CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Celexa ® (Citalopram)
NDA: 20-822 (b) (4) 016
21-046 (b) (4) 002
FORMULATION: Tablets/Solution
APPLICANT: Forest Labs.

PRIMARY REVIEWER: Vanitha J. Sekar, PhD

TYPE: Pediatric (b) (4) suppl (7-17 years)
STRENGTH: 10, 20, 40 mg, Solution 2 mg/ml
SUBMISSION DATE: 4-18-02

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Overall Summary of Findings: This submission (response to pediatric written request) contains results from 3 in-vivo studies: 1) Single dose (20 mg) pharmacokinetic study in 12 healthy children aged 7-11 years and in 12 adults, 2) multiple dose (40 mg/day maintenance dose) pharmacokinetic study in 13 pediatric depressed patients aged 10-17 years and in 12 adults, 3) Efficacy trial in pediatric depressed patients aged 7-17 years in which steady-state trough concentrations were measured (n=45 children 7-11 years and n=44 children aged 12-17 years). Only one of the 2 clinical efficacy studies demonstrated efficacy of Celexa in the pediatric population – the second study is a failed study. (b) (4) This Clinical Pharmacology/Biopharmaceutics review will therefore focus only on results from the traditional pharmacokinetic studies and the descriptive statistics for the pharmacokinetic information obtained in the clinical trial to evaluate whether the applicant has adequately evaluated the pharmacokinetics of Celexa in the pediatric population and if the pharmacokinetics of Celexa are similar in the pediatric population and in adults.

The sponsor has conducted 2 traditional pharmacokinetic studies – one single dose study (20 mg citalopram oral solution) in healthy children (aged 7-11 years) and adults, and a second multiple dose study in depressed adolescents (aged 10-17 years) and in depressed adults given 20 mg citalopram once daily with forced titration to 40 mg once daily for a total of four weeks. In the single dose study, higher C_{max} (114%), larger $AUC_{0-\infty}$ (33%), and smaller CL/F (28%) for citalopram were observed in children compared to adults. However, in the multiple dose study pharmacokinetic parameters of citalopram after a single dose of 20 mg citalopram and after multiple doses of 40 mg once daily were similar in depressed adolescents and adults. In addition, in efficacy trial CIT-MD-18 (in depressed children and adolescents aged 7-17 years), the sponsor has collected a blood sample (between 8-14 hours post dose) for the measurement of citalopram steady-state concentrations in plasma. In this study, the steady-state concentrations of citalopram were approximately 13% higher in the children as compared to the adolescents. Correlation analyses revealed no significant correlation between age and citalopram concentration (r=0.059, p=0.650) as well as body weight and citalopram concentration (r=-0.218; p=0.089).

These results suggest that the pharmacokinetics of Celexa are similar in adolescents and in adults. However for younger children (7-11 years of age), the single dose pharmacokinetic data suggest a higher exposure in the pediatric population compared to adults. Data from the sparse sampling pharmacokinetic study (in the efficacy trial) need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adults/adolescents.

Recommendation: The pharmacokinetic studies provided in this pediatric supplement for Celexa submitted to the Division of Neuropharmacological Drug Products to fulfil the pediatric written request provide an understanding of the pharmacokinetics of citalopram in pediatric patients between the ages of 7 and 17 years, inclusive. This submission is acceptable from OCPB perspective. Data from the sparse sampling pharmacokinetic study need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adolescents/adults.

Comment: At the time when data from the sparse sampling pharmacokinetic study are analyzed further, the sponsor will be requested to submit the exact sampling time relative to dosing for all of the sparse sampling data.

Introduction and Background: Celexa™ (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Celexa is available as 10 mg, 20 mg and 40 mg film coated tablets and also as an oral solution (2 mg/ml).

Celexa (citalopram HBr), in adults, is labeled to be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of not less than one week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). In vitro and in vivo studies in animals suggest that citalopram is a selective serotonin reuptake inhibitor with minimal effects on norepinephrine and dopamine neuronal reuptake. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer .

The single and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram, demethylcitalopram, and didemethylcitalopram to human plasma proteins is about 80%. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent. Following a single oral dose (40 mg tablet) of citalopram, peak blood levels occur at about 4 hours.

Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. Citalopram is metabolized to demethylcitalopram, didemethylcitalopram citalopram-N-oxide and a deaminated propionic acid. In humans, citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, demethylcitalopram and didemethylcitalopram in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. In vitro studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram is expected to be 2.5 times the plasma concentrations observed following a single dose. Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and demethylcitalopram was about 10% and 5%, respectively. The systemic clearance of citalopram is 330 ml/min, with approximately 20% of that due to renal clearance.

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2EI, but did suggest that it is a weak inhibitor of CYP-IA2, -2D6, and -2C19. However, in vivo data to address this question are limited. Coadministration of citalopram and the potent 3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple dose administration of Celexa.

Clinical Pharmacology

1 a. Has the sponsor adequately evaluated the pharmacokinetics of Celexa in the pediatric population?
1. b. Are the pharmacokinetics of Celexa similar in the pediatric population and in adults?

In a single dose pharmacokinetic study (PK-13) of 20 mg citalopram oral solution in healthy children (aged 7-11 years) and adults, the rate of absorption of citalopram was faster and the extent of absorption was larger in children compared to adults. A shorter t_{max} (24%), higher C_{max} (114%), larger $AUC_{0-\infty}$ (33%), and smaller CL/F (28%) for citalopram were observed in children compared to adults. Similar conclusions were obtained when adjustments were made for differences in body weights between the subject populations. No gender effects on pharmacokinetic parameters (except citalopram T_{max}) were found for citalopram in this study. T_{max} (11%) for citalopram was shorter in females than in males.

In a multiple dose pharmacokinetic study (PK-07) in children (aged 10-17 years) and in adults given 20 mg citalopram once daily with forced titration to 40 mg once daily for a total of four weeks, pharmacokinetic parameters of citalopram after a single dose of 20 mg citalopram and after multiple doses of 40 mg once daily were similar in depressed adolescents and adults. Comparison of pharmacokinetic parameters between male and female patients revealed no significant gender effects for citalopram.

Comparison of the pharmacokinetics of citalopram and demethylcitalopram following a single 20 mg dose across the above 2 studies (PK-13 and PK-07) suggests that younger children (aged 7-11 years) have higher AUC (approximately 30%) and Cmax (60-100%) than adolescents and adults following a single 20 mg dose of citalopram.

However, in efficacy trial CIT-MD-18 (in depressed children and adolescents aged 7-17 years), the sponsor has collected a blood sample for the measurement of citalopram steady-state concentrations in plasma. Wherever possible, the sample was collected between 8-14 hours after the last dose of study medication was taken. In this study, the steady-state concentrations of citalopram were approximately 13% higher in the children as compared to the adolescents. Correlation analyses revealed no significant correlation between age and citalopram concentration (r=0.059, p=0.650). Body weight also appeared to be uncorrelated with either citalopram concentration (r=-0.218; p=0.089). Tables and figures supporting these results are attached in the appendix. There is a variability in sampling times, no pharmacokinetic modeling was performed on this data, and (13%) increased concentrations were observed in children compared to adolescents. Therefore, data from the sparse sampling pharmacokinetic study need to analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adolescents/adults.

Conclusions: These results suggest that the pharmacokinetics of Celexa are similar in adolescents and in adults. However for younger children (7-11 years of age), the single dose pharmacokinetic data suggest a higher exposure in the pediatric population compared to adults. Data from the sparse sampling pharmacokinetic study (in the efficacy trial) need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adults.

(b) (4)

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, Ph.D.
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 20-822 (b) (4) 016
21-046 (b) (4) 002
/MO/ A. Mosholder
/CSO/P. David
/Biopharm/V. Sekar
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta

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APPENDIX

Study CIT-PK-013

Objective: This study was designed to evaluate the pharmacokinetics of citalopram and its metabolites in pediatric subjects (compared to adult subjects) following a single 20 mg dose.

Study Design: This was an open-label, parallel, single dose study in 12 pediatric (7 -11 years old) and 12 adult (18 -35 years old) healthy male and female subjects. Subjects were institutionalized for the entire study. Subjects received a single, oral dose of 20 mg of citalopram in a 10 ml oral solution at 0800 on Day 1, following which multiple plasma samples were obtained. Blood samples were collected for the measurement of plasma concentrations of each citalopram enantiomer and its respective metabolites. Safety was assessed throughout the study by monitoring of adverse events and by laboratory and physical examinations and vital sign and ECG measurements

On Day 1 subjects received a single 20 mg dose of citalopram in a 10 mL oral solution (10mg/5mL) at 0800 hours. Subjects remained ambulatory or seated upright and awake for the first four (4) hours following drug administration and did not engage in strenuous activity. Subjects were dosed under fasted conditions. During the study, standardized, bland, low-fat meals were provided to all subjects while institutionalized. Meals did not contain any caffeine containing food or beverages. Subjects did not eat grapefruit or drink grapefruit juice from 48 hours before; and throughout the study. Subjects were required to consume the entire contents of each meal and snack. When meal times coincided with the blood sampling schedule and vital sign measurement, the vital signs were measured first, then the blood samples were drawn before meals. No concomitant medication was permitted during the study.

Pharmacokinetic Sample Collection: Blood samples were collected at the following times.
Day 1, after 0800 drug administration at: 0 hour (pre-dose), 1, 2, 3, 4, 8, and 12 hours (post-dose); Days 2, 3, 4, 5, 6, 7, and 8 at: 24, 48, 72, 96, 120, 144, and 168 hours (post Day 1 dose).

Bioanalytical Procedure: The citalopram enantiomers and enantiomeric metabolites R-CT (R-citalopram), escitalopram (S-CT), R- and S-didemethylcitalopram (DCT), R- and S-didemethylcitalopram and their internal standard, D-4-R-citalopram (D-4-R-CT), were extracted from 0.5 ml human plasma using diethyl ether and then back extracted with 0.1N HCl. The mobile phase was 0.1 % ammonium trifluoroacetate in methanol. The enantiomers of citalopram, demethylcitalopram, and didemethylcitalopram were quantified using a triple quadrupole mass spectrometer in positive APCI/SRM (Atmospheric Pressure Chemical Ionization/Selective Reaction Monitoring) mode. The dynamic range of the assay was from 1 to 150 ng/ml for all analytes. The correlation coefficients of standard curves were greater than or equal to 0.99. Duplicate QC samples at three nominal concentrations (3.75, 15, and 75 ng/ml, for all analytes) were analyzed along with plasma samples. The following table summarizes the precision (%CV) and accuracy (% deviation) of the method during the study.

Table 5.1 Summarizes the Precision (%CV) and Accuracy (%Deviation) of the Analytic Method during the Study

Compound	Standard Curves		Quality Control Samples	
	% Deviation	% CV	% Deviation	% CV
S-CT	≤ 3.3	≤ 5.2	≤ 6.9	≤ 6.4
S-DCT	≤ 2.6	≤ 4.2	≤ 6.6	≤ 5.4
S-DDCT	≤ 3.3	≤ 4.3	≤ 8.6	≤ 5.3
R-CT	≤ 2.7	≤ 3.6	≤ 6.2	≤ 6.0
R-DCT	≤ 2.6	≤ 4.8	≤ 6.1	≤ 6.2
R-DDCT	≤ 3.4	≤ 4.5	≤ 7.5	≤ 7.8

Statistical Analysis: Statistical analyses were performed with the Statistical Analyses System (SAS) version 6.12 for the UNIX system microcomputers using the General Linear Models procedure (GLM). Analysis of variance (ANOY A) was performed on all of the pharmacokinetic parameters, including Cmax, AUC, Tmax, T1/2, and CL/F. AUC and Cmax were log-transformed in the analysis of variance comparison. Statistical comparison of pharmacokinetic parameters between children (7 to 11 years old) and adults (18 to 35 years old) were performed using ANOVA adjusted by gender (as the factor). Similarly, the impact of the gender effects on pharmacokinetic parameters adjusted by age (as the factor) was evaluated.

Patient Demographics: Twenty-four subjects, twelve adults (3 males and 9 females) and twelve children (6 males and 6 females) were enrolled and received citalopram. Patients' demographic characteristics are shown in the table below.

Table 8.1 Summary of Demographic Characteristics

	Adults N=12	Children N=12
Age, years		
Mean	30.3	9.4
Standard Deviation	3.8	1.1
Min – Max	23, 35	7,11
Weight, kg		
Mean	74	34
Standard Deviation	16.43	5.17
Min – Max	52.7, 102.7	26.8, 44.1
Height, cm		
Mean	165.1	137.0
Standard Deviation	12.11	7.28
Min – Max	149.9, 188	127.0, 149.9

Pharmacokinetic Results:. Pharmacokinetic data were analyzed for all 24 subjects: 12 adults (9 females and 3 males) and 12 children (6 males and 6 females) who entered the study. Didemethylcitalopram was below the limit of quantitation in all subjects at all time points except for one pediatric subject with concentrations above 1 ng/mL at 24 and 48 hours after citalopram administration. Since plasma concentrations of didemethylcitalopram were close to or below the limit of quantification (1 ng/mL), no discussion of didemethylcitalopram pharmacokinetics has been presented by the sponsor.

Effect of Age: The mean plasma concentration plots for citalopram and demethylcitalopram are shown in the figures below by age group.

Figure 11.1 Plasma Concentrations (mean±SD) of Citalopram after Administration of 20 mg Citalopram in Healthy Pediatric vs. Adult Volunteers.

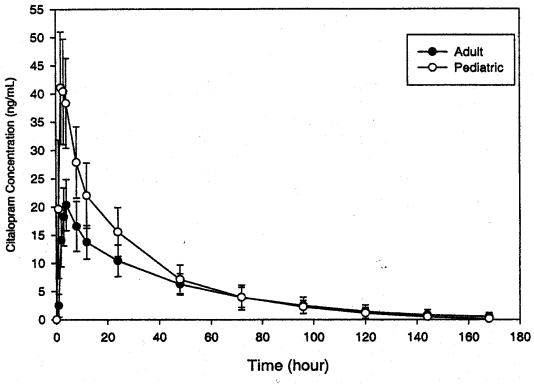
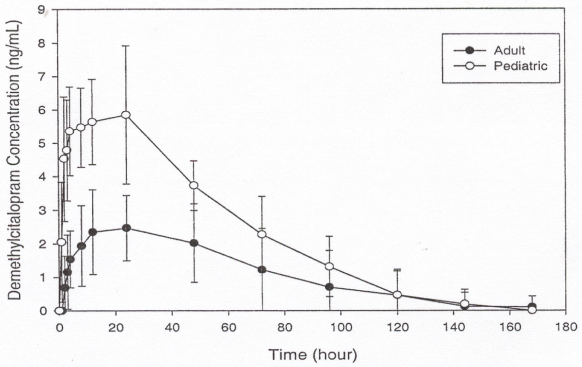


Figure 11.2 Plasma Concentrations (mean±SD) of Demethylcitalopram after Administration of 20 mg Citalopram in Healthy Pediatric vs. Adult Volunteers.



A summary of the mean pharmacokinetic parameters (Mean ± SD) of citalopram for the healthy adult and pediatric subjects following the administration of 20 mg citalopram oral solution is presented in the table below.

Table 9.1 Pharmacokinetic Parameters (Mean ± SD) of Citalopram following Administration of 20 mg Citalopram in Healthy Adult and Pediatric Volunteers.

	Citalopram		
PK Parameters	Adult (N=12)	Pediatric (N=12)	p
C_{max} (ng/mL)	20.5 ± 4.7	43.8 ± 8.4	0.000
T_{max} (hr)	3.8 ± 0.5	2.9 ± 0.8	0.002
AUC_{0-t} (hr* ng/mL)	805.8 ± 289.9	1110.1 ± 336.5	0.012
AUC_{0-inf} (hr* ng/mL)	871.5 ± 312.4	1161.7 ± 343.4	0.018
$t_{1/2}$ (hr)	34.2 ± 7.6	26.1 ± 4.0	0.007
CL/F (L/hr)	25.4 ± 8.0	18.3 ± 4.2	0.009
Vz/F (L)	1189.2 ± 234.0	675.0 ± 133.5	0.000

Following a single dose administration of 20 mg citalopram oral solution, a shorter Tmax (24%), higher Cmax (114%), larger AUC0-t (38%) and $AUC_{0-\infty}$ (33%) were observed in children compared to adults. These data suggest that the rate of absorption of citalopram was faster and the extent of absorption was higher in children compared to adults. Also, a shorter t1/2 (24%) and smaller CL/F (28%) were observed in children compared to adults. Similar conclusions were obtained when adjustments were made for differences in body weights between the subject populations.

A summary of the mean pharmacokinetic parameters ((Mean ± SD) of demethylcitalopram for the healthy adult and pediatric subjects following the administration of 20 mg citalopram oral solution is presented in the table below.

Table 9.2 Pharmacokinetic Parameters (Mean ± SD) of Demethylcitalopram following Administration of 20 mg Citalopram in Healthy Adult and Pediatric Volunteers.

Demethylcitalopram			
PK Parameters	Adult (N=12)	Pediatric (N=12)	p
C_{max} (ng/mL)	2.6 ± 1.1	6.3 ± 2.1	0.000
T_{max} (hr)	17.0 ± 7.7	13.9 ± 8.0	0.399
AUC_{0-t} (hr* ng/mL)	172.8 ± 124.4	369.6 ± 96.9	0.000
AUC_{0-inf} (hr* ng/mL)	369.6[a] ± 122.8	463.0[b] ± 107.1	0.136
$t_{1/2}$ (hr)	55.3[a] ± 24.0	41.3[b] ± 14.3	0.091

[a] N=7
[b] N=12

A higher Cmax (142%) and AUC0-t (114%) for demethylcitalopram was observed in children compared to adults. Tmax, tl/2 and AUC0-∞ for demethylcitalopram were not significantly different in children relative to adults.

Effect of Gender: The mean plasma concentration plots for citalopram and demethylcitalopram are shown in the figures below by gender.

Figure 11.3 Plasma Concentrations (mean±SD) of Citalopram after Administration of 20 mg Citalopram in Male vs. Female Volunteers.

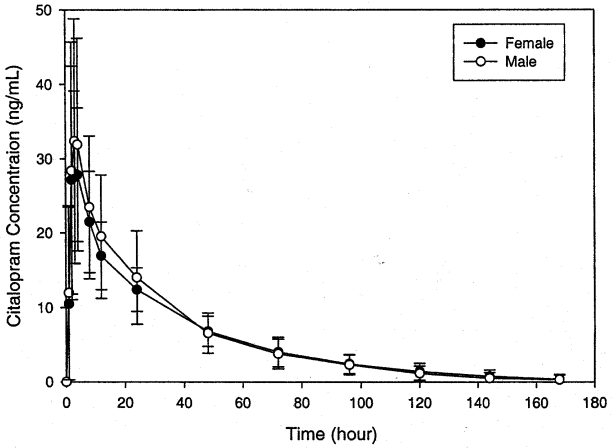
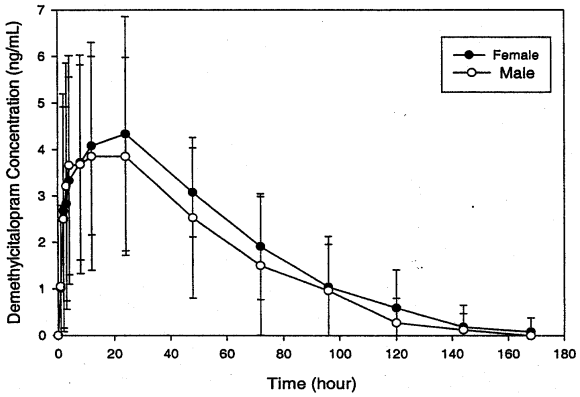


Figure 11.4 Plasma Concentrations (mean±SD) of Demethylcitalopram after Administration of 20 mg Citalopram in Male vs. Female Healthy Volunteers.



The table below shows the mean pharmacokinetic parameters of citalopram following administration of 20 mg citalopram in male and female (both adult and children) volunteers.

Table 9.3 Pharmacokinetic Parameters (Mean ± SD) of Citalopram following Administration of 20 mg Citalopram in Healthy Female and Male Volunteers.

Citalopram			
PK Parameters	Female (N=15)	Male (N=9)	p
C_{max} (ng/mL)	31.0 ± 13.0	34.2 ± 15.2	0.118
T_{max} (hr)	3.2 ± 0.9	3.6 ± 0.5	0.024
AUC_{0-t} (hr* ng/mL)	940.1 ± 276.6	987.7 ± 453.0	0.533
AUC_{0-inf} (hr* ng/mL)	1002.7 ± 288.3	1039.8 ± 461.7	0.514
$t_{1/2}$ (hr)	31.4 ± 7.4	28.1 ± 6.9	0.668
CL/F (L/hr)	21.6 ± 6.6	22.2 ± 8.5	0.347
Vz/F (L)	957.7 ± 295.1	889.3 ± 377.4	0.388

No gender effects were found for any of the pharmacokinetic parameters for citalopram between the female and male groups, except for 42% decrease in demethylcitalopram Tmax at steady state in male patients relative to female patients. The rate and extent of absorption as well as the disposition of escitalopram and S-demethylcitalopram were similar in both adult and pediatric patients. The PK parameters for males and females were compared for children separately (see table below). These data suggest no gender differences in citalopram PK in children following a single 20 mg dose.

	Males (n=6)	Females (n=6)
Cmax (ng/ml)	43.3 (8.2)	44.4 (9.2)
tmax (h)	3.3 (0.6)	2.5 (0.8)
t1/2 (h)	26.1 (4.6)	26.1 (3.7)
AUCinf (ng*h/ml)	1224.5 (455.8)	1098.9 (207.9)
CL/F (L/h)	17.9 (4.9)	18.8 (3.5)

For demethylcitalopram, Cmax (10%) and AUC0-t (19%) of S-demethylcitalopram was higher in female compared to male subjects. No gender effects were found for any of the other pharmacokinetic parameters.

Conclusions: Following a single dose of 20 mg citalopram oral solution, the rate of absorption of citalopram was faster and the extent of absorption was larger in children compared to adults. A shorter t_{max} (24%) and $t_{1/2}$ (24%), higher C_{max} (114%), larger $AUC_{0-\infty}$ (33%), and smaller CL/F (28%) for citalopram were observed in young children compared to adults. Similar conclusions were obtained when adjustments were made for differences in body weights between the subject populations. A higher C_{max} (142%) for demethylcitalopram was observed in children compared to adults. No gender effects on pharmacokinetic parameters (except citalopram T_{max}) were found for citalopram and demethylcitalopram in this study. T_{max} (11%) for citalopram was shorter in females than in males.

CIT-PK-07

Objective: The primary objective of this study was to evaluate the pharmacokinetics of citalopram, demethylcitalopram, didemethylcitalopram and their enantiomers in pediatric patients with depression (compared to adult patients with depression), following titration to a dose of 40 mg daily from a starting dose of 20 mg daily. The secondary objectives were to assess the safety and
efficacy of citalopram in pediatric patients.

Study Design: This study was a 4 week, open-label, parallel group, multiple-dose, dose-escalating study. The study was initially designed to include three groups of 12 depressed patients each, aged 7-11 years (children), 12-17 years (adolescents), and 21-45 years (adults). Because of difficulty recruiting depressed children, the protocol was amended to define a single group of pediatric patients from 10-17 years of age (n=13) for comparison with the adult patients (n=12). The patients received citalopram at a starting dose of 20 mg daily for one week and then received citalopram 40 mg daily for 3 weeks.

Blood and urine samples for pharmacokinetic analysis were collected throughout the study. Efficacy assessments in adult patients were performed by use of Clinical Global Impressions Severity Scale (CGI-S) and Clinical Global Improvement Scale (CGI-I). In the pediatric patients, Kiddie and Young Adult-Schizophrenia and Affective Disorders Schedule-Present and Lifetime (K-SADS-PL) and Children's Depression Rating Scale, Revised (CDRS-R) were used. Safety was assessed throughout the study by monitoring adverse events, laboratory tests, ECG's, physical examinations, and vital signs. Efficacy assessments were administered prior to the first dose of citalopram (Baseline) and after four weeks of treatment with citalopram.

The study drug was orally administered once daily between 0600 hours and 1000 hours. A single 20 mg cltalopram tablet from Day 1 to Day 7 was administered and a single 40 mg citalopram tablet from Day 8 to Day 28. While patients were housed (Days 1 and 28) in the clinic they were given standardized, bland, low fat, xanthine-free meals and snacks. No alcohol-containing foods or beverages was consumed for 72 hours prior to the first dose of study drug (Day 1) until the last blood sample was collected on Day 35. No grapefruit or grapefruit juice was consumed from Day -1 to Day 35, inclusive.

Pharmacokinetic Sample Collection: Blood samples were collected at the following times from all patients except those younger than 12 years of age:
Day 1: 0.0 hour (pre-dose) and 1.0,2.0,3.0,4.0,6.0,8.0, 12.0 hours post-dose
Day 2: 24.0 hours (post-dose)
Day 8: 0.0 hour (pre-dose)
Day 27: 0.0 hour (pre-dose)
Day 28: 0.0 hour (pre-dose), and 1.0,2.0,3.0,4.0,6.0,8.0, and 12.0 hours post-dose.
Days 29,30,32,34, and 35: 24.0,48.0,96.0, 144.0, and 168.0 hours post the Day 28 final drug dose.
For the patient under 12 years of age only 17 blood samples were collected, at the following time points:
Day 1: 0.0 hour (pre-dose) and 1.0,2.0,4.0,8.0, and 12.0 hours post-dose
Day 2: 24 hours post dose
Day 8: 0.0 hour (pre-dose)
Day 28: 0.0 hour (pre-dose), and 1.0,2.0,4.0,8.0, and 12.0 hours post-dose.
Days 29, 30, and 32: 24.0, 48.0, and 96.0, hours post the Day 28 final drug dose.

Bioanalytical Procedure: R- and S-citaloprarn and metabolites in human plasma were determined using a validated LC/MS/MS method. R-citalopram (R-CT), escitalopram (S-CT), R- and S-DCT, R- and S-DDCT and their internal standard, d4-R-CT, were extracted from 0.5 mL human plasma using diethyl ether and then back extracted with 0.1 N HCl. The mobile phase was 0.1 % ammonium trifluoroacetate in methanol. The enantiomers of citalopram, demethylcitalopram, and didemethylcitalopram were quantitated using a triple quadrupole mass spectrometer.

The dynamic ranges of the assays were from 1 to 150 ng/ml in plasma for all analytes. All analytical runs had standard curve correlation coefficients greater than 0.99. For plasma standards, the precision and accuracy for all analytes were within 5.3% and -3.5%, respectively, not including outliers. The precision and accuracy for all analytes were within 14.2% and 5.6%, respectively, including outliers. For quality control samples, the precision and accuracy for all analytes were within 16.7% and -9.7%, respectively, including outliers.

Statistical Analysis: Statistical analyses were performed with the Statistical Analyses System (SAS) version 6.12 for the UNIX system microcomputer using the General Linear Models procedure (GLM). Analysis of variance (ANOV A) was performed on the pharmacokinetic parameters including Cmax, AUC0-24 and Tmax after the initial doses, and Cmax, AUCss, Tmax, t1/2, CL/F after the final dose. AUC and Cmax were log-transformed in the analysis of variance.
Statistical comparison of pharmacokinetic parameters between pediatric and adult patients were performed using ANOV A adjusted for gender (as the factor). Similarly, gender effects on pharmacokinetic parameters were assessed using ANOVA adjusted for age (as the factor).

Patient Demographics: Twenty-five patients, twelve adult patients (4 males and 8 females) and thirteen pediatric patients (7 males and 6 females) were enrolled and received citalopram. Patients' demographic characteristics are shown in the table below.

Table 8.1 Summary of Demographic Characteristics

	Adult N=12	Pediatric N=13	All Patients N=25
Age, years			
Mean	36	14.2	24.7
Standard Deviation	6.4	1.9	12.0
Min – Max	21, 44	10, 17	10, 44
Weight, kg			
Mean	77.6	62.3	69.6
Standard Deviation	14.95	11.69	15.2
Min – Max	55.8, 102.5	41.2, 78.2	41.2, 102.5
Height, cm			
Mean	172.8	165.9	169.2
Standard Deviation	12.3	12.8	12.8
Min – Max	157.0, 193.0	146.0, 191.7	146.0, 193.0

Cross Reference: Table 1.1, Appendix F

Pharmacokinetic Results: Pharmacokinetic data were analyzed for all 23 patients [11 adults (7 females and 4 males) and 12 pediatric patients (7 males and 5 females)] who completed the study.

In general, none of the patients had detectable concentrations of didemethylcitalopram during the 24 hour period after the initial dose of 20 mg citalopram and the concentrations for didemethylcitalopram at steady-state were too low to estimate the pharmacokinetic parameters. No discussion of didemethylcitalopram pharmacokinetics has been presented by the sponsor.

Effect of Age:

Single Dose Pharmacokinetics: The mean plasma concentration plots for citalopram and demethylcitalopram following a single 20 mg dose of Celexa are shown in the figures below by age group.

Figure 12.1 Plasma Concentrations (mean±SD) of Citalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric vs. Adult Patients

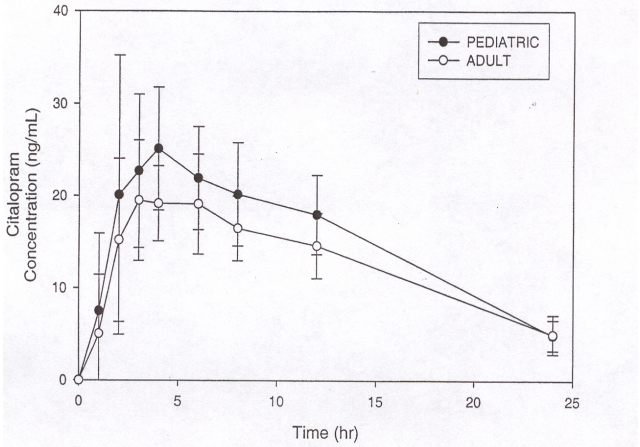
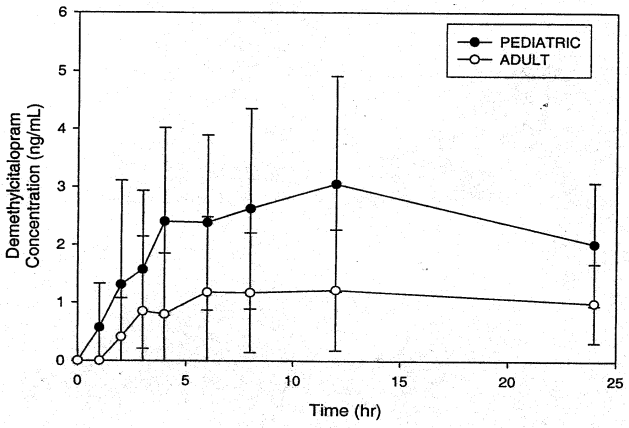


Figure 12.2 Plasma Concentrations (mean±SD) of Demethylcitalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric vs. Adult Patients.



A summary of the mean pharmacokinetic parameters (Mean ± SD) of citalopram and demethylcitalopram for the healthy adult and pediatric subjects following the administration of a single oral dose of 20 mg is presented in the table below.

No significant age effects were found for Cmax, Tmax, or AUC0-24 of citalopram or demethylcitalopram between the pediatric and adult groups after the initial dose of 20 mg citalopram. These data suggest that the rate and extent of absorption of citalopram and its rate of metabolism to demethylcitalopram following a single dose of 20 mg citalopram were similar in the two age groups following a single oral dose of Celexa administered as 20 mg tablet.

Comparison of the pharmacokinetics of citalopram and demethylcitalopram following a single 20 mg dose across studies (PK-13 and PK-07) suggests that younger children (aged 7-11 years) have higher AUC (approximately 30%) and Cmax (60-100%) than adolescents and adults following a single 20 mg dose of citalopram.

Multiple Dose Pharmacokinetics: The mean plasma concentration plots for citalopram and demethylcitalopram following multiple doses of Celexa 40 mg once daily are shown in the figures below by age group.

Figure 12.3 Plasma Concentrations (mean±SD) of Citalopram after a Multiple Dose Administration of 40 mg Citalopram in Pediatric vs. Adult Patients.

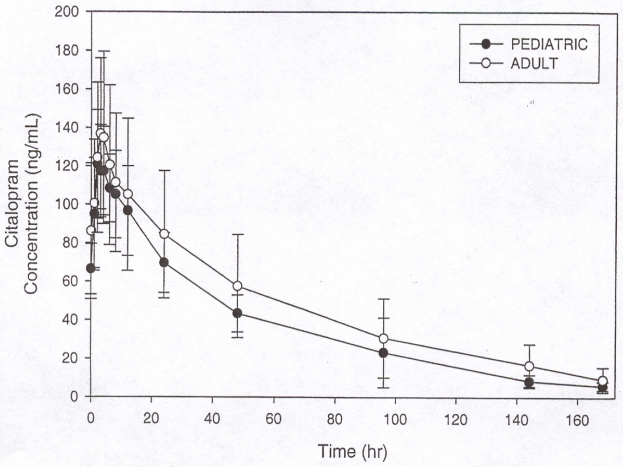


Figure 12.4 Plasma Concentrations (mean±SD) of Demethylcitalopram after a Multiple Dose Administration of 40 mg Citalopram in Pediatric vs. Adult Patients.

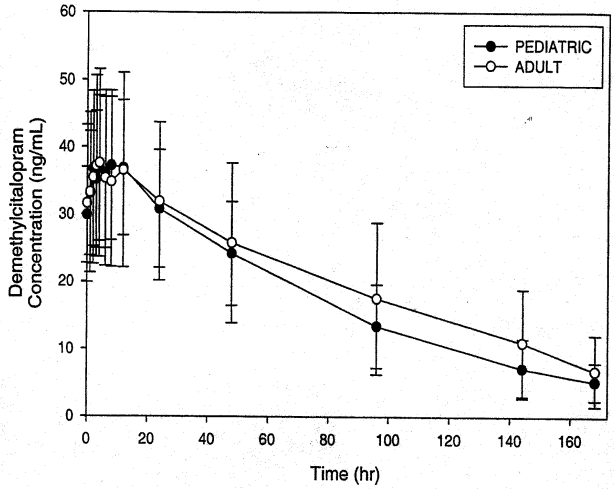


Table 10.1 Pharmacokinetic Parameters (Mean ± SD) of Citalopram and Demethylcitalopram Following a Single Dose of 20 mg Citalopram in Adult and Pediatric Patients.

Citalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	23.0 ± 5.5	27.9 ± 8.7	0.480
T_{max} (hr)	3.4 ± 1.8	3.7 ± 1.4	0.664
AUC_{0-24} (hr* ng/mL)	341.0 ± 73.3	418.9 ± 116.6	0.567
Demethylcitalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	1.5 ± 1.2	3.4 ± 1.7	0.099
T_{max} (hr)	13.4 [a] ± 9.5	15.8 ± 7.6	0.850
AUC_{0-24} (hr* ng/mL)	26.6 ± 22.6	63.8 ± 40.6	0.582

[a] N=8

A summary of the mean pharmacokinetic parameters ((Mean ± SD) of citalopram and demethylcitalopram for the healthy adult and pediatric subjects following multiple doses of 40 mg/day is presented in the table below.

Table 10.2 Pharmacokinetic Parameters (Mean ± SD) of Citalopram and Demethylcitalopram Following Multiple Dose of Administration of 40 mg Citalopram in Adult and Pediatric Patients

Citalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	144.8 ± 43.1	127.4 ± 27.4	0.393
T_{max} (hr)	2.9 ± 0.5	2.6 ± 1.4	0.540
AUC_{ss} (hr* ng/mL)	2527.8 ± 884.3	2273.1 ± 469.7	0.676
$t_{1/2}$ (hr)	43.6 ± 7.7	38.1 ± 8.4	0.930
CL/F (L/hr)	17.7 ± 6.1	18.3 ± 4.1	0.919
Vz/F (L)	1063.2 ± 242.7	1030.7 ± 445.0	0.667
Ae_{0-24} (mg)	9.7 [a] ± 5.3	7.7[a] ± 2.6	0.269
Demethylcitalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	40.1 ± 13.6	39.8 ± 11.2	0.985
T_{max} (hr)	6.8 ± 4.8	7.2 ± 4.2	0.360
AUC_{ss} (hr* ng/mL)	837.2 ± 310.1	842.3 ± 233.4	0.841
$t_{1/2}$ (hr)	67.9 ± 17.7	58.8 ± 19.7	0.230
Ae_{0-24} (mg)	5.7 [a] ± 1.2	7.4[a] ± 1.8	0.036

[a] N=10

No age effects were found for the pharmacokinetics of citalopram and demethylcitalopram between the pediatric and adult groups after a multiple daily dose of 40 mg citalopram.

Effect of Gender: The tables below show the mean pharmacokinetic parameters of citalopram and demethylcitalopram following a single dose of 20 mg citalopram and multiple dose administration of 40 mg once daily in male and female volunteers.

Table 10.3 Pharmacokinetic Parameters (Mean ± SD) of Citalopram and Demethylcitalopram Following a Single Dose of 20 mg Citalopram in Female and Male Patients.

Citalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	26.7 ± 7.7	24.3 ± 7.7	0.220
T_{max} (hr)	3.5 ± 1.6	3.5 ± 1.6	0.975
AUC_{0-24} (hr* ng/mL)	394.7 ± 115.5	367.4 ± 93.2	0.336
Demethylcitalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	2.5 ± 1.7	2.5 ± 2.0	0.898
T_{max} (hr)	12.5 [a] ± 8.3	17.8 [b] ± 7.8	0.215
AUC_{0-24} (hr* ng/mL)	45.9 ± 35.7	46.2 ± 41.5	0.582

[a] N=11
[b] N=9

Table 10.4 Pharmacokinetic Parameters (Mean ± SD) of Citalopram and Demethylcitalopram Following Multiple Dose Administration of 40 mg Citalopram in Female and Male Patients.

Citalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	138.7 ± 31.1	132.5 ± 42.1	0.726
T_{max} (hr)	2.8 ± 0.7	2.6 ± 1.4	0.790
AUC_{ss} (hr* ng/mL)	2463.1 ± 521.5	2320.6 ± 866.6	0.522
$t_{1/2}$ (hr)	40.1 ± 7.4	41.5 ± 9.6	0.431
CL/F (L/hr)	17.0 ± 4.1	19.1 ± 5.9	0.354
Vz/F (L)	976.6 ± 262.7	1122.3 ± 435.1	0.313
Ae_{0-24} (mg)	8.3 [a] ± 3.2	9.0 [a] ± 5.2	0.569
Demethylcitalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	39.1 ± 12.1	41.0 ± 12.6	0.662
T_{max} (hr)	8.8 ± 3.9	5.1 ± 4.2	0.015
AUC_{ss} (hr* ng/mL)	828.1 ± 267.8	852.7 ± 277.2	0.817
$t_{1/2}$ (hr)	62.1 ± 17.3	64.4 ± 21.3	0.582
Ae_{0-24} (mg)	5.9 [a] ± 1.3	7.3 [a] ± 1.9	0.122

[a] N=10

No gender effects were found for any of the pharmacokinetic parameters for citalopram and demethylcitalopram between the female and male groups after a single dose of 20 mg
Citalopram or multiple dose administration of 40 mg citalopram.

Conclusions: Pharmacokinetic parameters of citalopram and demethylcitalopram after a single dose of 20 mg citalopram and after multiple doses of 40 mg once daily citalopram were similar between depressed adolescents and adults.

Sparse Sampling data from Efficacy Trial CIT-MD-18

Summary: In efficacy trial CIT-MD-18 (in depressed children and adolescents aged 7-17 years), the sponsor has collected a blood sample for the measurement of citalopram steady-state concentrations in plasma. Wherever possible, the sample was collected between 8-14 hours after the last dose of study medication was taken. In this study, the steady-state concentrations of citalopram were approximately 13% higher in the children as compared to the adolescents. Correlation analyses revealed no significant correlation between age and citalopram concentration (r=0.059, p=0.650). Body weight also appeared to be uncorrelated with either citalopram concentration (r=-0.218; p=0.089). Tables and figures supporting these results are provided below. There is a variability in sampling times, no pharmacokinetic modeling was performed on this data, and (13%) increased concentrations were observed in children compared to adolescents. Therefore, data from the sparse sampling pharmacokinetic study need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adolescents/adults.

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Pharmacokinetic Results from Study CIT-MD-18 (Tables and Figures)

Forest Laboratories, Inc.
Protocol CIT-MD-18

Appendix Table 2A
Demogrphic Characteristics - Children
Safety Population

Demographic Parameter	Placebo (N=38)	Citalopram (N=45)
Age (Year)		
Mean	9.6	9.3
N	38	45
SD	1.31	1.13
Median	10.0	9.0
Range	7, 11	7, 11
Gender (n, %)		
Female	16 (42.1)	19 (42.2)
Male	22 (57.9)	26 (57.8)
Race (n, %)		
Caucasian (White)	31 (81.6)	36 (80.0)
Non-Caucasian	7 (18.4)	9 (20.0)
Other	3 (7.9)	6 (13.3)
Black	4 (10.5)	3 (6.7)
Weight (lb)		
Mean	97.6	98.9
N	38	45
SD	37.99	43.01
Median	95.8	88.6
Range	48.0, 219.0	50.0, 247.0
Height (in)		
Mean	56.1	55.7
N	38	45
SD	4.23	4.72
Median	56.3	55.5
Range	47.5, 64.0	48.0, 68.2

Note: Age = (Date of randomization - Date of birth)/365.25.
p-values for between-treatment comparisons are from two-way ANOVA additive model (treatment, center) for continuous vari
test (controlling for center) for categorical variables.
For race, comparison was done for Caucasian vs. Non-Caucasian.

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Appendix Table 2B
Demogrphic Characteristics - Adolescents
Safety Population

Demographic Parameter	Placebo (N=47)	Citalopram (N=44)	p-value
Age (Year)			
Mean	14.1	14.9	0.079
N	47	44	
SD	1.77	1.73	
Median	14.0	15.0	
Range	12, 17	12, 17	
Gender (n, %)			
Female	30 (63.8)	28 (63.6)	0.893
Male	17 (36.2)	16 (36.4)	
Race (n, %)			
Caucasian (White)	31 (66.0)	36 (81.8)	0.028
Non-Caucasian	16 (34.0)	8 (18.2)	
Other	9 (19.1)	3 (6.8)	
Black	7 (14.9)	5 (11.4)	
Weight (lb)			
Mean	148.2	149.1	0.888
N	47	44	
SD	60.31	46.19	
Median	138.5	143.3	
Range	72.0, 396.0	74.5, 280.1	
Height (in)			
Mean	63.5	64.7	0.290
N	47	44	
SD	4.37	3.99	
Median	64.0	64.6	
Range	54.0, 74.5	56.5, 74.0	

Note: Age = (Date of randomization - Date of birth)/365.25.
p-values for between-treatment comparisons are from two-way ANOVA additive model (treatment, center) for continuous variables and from CMH test (controlling for center) for categorical variables.
For race, comparison was done for Caucasian vs. Non-Caucasian.

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Forest Laboratories, Inc.
Protocol CIT-MD-18

Citalopram
09/17/2001 (Page 1 of 1)

Appendix Table 13A
Descriptive Statistics for Plasma Concentration of Citalopram by Previous Dose
Safety Population

	Citalopram 20 mg			Citalopram 40 mg			Overall		
	Children	Adolescents	Total	Children	Adolescents	Total	Children	Adolescents	Total
Citalopram (ng/mL)									
MEAN	50.20	37.26	49.39	65.67	77.34	80.81	71.90	63.56	67.63
N	15	11	26	15	21	36	30	32	62
SD	42.806	27.973	37.900	60.941	70.630	69.071	57.971	62.022	59.794
MIN	1.00	2.75	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MAX	124.89	99.51	124.89	289.77	279.18	289.77	289.77	279.18	289.77
DCT (ng/mL)									
MEAN	24.93	14.68	20.60	46.01	26.52	35.81	35.47	23.77	29.43
N	15	12	26	15	21	36	30	32	62
SD	14.445	9.487	13.389	26.140	19.263	23.703	23.357	17.688	21.287
MIN	1.00	2.40	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MAX	54.09	29.51	54.09	85.73	67.36	85.73	85.73	67.36	85.73
DDCT (ng/mL)									
MEAN	3.12	2.87	3.02	8.50	5.51	6.76	5.81	4.60	5.19
N	15	11	26	15	21	36	30	32	62
SD	1.672	1.950	1.761	6.359	4.394	5.426	5.324	3.912	4.651
MIN	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MAX	5.75	6.62	6.62	22.15	13.92	22.15	22.15	13.92	22.15

Figure 3.3
Scattergrams: Weight vs. Citalopram Plasma Concentration
Safety Population

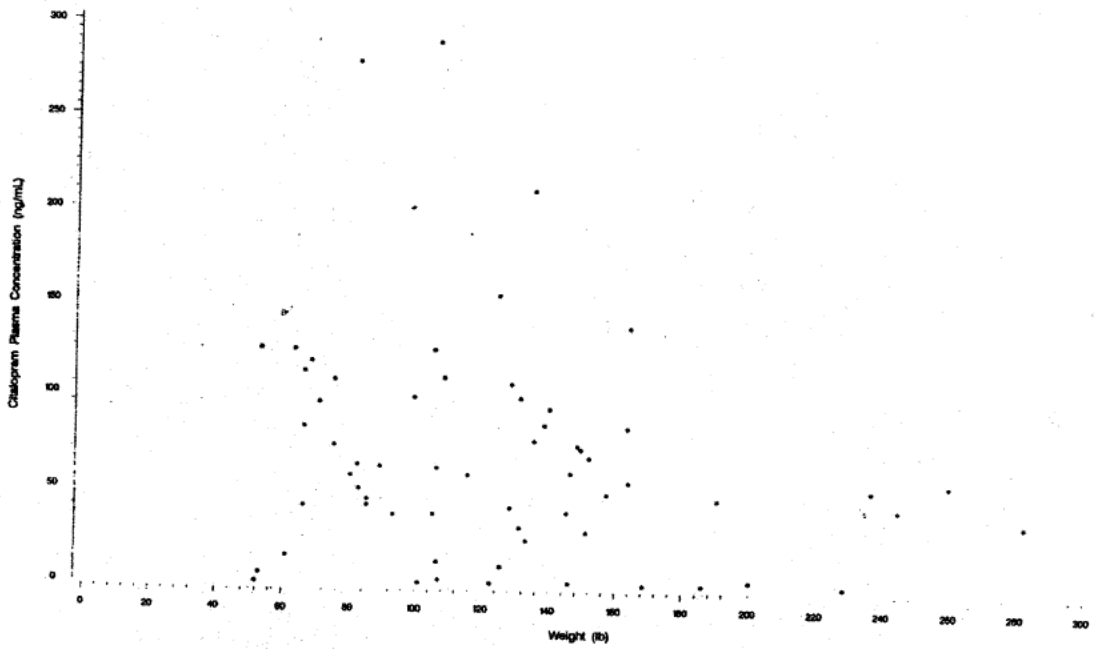
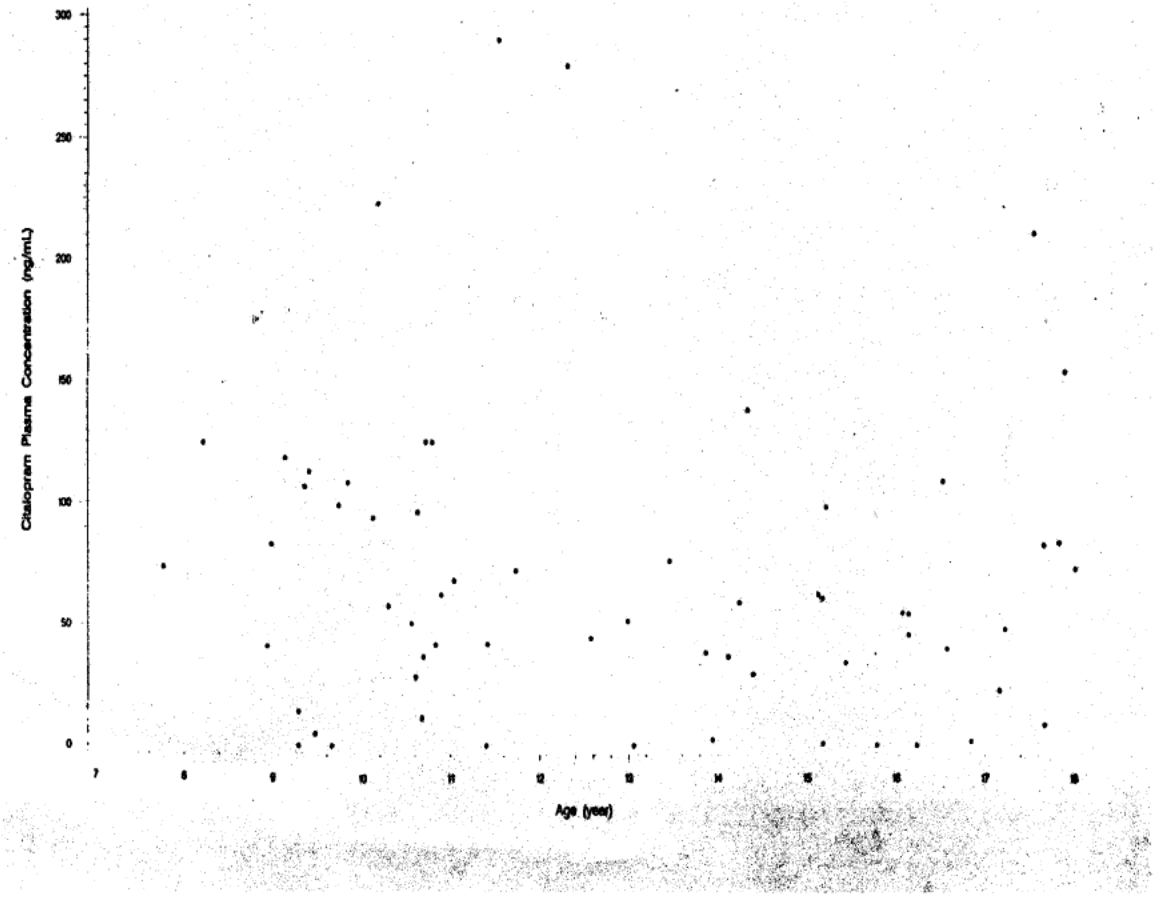


Figure 3.1
Scattergrams: Age vs. Citalopram Plasma Concentration
Safety Population



Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-822 (b) (4) 016 21-046 (b) (4) 002	**Brand Name**	Celexa
OCPB Division (I, II, III)	I	**Generic Name**	Citalopram
Medical Division	Neuropharm	**Drug Class**	Antidepressant
OCPB Reviewer	Vanitha J. Sekar	**Indication(s)**	Depression
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	IR tablets 10 mg, 20 mg, 40 mg Oral Solution 2 mg/ml
		Dosing Regimen	20-60 mg/day in adults
Date of Submission	4-18-02	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	9-1-02	**Sponsor**	Forest Labs
PDUFA Due Date	10-19-02	**Priority Classification**	Priority (Pediatric supplement)
Division Due Date	9-15-02		Age range 7-17 years

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	**X**			
HPK Summary				No overall summary provided
(b) (4)				
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

Data sparse:	**X**	**1**		No formal analysis performed. Descriptive data analysis performed.
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	This submission contains results from 3 in-vivo studies: 1) Single dose (20 mg) pharmacokinetic study in 12 healthy children aged 7-11 years and in 12 adults, 2) multiple dose (40 mg/day maintenance dose) pharmacokinetic study in 13 pediatric depressed patients aged 10-17 years and in 12 adults, 3) Efficacy trial in pediatric depressed patients aged 7-17 years in which steady-state trough concentrations were measured (n=45 children 7-11 years and n=44 children aged 12-17 years).
Comments sent to firm ?		
QBR questions (key issues to be considered)	Only one of the 2 clinical efficacy studies demonstrate efficacy of Celexa in the pediatric population – the second study is a failed study. The CPB review will therefore focus only on traditional pharmacokinetic studies and descriptive statistics in the clinical trial to evaluate whether the applicant has adequately evaluated the pharmacokinetics of Celexa in the pediatric population and if the pharmacokinetics of Celexa are similar in the pediatric population and in adults.	
Other comments or information not included above	The purpose of this filing meeting in addition to determining filability is to determine whether it fully responds to the pediatric written request so that the applicant may obtain an additional 6 months of exclusivity. The sponsor has satisfactorily addressed issues in the written request pertaining to evaluating the pharmacokinetics of Celexa in the pediatric population	
Primary reviewer Signature and Date	Vanitha J Sekar 5/31/02	
Secondary reviewer Signature and Date		

CC: NDA 20-822, 21-046 HFD-850(Lee), HFD-120(David), HFD-860(Uppoor, Mehta, Marroum), CDR (B. Murphy)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Vanitha Sekar
7/19/02 01:59:13 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/19/02 03:38:51 PM
BIOPHARMACEUTICS