

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20822

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

RECEIVED MAY 05 1998

Citalopram Hydrobromide

Forest Laboratories MAY 5 1998

10, 40, and 60 mg Tablets

New York, NY 10022

NDA 20-822

Submission Date: March 30, 1998

Reviewer: Iftexhar Mahmood, Ph. D.

Indication: Antidepression

Forest Laboratories have submitted the following 2 studies as part of their previously submitted NDA (review dated 3/20/98). The summary of these two studies can be found in Appendix 1 and 2.

Study 1. A dose proportionality and pharmacokinetic study of citalopram in healthy young volunteers (CIT-PK1-97-02-000).

This was a randomized, single dose, cross-over dose proportionality study conducted in 30 subjects (24 completed). The subjects were given 10 to 60 mg citalopram tablets following an overnight fast and each dose was separated by a 14-day washout period. Blood samples were collected till 192 hours. The results of this study indicated that citalopram tablets are linear over a dose range of 10 to 60 mg. In this study, no gender difference was found in citalopram pharmacokinetics.

Study 2. A single-dose, open label, bioequivalence study comparing citalopram tablets with Forest Ireland citalopram tablets in human volunteers (CIT-PK1-97-03-000).

This was open-label, randomized, single dose, two-way cross-over bioequivalence study in 24 subjects. Each subject received either a 60 mg tablet manufactured by or Forest Ireland following an overnight fast. There was a 14-day washout period between the two treatments. Blood samples were collected till 192 hours. The results of this study indicated that the formulations are bioequivalent.

Recommendation:

The results and the conclusions of this study are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

/S/

5/5/98

Iftakhar Mahmood, Ph. D.

Division of Pharmaceutical Evaluation I

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RD/FT initialed by Chandra Sahajwalla, Ph. D. _____

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CC: NDA 20-822

HFD-120, HFD-860 (Mahmood, Sahajwalla, Malinowski), CDR (Barbara Murphy for Drug Files).

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APPENDIX 1

FOREST LABORATORIES, INC.

Name of Company	Individual study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority use only)</i>
Forest Laboratories, Inc.		
Name of Finished Product		
Citalopram		
Name of Active Ingredient		
Citalopram		

Title of Report		
A Dose Proportionality and Pharmacokinetics Study of Citalopram in Healthy Young Volunteers (CIT-PK1-97-02-000)		
Purpose of Study		
The objective of this study was to evaluate the dose proportionality of citalopram plasma levels after administration of single doses of 10, 20, 40 and 60 mg citalopram tablets under fasted conditions in healthy, young male and female volunteers.		
Date of the Report	Studies were carried out	
March 25, 1998	From	To
	September 15, 1997	December 15, 1997
Statistical Methodology	Phase of Study	Number of Subjects
Statistical Analysis System (SAS) Version 6.09: ANOVA used to compare PK parameters, the statistical model contained terms for subject, period, treatment and residual effects. Gender differences assessed using Kruskal-Wallis Test (Chi Square Approximation)	Phase I	30 (24 completed)
Design of Study	Analytical Site (1)	Mode of Administration
open-label, single dose, randomized four-way crossover design	Forest Laboratories, Inc.	oral
Clinical Site	Formulations	
	Citalopram hydrobromide 10 mg (Lot #1235), 20 mg (Lot #1228), 40 mg (Lot #1229), and 60 mg (Lot # 1230), Forest	



FOREST LABORATORIES, INC.

Name of Company	Individual study Table Referring to Part of the Dossier	<i>(For National Authority use only)</i>
Forest Laboratories, Inc.		
Name of Finished Product		
Citalopram		
Name of Active Ingredient		
Citalopram	Volume:	
	Page:	

Test Formulation Administration (CIT-PK1-97-02-000)
Treatment
Subjects were randomized to receive each of the following four (4) treatments with a 14 day wash out period between treatments: Treatment A: A single oral administration of citalopram 10 mg tablet, following a 10 hour overnight fast. Treatment B: A single oral administration of citalopram 20 mg tablet, following a 10 hour overnight fast. Treatment C: A single oral administration of citalopram 40 mg tablet, following a 10 hour overnight fast. Treatment D: A single oral administration of citalopram 60 mg tablet, following a 10 hour overnight fast.

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FOREST LABORATORIES, INC.

Name of Company	Individual study Table Referring to Part of the Dossier	<i>(For National Authority use only)</i>
Forest Laboratories, Inc.		
Name of Finished Product		
Citalopram		
Name of Active Ingredient		
Citalopram	Volume:	
	Page:	

Summary and Conclusions (CIT-PK1-97-02-000)

In this dose proportionality study conducted in 24 normal male and female subjects, single doses of citalopram over a range of 10 to 60 mg were well tolerated. Citalopram was rapidly absorbed, with peak plasma concentrations occurring at approximately 5^h hours for all doses tested (10 - 60 mg). No statistically significant differences were observed in the dose-normalized C_{max} and $AUC_{0-\infty}$ values across the 10, 20, 40 and 60 mg doses suggesting a proportional increase in plasma citalopram concentrations with dose. There was also a linear relationship between these parameters and dose. Further, there was a linear relationship observed between the citalopram dose and the C_{max} and AUC_{0-t} values of demethylcitalopram. Citalopram half-life values of approximately 36-40 hours were obtained in this study. There were no statistically significant differences in the half-life values obtained for all four doses tested; i.e., half-life was independent of dose. No gender differences were observed in the C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$ and CL/F values over a citalopram dose range of 10 to 60 mg. These results support previous steady-state pharmacokinetic findings in patients suggesting the dose-proportionality of citalopram pharmacokinetics over a daily dose range of 10 to 60 mg.

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Safety Summary:

Single oral administration of 10 mg, 20 mg, 40 mg and 60 mg citalopram tablets was well tolerated and safe. No clinically important abnormalities or events were associated with citalopram administration.

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statistically significant differences ($p = 0.525$). The $t_{1/2}$ values obtained in this study are similar to those obtained in other single dose studies in young subjects.^{1,2}

The oral clearance (CL/F) values obtained for all dose levels were approximately 20 L/hr and were not significantly different from each other ($p = 0.910$). These values are also similar to those previously reported in another study where young healthy subjects received a single dose of 2 x 20 mg citalopram tablet.¹

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There were no period effects observed in this study.

The plasma DCT concentrations following administration of 10, 20, 40 and 60 mg citalopram tablets in healthy young male and female subjects are listed in Tables A-7 through A-10, respectively (Appendix A). For visual comparison, the mean plasma DCT concentrations for the 10, 20, 40 and 60 mg citalopram tablets are illustrated in Figure A-9 (Appendix A). The mean pharmacokinetic parameters for DCT are listed in Table 2 below. The individual pharmacokinetic parameters (AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} and $t_{1/2}$) for DCT are listed in Tables A-15 through A-17 (Appendix A) for the 20, 40 and 60 mg citalopram tablets, respectively. Pharmacokinetic parameters for DCT (10 mg dose level) were not calculated since 95% of the plasma concentration values were below the limit of quantification (Table A-7, Appendix A).

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Table 2
Pharmacokinetic Parameters (Mean \pm SD) of DCT Following Single Dose Oral Administration of Citalopram Hydrobromide 20, 40 and 60 mg Citalopram Tablets in Young Healthy Subjects

	20 mg	40 mg	60 mg
C_{max} (ng/mL)	3.2 \pm 0.9	6.1 \pm 1.9	8.5 \pm 2.3
T_{max} (hours)	17.3 \pm 13.2	17.9 \pm 11.1	25.0 \pm 22.3
AUC_{0-t} (ng•hr/mL)	204.5 \pm 77.0	575.1 \pm 162.6	879.2 \pm 208.9
$AUC_{0-\infty}$ (ng•hr/mL)	-- ^a	843.7 \pm 193.7	1153.2 \pm 233.0
$t_{1/2}$ (hours)	-- ^a	79.3 \pm 19.6	77.5 \pm 27.7

^a plasma concentrations were generally at or below the limit of quantification and estimation of the half-life was not feasible

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As was shown previously for citalopram, the mean C_{max} and AUC_{0-t} values of demethylcitalopram increased linearly with increasing dose (with correlation factors of 0.997 for both parameters, Figures A-10 and A-11, respectively). These data suggest that

Table 1
Pharmacokinetic Parameters (Mean ± SD) of CT Following Single Dose Oral Administration of Citalopram Hydrobromide 10, 20, 40 and 60 mg Citalopram Tablets in Young Healthy Subjects

	10 mg	20 mg	40 mg	60 mg
C_{max} (ng/mL)	10.6 ± 2.4	21.7 ± 3.9	43.7 ± 7.2	65.6 ± 10.2
T_{max} (hours)	5.8 ± 2.3	4.9 ± 2.3	5.3 ± 2.4	4.5 ± 1.4
AUC_{0-t} (ng•hr/mL)	378.6 ± 128.9	861.4 ± 264.9	1901.6 ± 464.3	2774.5 ± 633.0
$AUC_{0-∞}$ (ng•hr/mL)	533.2 ± 248.5	1010.4 ± 283.5	2070.3 ± 504.6	2946.5 ± 689.1
$t_{1/2}$ (hours)	36.3 ± 11.5	38.5 ± 10.2	40.0 ± 9.9	39.5 ± 8.0
CL/F (L/hr)	20.9 ± 5.7	21.6 ± 6.3	20.6 ± 4.6	21.4 ± 4.7

No statistically significant differences were observed for the dose-normalized C_{max} ($p = 0.932$) and dose-normalized $AUC_{0-∞}$ ($p = 0.845$) values, suggesting a proportional increase in plasma citalopram concentrations with dose. In addition, the mean C_{max} , AUC_{0-t} and $AUC_{0-∞}$ values increased linearly (correlation factors (r) of 0.999) with increasing dose (Figures A-6 through A-7, respectively).

A statistically significant difference was observed between the dose-normalized AUC_{0-t} values for the 10 mg compared to the 40 ($p = 0.005$) and 60 mg tablets ($p = 0.015$) but not the 20 mg tablet ($p = 0.145$). This may be due to the fact that the plasma CT concentrations were at or just below the limit of quantification following administration of the 10 mg tablet and were assigned a value of zero resulting in lower AUC_{0-t} values. However, there were no statistically significant differences in the dose-normalized AUC_{0-t} values for the 20, 40 and 60 mg tablets ($P = 0.282$) suggesting a proportional increase in plasma citalopram concentrations with dose for this dose range. Also, the mean AUC_{0-t} values increased linearly (correlation factor (r) of 0.999) with increasing dose over the dose range tested (10 to 60 mg) (Figure A-8). Collectively, these data suggest that at the dose levels tested, there is a linear relationship between dose and citalopram levels and that an increase in dose results in a proportional increase in plasma citalopram concentrations; e.g., doubling the dose (within a dose range of 10 to 60 mg) results in a doubling of citalopram concentrations in the plasma.

Citalopram was fairly rapidly absorbed, with peak plasma concentrations occurring at approximately 5 hours. There were no statistically significant differences observed in the T_{max} values ($p = 0.128$) obtained for all four dose levels.

Comparison of the half-life values obtained for the four doses levels did not show any

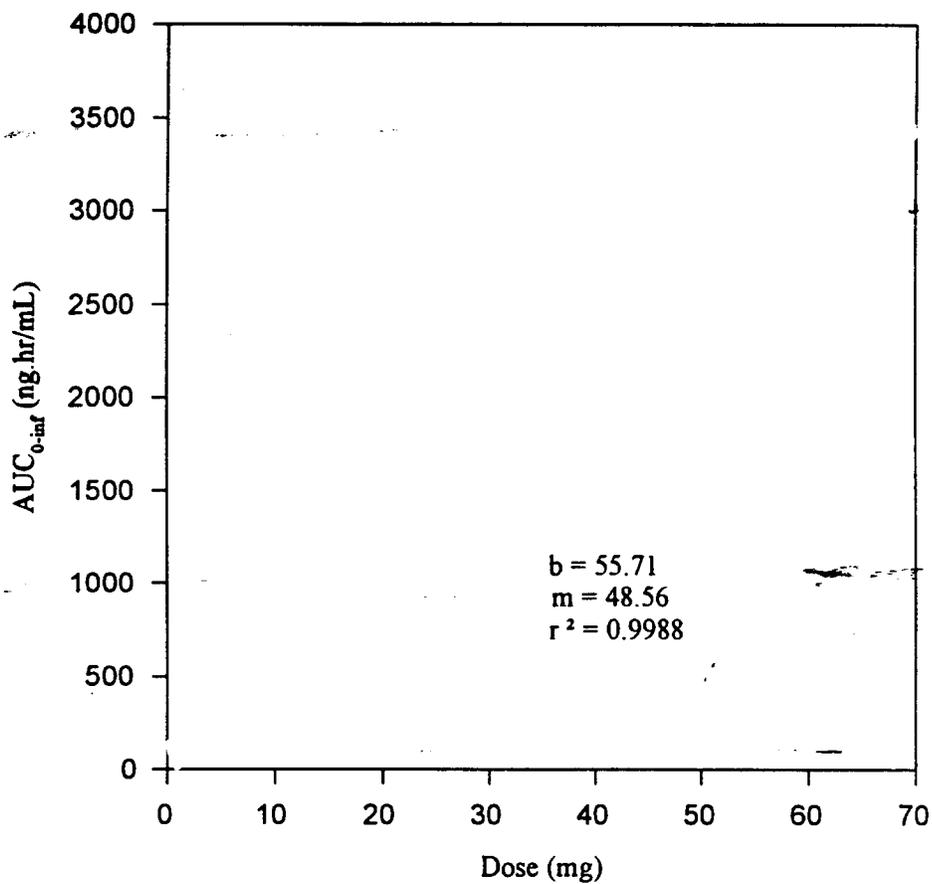
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Figure A-7
Dose-AUC_{0-inf} Relationship for Citalopram Following Single Dose
Oral Administration of 10, 20, 40 and 60 mg Citalopram Tablets
in Young Healthy Male and Female Subjects



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Figure A-8
Dose-AUC_{0-t} Relationship for Citalopram Following a Single Dose
Oral Administration of 10, 20, 40 and 60 mg Citalopram Tablets
in Young Healthy Male and Female Subjects

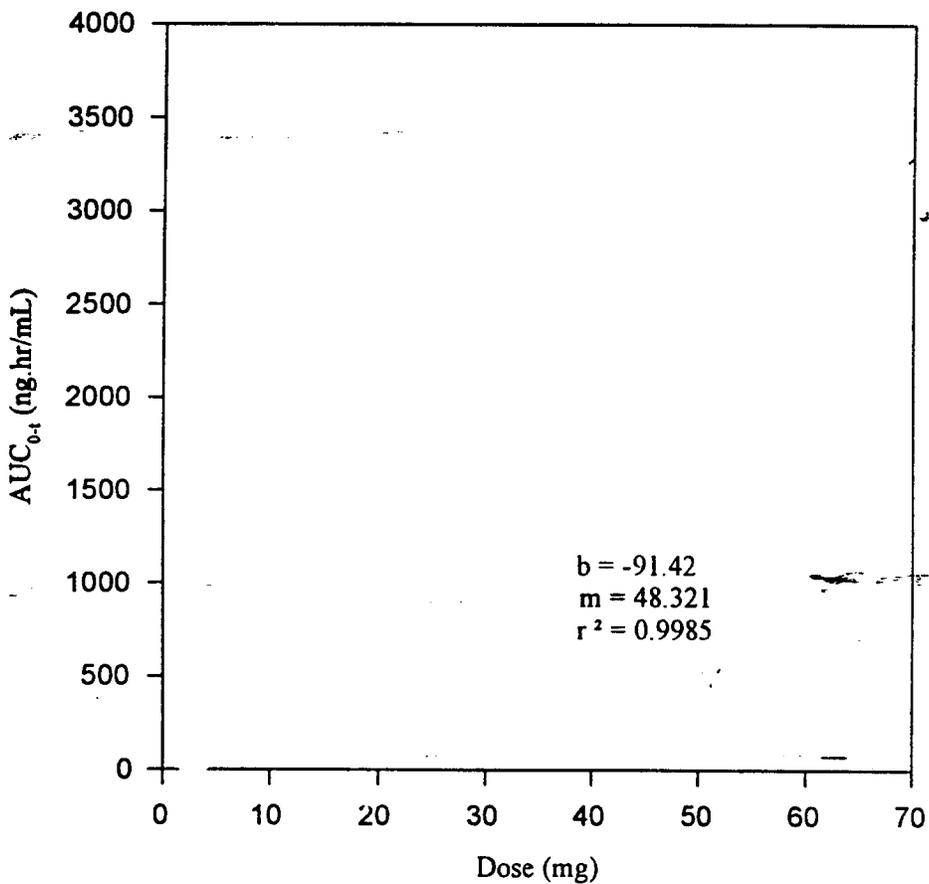
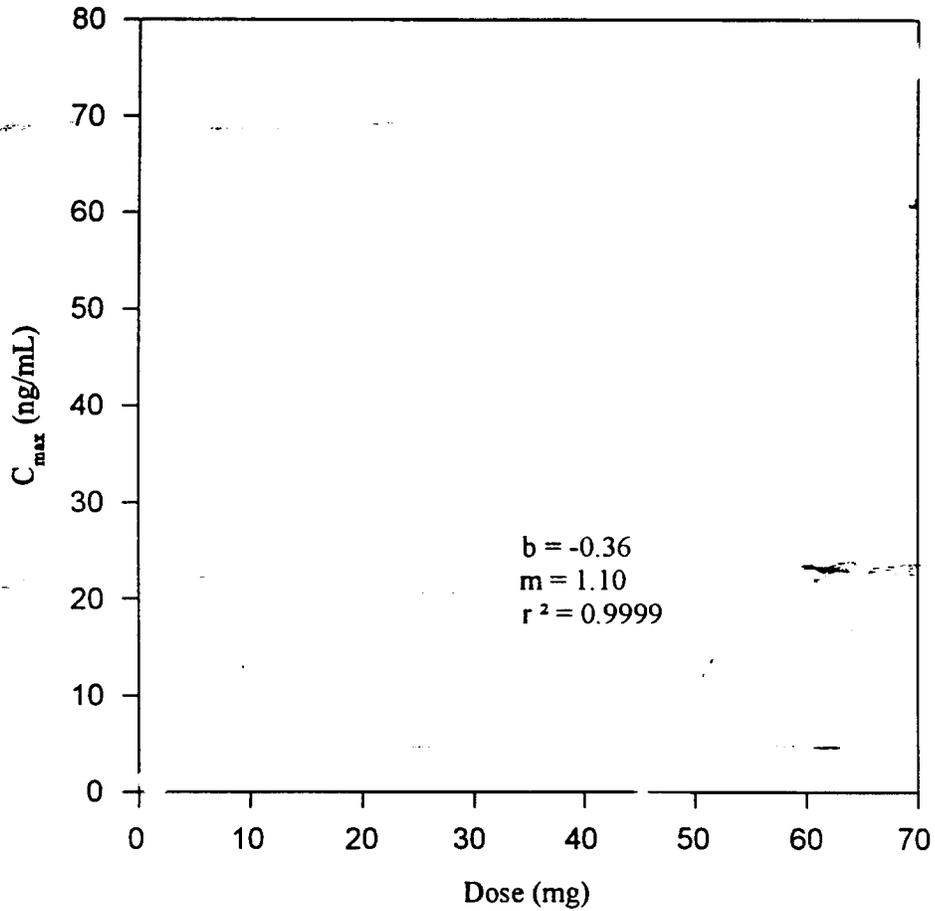


Figure A-6
Dose- C_{max} Relationship for Citalopram Following Single Dose Oral Administration of 10, 20, 40 and 60 mg Citalopram Tablets in Young Healthy Male and Female Volunteers



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Figure A-10
Dose- C_{max} Relationship for Demethylcitalopram Following
a Single Dose Oral Administration of 20, 40 and 60 mg Citalopram
Tablets in Young Healthy Male and Female Subjects

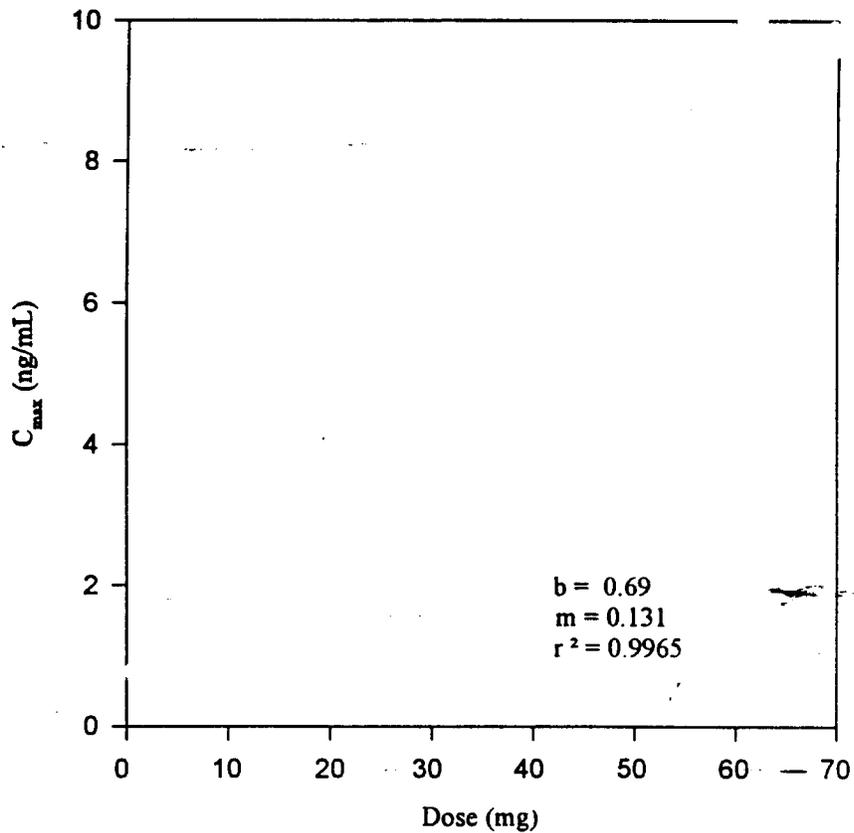
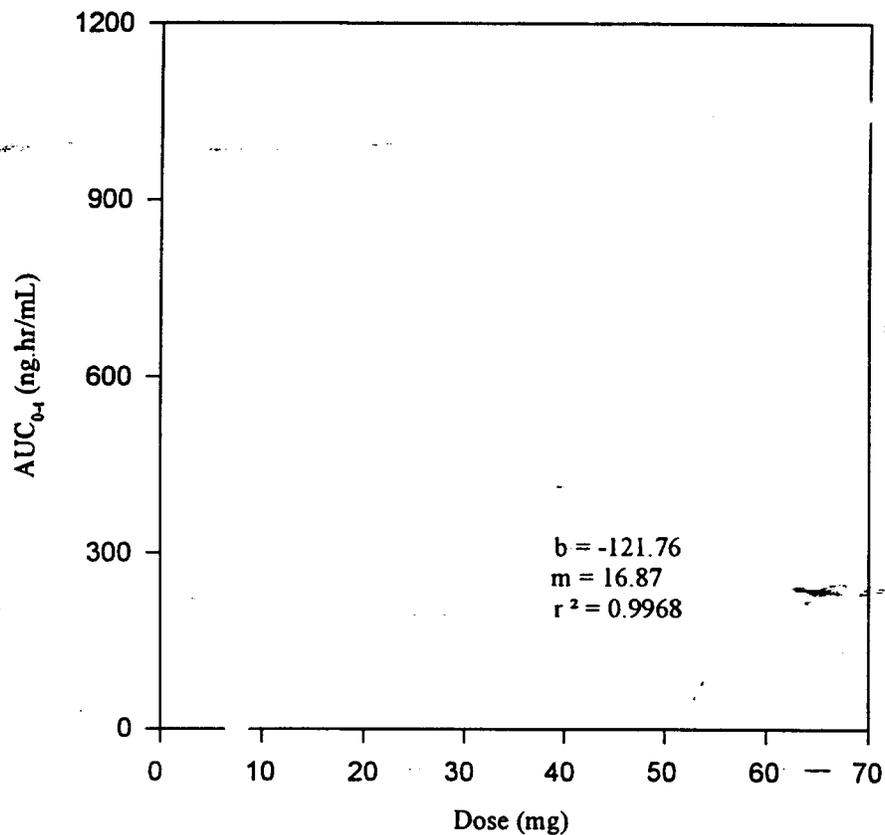


Figure A-11
Dose-AUC_{0-t} Relationship for Demethylcitalopram Following
a Single Dose Oral Administration of 20, 40 and 60 mg Citalopram
Tablets in Young Healthy Male and Female Subjects



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Appendix 2

Citalopram Hydrobromide
10, 20, 40 and 60 mg tablets
NDA 20-822

Forest Laboratories
New York, NY 10022

MAR 20 1998

Submission Date: May 7, 1997, November 18 and 26, 1997, January 21, 1998.

Reviewer: Iftexhar Mahmood, Ph. D.

Indication: Antidepression

INTRODUCTION

Citalopram (CT) is an orally administered selective serotonin reuptake inhibitor. Citalopram is a racemic bicyclic phthalane derivative. Molecular formula of citalopram is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405. Citalopram is a white powder and is sparingly soluble in water. The pK_a of citalopram is 9.5.

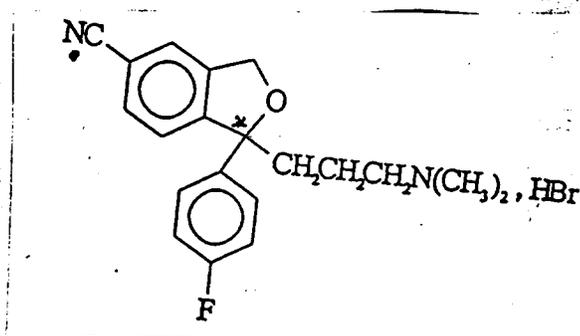
Citalopram is absorbed with a T_{max} of _____ in healthy subjects. The absolute bioavailability of citalopram is 80%. Following a single oral dose (30 mg tablet) of citalopram, the mean C_{max} and T_{max} were 42.2 ng/mL and 4.5 hours, respectively. The mean C_{max} and T_{max} of demethylcitaloprim (a metabolite of citalopram) were 5.3 ng/mL and 24.8 hours, respectively. Food has no effect on the pharmacokinetics of citalopram tablets. The volume of distribution of citalopram is 12.3 L/kg. Citalopram is 82% bound to human plasma proteins over the concentration range of 100 to 2400 ng/mL. The major metabolites of citalopram are desmethylcitalopram (DCT) and didesmethyl citalopram (DDCT). Minor metabolites of citalopram are N-Oxide and propionic acid. Approximately 85% of the radioactivity was recovered in urine (75%) and feces (10%). CT, DCT, DDCT, CT-glucuronide + DDCT-glucuronide, deaminated propionic acid-glucuronide, and N-oxide accounted for 26%, 19%, 9%, 20%, 12% and 7% of the radioactivity recovered in urine, respectively. The systemic clearance of citalopram is 330 mL/min. Renal clearance is about 60 mL/min. The elimination half-life of citalopram is approximately 35 hours.

Based on the inhibition of the accumulation of radiolabelled serotonin (5-HT) into rat whole brain synaptosomes and the potentiation of 5-HTP in vivo in mice, the pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. Human studies have shown that higher concentrations of the (R)-enantiomer are achieved in the plasma compared to the (S)-enantiomer, possibly due to the larger clearance of the (S)- compared to the (R)-enantiomer. Gender-related pharmacokinetic differences resulted in higher serum concentrations of CT (though not its metabolites) in females. This difference was more pronounced for the (S)- than for the (R)-enantiomer.

Compared to a single oral dose study (40 mg), following multiple dosing the C_{max} and AUC (0-24 h) increased by 230% and 40%, respectively, whereas the oral clearance decreased by 25%. The percent of dose excreted unchanged in urine was 23% following multiple dosing compared to 10% after a single dose. The elimination half-life of CT; DCT and DDCT following multiple dosing was 41, 49 and 102 hours, respectively.

In hepatically impaired patients, the oral clearance of citalopram was decreased by 40% and the half-life increased more than 100%. Mild and moderate renal impairment was associated with a 20% decrease in oral clearance. The systemic clearance in the elderly was 25 to 75% lower than the young subjects. Approximately 1.5 to 2 fold higher AUC of citalopram was observed in females than males.

Drugs which may be coadministered with citalopram including digoxin, carbamazepine, imipramine, lithium, levomepromazine and warfarin did not appear to have any significant pharmacokinetic interactions with citalopram. Coadministration of citalopram with psychotropic drugs such as tricyclic antidepressants, benzodiazepines and neuroleptics produced minimal effects on the pharmacokinetics of citalopram, with the possible exception of alprazolam, clomipramine and fluvoxamine.



Citalopram Hydrobromide

● ^{14}C -Radiolabeled

* Chiral Center

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A total number of 32 studies were submitted of which 25 were reviewed.

SUMMARY

Bioequivalence Study:

In a bioequivalence study, 14 male subjects received either 4 x 10 mg sugar coated (old formulation) or 1 x 40 mg film-coated citalopram hydrobromide tablets to compare the two formulations. The study indicated that the 90% confidence interval was within the required range of 80% to 125% for C_{max} and AUC (Study #1).

Earlier studies using sugar-coated tablets did not differ from the later used film-coated tablets with respect to their pharmacokinetic parameters with relative bioavailabilities of almost 100%. Subsequent studies were therefore conducted using the technically-improved film-coated tablets.

Absorption:

Following a single oral dose (30 mg tablet) of citalopram, the mean C_{max} and T_{max} were 42.2 ± 5.6 ng/mL and 4.5 ± 1.7 hours, respectively. The mean C_{max} and T_{max} of demethylcitalopram (a metabolite of citalopram) were 5.3 ± 1.0 ng/mL and 24.8 ± 19.6 hours, respectively (Study #3). The absolute bioavailability of citalopram (2 x 20 mg oral dose) was $80 \pm 13\%$ ($n = 12$) relative to an intravenous dose (40 mg solution infused over 2 hours) (Study #2). The relative bioavailability of citalopram tablet against solution was approximately 100% (Study #3).

Distribution:

The volume of distribution of citalopram following 40 mg IV infusion over 2 hours was 12.3 ± 2.4 L/kg (study #2).

The binding values of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins are approximately 82, 74 and 78%, respectively, as measured using ultrafiltration techniques

Metabolism:

volunteers ($n = 4$). Approximately 75%

CT, DCT, DDCT, CT-glucuronide + DDCT-glucuronide, deaminated

propionic acid-glucuronide, and N-oxide accounted for 26%, 19%, 9%, 20%, 12% and 7% of the radioactivity recovered in urine, respectively (Study #4).

Citalopram in man is the dominant compound in plasma after single or multiple doses. The two most predominant metabolites of citalopram are the demethylated compounds, DCT and DDCT. The DCT levels are approximately that of the parent compound whereas DDCT levels are only about 10% of citalopram levels. The other less predominant metabolites of citalopram include citalopram-N-oxide (CNO) and deaminated propionic acid (DPA). Following a 40 mg/day dose, all of the metabolites with the exception of CNO were detected in the plasma whereas all metabolites were detected in the urine.

In-vitro studies using human liver microsomes indicated that CYP3A4 is a major isozyme involved in the N-demethylation of CT, while CYP2C19 plays a minor role in this metabolic pathway. In vitro human liver studies have also shown that CT is a weak inhibitor of CYP1A2, CYP2D6, CYP2C19 and CYP3A4 whereas DCT is an intermediate inhibitor of CYP2D6. CT is approximately 32 times a weaker inhibitor of 2D6 than fluoxetine and 240 times a weaker inhibitor of 1A2 than fluvoxamine (Study #4a).

Elimination:

Both single oral dose (40 mg) and intravenous infusion in healthy subjects yielded half-lives of approximately 35 hours for citalopram and 78 hours for DCT. Following single intravenous administrations of 40 mg citalopram to healthy male volunteers, the systemic clearance of citalopram was 330 mL/min. The fraction of drug recovered in the urine as citalopram and DCT was 11% and 4%, respectively. The renal clearance of citalopram in normal healthy volunteers is 60 mL/min (Study #2).

Enantiomers of citalopram:

Citalopram is available orally as a racemic mixture. Based on the inhibition of the accumulation of serotonin (5-HT) into rat whole brain synaptosomes and the potentiation of -5-HTP in vivo in mice, the pharmacological effect of citalopram resides in the (S)-(+)-enantiomer.

When a multiple dosing regimen of 40 (2 x 20 mg) mg/day for 8 weeks of CT was administered to young male and female subjects, statistically higher (2.2 fold in males and 1.5 fold in females) levels of the (R)- compared to the (S)- enantiomer for CT, DCT and DDCT were observed (Study #5). Similar results were obtained in another study in which a multiple dose regimen of 40 mg/day of CT administered in healthy male and female subjects yielded statistically higher levels of the (R)- compared to the (S)- enantiomer for

CT, DCT and DDCT. In this study, generally larger $t_{1/2}$ values were observed for the (R)- compared to the (S)-enantiomer. Moreover, the oral clearance (CL/F) of the (S)- enantiomer was significantly higher than the (R)- enantiomer for CT which may have contributed to the lower serum levels of the (S)- enantiomer. Also, higher amounts of the (R)-enantiomer of CT, DCT and DDCT were excreted in the urine reflecting the greater serum content compared with the (S)-enantiomer. Additionally, enantiomeric (R/S) ratios for AUC_{SS} and $A_{e,SS}$ were lower for DCT than for CT indicating less stereoselectivity in the disposition of DCT or reflecting a lower demethylation rate of the (R)- relative to the (S)- enantiomer. DCT (S) activity is about 12% to 14% of the parent compound.

A gender difference in the pharmacokinetics of CT was observed. Higher serum CT levels were found in females, a difference which was not accounted for by body weight alone. The AUC_{SS} of CT was approximately 1.5, 2.3, 1.8 fold higher in females (n = 6) than males (n = 5) for the (R), (S) and the racemic CT, respectively. Also the serum concentrations of the (R)-enantiomer of CT were higher in males relative to the (S)- enantiomer as reflected in the (R/S) ratios for AUC_{SS} and $A_{e,SS}$. Adjusted for weight, Cl_{oral} and V_{SS}/F were both approximately 30% lower for females than for males. Lower values for these parameters were observed for both the (S)- and (R)- enantiomers in the females compared to the males. There were no gender differences in the pharmacokinetics of DCT and DDCT.

Dose Proportionality:

There is no information on dose proportionality of citalopram ranging from 10 to 60 mg tablets (strengths intended to be marketed).

Food Effect:

The effect of food (30 mg single dose immediately after a high fat meal diet) was assessed in healthy male volunteers (n =4 in fasting and 5 in fed state). Food had no effect on the pharmacokinetics of citalopram (Study # 6).

Multiple Dose Kinetics:

In a multiple dose study, citalopram was given as 40 mg/day tablet orally to 10 healthy subjects for 29 days. Blood and urine samples were collected till 240 hours and 360 hours, respectively. Citalopram and its metabolites concentrations were measured in serum and urine. Compared to a single oral dose study (40 mg), the C_{max} and AUC (0-24 h) increased by 230% and 40%, respectively, whereas the oral clearance decreased by 25%. The percent of dose excreted unchanged in urine was 23% following multiple dosing

compared to 10% after a single dose. The C_{max} , AUC and percent of dose excreted unchanged in urine of DCT was 9 fold, 1.3 fold and 4 fold higher following multiple dosing compared to a single dose. The elimination half-life of CT, DCT and DDCT following multiple dosing was 41, 49 and 102 hours, respectively (Study #7).

SPECIAL POPULATION:

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Hepatic Impairment:

The pharmacokinetics of citalopram was assessed in 9 subjects (6 alcoholic cirrhosis and 3 chronic active hepatitis) with reduced hepatic function (Study #8). The subjects received 20 mg citalopram as a single oral dose. The oral clearance of citalopram was 0.26 l/min in subjects with reduced hepatic function as compared to 0.41 l/min in healthy volunteers. The half-life of citalopram was doubled in subjects with reduced hepatic function as compared to healthy volunteers. This study is inconclusive (please see comment on page #19).

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Renal Impairment:

The pharmacokinetics of citalopram was assessed in 8 subjects with reduced renal function (Study #9). The subjects received 20 mg citalopram as a single oral dose. The creatinine clearance ranged The oral clearance of citalopram was 17% lower in subjects with reduced renal function as compared to healthy volunteers. The half-life of citalopram was almost 12 hours longer in subjects with reduced renal function as compared to healthy volunteers.

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Age and Gender:

The studies conducted by the Sponsor to determine the effect of age on the pharmacokinetics of citalopram are inconclusive due to small sample size (Study #10). However, when data were analyzed from two separate studies (mean age = 26 years (n = 16), 71 years (n = 25)), it was found that there was no difference in C_{max} and T_{max} of citalopram between young and elderly. But the AUC was 37% higher and half-life was 18 hours longer in the elderly compared to young. Another pooled study indicated that AUC of citalopram can be more than 50% higher and half-life can be longer by 24 hours in the elderly compared to young.

There may be gender difference in the pharmacokinetics of citalopram (Study #10). Due to small sample size (n = 3), no conclusion can be drawn about the effect of gender on the pharmacokinetics of citalopram (Study #10). From the analysis of pooled data (n = 26

males, 29 females), it was observed that C_{max} and AUC were higher in females by 32% and 35%, respectively.

The pharmacokinetic study of enantiomers of citalopram also indicated that serum CT levels were higher in females than males. The AUC_{SS} of CT was approximately 1.5, 2.3, 1.8 fold higher in females (n = 6) than males (n = 5) for the (R), (S) and the racemic CT, respectively.

Drug-Interaction Studies:

(i) Citalopram-cimetidine interaction:

The metabolism of citalopram is mediated by CYP2D6, CYP2C19 and possibly CYP3A4. Cimetidine has been shown to be a potent inhibitor of several CYP enzymes including CYP2D6, CYP3A4, CYP1A2, and a weak inhibitor of CYP2C9. To investigate the possible interaction of Citalopram with another inhibitor of the CYP enzymatic system, the effects of cimetidine on steady-state citalopram pharmacokinetics was studied in young healthy male (n = 12) and female (n = 2) subjects. Subjects received 1x40 mg citalopram tablet per day during the first 21 days. One tablet of 40 mg citalopram and 800 mg (400 mg twice a day) of cimetidine from day 22 to day 29. Concomitant administration of cimetidine caused a significant increase in the average steady-state levels of citalopram and DCT by 43% and 11%, respectively as determined by AUC values and a significant decrease (30%) in the oral clearance of citalopram. In addition, the renal clearances of DCT and DDCT were decreased by approximately 26%. The data suggest that dosage adjustment of citalopram may be warranted when given with cimetidine. The effect of citalopram on the pharmacokinetics of cimetidine was not evaluated ((Study #11).

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(ii) Citalopram-warfarin interaction:

Warfarin is metabolized entirely by the hepatic CYP systems with the CYP2C9 and CYP1A2 responsible for the metabolism of the S(-) and the R(+)-enantiomers, respectively. A single dose of warfarin was administered to young healthy male subjects (n = 12) before and after subjects achieved steady-state plasma levels of citalopram. There were no statistically significant differences in the pharmacokinetic parameters for both (R) and (S) warfarin when warfarin was administered alone or in combination with citalopram. Although the prothrombin times are higher in the presence of citalopram than with warfarin alone, the magnitude of this difference was small (approximately 5%) (Study #12).

(iii) Citalopram-digoxin interaction:

To investigate the possible interaction of digoxin and citalopram, a single oral dose of digoxin (1 mg) was administered to healthy subjects (n =12) before administration of citalopram and then again after the same subjects had achieved steady-state levels of citalopram. There were no statistically significant changes in the pharmacokinetics of digoxin when given alone or in combination with citalopram. Serum concentrations of citalopram, DCT and DDCT were not affected by single dose of digoxin (Study #13).

(iv) Citalopram-metoprolol interaction:

Metoprolol is predominantly metabolized by the CYP2D6 enzyme to hydroxy metoprolol. A single dose of metoprolol (150 mg) was administered in young subjects (n = 13) before administration of citalopram and then again after the same subjects had achieved steady-state levels of citalopram. Only extensive metabolizers of dexamethorphan (CYP2D6) and mephenytoin (CYP2C19) were included in the study. Pharmacokinetic analysis showed that the AUC and C_{max} of metoprolol in plasma was increased approximately two-fold after multiple dose administration of citalopram (40 mg/day for 21 days) whereas a decrease in the plasma concentration of hydroxy metoprolol was observed, suggesting a moderate inhibition of metoprolol metabolism. Adjustment in metoprolol dose when given with citalopram is needed. The effect of metoprolol on the pharmacokinetics of citalopram was not evaluated (Study #14).

(v) Citalopram-carbamazepine interaction:

Citalopram was coadministered with carbamazepine (CBZ) to healthy subjects (n =12) who had achieved steady-state plasma levels of CBZ. There were no statistically significant differences between the C_{max} , AUC, T_{max} and CL/F values of CBZ and carbamazepine-10,11-epoxide (CBZE) before and during citalopram coadministration. The effect of CBZ on the pharmacokinetics of citalopram was not evaluated. Considering that CBZ is hepatic enzyme inducer, the pharmacokinetics of citalopram is expected to be altered during the continuous administration of CBZ (Study #15).

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(vi) Citalopram-lithium interaction:

In a study conducted in 8 healthy volunteers (sparteine and mephenytoin extensive metabolizers), there was no pharmacokinetic (AUC, C_{max} , T_{max}) interaction between citalopram and lithium. Lithium did not affect the serum level of citalopram, DCT or DDCT, and citalopram did not affect serum levels of lithium (Study #16).

(vii) Citalopram-imipramine and citalopram-levomepromazine interaction:

The effects of imipramine and levomepromazine on the steady-state pharmacokinetics of citalopram were investigated in young healthy male subjects (n=8). Results show that imipramine had no effect on steady-state citalopram pharmacokinetics. Although citalopram did not affect the pharmacokinetics of imipramine, it caused a significant increase in desipramine levels (52%) and a significant reduction in 2-hydroxydesipramine (AUC₀₋₂₄). In addition, a 35% prolongation of desipramine t_{1/2} was observed (Study #17). Since desipramine is pharmacologically active, caution should be exercised when citalopram is administered with imipramine or desipramine.

There was no pharmacokinetic interactions between citalopram and levomepromazine. Levomepromazine did not affect the serum level of citalopram, DCT (20% increase in AUC) or DDCT, and citalopram did not affect serum levels of levomepromazine (Study #18).

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(viii) Citalopram-ethanol and citalopram-amitriptyline interaction:

Twelve healthy volunteers (6 males, 6 females) received 20 to 40 mg citalopram and 37.5 to 75 mg amitriptyline for 8 days. A test dose of alcohol to reach a blood level of 80 mg/100 mL was administered on day 8 and repeated at 1 and 3 hours later. Compared to placebo, both drugs impaired coding skills and immediate memory recall and increased body sway. Subjects became more drowsy, feeble, lethargic and drowsy. Physical tiredness, headach, indigestion, restlessness, dizziness and sweating were also increased. Symptoms were more pronounced with amitriptyline than citalopram (Study #19). It is suggested that citalopram should not be administered either with alcohol or amitriptyline.

Sponsor's proposed Specifications

Formulation:

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DRAFT LABELING

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the 'Labeling' changes.

APPROVED
DATE

Iftexhar Mahmood, Ph.D. /S/ 3/20/98

RD/FT initialed by Chandra Sahajwalla, Ph.D. /S/ 3/20/98

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CPB Briefing: March 3, 1998

CC: NDA 20-789, HFD-120, HFD-860 (Mahmood, Sahajwalla, Malinowski), HFD-340 (Viswanathan), CDR (Barbara Murphy) and FOI (HFD-19) files.

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