

SYNOPSIS

<u>NAME OF SPONSOR/COMPANY:</u> Johnson & Johnson Pharmaceutical Research & Development, L.L.C. <u>NAME OF FINISHED PRODUCT:</u> LEVAQUIN® <u>NAME OF ACTIVE INGREDIENT(S):</u> RWJ-25213-097 (levofloxacin)	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
Protocol No.: LOFBO-PHI-117		
Title of Study: An Open-Label, Randomized 2-Way Crossover Study to Evaluate the Effect of Food on Levofloxacin Pharmacokinetics From an Oral Solution Formulation		
Principal Investigator: F. Vanhoutte, M.D., Clinical Pharmacology Unit, AZ Jan Palfijn, Merksem; Belgium		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: November 12, 2002 – December 14, 2002 Sample Analysis: December 20, 2002 – January 1, 2003	Phase of development: 1	
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, 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 a 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 were collected at scheduled times through 48 hours after study drug administration 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.		
Number of Subjects (planned and analyzed): 24 subjects planned (12 subjects [6 men and 6 women] in each treatment-sequence group), 24 subjects enrolled, 24 subjects evaluated for pharmacokinetics, 24 subjects evaluated for safety.		
Diagnosis and Main Criteria for Inclusion: Healthy men and women, between the ages of 18 and 55 years, inclusive.		
Test Product, Dose and Mode of Administration, Batch No.: 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)		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.		
Duration of Treatment: Each subject received 2 single oral doses of 500 mg levofloxacin solution, 1 in each treatment period at least 4 days apart.		

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<p>Criteria for Evaluation:</p> <p><u>Pharmacokinetics:</u> The following pharmacokinetic parameters were estimated by model independent methods and summarized: C_{max}, t_{max}, $t_{1/2}$, AUC_{∞}, CL/F, Vd/F.</p> <p><u>Safety:</u> Safety evaluations included: adverse event monitoring, standard clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital sign measurements, physical examinations, and pregnancy tests for women of childbearing potential.</p>		
<p>Statistical Methods:</p> <p><u>Pharmacokinetics:</u> Plasma concentration and pharmacokinetic parameter (C_{max}, t_{max}, $t_{1/2}$, AUC_{∞}, CL/F, and Vd/F) data were summarized. The primary parameters of interest for the statistical analysis were AUC_{∞} and C_{max}. The analysis was performed on the log-transformed 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.</p> <p><u>Safety:</u> The incidence, relationship to therapy, and severity of treatment-emergent adverse events were summarized by treatment condition using a standard adverse-event dictionary based on WHOART. Changes in clinical laboratory tests and vital signs were assessed by descriptive statistics and summarized by treatment condition. Results of physical examination findings were listed.</p>		

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SUMMARY – CONCLUSIONS							
<u>PHARMACOKINETIC RESULTS:</u>							
Mean (±SD) levofloxacin pharmacokinetic parameters (fed and fasted) following a single 500 mg oral dose of levofloxacin solution are presented in the table below.							
Mean (±SD) Pharmacokinetic Estimates (Fed and Fasted) Following a Single 500-mg Oral Dose of Levofloxacin Solution							
Parameter	Solution Fed N=24	Solution Fasted N=24					
C_{max} , µg/mL	3.78 ± 0.884	5.24 ± 2.01					
t_{max} , hr	1.5 ± 1.1	0.81 ± 0.52					
$t_{1/2}$, hr	6.2 ± 1.1	6.2 ± 1.0					
AUC_{∞} , µg•h/mL	34.1 ± 8.23	39.4 ± 10.9					
CL/F, L/hr	15.4 ± 3.51	13.6 ± 3.76					
Vd/F, L	137 ± 35.4	121 ± 35.2					
The table below summarizes the results obtained from ANOVA in testing for sequence group effect and period effect.							
Summary of Results From ANOVA – Test for Sequence Group Effect and Period Effects							
Parameter	Sequence Group Effect			Period Effect			Intrasubject %CV
	F	df	p value	F	df	p value	
AUC_{∞} , µg•h/mL	0.34	(1,22)	0.565	1.66	(1,22)	0.211	5.3
C_{max} , µg/mL	0.06	(1,22)	0.805	1.06	(1,22)	0.315	18.3
F = Test statistic; df = degrees of freedom; CV = coefficient of variation							
For AUC_{∞} and C_{max} there was no significant sequence group effect at a 10% level of significance and there was no significant period effect at a 5% level of significance.							
The table below summarizes the ratio of means and the 90% confidence intervals for the mean pharmacokinetic parameters AUC_{∞} and C_{max} .							
Ratio of Means and 90% Confidence Intervals of the Ratio of the Means for Pharmacokinetic Parameters of Levofloxacin Solution Administered Under Fed (Test) to Fasting (Reference) Condition.							
Parameter	Geometric Mean		Ratio (%)	90% Confidence Intervals			
	Solution Fed	Solution Fasted		Lower Limits (%)		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	
The 90% confidence intervals for the ratio of mean AUC_{∞} between fed and fasted conditions fell within the 80% to 125% bioequivalence acceptance criteria. The 90% confidence intervals for the ratio of mean C_{max} between fed and fasted conditions fell outside the 80% to 125% limits.							

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<p><u>SAFETY RESULTS:</u></p> <p>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.</p> <p>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.</p> <p>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.</p> <p>There were no clinically meaningful changes in vital signs or physical examination findings.</p> <p><u>CONCLUSION:</u></p> <p>The study results show that a high-fat meal slightly delays the absorption of levofloxacin from the oral solution formulation in healthy subjects (t_{max} of 1.5 ± 1.1 versus 0.8 ± 0.5 hours, with or without food, respectively) and decreases C_{max} (3.78 ± 0.884 versus 5.24 ± 2.01 $\mu\text{g/mL}$, with and without food, respectively); however, the total bioavailability, as indicated by AUC_{∞} (34.1 ± 8.23 versus 39.4 ± 10.9 $\mu\text{g}\cdot\text{h/mL}$), is not affected by food. A single 500 mg dose of levofloxacin solution formulation administered under fed and fasted condition was safe and well-tolerated by healthy subjects.</p> <p>Date of the report: 20 May 2003</p>		