•h/mL) Geometric Mean (CV%)	T _{max} (h) Median (min. max)	T-1/2 (h) Mean (S.D.)
Fasted (n = 14)	3.12 (19%)	29.08 (29%)	28.88 (29%)	1.25 (0.50, 4.00)	8.49 (1.06)
With high fat meal (n = 14)	2.34 (22%)	26.05 (26%)	25.80 (26%)	4.00 (2.50, 8.00)	8.78 (1.26)
With Omeprazole (n = 14)	2.57 (32%)	28.68 (20%)	28.26 (20%)	2.25 (1.50, 5.00)	9.12 (1.07)

Table 2 summarized statistical analysis results for gatifloxacin C_{max} and AUC_{0-∞}. The geometric mean AUC_{inf} was reduced by 10% in the fed state compared with fasted conditions. Based on the confidence intervals, the food does not seem to affect the extent of oral bioavailability. However, compared with fasted conditions, the median T_{max} was prolonged from 1.25 hr to 4 hr in the fed state and, accordingly, the geometric mean C_{max} in the fed state was reduced by 25% compared with fasted conditions, suggesting that food can affect the rate of oral bioavailability of gatifloxacin.

When gatifloxacin was taken with omeprazole, the geometric mean AUC_{inf} of gatifloxacin was not changed by omeprazole. However, the geometric mean gatifloxacin C_{max} was reduced by 18% when gatifloxacin was taken with omeprazole as compared with administration under fasted conditions, suggesting that co-administration with omeprazole can affect the rate of oral bioavailability of gatifloxacin.

Mean $T_{1/2}$ was substantially identical (8.5 or 9.1 hours) for all treatment groups and comparable with the values obtained from other studies.

Table 2. Statistical analysis results for gatifloxacin C_{max} and AUC_{inf}

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Reference (Fasted)	Test Treatment	Point Estimate	90% Confidence Limits
C_{max} ($\mu\text{g/mL}$)	3.12	High fat meal	2.34	0.75 (0.65, 0.87)
		Omeprazole	2.57	0.82 (0.71, 0.96)
AUC_{inf} ($\mu\text{g}\cdot\text{h/mL}$)	29.08	High fat meal	26.05	0.90 (0.82, 0.98)
		Omeprazole	28.68	0.99 (0.90, 1.08)

Reviewer's comment: It was not addressed whether the difference in the rate of oral bioavailability of gatifloxacin Trade POS, i.e., lower C_{max} and prolonged T_{max} , due to high fat meal is clinically significant or not. However, AUC_{inf} is considered to be a major determinant for the antibacterial efficacy of fluoroquinolones. Thus, based on the above data, i.e., similar AUC_{inf} regardless of food intake, it seems appropriate to recommend that gatifloxacin oral suspension can be given without regard to food.

Safety and Tolerability Results:

There were no deaths or other Serious Adverse Events (SAEs). All 14 subjects completed the study as designed. There were no discontinuations in this study. There were 19 treatment emergent AEs reported in 9 (64.3%) of 14 subjects. Most AEs were categorized in the digestive system (GI bleeding, diarrhea, flatulence, and constipation) **with a slightly higher incidence noted for gatifloxacin under fasted conditions (5 events versus 1 event for gatifloxacin under fed conditions, 2 events for omeprazole alone, and none for omeprazole plus gatifloxacin). Two cases of GI bleeding were observed only when gatifloxacin Trade POS was administered under fasted condition.** The incidence of AEs by body system was similar between the different treatment groups for other AEs, with the incidence generally among 1 to 2 subjects. All AEs resolved prior to discharge. There were 3 marked laboratory abnormalities (MAs) (decreased neutrophils, increased serum potassium, and increased uric acid) reported by 3 subjects, none of which were considered clinically significant according to the Investigator.

No clinically meaningful changes were apparent in physical examinations, vital signs, and ECGs.

Reviewer's comment: Although the safety data are based on the limited number of subjects, it should be noted that the incidence of GI irritation is higher under fasted conditions compared with when gatifloxacin POS Trade was administered with high fat meal. However, based on the discussion with the medical officer, Dr. Ekopimo Ibia, who reviewed other clinical studies, the greater incidence of GI irritation under fasted condition than when administered with a high fat meal does not appear to be a significant safety concern.

Conclusion:

Food Effect

Single doses of 400 mg of gatifloxacin administered as the gatifloxacin Trade POS appeared to be safe and well tolerated in normal healthy subjects. Although gatifloxacin administered under fasted condition caused a higher incidence of GI irritations, including GI bleeding, compared with administered with a high fat meal, it does not appear to be a safety concern considering other clinical study data.

When compared with administered under fasted condition, the extent of oral bioavailability of gatifloxacin, i.e., AUC, was not changed by a high fat meal. However, a high fat meal decreased the rate of oral bioavailability from Tequin Oral Suspension; C_{max} was decreased from 3.12 $\mu\text{g/mL}$ to 2.34 $\mu\text{g/mL}$ and T_{max} was prolonged from 1.25 hr to 4 hr when gatifloxacin POS was administered with a high fat meal compared with when administered under fasted condition. Because AUC_{inf} is considered to be a major determinant for the antibacterial efficacy of fluoroquinolones, it seems appropriate to recommend that gatifloxacin oral suspension can be given without regard to food.

Effect of Omeprazole

Co-administration of gatifloxacin oral suspension with omeprazole did not change the extent of oral bioavailability of gatifloxacin, but resulted in a modest decrease in the rate of oral bioavailability of gatifloxacin, i.e., lower C_{max} (2.57 $\mu\text{g/mL}$ vs. 3.12 $\mu\text{g/mL}$) and greater T_{max} (2.25 hr vs. 1.25 hr), compared with gatifloxacin POS alone under fasted condition. Since AUC is a major determinant for antimicrobial efficacy of fluoroquinolones, gatifloxacin POS can be coadministered with omeprazole.

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/s/

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