CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/SE5-064

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Vanitha Sekar			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 3/14/02	IND No.: Serial No.	NDA No. 18-936 SE5-064	DATE OF DOCUMENT 10/4/01	
NAME OF DRUG Prozac (Fluoxetine HCl)	PRIORITY CONSIDERATION		Date of informal/Formal Consult 10/22/01	

NAME OF THE SPONSOR: [Eli Lilly]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- ☐ PHASE III PROTOCOL
- ☐ DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☐ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☒ OTHER *(SPECIFY BELOW)*:

Response to approvable letter

[Meeting to clarify RTF issues]

REVIEW ACTION

- ☐ NAI (No action indicated)
- ☐ E-mail comments to:

☐Medical ☐Chemist ☐Pharm-Tox
☐Micro ☐Pharmacometrics ☐Others
(Check as appropriate and attach e-mail)

- ☐ Oral communication with

Name: [ ]

- ☐ Comments communicated in meeting
- ☐ Formal Review/Memo (attached)
- ☒ See comments below
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*:

[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Please see attachment for comments

SIGNATURE OF REVIEWER: Vanitha J Sekar	Date 3/14/02
SIGNATURE OF TEAM LEADER:	Date
CC.: HFD # [860]; TL: [Uppoor]; DD: [Mehta]	**Project Manager:** Paul David **Date**

Background: This submission consists of the sponsor's response to the approvable letter sent by the Agency for the use of Prozac in children and adolescents with depression and OCD. The approvable letter contained revised labeling proposed by the Agency as well as other issues. This review will discuss of the responses from the sponsor to the clinical pharmacology issues addressed in the approvable letter.

Labeling: Barring minor editorial changes, the sponsor is in agreement with all of OCPB's proposed changes to the following sections of the label: Clinical Pharmacology-Pediatric Pharmacokinetics, Precautions-Pediatric Use. The sponsor's proposed changes to these two sections of the (approvable) label are acceptable.

In addition, the sponsor has also made changes to the Dosage and Administration section (for major depressive disorder) as follows:

Approvable letter:
Pediatric (Children and Adolescents)- In the, short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of ——— patients were administered fluoxetine doses of 10 to 20 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). ——— treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day. ———
A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

Sponsor's proposal:
In the, short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of ——— , patients were administered fluoxetine doses of 10 to 20 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day. However, due to higher plasma levels in lower weight children, the starting and target dose of fluoxetine in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

The sponsor's proposed change in wording to the above section of the label is acceptable.

Phase 4 Commitment for a PK-PD study of fluoxetine at higher doses:

———
———
———

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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
3/14/02 06:31:04 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/14/02 06:47:11 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	18-936 SE5-064	Brand Name	Prozac
OCPB Division (I, II, III)	I	Generic Name	Fluoxetine
Medical Division	Neuropharm	Drug Class	Antidepressant (SSRI)
OCPB Reviewer	Vanitha J. Sekar	Indication(s)	Depression and OCD
OCPB Team Leader	Ramana Uppoor	Dosage Form	Capsules
		Dosing Regimen	20 t[illegible] mg/day
Date of Submission	9-14-2000, 1/5/2001, 3/16/2001, 3/19/2001, 5/22/2001	Route of Administration	Oral
Estimated Due Date of OCPB Review	6-15-2001	Sponsor	Eli Lilly
PDUFA Due Date	7-14-2001	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE		2	2	
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
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:				
multiple dose				
Patients-				
single dose:				
multiple dose	x	1	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:				
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	1	

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-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	2	2	2	

Filability and QBR comments

	"X" if yes	Comments to be sent to firm
Application filable ?	X	1. Please submit data sets for individual patients in electronic format. We request that the following information be provided for the data sets from each of the studies, HCIU (pediatric), HCJE (pediatric), HCFB (adult), HCFC (adult): Subject ID, Dose, Time of dose administration (h), Time of sampling(h), Plasma fluoxetine conc, Plasma norfluoxetine conc., Age, Weight, Height, BSA, Gender, Race, Creatinine CL, Phenotype 2. Please submit electronically, the control files and data sets that were used for each of the models evaluated using population pharmacokinetic analysis
Comments sent to firm ?		
QBR questions (key issues to be considered)	1. Do the studies provide adequate PKinformation for the use of fluoxetine in the pediatric population (6 -17 years) across the recommended dose range? 2. Are the PK of fluoxetine similar in the pediatric population and in adults? 3. Is there an exposure-response relationship forfluoxetine with respect to QTc prolongation in the pediatric population?	
Other comments or information not included above		
Primary reviewer Signature and Date	Vanitha Sekar, PhD	
Secondary reviewer Signature and Date	Ramana Uppoor, PhD	

CC: NDA 18-936 SE5-064, HFD-850(Lee), HFD-120(David), HFD-860(Sekar, Uppoor, Mehta, Sahajwalla), CDR (B. Murphy)

TABLE OF CONTENTS

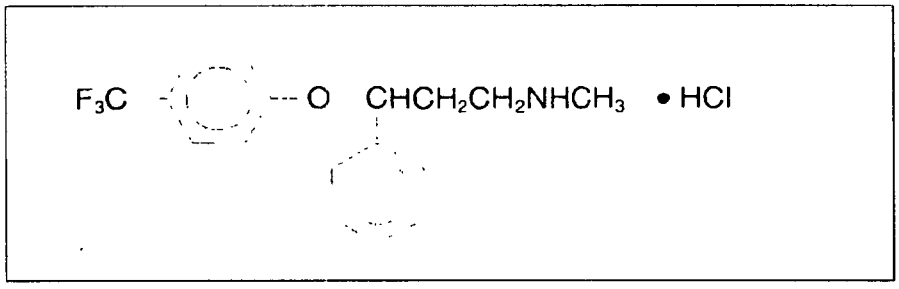
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Prozac® (Fluoxetine)
NDA: 18936-SE5-064
FORMULATION: Capsules
APPLICANT: Eli-Lilly

PRIMARY REVIEWER: Vanitha J. Sekar, PhD
TYPE: Pediatric efficacy suppl (6-17 years)
STRENGTH: 10, 20, 40 mg
SUBMISISON DATE: 9/14/00, 1/5/01, 3/16/01, 3/19/01, 5/22/01

Background: Fluoxetine HCl is a selective serotonin (5-HT) reuptake inhibitor (SSRI). It is chemically unrelated to other tricyclic, tetracyclic or other available antidepressants. Its molecular weight is 345.79. The structural formula is:

Figure 1



Prozac® capsules are available in 10 mg, 20 mg and 40 mg strengths for oral administration. Prozac is indicated for the treatment of depression and Obsessive Compulsive Disorder (OCD) in adults. The mechanism of action of fluoxetine in depression and OCD is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons.

Fluoxetine is a racemic mixture (50/50) of R-fluoxetine and S-fluoxetine. Animal studies suggest that the two are equipotent in their pharmacologic activity. Fluoxetine is approximately 94% plasma protein bound. Food does not appear to affect the bioavailability of fluoxetine, but absorption may be delayed. Fluoxetine is metabolized (via CYP2D6) to norfluoxetine, which is an active metabolite. The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state. Plasma concentrations of fluoxetine following chronic dosing are higher than those predicted by single-dose studies, because fluoxetine pharmacokinetics are not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics.

This submission contains results from 3 studies that have been submitted as a response to a pediatric written request from the Agency. Two of these studies are efficacy/safety trials in pediatric patients with OCD (HCJW)and depression (HCJE). The third study (HCIU) is a pharmacokinetic study of fluoxetine in the pediatric population. The pharmacokinetic results from studies HCIU and HCJE are reviewed as part of this clinical pharm/biopharmaceutics review.

Analytical Methods: Studies HCIU and HCJE: Plasma concentrations of fluoxetine and norfluoxetine were analyzed using a validated ——— method. The limit of detection for both fluoxetine and norfluoxetine was 1 ng/ml. No interfering peaks were observed. The method was linear in the range of ——— for fluoxetine and norfluoxetine. Intra-day precision and accuracy of quality control samples were within acceptable limits. Precision (%RSD) ranged from ——— for fluoxetine and ——— for norfluoxetine, respectively. Accuracy (%RE) ranged from - ——— for fluoxetine and from - ——— for norfluoxetine. Inter-day

precision and accuracy of quality control samples were within acceptable limits. Precision (%RSD) ranged from — for fluoxetine and —— for norfluoxetine, respectively. Accuracy (%RE) ranged from —— for fluoxetine and from —— for norfluoxetine.

Overall Summary: Plasma concentrations of fluoxetine and norfluoxetine in children were 2-fold and 1.5 fold higher, respectively, than those observed in adolescents. Steady state fluoxetine concentrations in children and adolescents were 171 ng/mL and 86 ng/mL, respectively. Steady state norfluoxetine concentrations in children and adolescents were 195 ng/mL and 113 ng/mL, respectively. These differences in concentrations between children and adolescents were mainly attributed to differences in body weight. The mean overall steady state concentrations of fluoxetine and norfluoxetine in adults were 96.86 and 110.42 ng/mL. Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however these concentrations were within the range of concentrations observed in the adult population. There were no gender-related differences in the pharmacokinetics of fluoxetine in the pediatric population. The population PK modeling (using pediatric and adult PK data) conducted by the applicant and reviewed by the Agency also supports these conclusions (Refer Pharmacometrics review in appendix).

There were other similarities in the pharmacokinetics of fluoxetine between the pediatric population and adults:
Ratio of norfluoxetine:fluoxetine was similar in both groups (1.2-1.3)
Steady state was achieved approximately at the same time, 3-4 weeks after the start of dosing
Fluoxetine t1/2 was similar in both groups (4-6 days)
Accumulation ratio in the pediatric population was approx. 15, similar to that in adults (10-20)

The higher plasma concentrations observed in children compared to adults may have warranted a dose adjustment (starting dose of 10 mg/day for several weeks before titration to higher dose if necessary) in this population. However clinical trials were conducted using maintenance doses of 20 mg/day with an initiation dose of 10 mg/day.

The applicant has not studied the pharmacokinetics of fluoxetine following doses greater than 20 mg daily in the pediatric population. ——

The effect of administration of Prozac on QT prolongation in the pediatric population evaluated in these studies was analyzed. The analysis suggested a lack of influence of fluoxetine exposure on QTc prolongation in the pediatric population following administration of 20 mg/day Prozac.

Proposed Dosing Regimen for Pediatric Population (children and adolescents):
Depression: The applicant's recommended starting dose for Prozac in the pediatric population —— is 10 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day. A dose increase may be considered after several weeks if insufficient clinical improvement is observed. ——

OCD: The applicant's recommended starting dose for Prozac in the pediatric population —— is 10 mg/day. After 2 weeks at 10 mg/day, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several weeks if insufficient clinical improvement is observed. ——

Labeling comments: See attached annotated label with OCPB recommendations.

Recommendation: The pharmacokinetic studies provided in this pediatric supplement for NDA 18936 SE5-064 submitted to the Division of Neuropharmacological Drug Products to fulfil the pediatric written request provide an understanding of the pharmacokinetics of fluoxetine in pediatric patients between the ages of [redacted] inclusive. The information on the pharmacokinetics of fluoxetine (Prozac®) provided in the pediatric population is adequate to support approval.

Comments to Medical Officer:

1. The higher plasma concentrations of fluoxetine/norfluoxetine observed in children compared to adults may warrant a dose adjustment (starting dose of 10 mg/day for several weeks before titration to higher dose if necessary) in this population.
2. [redacted]
3. We recommend that the applicant attempt to characterize pharmacokinetics of both enantiomers R- and S-fluoxetine in the above-mentioned pharmacokinetic study.
4. We recommend that the applicant collect EKG data at the time of pharmacokinetic assessments in an attempt to evaluate the presence (or lack of) a concentration-response relationship for R- and S-fluoxetine and QTc changes in the above mentioned study.

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 18936 SE5-064
/MO/ A. Mosholder
/CSO/P. David
/Biopharm/V. Sekar
/Acting TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta

APPENDIX

Study HCJE: Fluoxetine versus placebo in childhood/adolescent depression.

Objectives: The primary objective was to compare the safety and efficacy of fluoxetine 20 mg/day and placebo in treatment of major depression in children and adolescents. A secondary objective was to determine the pharmacokinetics of fluoxetine and norfluoxetine in this patient population following a dose of 20 mg/day.

Study Design: The study was a randomized, double-blind parallel group study in depressed children and adolescents between the ages of 8 and 17 years, inclusive. There were 6 study periods: Period 1 was a diagnostic evaluation period for 2 weeks; Period 2 was a single blind placebo wash-out period for 1 week; Period 3 was a double blind adaptation period for 1 week where patients were randomized to receive placebo or fluoxetine 10 mg/day; Period 4 was a double-blind fixed dose acute treatment period for 8 weeks where patients were randomized to receive fluoxetine 20 mg/day; Period 5 was a double blind nonresponder rerandomization period for 10 weeks; Period 6 is the ongoing 32 week relapse prevention phase. See figure below.

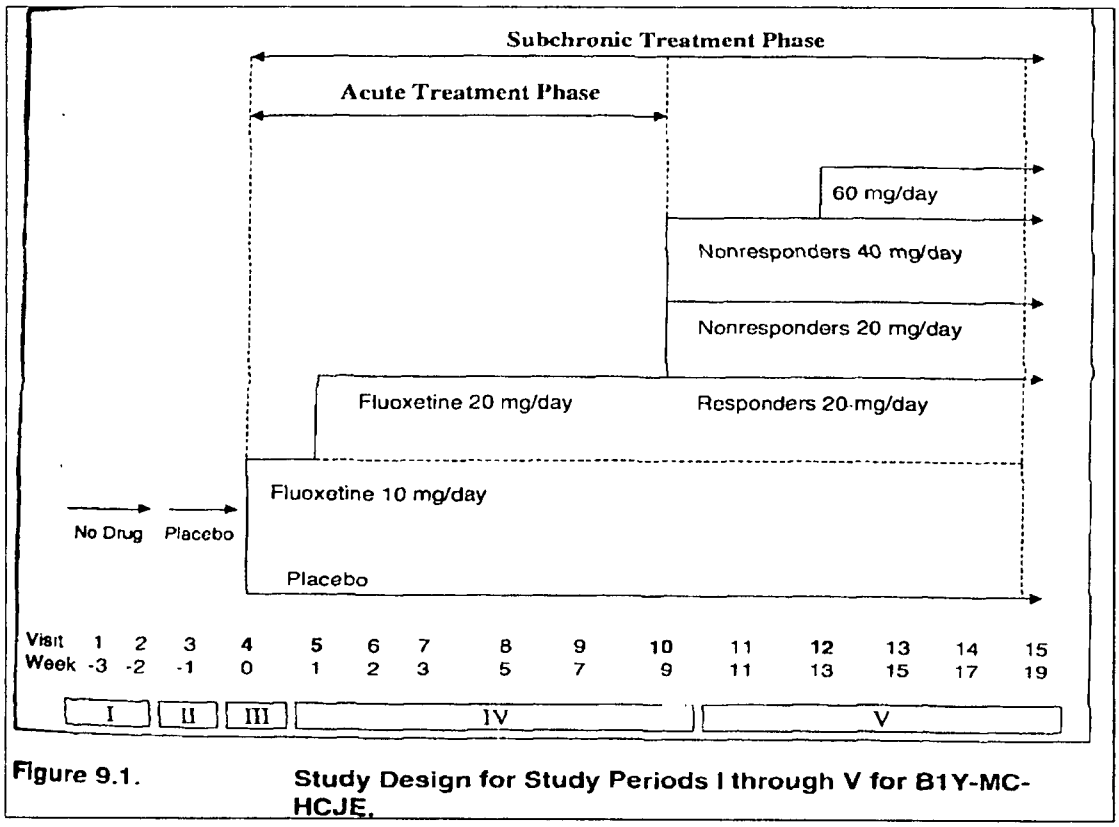


Figure 9.1. Study Design for Study Periods I through V for B1Y-MC-HCJE.

Formulation characteristics: Fluoxetine HCl 10 mg (Lot # CT07620, CT12697)), 20 (Lot # CT09678, CT10738)), and placebo (Lot # CT09679, CT10799) capsules were given orally.

Pharmacokinetics:
Pharmacokinetic Sample Collection: A blood sample was obtained at baseline and steady state blood samples were obtained at Visits 10 and 15 following at least 4 weeks of fixed fluoxetine dosing at 20 mg/day. All blood samples were collected randomly within the dosing interval of 24 hours. Blood samples were also obtained from patients who discontinued early

from the study. One blood sample was collected from 53% of patients and 47% patients provided two blood samples. There were a total of 138 observations (concentrations), of which 79 were from children and 59 were from adolescents. Patients were not phenotyped or genotyped for their CYP2D6 status.

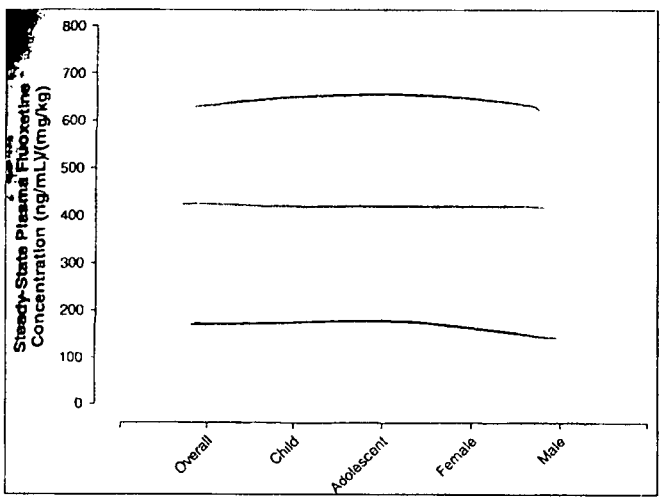
Pharmacokinetic Patient Sample: The pharmacokinetic data set consisted of 94 patients of which 52 were children (8-12 years; mean 10.8 years) and 42 were adolescents (13 to 17 years; mean 15.1 years). The demographic characteristics of the patients included in the pharmacokinetic analysis are shown in the table below.

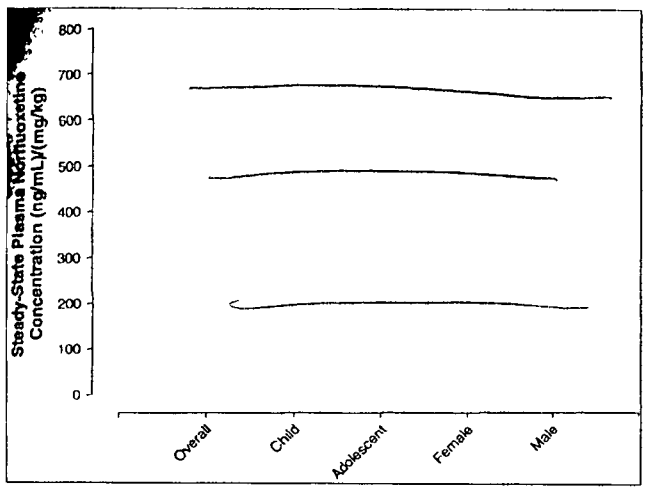
Demographic	Category	Subcategory	N	Mean	SD	Range
Age (years)	Overall	-	94	12.8	2.5	8-17
	Children	-	52	10.8	1.3	8-12
	Adolescents	-	42	15.1	1.3	13-17
Ethnic Origin	Overall	Caucasian	85	-	-	-
		Other	9	-	-	-
	Children	Caucasian	49	-	-	-
		Other	3	-	-	-
	Adolescents	Caucasian	36	-	-	-
		Other	6	-	-	-
Gender	Overall	Male	47	-	-	-
		Female	47	-	-	-
	Children	Male	28	-	-	-
		Female	24	-	-	-
	Adolescents	Male	19	-	-	-
		Female	23	-	-	-
Weight (kg)	Overall	-	93	57.7	18.4	24-103
	Children	-	52	49.2	16.0	24-102
	Adolescents	-	41[a]	68.6	15.4	34-103
Height (cm)	Overall	-	93	155.8	14.3	124-188
	Children	-	52	146.9	11.0	124-188
	Adolescents	-	41[a]	167.2	8.9	135-188
Body Mass Index (kg/m^2)[b]	Overall	-	93	23.4	5.7	15-40
	Children	-	52	22.5	5.7	15-39
	Adolescents	-	41[a]	24.6	5.7	16-40

Pharmacokinetic Results:. The pharmacokinetic data suggest that the mean steady state fluoxetine concentration in the pediatric population is approximately 117 ng/ml and that for norfluoxetine is 144 ng/ml. The observed fluoxetine and norfluoxetine concentrations at steady state after dosing with fluoxetine 20 mg/day are shown in the table below.

Category	N (No. of observations)	Mean (ng/mL)	SD	%CV	Range (ng/mL)
Fluoxetine					
All patients	138	116.6	73.7	63 2	
Children	79	144.8	76.4	52.8	
Adolescents	59	78.8	49.4	62.7	
Gender					
Male	66	115 0	59.9	52.1	
Female	72	118 0	84 9	71.9	
Children					
Male	41	144 5	53.2	36 8	
Female	38	145.2	96.2	66.3	
Adolescents					
Male	25	66.6	32.7	49	
Female	34	87.7	57.6	65.7	
Norfluoxetine					
All patients	138	144.1	58.9	40.9	
Children	79	167.2	59 6	35.7	
Adolescents	59	113.1	41.4	36.6	
Gender					
Male	66	143.1	61.9	43.2	
Female	72	144.9	56.5	38.9	
Children					
Male	41	168.9	62.1	36.8	
Female	38	165.3	57.6	34.9	
Adolescents					
Male	25	100.9	30.9	30.6	
Female	34	122.1	46	37.7	

Steady state fluoxetine concentration in children is approximately 2-fold that observed in adolescents. Steady state norfluoxetine concentration in children is approximately 1.5 -fold that observed in adolescents. Normalizing the observed concentrations by body weight suggests that the concentrations in children are comparable to those in adolescents (see figure below). Thus, body weight explains a major portion of the variability explained in the plasma concentrations of fluoxetine and norfluoxetine. There were no significant gender differences in fluoxetine and norfluoxetine concentrations in either age group. These concentrations and results are comparable to those observed in the intensive pharmacokinetic study HCIU.





Pharmacokinetic Analysis during the Relapse–Prevention Phase: During the relapse prevention phase of the study, 12 blood samples from 12 fluoxetine-treated (20 mg/day) patients were used in the pharmacokinetic analysis. Patient demographics are shown below.

Table HCJEr.11.11. Patient Demographics Pharmacokinetic Dataset

Demographic	Category	Subcategory	N	Mean	SD	Range
Age (years)	Overall	-	12	13.8	2.5	10-17
	Children	-	4	10.8	1.0	10-12
	Adolescents	-	8	15.3	1.3	13-17
Ethnic Origin	Overall	Caucasian	10	-	-	-
		Other	2	-	-	-
	Children	Caucasian	4	-	-	-
		Other	0	-	-	-
	Adolescents	Caucasian	6	-	-	-
		Other	2	-	-	-
Gender	Overall	Male	7	-	-	-
		Female	5	-	-	-
	Children	Male	3	-	-	-
		Female	1	-	-	-
	Adolescents	Male	4	-	-	-
		Female	4	-	-	-
Weight (kg)	Overall	-	12	65.3	17.4	34-102
	Children	-	4	49.5	11.1	34-59
	Adolescents	-	8	73.2	14.5	60-102
Height (cm)	Overall	-	12	161.3	11.4	142-173
	Children	-	4	146.7	3.2	142-150
	Adolescents	-	8	168.6	4.3	160-173
Body Mass Index (kg/m^2)[a]	Overall	-	12	24.8	4.7	17-35
	Children	-	4	22.8	4.3	17-26
	Adolescents	-	8	25.7	4.9	21-35

The mean observed fluoxetine plasma concentrations were 3-fold higher in children than in adolescents, and mean norfluoxetine concentrations were 1.5-fold higher in children than in adolescents (see below). These differences in concentrations in children and adolescents were mainly related to body-weight. The pharmacokinetic results obtained for the relapse-prevention phase are consistent with those obtained from the subchronic phase of this study.

Table HCJEr.11.12. Observed Fluoxetine and Norfluoxetine Concentrations at Steady-State After Dosing with Fluoxetine 20 mg/day

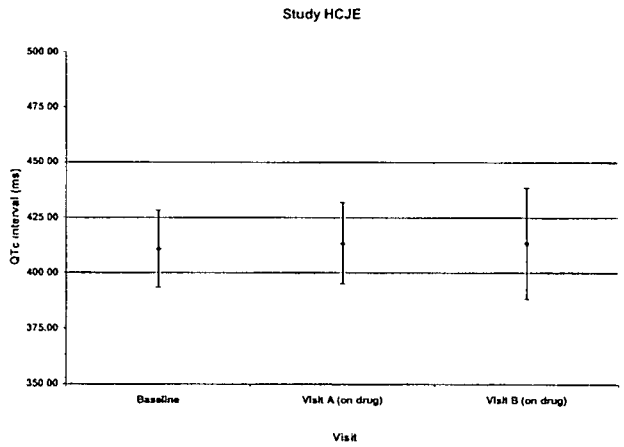
Category	N	Mean (ng/mL)	SD	%CV	Range (ng/mL)
Fluoxetine					
All patients	12	92.0	104.4	113.5	
Children	4	167.7	162.4	96.8	
Adolescents	8	54.2	30.4	56.1	
Gender					
Male	7	62.3	42.3	67.9	
Female	5	133.6	153.6	115.0	
Children					
Male	3	89 0	48.5	54 6	
Female	1	403.84	-	-	
Adolescents					
Male	4	42.3	27.5	65.1	
Female	4	66.1	32.0	48.4	
Norfluoxetine					
All patients	12	109.7	41.5	37.8	
Children	4	144.4	28.8	19.9	
Adolescents	8	92.3	36.3	39.4	
Gender					
Male	7	109.9	41.6	37.8	
Female	5	109.4	46.3	42.4	
Children					
Male	3	132.1	18.3	13.9	
Female	1	181.32	-	-	
Adolescents					
Male	4	93.3	48.7	52.2	
Female	4	91.4	26.6	29.1	

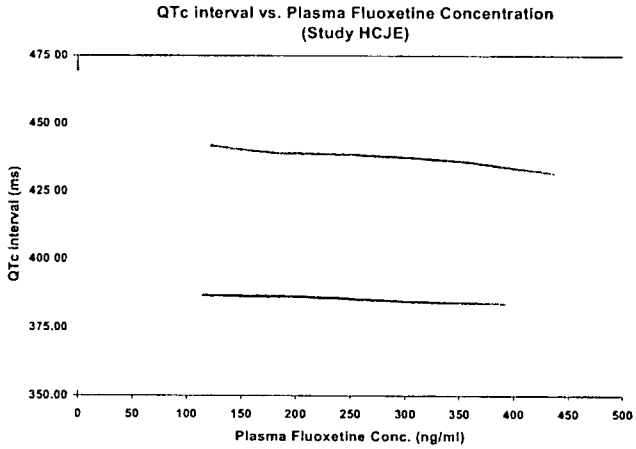
Conclusions: The mean observed steady state concentrations of fluoxetine in children were 2-3 fold higher than those observed in adolescents, and the mean observed steady state concentrations of norfluoxetine in children were 1.5-fold higher than those observed in adolescents. These differences in concentrations between children and adolescents were mainly attributed to differences in body weight.

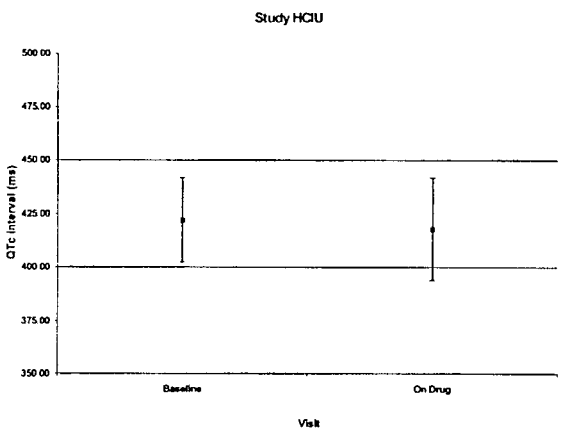
Effect of Prozac on QT interval prolongation in the Pediatric Population

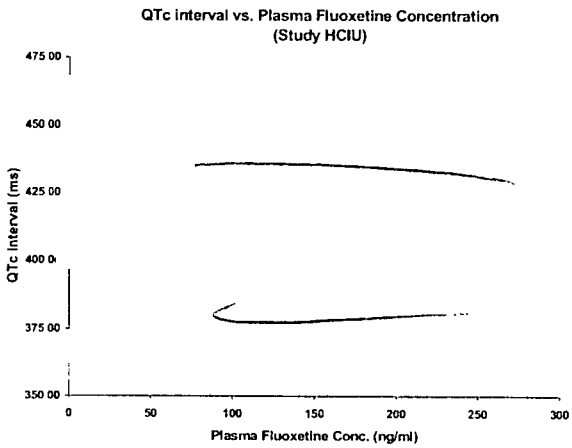
Following administration of Prozac, the following cardiovascular adverse reactions were reported as rare: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation. Recent reports showed that administration of only R-isomer of fluoxetine was associated with QT prolongation. Prozac is a racemic mixture of R and S-isomers of fluoxetine. The effect of administration of Prozac on QT prolongation in the pediatric population evaluated in these studies was analyzed. Agency requested the applicant to obtain ECG data at baseline and on drug in both Studies HCIU and HCJE .

The applicant analyzed ECG data from Study HCJE by three blinded and independent contract vendors/consultants at different points in time. The last reading performed by [redacted] accounted for the events of sinus arrhythmia, which is frequent in pediatric population. The applicant considered these readings as the most precise and accurate interpretation of the QTc data. A plot of QTc interval versus Visit (baseline and on drug) shows no effect of drug on QTc. Furthermore, a plot of QTc versus plasma fluoxetine concentrations shows lack of a relationship between QTc and plasma fluoxetine concentrations. (Refer to Pharmacometrics Review, page 28 for additional details). Similar results were obtained from ECG data obtained for Study HCIU. See plots below.









PHARMACOMETRICS REVIEW

NDA 18,936	**Submission Date:** January 2, 2001 March 19, 2001
Drug Name:	Prozac (fluoxetine hydrochloride)
Formulation:	20 mg capsules
Applicant:	Eli Lilly and Co
Consult:	Reports of the Studies B1Y-MC-HCIU "Pharmacokinetic assessment of Fluoxetine and norfluoxetine in preadolescent and adolescent patients" and B1Y-MC-HCJE "Fluoxetine versus placebo in childhood/ adolescent depression"
Pharmacometrics Specialist:	Elena V. Mishina, Ph.D.

Preamble/Background:

Fluoxetine is a selective serotonin re-uptake inhibitor (SSRI) that has been approved for the treatment of depression, obsessive-compulsive disorder (OCD), and bulimia nervosa in adults. The pharmacokinetics and bioavailability of fluoxetine and norfluoxetine (active metabolite) have been extensively studied in adults (healthy and patient's populations) in NDA 18,936.

A supplemental NDA 18,936 for fluoxetine hydrochloride was submitted for review in response to the Written Request for Pediatric Studies. This NDA supports the use of fluoxetine for the treatment of major depressive disorder (MDD) in children and adolescents, and for the treatment of OCD in children and adolescents. In support of labeling recommendations in the pediatric population, the sponsor conducted two clinical studies. Pharmacokinetics of fluoxetine in pediatric patients (children and adolescents) from Study B1Y-MC-HCIU (HCIU) and population data analysis of this study were submitted for review. Additionally, plasma fluoxetine and norfluoxetine concentrations were available from the larger efficacy Study B1Y-MC-HCJE (HCJE) in children and adolescents. Population model was not developed for the later study but the data were summarized descriptively and submitted for review. The results of these data analyses were used for the labeling changes for Prozac.

Overall Objective/Rationale:

To evaluate the safety and efficacy of fluoxetine in the treatment of pediatric depression and/or OCD, and to develop pharmacokinetic information pertinent to using the drug in the pediatric population.

Pharmacokinetic Objectives:

Assess the pharmacokinetics of fluoxetine (20 mg/day) and its metabolite norfluoxetine in pediatric patients (preadolescents and adolescents);

Compare the steady state plasma concentrations achieved and pharmacokinetics attained in preadolescent and adolescent patients on a fixed dose of fluoxetine 20 mg/day to the steady state plasma concentrations achieved and pharmacokinetics attained in adult patients from prior pharmacokinetic studies (Protocols HCFB and HCFC).

Methods:

Study HCIU

This was a single-site, open-label, two-period treatment study to assess the pharmacokinetic profiles of fluoxetine dosed at 20 mg/day and its metabolite, norfluoxetine in preadolescent and adolescent patients. Period I was a screening, washout, and study preparation phase. Period II was a 60-day (58 to 62 days), open-label, acute therapy, and pharmacokinetic data collection (up to 10 blood samples per patient at various times during the treatment interval of 60 days) phase. The data from pediatric patients were compared with historical data obtained from two studies with adults:

Protocol HCFB: "Disposition of fluoxetine in depressed, renal-dialysis patients" (data from patients with normal renal function)

Protocol HCFC: "Pharmacokinetics of fluoxetine in patients with reduced renal function".

The data from these two studies were combined (data from these 2 studies are considered to be representative, in that the PK parameters from these studies were comparable to those from other studies in adults). Pediatric data consisted of 21 patients and 168 fluoxetine and norfluoxetine plasma concentrations. Only fluoxetine plasma concentrations were used for population pharmacokinetic modeling.

Study HCJE

This was a multi-center, double blind, randomized, parallel-group study. Fluoxetine was compared with placebo for efficacy and safety in children and adolescents diagnosed with major depressive disorder (MDD) according to DSM-IV criteria. There were 6 periods in this study.

Period I was a diagnostic evaluation period (2 weeks).

Period II was a wash-out period (1 week), placebo responders were discontinued.

Period III was a double-blind adaptation period (1 week), patients were randomized to receive fluoxetine (10 mg/day) or placebo.

Period IV was a double-blind, fixed dose acute treatment (8 weeks), patients were randomized to receive fluoxetine (20 mg/day) or placebo.

Period V was a double-blind nonresponder rerandomization period (10 weeks). Nonresponders got higher (40 or 60 mg/day) doses of fluoxetine.

Period VI was a double-blind relapse prevention period (32 weeks).

Patients were screened at the first visit. Blood samples were obtained at baseline and at steady state at visits 10 and 15 following at least 4 weeks of fixed fluoxetine dosing at random times within a dosing interval.

Data Analyses:

Assay Method:

Plasma samples were analyzed at [redacted] by a validated [redacted] method.

Data:

HCIU: Quantifiable plasma concentration (170 blood samples) data from 21 patients were available for the analyses. Two data records were omitted due to missing or questionable dosing and/or sample data/time information.

HCJE: Quantifiable plasma fluoxetine and norfluoxetine concentrations were available from 101 patients (total 174 samples). The data from the patients on 20 mg/day fluoxetine were summarized (138 observations from 94 patients).

Pharmacokinetic Analysis:

Observed fluoxetine and norfluoxetine plasma concentration data from pediatric patients (Studies HCIU and HCJE) and adults patients (Studies HCFB and HCFC) were tabulated and descriptive statistics were summarized.

Population Data Analyses

Study HCJE:

The sponsor did not attempt to perform population modeling.

Study HCIU:

Pharmacokinetic parameters were estimated only for fluoxetine using NONMEM version V with PREDPP. The sponsor did not attempt to perform population modeling accounting for the metabolite, norfluoxetine.

Model Building and Validation:

First step of model building was selection of the structural model followed by statistical models for inter-patient variability and residual variability.

Structural model for fluoxetine was one-compartmental model with first order input with estimation of the physiologic parameters (clearance, CL/F, volume of distribution, V/F and absorption rate constant ka).

Inter-subject variability was assumed to be distributed log-normally and modeled as proportional term:

$$P_j=\vartheta \cdot e^{\eta}$$

where Pj is the individual value for the model parameter in j^{th} individual, ϑ is typical value of the parameter and η is an independent random variable with mean zero and variance of ω_p^2.

Residual variability was modeled as a proportional residual error model:

$$Y_{ij} = F_{ij} \cdot (1 + \varepsilon_{ij})$$

where Y_{ij} is the observed plasma concentration and F_{ij} is the predicted plasma concentration based on the pharmacokinetic model; the random variable ε_{ij} that defined residual variability had a normal probability distribution with mean 0 and variance denoted as σ^2.

Comparison of two nested models (where one model is entirely contained within a second model) was based on change in the minimal objective function (MOF) value, agreement between predicted and observed concentrations and the magnitude and randomness of residual values. Covariates retained in the final model were those that produced a statistically significant ($p < 0.001$) increase in the NONMEM objective function (>10 units for one degree of freedom) when removed from the full model. In this analysis, POSTHOC estimates were used to select patient's factors for further model development.
Comparison of different covariate models was based on comparison of MOF (statistics computed by NONMEM that is proportional to the -2log likelihood) and inspection of various diagnostic plots. For the convergence, 3 significant digits were required on all parameters.
Pharmacostatistical models were evaluated using either first order (FO) or first order conditional (FOCE) methods.

After the additional request from the Agency, the applicant performed the validation of population pharmacokinetic model developed for the study HCIU using the data from study HCJE. These data were sparse (many patients have only one blood draw during the study) and taken only from the patients who received the 20 mg dose of fluoxetine.
The distribution of clearances calculated from the patients in study HCIU and the same from study HCJE were compared using Kolmogorov-Smirnov test. The test statistics was estimated as 0.221, less than critical value of 0.327 (α=0.05). Therefore, these two distributions are similar. In addition, graphical comparison of the frequency distribution of individual clearance values obtained from study HCJE with the same for the study HCIU shows significant overlap of two areas (Figure 1).

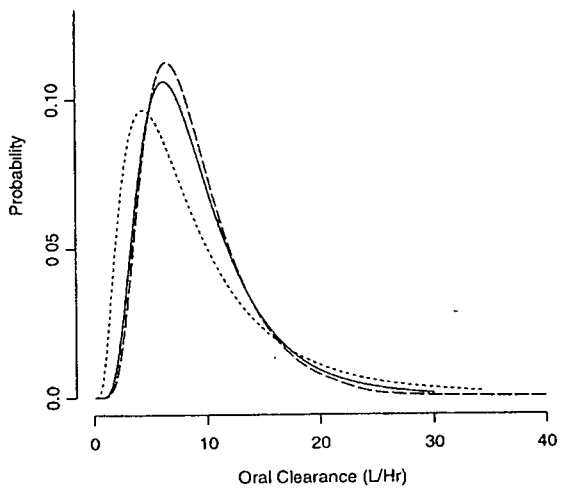


Figure 1. **Frequency Distribution of Individual Estimates of Oral Clearance**
The fitted curve (solid line) represents a log-normal distribution of predicted individual clearances in Study HCJE (20-mg dose) based on final parameters from the population pharmacokinetic model developed for Study HCIU. The fitted curve (dashed line) represents individual estimates of oral clearance for pediatric patients in Study HCJE (20-mg dose). The fitted curve (dotted line) represents clearance estimates from pediatric patients in Study HCIU.

Comment:
Model validation is acceptable from the FDA's point of view.

Results:
Study HCIU

Data Collection:
The majority of plasma samples were collected between 8 and 12 hours post-dose. The sampling frequency for all patients in this study was quite similar.
Descriptive Statistics:
The mean steady state fluoxetine plasma concentrations were 127 ng/mL in pediatric patients, preadolescents have them 2-fold higher than adolescents. Mean fluoxetine plasma concentrations were 3.5-fold higher in preadolescent females in comparison with adolescent females. The summary of descriptive statistics is shown in Table 8.2. The influence of the disease (depression or OCD) and its state could not be assessed by such comparisons due to the small sample size. In both pediatric groups plasma fluoxetine concentrations were highly variable, the range of the observed fluoxetine concentrations was similar in both groups.

Table 8.2. **Observed Fluoxetine Concentrations at Steady-State In Pediatric Patients**

Category	Mean[a] (ng/mL)	SD	%CV	Range
All patients	126.6	75.0	59.2	
Preadolescent	170.9	73.3	42.9	
Adolescent	86.3	51.6	59.8	
Gender				
Male	130.9	64.1	48.9	
Female	119.5	94.5	79.1	
Preadolescent				
Male	151.3	65.1	43.0	
Female	216.6	83.5	38.6	
Adolescent				
Male	107.2	59.3	55.3	
Female	61.2	28.7	46.8	
Disease State				
Overall				
Depression (n=18)	115.8	62.2	53.7	
OCD[b] (n=2)	257.2	-	-	
Depression & OCD (n=1)	59.6	-	-	
Preadolescent				
Depression (n=9)	155.2	57.4	37.0	
OCD (n=1)	311.6	-	-	
Depression & OCD (n=0)				
Adolescent				
Depression (n=9)	76.3	37.8	49.5	
OCD (n=1)	202.8	-	-	
Depression & OCD (n=1)	59.6	-	-	

The mean steady state norfluoxetine plasma concentrations were 152 ng/mL in pediatric patients, preadolescents have them 1.7-fold higher than adolescents. Mean fluoxetine plasma concentrations were 1.8-fold higher in preadolescent females in comparison with adolescent females (Tables 8.2 and 8.3). Normalizing fluoxetine and norfluoxetine concentrations by body weight suggests that exposures in preadolescents and adolescents are similar (see figure 8.9).

Table 8.3. Observed Norfluoxetine Concentrations at Steady-State in Pediatric Patients

Category	Mean[a](ng/mL)	SD	%CV	Range
All patients	151.8	76.3	50.3	
Preadolescent	195.0	89.2	45.8	
Adolescent	112.5	30.4	27.0	
Gender				
Male	155.6	79.7	51.2	
Female	145.6	75.5	51.8	
Preadolescent				
Male	192.3	94.8	49.3	
Female	201.4	93.7	46.5	
Adolescent				
Male	112.9	19.5	17.2	
Female	112.1	42.8	38.2	
Disease State				
Overall				
Depression (n=18)	147.2	72.1	49.0	
OCD[b] (n=2)	207.7	-	-	
Depression & OCD (n=1)	122.6	-	-	
Preadolescent				
Depression (n=9)	182.3	84.5	46.4	
OCD (n=1)	309.5	-	-.	
Depression & OCD (n=0)	-.	-.	-.	
Adolescent				
Depression (n=9)	112.2	33.7	30.0	
OCD (n=1)	105.8	-	-.	
Depression & OCD (n=1)	122.6	-.	-.	

The visual presentation of the observed steady state plasma concentrations for fluoxetine is shown in Figure 2 (FDA). Based on graphical evaluation, the patients were properly assumed to be at steady state within 3-4 weeks.

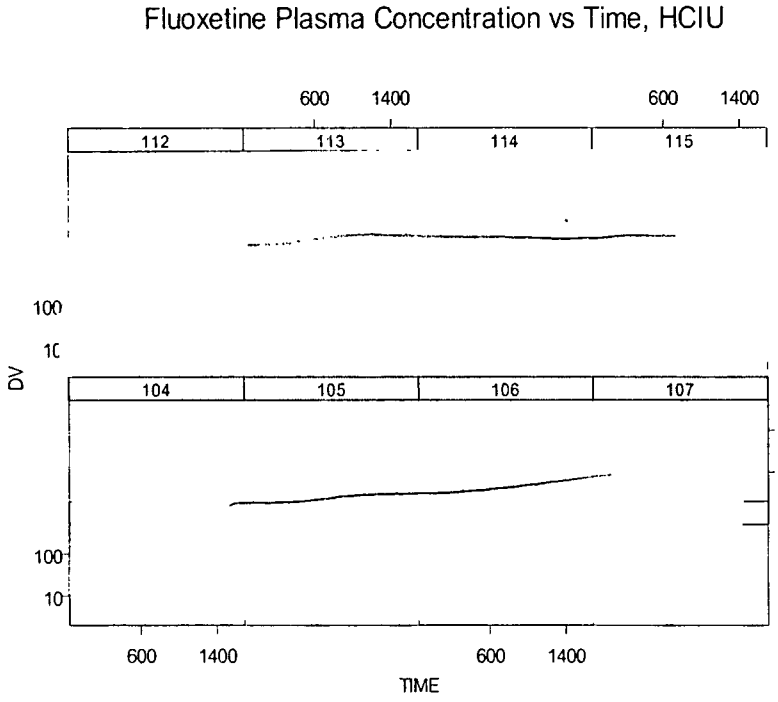


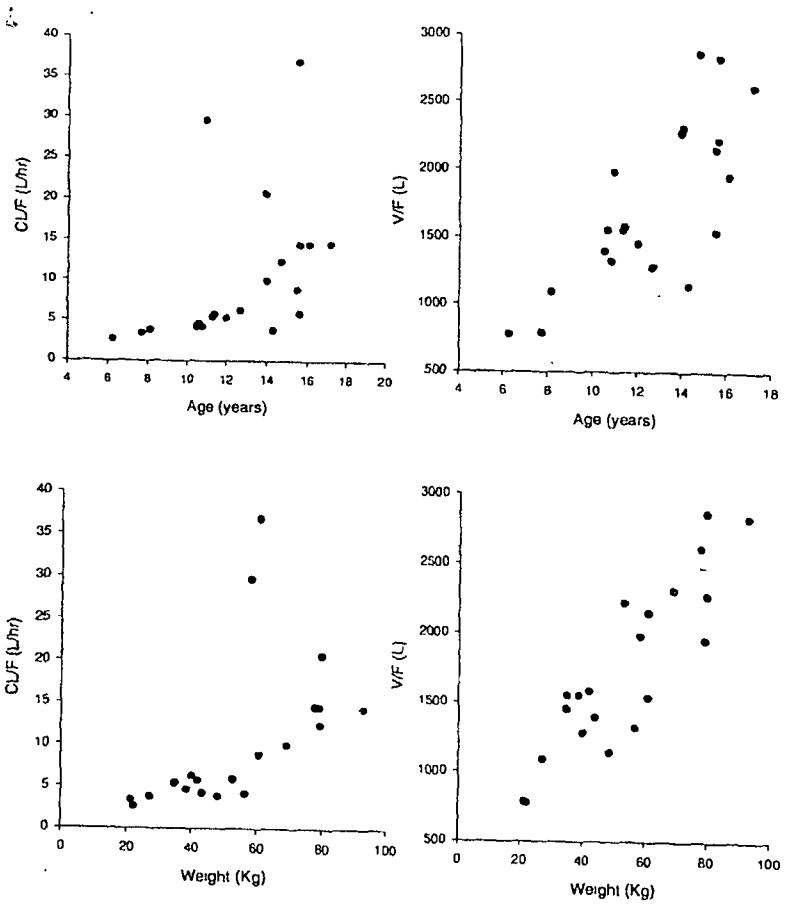
Figure 2. Example of Fluoxetine plasma concentration vs time (hours) for 16 patients, Study HCIU. Light color of circles corresponds to female, dark color - to male patients.

Population model:

Based on the goodness of fit criteria and other model diagnostics, one-compartmental model was chosen for the description of fluoxetine plasma concentration profiles. The applicant presented the final base model output and all model run outputs. These model runs show the logical steps leading to the final model selection. Best results were obtained with the use of FOCE estimation method.

Oral clearance was estimated as 11.8 L/kg, and volume of distribution as 1480 L with variabilities of 85.7 and 44.2% respectively. The variability for ka was not obtained in the model most likely due to a small number of observations in the absorption phase. The value of ka to 0.666 hr^{-1} was fixed across the population for the simplification of the model for this limited data set.

Empirical Bayes estimates of CL/F and V/F obtained from the fit were used for the graphical evaluation of the covariates by plotting the individual patient's parameter values vs covariates. Apparently, body weight and age had a strong relationship with V/F while CL/F relationship with these covariates was not that pronounced (Figure 3).



Relationship between oral clearance (CL/F) and apparent volume of distribution (V/F) with age or weight.

Figure 3. Estimates for clearance and volume of distribution are POSTHOC estimates from the base models.

Therefore, covariate analysis was focused on the surrogates of body size (weight and body mass index). Age, body weight and body mass index modeled as continuous variables significantly improved the fit and decreased the inter-patient variability. Body weight was modeled without centering.

The applicant reported that gender modeled as a categorical variable was not significant in the model. Graphical evaluation of gender effect (Figure 4, FDA) confirms that conclusion. Figure 3 shows that the distribution of fluoxetine plasma concentrations vs time for female (left panel) and male (right panel) patients is similar.

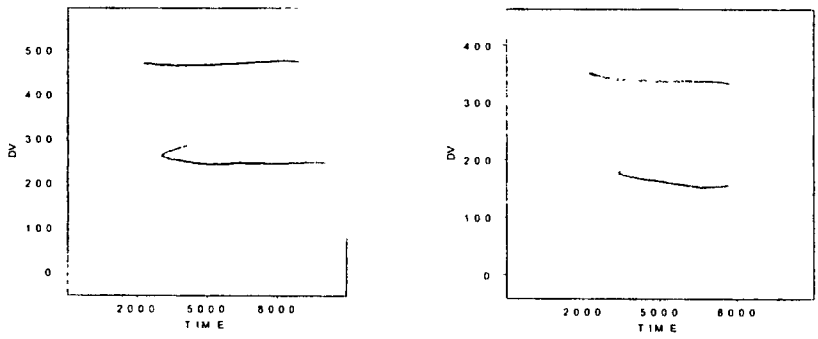


Figure 4. Distribution of fluoxetine plasma concentrations for female (left panel) and male (right panel) patients.

The applicant presented the summary of the covariate analyses (Table 8.5).

Table 8.5. Pharmacokinetic and Covariate Parameters in the Final Population Model for Fluoxetine in Pediatric Patients

Hypothesis	Model	Change in $-2\log L^a$	Estimate of between patient variability; ω_{CL} or ω_V (as %CV) [b]	Comments
Gender				
Influence on CL	Categorical	0.06	86%	Not significant
Influence on V	Categorical	0	→	Not significant
Age (years)				
Influence on CL	$\theta_1 + \theta_2 \times$ Age	-23.58 ↓	72 %	Significant; $p < 0.001$; $\theta_1 = 0.397$; $\theta_2 = 0.879$
Influence on V	$\theta_1 \times$ Age $^{\theta 2}$	-43.20 ↓	26 %	Significant; $p < 0.001$; $\theta_1 = 16.6$; $\theta_2 = 1.86$
Body Weight (kg)				
Influence on CL	$\theta_1 + \theta_2 \times$ Weight	-35.08 ↓	55 %	Significant; $p < 0.001$; $\theta_1 \cong 0$; $\theta_2 = 0.193$
	$\theta_1 \times$ Weight	-35.14 ↓	55 %	Significant; $p < 0.001$; $\theta_1 = 0.194$
Influence on V	$\theta_1 \times$ Weight $^{\theta 2}$	-59.10 ↓	22 %	Significant; $p < 0.001$; $\theta_1 = 11.1$; $\theta_2 = 1.31$
	$\theta_1 + \theta_2 \times$ Weight	-54.63 ↓	20 %	Significant; $p < 0.001$; $\theta_1 \cong 0$; $\theta_2 = 37.0$
Influence on both CL &V	$\theta_{CL} \times$ Weight; $\theta_V \times$ Weight	-77.08 ↓	52 % 21 %	Significant; $p < 0.001$; $\theta_{CL} = 0.181$; $\theta_V = 37.4$
Body Mass Index (BMI, kg/m²)				
Influence on both CL &V	$\theta_{CL} \times$ BMI; $\theta_V \times$ BMI	-54.67 ↓	60 % 26 %	Significant; $p < 0.001$, $\theta_{CL} = 0.446$; $\theta_V = 82.9$

Although both age and body mass index were significant covariates, the decrease in the inter-patient variability was more pronounced when body weight was included as linear function affecting both clearance and volume of distribution.

Based on the results of all model runs (change in MOF and interpatient variabilities), body weight proportionally affecting both CL and V was included in the final model. This improvement of the model was additionally supported by the visual inspection of the plots of predicted vs observed plasma concentrations and weighted residuals vs parameter. In comparison with the base model, including the weight factor in the final

model decreased the inter-patient variability for clearance from 85.7 t0 52%, and for V from 44.2 to 20.5%, respectively.

However, this final model did not explain about 50% of variability for oral clearance in the pediatric population. The applicant did not perform exploration of any other covariates, which may influence the oral clearance of fluoxetine.

Comparison to Adult Data

The pharmacokinetic data on 16 adult patients from studies HCFB and HCFC were compared to the pediatric patient's data from study HCIU. The applicant has not attempted to model the data from children and adult's together accounting for the influence of age in the model. The applicant's comparison was based on the descriptive statistics of observed plasma concentrations for fluoxetine and norfluoxetine, Table 8.8. The mean overall steady state concentrations of fluoxetine and norfluoxetine in adults were 96.86 and 110.42 ng/mL, respectively, and interpatient variabilities were high in both pediatric and adult population.

Table 8.8. Observed Fluoxetine and Norfluoxetine Concentrations at Steady-State

Category	Mean (ng/mL)	SD	%CV	Range
Fluoxetine				
Overall Pediatric	126.6	75.0	59.2	
Preadolescent	170.9	73.3	42.9	
Adolescent	86.3	51.6	59.8	
Overall Adult	96.9	54.0	55.8	
Study HCFB	62.2	33.0	53.0	
Study HCFC	137.3	45.5	33.1	
Norfluoxetine				
Overall Pediatric	151.8	76.3	50.3	
Preadolescent	195.0	89.2	45.8	
Adolescent	112.5	30.4	27.0	
Overall Adult	110.5	57.9	52.4	
Study HCFB	120.9	72.0	59.6	
Study HCFC	98.2	38.7	39.4	

There were other similarities in these two populations: the ratio between the parent drug and metabolite was 1.2-1.3, the steady state was achieved approximately at the same time, 3-4 weeks after the start of dosing, half-life for fluoxetine was estimated between 4 and 6 days. Accumulation ratio in the pediatric population was about 15 fold, consistent with adults (10-20 fold).

Normalized by body weight plasma fluoxetine concentrations in pediatric population were comparable with the same in adults (Figure 8.9).

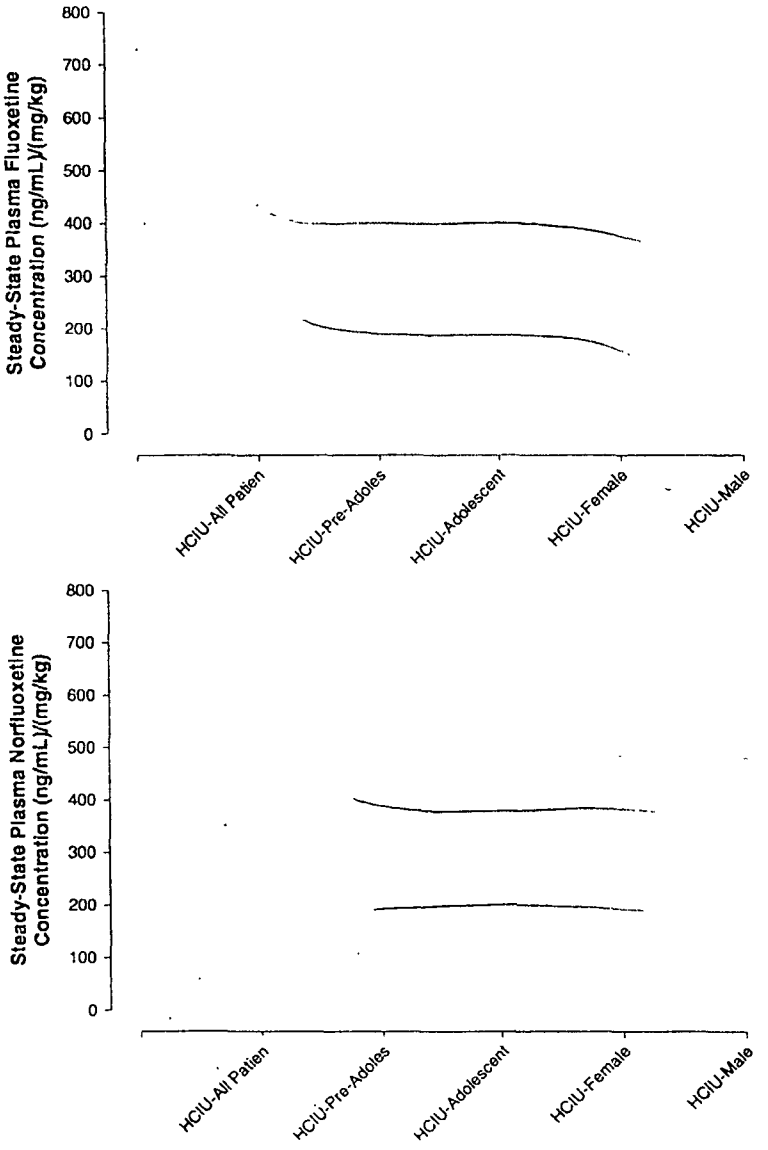
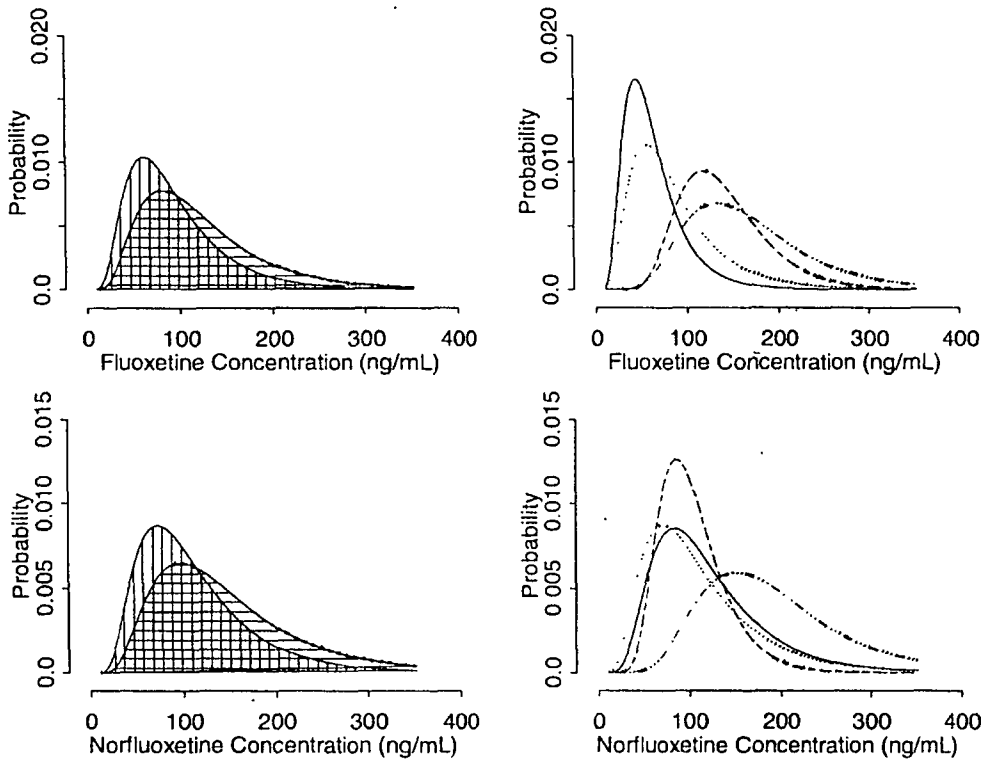


Figure 8.9. **Study HCIU: Dose weight normalized fluoxetine and norfluoxetine observed steady-state concentrations**

Additionally, the applicant presented graphically the distribution of individual estimates of fluoxetine and norfluoxetine plasma concentrations and properly concluded that they are similar (Figure 8.10). (Note: Average steady-state fluoxetine and norfluoxetine concentrations observed in children were higher relative to adults; however these concentrations were within the range of concentrations observed in the adult population.)



Left panel: Vertical hatches: All adults; Horizontal hatches: All pediatric patients.

Right panel:

—— Study HCFB — — Study HCFC —— Pre-adolescent · · Adolescent

Figure 8.10. Distributions of individual estimates of fluoxetine and norfluoxetine steady-state concentrations

The fitted curves represents a log-normal distribution of individual mean steady-state concentrations from the pediatric and adult populations. Oral clearance at steady-state can be approximated as F•Dose/Css•τ; where, F is the fraction absorbed and τ is the dosing interval.

For the additional verification of the applicant findings, the FDA assessed the influence of the age as a covariate on clearance and volume of distribution when the data from

pediatric and adult patients was combined. Rerun of the final applicant's model using the combined data from studies HCIU, HCFC, and HCFB led to the estimation of pharmacokinetic parameters, which were very similar with the ones obtained for the pediatric population.

Drug: Fluoxetine Protocol: HCIU
Subject: - Run. 001

Subroutines: ADVAN2 TRANS2 Method: 1 PRINT=5
1323 Records 168 Observations 21 Patients
Obj Func: 1082.272 # EVALS: 143 Sig Digits: 3.1

Parameter	Initial Estimate	Estimate	StdErr	%SE
THETA #1 -	(001,1,10),	0.181	0.0228	12.60
THETA #2 -	(1,50,100);	37.4	2.08	5.56
THETA #3 -	0.666 FIXED,	0.666	Fixed	-
OMEGA #1 -	0.8	0 271	0.124	45 76
OMEGA #2 -	0.5	0.0422	0 0174	41.23
SIGMA #1 -	2	0 0341	0 00767	22.49

Combined Data File for HCIU, HCFC, and HCFB studies, FDA run

Parameter	Initial Estimate	Estimate	StdErr	%SE
THETA #1 -	(.001,1,10),	0.148	0.0109	7.30
THETA #2 -	(1,50,100),	29.1	3.42	11.75
THETA #3 -	0.666 FIXED;	0.666	Fixed	-
OMEGA #1 -	0.8	0.22	0 0617	28.0
OMEGA #2 -	0 5	0.376	0.121	32 2
SIGMA #1 -	1	0.0372	0.00775	20.83

FDA performed a graphical evaluation of the relationship between AGE and individual patient's pharmacokinetic parameters estimated using the combined data file (Figure 6). The light colored circles are for female, and dark colored circles are for male patients, the lines are the result of linear regression. There is no obvious trend in the clearance (CL) and volume of distribution (V) versus AGE for this data set.

Using the data file from studies HCIU and historic adult data, FDA added into the final applicant's model new parameter AGE as linear or power function of CL or V. The AGE effect for each run were estimated to be negligible. Standard errors of the estimates were very large.

Model	AGE, estimation	AGE, SE
$CL=\theta_1*WT+\theta_2*AGE$	1.59E-9	0.0411
$CL=\theta_1*WT*AGE^{\theta 2}$	6.29E-9	0.176
$V=\theta_1*WT+\theta_2*AGE$	1.63E-11	-
$V= CL=\theta_1*WT * AGE^{\theta 2}$	3.17E-10	0.0194

This is an additional support to the applicant's statement that the pharmacokinetics of fluoxetine is similar both in pediatric and adult population.

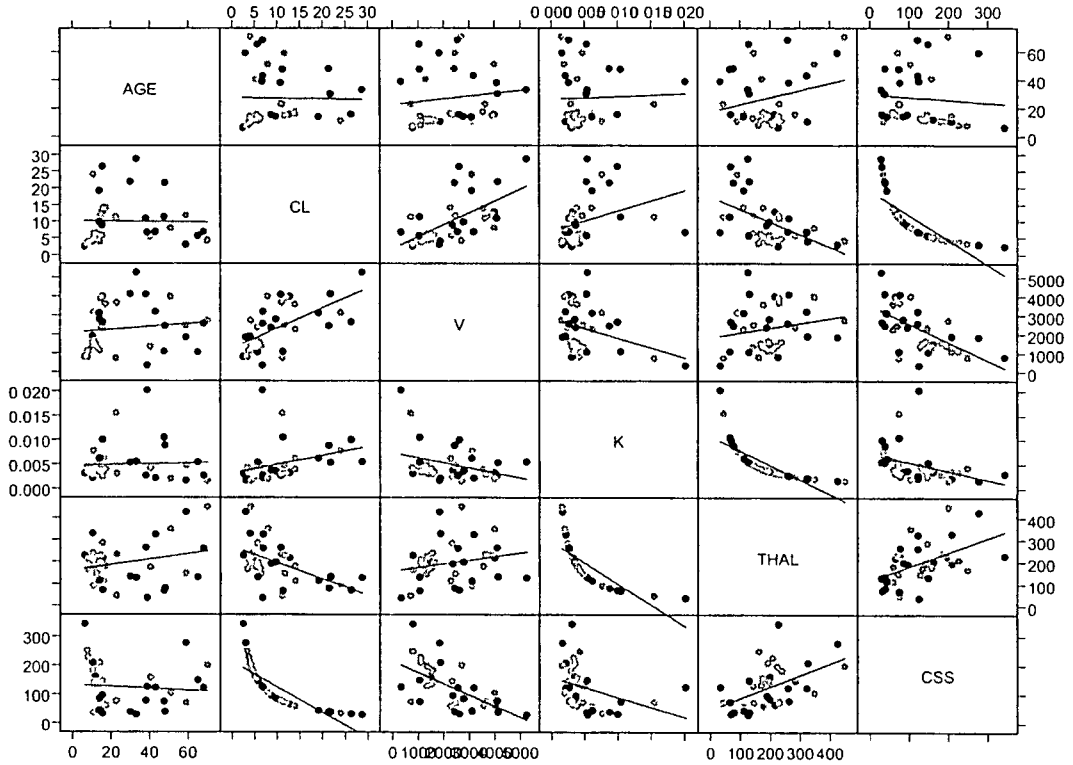


Figure 6a. Matrix plot for the relationship between pharmacokinetic parameters and age (final applicant's model fitted to pediatric and adult population data simultaneously). The light colored circles are for female, and dark colored circles are for male patients, the lines are the result of linear regression.

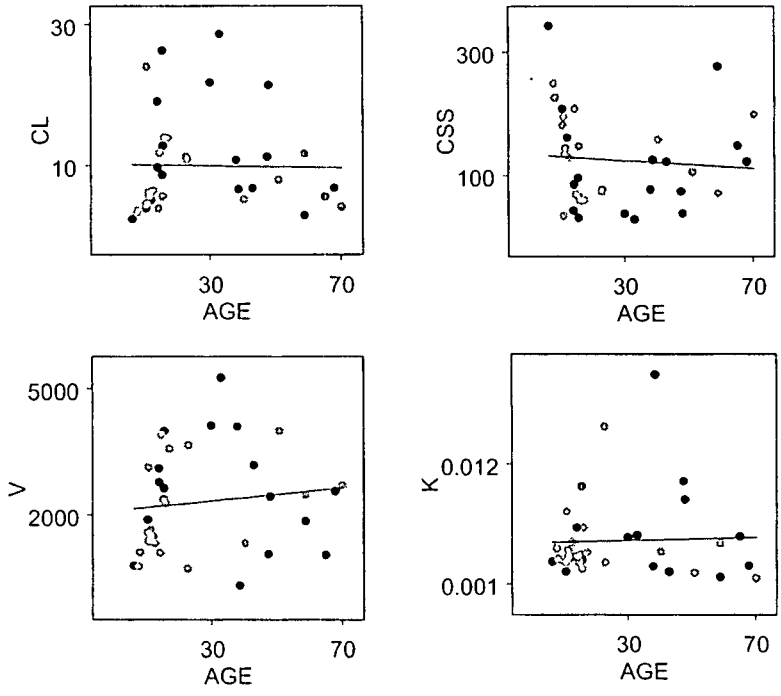


Figure 6b. Plots for the relationship between CL, V, Css, K and age (final applicant's model fitted to pediatric and adult population data simultaneously). The light colored circles are for female, and dark colored circles are for male patients, the lines are the result of linear regression.

APPEARS THIS WAY
ON ORIGINAL

Issues on QT interval prolongation

Over 20 years of the Prozac administration, the following cardiovascular adverse reactions were reported as rare: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation. Recent reports showed that administration of only R-isomer of fluoxetine was associated with QT prolongation. Although Prozac is a racemic mixture of R and S-isomers of fluoxetine, the information on possible QT prolongation in the new (pediatric) population is very important. The Agency requested the applicant to obtain ECG at the start and at the end of treatment in both Studies HCIU and HCJE and to calculate QTc values.

The applicant performed read of ECGs from Study HCJE by three blinded and independent contract vendors/consultants at different points in time. The last reading performed by [redacted] accounted for the events of sinus arrhythmia, which is frequent in pediatric population. The applicant considered these readings as the most precise and accurate interpretation of the QTc data. FDA plotted all QTc data from three readings vs fluoxetine plasma concentrations, Figure 7.

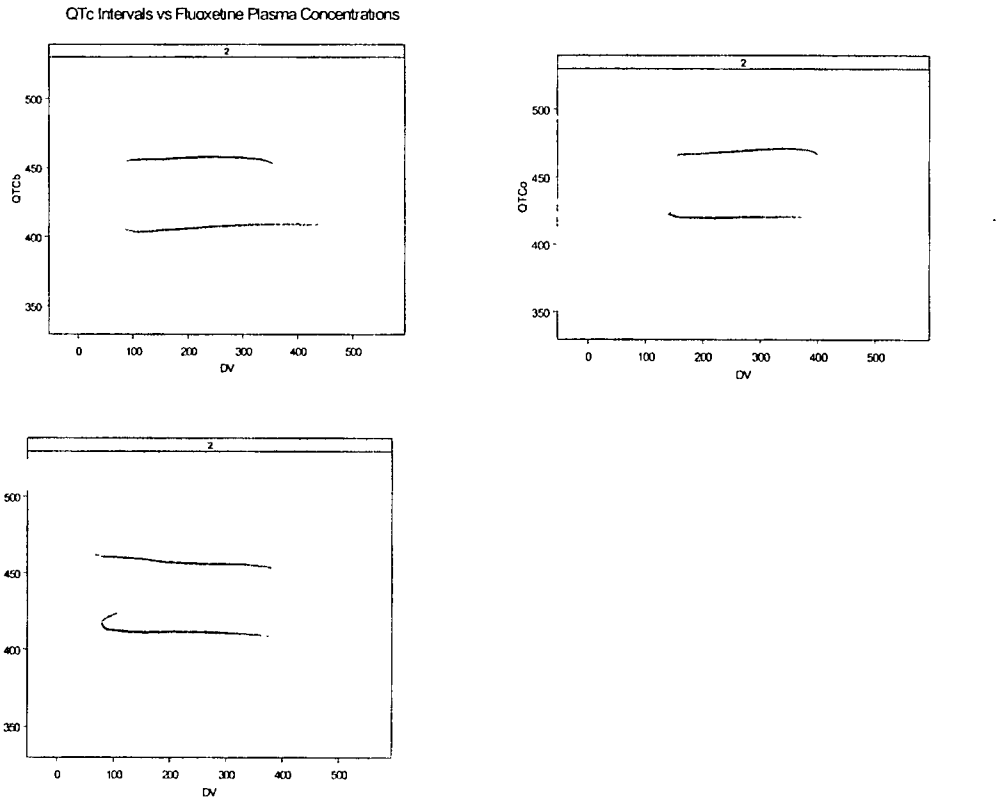


Figure 7. QTc intervals vs fluoxetine plasma concentrations. Light colored symbols refer to female and dark colored symbols to male patients. Circles are for the [redacted] squares for [redacted] and triangles are for [redacted] readings.

These plots show no apparent trend in the relationship between QTc and fluoxetine plasma concentration. One patient (#415) had QTc of 514 msec when calculated by [redacted]. The other consultants calculated this patient's QTc as 452 and 460 msec.
Gender differences were not pronounced for this population, Figure 8.

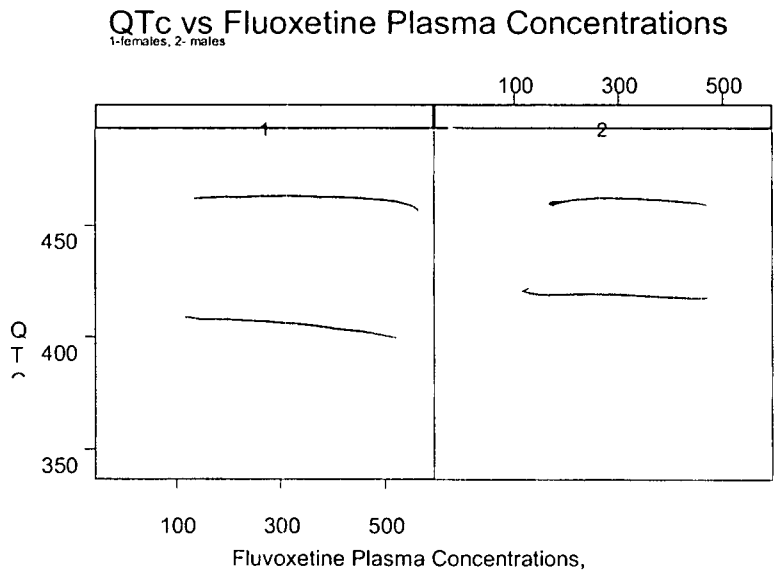


Figure 8. QTc intervals vs fluoxetine plasma concentrations. Circles are female patients' data, triangles are male patients' data.

The main concern with changes in QTc interval is its prolongation during the course of fluoxetine administration. Changes in QTc interval measurements in comparison with the baseline values were plotted vs time in course of the study (Figure 9). The changes in QTc were not significant during the study.
Figure 10 compares the QTc values measured at the different occasions. Majority of patients have only 2 measurements: at baseline and at the end of the study, some patients had the third ECG and only one patient had the fourth and fifth ECG (at the same day as #3). Therefore, for ECG #4 and #5 confidence interval is larger than 1st and 3rd quartiles. Otherwise, the difference between occasions was not significant.

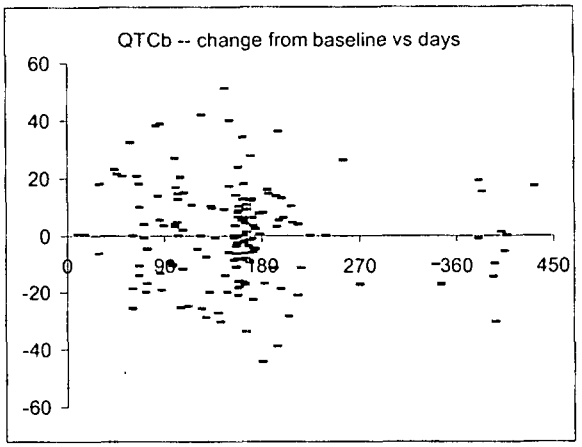


Figure 9. Change in QTcb values from the baseline vs the time (days) after the start of the study

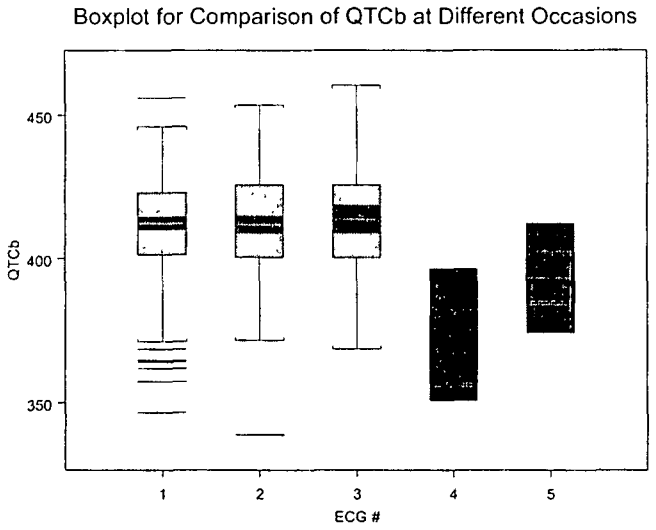


Figure 10. Boxplot comparing QTcb obtained at different occasions. The ends of the box are at the 1st and 3rd quartiles, line is at the median (50^{th} percentile), dark space around the median shows 95% confidence interval, the lines outside the whiskers show the outliers. At occasion 4 and 5 only one measurement was made.

In conclusion, this graphical data exploration shows that QTc prolongation (based on QTc values) was not an issue in this pediatric patient population, who were receiving the dose of racemic fluoxetine of 20 mg/day over approximately 60 weeks.

Comments:

1. The applicant properly developed the population model describing the fluoxetine pharmacokinetics in pediatric patients. Based on the results of all model runs (change in MOF and interpatient variabilities), body weight proportionally affecting both CL and V was included in the final model. This improvement of the model was additionally supported by the visual inspection of the plots of predicted vs observed plasma concentrations and weighted residuals vs parameter. However, this final model did not explain about 50% of variability for oral clearance in the pediatric population. The applicant did not perform exploration of any other covariates, which may influence the oral clearance of fluoxetine.

2. Modeling did not consider the active metabolite, norfluoxetine.

3. The applicant adequately performed pharmacokinetic model validation.

4. The mean observed plasma concentrations of fluoxetine and norfluoxetine were compared with the same data from the historical control studies in adults. Both adult and pediatric patients exhibit high inter-patient variability. In both populations, the ratio of norfluoxetine to fluoxetine was 1.2-1.3, steady state was achieved within 3-4 weeks after multiple daily dosing, the accumulation ratio in pediatrics was 15, and in adults was 10-20. When the observed fluoxetine and norfluoxetine plasma concentrations were normalized by body weight, they were comparable with the same in adults.

5. The Agency applied the applicant's population model to the combined data from study HCIU (pediatric), HCFC, and HCFB (adults). The pharmacokinetic parameters estimated for the combined data were very similar with the pediatric patient's parameters. The incorporation of AGE as a covariate into the model led to the negligible estimates of this covariate, indicating that the influence of age was not significant.

6. Based on above comments 4 and 5, the pharmacokinetic differences between pediatric and adult patients are not significant.

7. This reviewer analyzed graphically the changes in QTc intervals from the efficacy and safety Study HCJE and concluded that these changes are not major.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the Reports of the Studies B1Y-MC-HCIU "Pharmacokinetic assessment of Fluoxetine and norfluoxetine in preadolescent and adolescent patients" and B1Y-MC-HCJE "Fluoxetine versus placebo in childhood/ adolescent depression" The changes in Package Insert proposed by the applicant are acceptable (see Primary Reviewer's Labeling Comments).

Date_____

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23 page(s) of revised draft labeling has been redacted from this portion of the review.

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
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