CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-721

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-721	Submission Date(s): December 19, 2003
Brand Name	Levaquin®
Generic Name	Levofloxacin
Reviewer	Seong H. Jang, Ph.D.
Team Leader	Phil M. Colangelo, Pharm.D., Ph.D.
Clinical Review Division	DSPIDP (HFD-590)
Sponsor	Johnson & Johnson
Submission Type; Code	Original NDA
Formulation; Strength(s)	Oral solution; 25 mg/mL, 480 mL
Proposed Indications	All approved indications for Levaquin® tablets

I. Executive Summary

On December 19, 2003, the applicant submitted an original NDA for Levaquin® (levofloxacin) Oral Solution. This new oral solution formulation of Levaquin has been developed for use in the treatment of the same approved indications for Levaquin Tablets filed under NDA 20-634 and Levaquin Injection filed under NDA 20-635. Thus, the approval of this current NDA is mainly dependent upon the bioequivalence of the oral solution to the tablets, since no new pivotal clinical efficacy and safety studies using the oral solution formulation were submitted.

In this NDA, two biopharmaceutics studies were submitted and reviewed for the new oral solution: (1) bioequivalence of oral solution vs. Levaquin Tablet; (2) effect of food on the bioavailability of the oral solution. The major findings of these studies are as follows:

1. The Levaquin oral solution was bioequivalent to the commercial Levaquin tablet formulation for both total exposure (AUC_{inf}) and peak exposure (C_{max}). The oral solution formulation was

This bioequivalence data supports the use of the oral solution to treat indications approved for Levaquin Tablets in adults.

2. A high fat meal slightly decreases the rate of absorption of levofloxacin from the oral solution formulation in healthy subjects, as indicated by a prolonged T_{max} (1.5 *vs.* 0.8 hr) and a 25% lower mean C_{max} (3.78 vs. 5.24 μg/mL); however, the extent of

absorption, i.e., AUC, is not affected by food. Based on the results, levofloxacin solution formulation is recommended to be taken 1 hour before or 2 hours after eating.

I-1. Recommendation

The OCPB reviewer finds the clinical pharmacology/biopharmaceutics information provided in this NDA for Levaquin (levofloxacin) Oral Solution to be acceptable.

II. Labeling Comments

Labeling comments from the OCPB reviewers are incorporated into the 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

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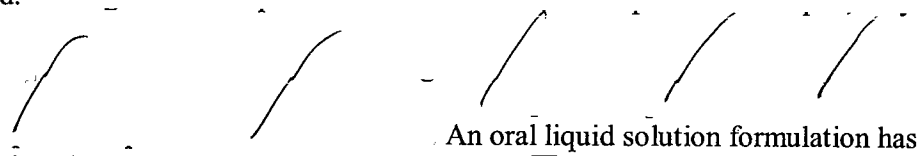
Summary of Clinical Pharmacology and Biopharmaceutics Review

Detailed reviews of individual studies are incorporated in Appendix 2.

1. Bioequivalence of Levofloxacin Oral Solution to Levaquin® Tablets (LOFBO-PHI-116)

Levofloxacin (Levaquin®) is available for oral and intravenous administration. The high absolute bioavailability of the tablet permits an interchangeable oral and intravenous levofloxacin therapy with the same dose. — for adult patients who have difficulty swallowing tablets, a liquid formulation was developed.



An oral liquid solution formulation has been developed — The sponsor intends to market the oral solution formulation for use in adults — The present study was designed to evaluate the bioequivalence of 3 levofloxacin oral formulations: the — formulation — — the newly developed oral solution formulation, and the marketed tablet. **The results showed — ormulations of levofloxacin satisfied the criteria for bioequivalence — (See Tables 1 and 2).**

Table 1. Pharmacokinetic parameters of levofloxacin after administration of 500 mg oral tablet, — and solution in healthy subjects (n=34).

	Tablet	Solution
C_{max} (µg/mL)[a]	5.18±1.52 (2.99 to 8.21)	5.76±1.77 (2.51 to 8.57)
AUC_{inf} (µg·hr/mL)[a]	48.5±12.6 (31.4 to 78.2)	47.8±10.8 (31.9 to 77.5)
T_{max} (hr)[b]	1.5 (0.52 to 4.0)	0.5 (0.25 to 4.0)
$T_{1/2}$ (hr)[a]	6.9±1.3 (4.4 to 9.3)	7.0±1.4 (4.2 to 9.8)
CL/F (L/hr)[a]	11.0±2.72 (6.39 to 15.9)	11.0±2.42 (6.45 to 15.7)
V_d/F (L)[a]	110±39.5 (53.8 to 205)	112±37.2 (61.6 to 191)

[a]:Mean±SD (range); [b]:Median (range)

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

	Ratio	Point estimate of Geometric means	90% CI of Point estimate
C_{max}			
	Solution:Tablet	1.10	(1.05, 1.15)
AUC_{inf}			
	Solution:Tablet	0.993	(0.970, 1.02)

2. Effect of food on pharmacokinetics of levofloxacin oral solution (Study LOFBO-PHI-117)

This study was designed to evaluate the effect of food on oral bioavailability of levofloxacin from the oral solution. **The results show that a high fat meal slightly decreases the rate of oral bioavailability of levofloxacin from the oral solution formulation in healthy subjects, as indicated by a prolonged T_{max} (1.5 *vs.* 0.8 hr) and lower C_{max} (3.78 vs. 5.24 µg/mL); however, the extent of oral bioavailability, i.e., AUC, is not affected by food (Tables 3 and 4).** Based on the results, levofloxacin solution formulation is recommended to be taken 1 hour before or 2 hours after eating.

Table 3. Pharmacokinetic parameters of levofloxacin after oral administration of 500 mg levofloxacin solution under fed (a high fat and high calories) and fasted conditions to healthy subjects (n=24).

	Solution Fed	Solution Fasted
C_{max} (µg/mL)[a]	3.78±0.884 (1.99 to 5.33)	5.24±2.01 (2.98 to 11.2)
AUC_{inf} (µg·hr/mL)[a]	34.1±8.23 (21.3 to 57.0)	39.4 ±10.9 (20.4 to 68.6)
T_{max} (hr)[b]	1.5 (0.5 to 4.0)	0.81 (0.25 to 2.0)
$T_{1/2}$ (hr)[a]	6.2±1.1 (4.3 to 8.6)	6.2±1.0 (4.6 to 8.4)
CL/F (L/hr)[a]	15.4±3.51 (8.77 to 23.7)	13.6±3.76 (7.28 to 24.5)
V_d/F (L)[a]	137±35.4 (71.6 to 195)	121±35.2 (60.6 to 210)

[a]:Mean±SD (range); [b]:Median (range)

Table 4. Ratio of means and 90% Confidence Intervals of the ratio of the means for AUC_{inf} and C_{max} of levofloxacin solution administered under fed (Test) to fasting (Reference) condition.

	Geometric Mean			90% CIs	
Parameter	Solution Fed	Solution Fasted	Ratio (%)	Lower Limit (%)	Upper Limit (%)
AUC_{∞}, µg•h/mL	33.25	38.04	87.43	85.17	89.75
C_{max}, µg/mL	3.67	4.92	74.52	68.07	81.58

Appendix 1

Proposed Labeling with OCPB Reviewer Revision

NDA-21-721: Levaquin®

(Levofloxacin)

Version: October 13, 2004

54 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Appendix 2

Individual Study Reviews

NDA-21-678: Levaquin®

(Levofloxacin)

1. An Open-Label, Randomized, 3-Way Crossover Study to Evaluate the Bioequivalence of an Oral — Formulation, an Oral Solution Formulation, and the Marketed Tablet Formulation of Levofloxacin in Healthy Subjects. [LOFBO-PHI-116]

LOFBO-PHI-116.pdf, pp 1-696

Levofloxacin (Levaquin®) is available for oral and intravenous administration. The high absolute bioavailability of the tablet permits an interchangeable oral and intravenous levofloxacin therapy with the same dose. — for adult patients who have difficulty swallowing tablets, a liquid formulation was developed.

An oral liquid solution formulation has been developed — . The sponsor intends to market the oral solution formulation for use in adults — The present study was designed to evaluate the bioequivalence of 3 levofloxacin oral formulations: — formulation the newly developed oral solution formulation, and the marketed tablet. ***The results showed that formulations of levofloxacin satisfied the criteria for bioequivalence***

Study period: Clinical conduct:
First conduct: 02 Nov. 2002 to 04 Nov. 2002;
Second conduct: 15 Nov. 2002 to 25 Nov. 2002

Sample analysis: 4 Dec. 2002 to 17 Dec. 2002

Objectives:
The primary objective of this study was to assess the bioequivalence of an — an oral solution formulation of levofloxacin, and the 500 mg marketed LEVAQUIN® (levofloxacin) tablet, with the tablet formulation as the reference.

Methodology:
This was a randomized, open-label, single-center, 500 mg single-dose, 3-way crossover, definitive bioequivalence study of 3 oral formulations of levofloxacin (tablet, — and solution) in healthy men and women. It was planned to enroll 36 subjects and to randomly assign each to 1 of 6 treatment-sequence groups (6 subjects in each, 3 men and 3 women). The study comprised a screening period, 3 open-label treatment periods

(Periods I, II, and III) separated by washout periods of at least 4 days between doses, and a post-treatment (or early withdrawal) period. The subjects who completed the study received a single dose of all 3 study drug formulations, 1 formulation on Day 1 of each of Periods I, II, and III. In each treatment period, subjects fasted 10 hours before drug administration and continued fasting until 4 hours after dose administration. Blood samples were collected on Days 1, 2, and 3 of each treatment period immediately before dose administration (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 10, 14, 24, 30, 36, and 48 hours after dose administration for measurement of levofloxacin concentration. For all treatment periods, subjects were sequestered at the study site from 6:00 p.m. on Day 0 through the collection of the 48-hour blood sample on Day 3. The post-treatment period consisted of procedures, such as a physical examination and clinical laboratory testing, to ensure the safety of the subjects before they were discharged from the study. Safety was monitored throughout the study.

Study Population and Demographic Data:
Two cohorts of 36 subjects each were enrolled in this study. The first cohort received 1 dose of study drug and completed Period 1. Because many errors occurred in the handling of study procedures by the study site, the study was stopped and reinitiated. The most critical reason for the termination is failing to collect a blood sample 0.5 hour after dose administration, which is critical to the analysis of bioequivalence, for all 36 subjects. The subjects completed early termination procedures. Their data were included in safety analyses; however, no blood samples collected to measure levofloxacin concentrations were analyzed, and no data were included in pharmacokinetic analyses.

Thirty-four subjects of the second cohort completed all study procedures. Eighteen subjects were male, and 16 were female. Nine were Caucasian; 1 was black; and 24 were other races. Their ages ranged from 19 to 55 years, with an average of 30 years. The weight ranged from 51.3 to 99.0 kg, with an average of 75.16 kg. The height ranged from 147 to 193 cm, with an average of 169 cm.

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

— Levofloxacin 125 mg/5 mL oral solution GFI 25213-097-EA-006, Bulk lot: D02LK0977. Levofloxacin 500-mg tablets, commercial product, NDC 0045-1525-50, Bulk lot: D00LK0530.

Safety Parameters:
Safety evaluations included adverse event monitoring, standard clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs measurements, physical examinations, and pregnancy tests for women of childbearing potential.

Pharmacokinetic Parameters:
Plasma samples were assayed for levofloxacin by a validated HPLC/fluorescence method. The lower and upper limits of quantification for this method were 0.05 and 15.0 µg/mL, respectively. Model-independent 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_{inf}), and the apparent terminal half-life ($T_{1/2}$).

Statistical Methods:
For each subject, plasma concentration-time profiles were plotted for all treatments received. The primary pharmacokinetic parameters of interest for the statistical analysis were AUC_{inf} and C_{max}. The analysis was performed on log-transformed estimated pharmacokinetic parameters. Only data from subjects who completed the 3 treatment periods were included in the statistical analysis. Analysis of variance (ANOVA) models were fit to the data with 1 of the parameters of interest (AUC_{inf} or C_{max}) as the dependent variable and the effects due to treatment-sequence group, treatment, and period as fixed effects, and subjects nested within the treatment-sequence groups as a random effect. Testing for the treatment-sequence group and period effects was carried out at the 10% and 5% levels of significance, respectively, using the appropriate error terms. The estimated least square means and intrasubject variability from the above model were used to construct 90% confidence intervals (CIs) for the difference in means on the logarithmic scale between the following pairs of treatments:

2. Oral solution formulation (Test) to marketed tablet (Reference)

In the treatment pairs listed above, a test formulation was considered to be bioequivalent to the reference formulation if the corresponding 90% CIs fell within the 80% to 125% limits of bioequivalence.

Pharmacokinetic Results:
Mean plasma concentrations and the relevant pharmacokinetic parameters of levofloxacin oral tablet [redacted] and solution to healthy subjects were described in Figure 1 and Table 2, respectively.

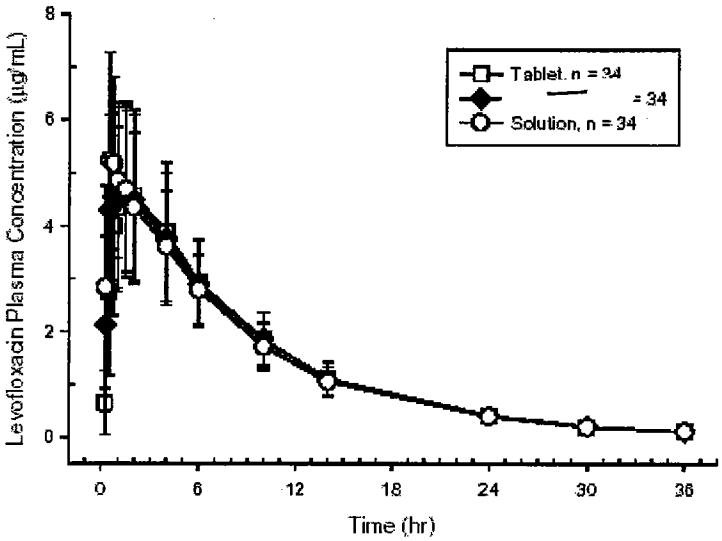


Figure 1. Plasma concentration of levofloxacin after oral administration of 500 mg tablet, and solution to healthy subjects (n=34). Bars represent standard deviation.

Table 1. Pharmacokinetic parameters of levofloxacin after administration of 500 mg oral tablet, and solution in healthy subjects (n=34).

	Tablet	Solution
C_{max} (µg/mL)[a]	5.18±1.52 (2.99 to 8.21)	5.76±1.77 (2.51 to 8.57)
AUC_{inf} (µg·hr/mL)[a]	48.5±12.6 (31.4 to 78.2)	47.8±10.8 (31.9 to 77.5)
T_{max} (hr)[b]	1.5 (0.52 to 4.0)	0.5 (0.25 to 4.0)
$T_{1/2}$ (hr)[a]	6.9±1.3 (4.4 to 9.3)	7.0±1.4 (4.2 to 9.8)
CL/F (L/hr)[a]	11.0±2.72 (6.39 to 15.9)	11.0±2.42 (6.45 to 15.7)
V_d/F (L)[a]	110±39.5 (53.8 to 205)	112±37.2 (61.6 to 191)

[a]:Mean±SD (range); [b]:Median (range)

Table 2 summarizes the statistical results for levofloxacin C_{max} and AUC_{inf}. The relative bioavailability of of solution with respect to the marketed tablet was 99.3%. satisfied the criteria for bioequivalence to the marketed tablet for both C_{max} and AUC_{inf} (Table 2). Similar findings were observed when the levofloxacin solution was compared to the marketed tablet. (Table 2).

The median T_{max} of levofloxacin for solution formulation was shorter compared with he marketed tablets (Table 1). Mean $T_{1/2}$, CL/F, and V_d/F were nearly identical for (Table 1).

Reviewer's comment: A modest decrease in T_{max} of — solution formulations compared with tablet formulation may be due to the time for disintegration of tablet formulation and does not seem clinically significant since the total exposure, i.e., AUC, is considered to be a major determinant for the antibacterial efficacy of fluoroquinolones. In addition, the substantially identical C_{max} values of different formulations support the insignificance of the difference in T_{max} values among the formulations.

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

	Ratio	Point estimate of Geometric means	90% CI of Point estimate
C_{max}			
	Solution:Tablet	1.10	(1.05, 1.15)
AUC_{inf}			
	Solution:Tablet	0.993	(0.970, 1.02)

Safety and Tolerability Results:
No deaths or other serious adverse event occurred during this study. Twenty subjects (28%) experienced adverse events: 10 (21%) after receiving the solution, 10 (21%) after the — and 8 (17%) after the tablet. All events, except 1 moderately severe event, were mild. Twenty were possibly related to study drug, 19 doubtfully related, and 7 not related. One subject withdrew from the study because of the adverse events of mildly severe chest pain and moderately severe syncope after receiving the — The number of incidents and the types of adverse events were about equally distributed among the 3 treatments. All adverse events were resolved. No clinically significant changes in clinical laboratory results, vital signs measurements, or physical examinations were seen, and all pregnancy tests were negative.

Reviewer's comment: The study design and interpretation of the results are acceptable from the perspective of Clinical Pharmacology and Biopharmaceutics.

Conclusion:
The levofloxacin oral solution — bioequivalent to the tablet formulation for both total exposure (AUC_{inf}) and peak exposure (C_{max}). — The 3 single 500-mg doses of levofloxacin administered orally in this study as a solution, — and tablet were well-tolerated by the healthy adult subjects.

2. An Open-Label, Randomized 2-Way Crossover Study to Evaluate the Effect of Food on Levofloxacin Pharmacokinetics From an Oral Solution Formulation [LOFBO-PHI-117]

LOFBO-PHI-117.pdf, pp 1-393

Levofloxacin (Levaquin®) is available for oral and intravenous administration. The high absolute bioavailability of the tablet permits an interchangeable oral and intravenous levofloxacin therapy with the same dose. —— for adult patients who have difficulty swallowing tablets, a liquid solution formulation was developed. The current study was designed to evaluate the effect of food on oral bioavailability of levofloxacin from the oral solution. ***The results show that a high fat meal slightly decreases the rate of oral bioavailability of levofloxacin from the oral solution formulation in healthy subjects, as indicated by a prolonged T_{max} (1.5 vs. 0.8 hr) and lower C_{max} (3.78 vs. 5.24 µg/mL); however, the extent of oral bioavailability, i.e., AUC, is not affected by food.*** *Based on the results, levofloxacin solution formulation is recommended to be taken 1 hour before or 2 hours after eating.*

Clinical data showed that the extent of levofloxacin absorption from the **marketed levofloxacin tablet** was not statistically significantly affected by food (AUC_{inf} of 45.6 *vs.* 50.5 µg·hr/mL, with and without food, respectively). Food slightly reduced the rate of oral bioavailability of levofloxacin from the tablet formulation, as indicated by a prolonged T_{max} (1.5 *vs.* 2.4 hr) and lower C_{max} (5.09 *vs.* 5.93) compared with under fasted condition, but these differences are not considered clinically significant.

Study period: Clinical conduct: 12 Nov. 2002 to 14 Dec. 2002;
Sample analysis: 20 Dec. 2002 to 1 Jan. 2003

Objectives:
The objective of this study was to evaluate the effect of food on the single-dose pharmacokinetics of an oral solution of levofloxacin. Safety was also assessed.

Methodology:
This was an open-label, randomized, 2-way crossover, 500 mg single-dose, single-center, food-effect study. The study consisted of 3 phases: a screening phase, an open-label treatment phase consisting of 2 treatment periods (also referred to as Period I and Period II), and a posttreatment phase. Subjects who met the prestudy eligibility criteria were randomly assigned to 1 of 2 treatment sequence groups. In each treatment period, subjects were admitted to the study unit the evening of Day 0, before study drug was administered on Day 1, and housed through 48 hours after dosing with study drug (i.e., until Day 3). Subjects received study drug as a single oral dose under both fed (within 10 minutes after completion of the FDA-recommended high–fat, high-calorie breakfast) and fasted (10-hour overnight fast) conditions according to their randomized treatment sequence, 1 condition in each treatment period. Each dosing day was separated by a washout period of at least 4 days. In each treatment period, serial pharmacokinetic blood samples (5 mL each) were collected immediately before dosing, and at 0.25, 0.5, 0.75, 1,

1.5, 2, 4, 6, 10, 14, 24, 30, 36, and 48 hours after each administration of study drug for determination of plasma concentrations of levofloxacin. Safety procedures were performed on Days 1 and 3 of Period I and on Day 1 of Period II. The posttreatment phase consisted of safety evaluations performed after collection of the final pharmacokinetic blood sample in the second treatment period. Adverse events were monitored from the time of the first study related procedure through completion of posttreatment study procedures, or until the time of early withdrawal.

Study Population and Demographic Data:
Twenty-four subjects planned (12 subjects [6 men and 6 women] in each treatment-sequence group), 24 subjects enrolled, 24 subjects evaluated for pharmacokinetics and safety. Twenty four subjects were Caucasian. Their ages ranged from 18 to 54 years, with an average of 35 years. The weight ranged from 53 to 109 kg, with an average of 74 kg. The height ranged from 156 to 195 cm, with an average of 174 cm.

Reviewer's comment: In this study, inclusion criteria include 'smoker who smoked no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 6 months prior to the screening' with the condition that smokers had to agree not to change his or her smoking habit during the study. In general, smokers are excluded for PK study because smoking is considered one of the compounding factors that affect drug metabolizing enzyme activity. However, the contribution of metabolism to the overall elimination of levofloxacin is very limited; following oral administration, approximately 87% of levofloxacin is recovered as unchanged drug in urine within 48 hours. In addition, the smoking habit would not be changed for the study. Thus, the inclusion criteria including light smoker is acceptable.

Test Product, Dose and Mode of Administration, Batch Numbers:
Single oral dose of levofloxacin (500 mg) given as 20 mL of the solution formulation (125 mg/5 mL). Batch: R11943 (GFI-25213-097-EA-006)

Safety Parameters:
Safety evaluations included adverse event monitoring, standard clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs measurements, physical examinations, and pregnancy tests for women of childbearing potential.

Pharmacokinetic Parameters:
Plasma samples were assayed for levofloxacin by a validated HPLC/fluorescence method. The lower and upper limits of quantification for this method were 0.05 and 15.0 μg/mL, respectively. Model-independent 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_{inf}), and the apparent terminal half-life ($T_{1/2}$).

Statistical Methods:
For each subject, plasma concentration-time profiles were plotted for all treatments received. The primary pharmacokinetic parameters of interest for the statistical analysis were AUC_{inf} and C_{max}. The analysis was performed on log-transformed estimated pharmacokinetic parameters. The estimated least square means and intrasubject

variability from an analysis of variance (ANOVA) model was used to construct 90% confidence intervals (CIs) for the ratio of the mean pharmacokinetic parameters obtained when administered in a fed state to those obtained when administered in a fasted state. Absence of food effect would be concluded if the 90% CIs fell within the 80% to 125% limit.

Pharmacokinetic Results:
Mean plasma concentrations and the relevant pharmacokinetic parameters of levofloxacin oral tablet, — and solution to healthy subjects were described in Figure 1 and Table 1, respectively.

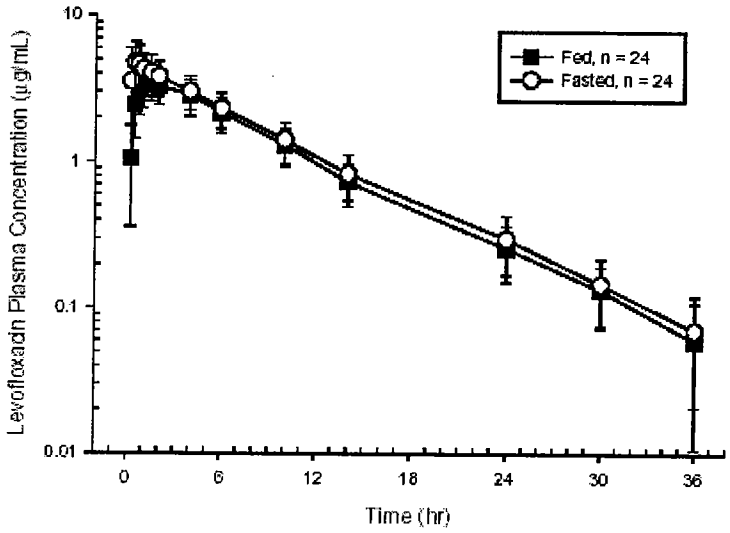


Figure 1. Plasma concentration of levofloxacin after oral administration of 500 mg levofloxacin solution under fed (a high fat and high calories) and fasted conditions to healthy subjects (n=24). Bars represent standard deviation.

Table 1. Pharmacokinetic parameters of levofloxacin after oral administration of 500 mg levofloxacin solution under fed (a high fat and high calories) and fasted conditions to healthy subjects (n=24).

	Solution Fed	Solution Fasted
C_{max} (µg/mL)[a]	3.78±0.884 (1.99 to 5.33)	5.24±2.01 (2.98 to 11.2)
AUC_{inf} (µg·hr/mL)[a]	34.1±8.23 (21.3 to 57.0)	39.4 ±10.9 (20.4 to 68.6)
T_{max} (hr)[b]	1.5 (0.5 to 4.0)	0.81 (0.25 to 2.0)
$T_{1/2}$ (hr)[a]	6.2±1.1 (4.3 to 8.6)	6.2±1.0 (4.6 to 8.4)
CL/F (L/hr)[a]	15.4±3.51 (8.77 to 23.7)	13.6±3.76 (7.28 to 24.5)
V_d/F (L)[a]	137±35.4 (71.6 to 195)	121±35.2 (60.6 to 210)

[a]:Mean±SD (range); [b]:Median (range)

Table 2 summarizes the ratio of means and the 90% CIs for the mean AUC_{inf} and C_{max}. The 90% CIs for the ratio of mean AUC_{inf} between fed and fasted conditions fell within the 80% to 125% bioequivalence acceptance criteria, indicating the absence of food

effect on the extent of oral bioavailability of levofloxacin from solution formulation. The 90% CIs for the ratio of mean C_{max} between fed and fasted conditions fell outside the 80% to 125% limits. Together with a prolonged T_{max} under fed conditions compared with under fasted conditions (1.5 *vs.* 0.8 hr, Table 1), a lower mean C_{max} value under fed conditions indicates that food may decrease the rate of oral bioavailability of levofloxacin from solution formulation. Other pharmacokinetic parameters including $T_{1/2}$, CL/F and Vd/F were nearly identical between fed and fasted conditions. The sequence group effect and the period effect were found not to be significant at a 10% and 5 % level of significance, respectively.

Reviewer's comment: It is not addressed whether the difference in C_{max} and T_{max} are clinically significant or not. There are no additional clinical data to support the absence of clinical significance of this difference in the rate of oral bioavailability due to food. Thus, based the results of this study, levofloxacin solution formulation is recommended to be taken without food, i.e., 1 hour before or 2 hours after eating.

Table 2. Ratio of means and 90% Confidence Intervals of the ratio of the means for AUC_{inf} and C_{max} of levofloxacin solution administered under fed (Test) to fasting (Reference) condition.

	Geometric Mean			90% CIs	
Parameter	Solution Fed	Solution Fasted	Ratio (%)	Lower Limit (%)	Upper Limit (%)
AUC_{∞}, µg•h/mL	33.25	38.04	87.43	85.17	89.75
C_{max}, µg/mL	3.67	4.92	74.52	68.07	81.58

Safety and Tolerability Results:

The number of subjects experiencing adverse events was the same for each treatment condition with 7 (29%) subjects each having adverse events following treatment under fed and fasted conditions. The only adverse events reported by more than 1 subject were headache (n=6) and purpura (n=2). The majority of the adverse events were considered by the investigator to be mild or moderate in severity and not or doubtfully related to study drug. There were no deaths and no serious adverse events reported during the study, and no subjects withdrew from the study due to an adverse event. There were no clinically relevant changes in mean values for serum chemistry, hematology, and urinalysis laboratory results, and there were no subjects with markedly abnormal values. There were no clinically meaningful changes in vital signs or physical examination findings.

Reviewer's comment: The study design and interpretation of the results are acceptable from the perspective of Clinical Pharmacology and Biopharmaceutics.

Conclusion:

The results show that a high fat meal slightly decreases the rate of oral bioavailability of levofloxacin from the oral solution formulation in healthy subjects, as indicated prolonged T_{max} (1.5 *vs.* 0.8 hr) and a 25% lower mean C_{max} (3.78 vs. 5.24 µg/mL); however, the extent of oral bioavailability, i.e., AUC, is not affected by food.

A single 500 mg dose of levofloxacin solution formulation administered under fed and fasted conditions was safe and well-tolerated by healthy subjects.

Based on the results, levofloxacin solution formulation is recommended to be taken 1 hour before or 2 hours after eating.

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Seong Jang
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Phil Colangelo
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