CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-365

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-365	Submission Date(s): November 2, 2001; August 1, 2002 Received: April 4, 2002; August 1, 2002
Brand Name	Lexapro™
Generic Name	Escitalopram Oxalate Oral Solution
Reviewer	Carol Noory
Team Leader	Ramana Uppoor
OCPB Division	HFD-860 (DPE 1)
OND division	Neuropharmacology HFD-120
Sponsor	Forest Laboratory, Jersey City, NJ 07311
Relevant INDs/NDA(s)	I58-380; I22-363; N21-323
Submission Type; Code	Original NDA
Formulation; Strength(s)	Oral Solution, 5 mg/5mL
Indication	For the [redacted] of major depressive disorders

I. Executive Summary

Forest Laboratories proposes to market escitalopram oxalate (ESC) as a 5mg/5mL oral solution. The sponsor developed the oral solution as an alternate dosage form to the escitalopram oxalate tablet formulation submitted under NDA 21-323, which was approved August 14, 2002.

The application includes no clinical trials, but does include a single dose bioequivalence study (Study SCT-PK-06) designed to evaluate the rate and extent of absorption of the oral solution (2mg/mL) formulation of escitalopram compared to the tablet formulation of the same drug. The tablet formulation used as the reference in this study has also been used in two pharmacokinetic studies and one clinical study in support of NDA 21-323. A dose proportionality study using the approved 10 mg tablet formulation in both young and elderly healthy volunteers was also submitted and reviewed.

The clinical pharmacology and biopharmaceutics section of NDA 21-365 is acceptable based on the following:

1. The firm demonstrated bioequivalence of a 10mL dose of ESC solution (2mg/mL) to the ESC 20 mg tablets batch used in clinical studies to support approval of NDA 21-323.
2. The to-be-marketed 1 mg/mL oral solution formulation is similar in composition to the 2 mg/mL oral solution formulation used in the bioequivalence study, the main difference being the amount of malic acid in the formulation.
3. An establishment inspection made May 28 through June 4, 2002 at the [redacted] (formerly [redacted] and March 26-28, 2002 at Forest Laboratories, did not reveal any violation that would render the biostudies invalid. There was a discrepancy to be addressed by the Medical Officer. The sponsor substituted the QTc values using the Bazett's correction [$QTc=QT\sqrt{60/HR}$]. This has been communicated to Dr. Karen Brugge, the Medical Officer, and Dr. Judith Racoosin to be addressed appropriately. Dr. Racoosin indicated that this was not a major issue for this NDA, although the use of Fredericia's correction would have been a better choice.

Labeling Comments:

1. The oral solution is bioequivalent to the tablet and this should be incorporated into the labeling.

II. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-365 and finds the clinical pharmacology and biopharmaceutics section acceptable. The above labeling comment should be incorporated in the approved label of escitalopram oxalate tablets.

OCPB briefing was August 19, 2002.

A. Carol Noory
Division of Pharmaceutical Evaluation I

FT: Initialed by Ramana Uppoor, Ph.D._____

cc list: NDA 21-365; HFD-860: (Noory, Uppoor, Marroum, Mehta, Sahajwalla); HFD-120 (Paul David); CDER Central Document Room

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IV. Summary of Clinical Pharmacology and Biopharmaceutic Findings

A. Background

Citalopram is a selective serotonin reuptake inhibitor. Citalopram (Celexa™) was approved for the treatment of depression in 1998 (NDA-20-822). Citalopram is a 50/50 racemic mixture of the S- and R-enantiomers. The pharmacological effect of citalopram resides in the S-enantiomer which is twice as potent as racemic citalopram and more than 100 times as potent as the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. The firm decided to market the S-enantiomer, escitalopram, for major depression. The tablet formulation was submitted under NDA 21-323. The general pharmacokinetic parameters of orally dosed escitalopram are summarized from the ESC tablet formulation (NDA 21-323) and the NDA for citalopram tablets (NDA-20-822), as follows:

- ESC is rapidly absorbed (t_{max} of 3-5 hours after single dose)
- Food does not affect the absorption of ESC.
- Distribution: The apparent volume of distribution (Vz/F) following a dose of ESC solution is 13L/kg.
- Plasma Protein binding: Approximately 50-80% of ESC and S-DCT is bound to plasma proteins.
- Metabolism: The major metabolites of escitalopram are S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT) which are mediated by CYP2C19, CYP2D6 and

CYP3A4. At steady-state, the plasma concentration of S-DCT is approximately one-third of the parent compound and S-DDCT is approximately one-twentieth of the parent compound.

- Elimination half-life: The elimination half-life for escitalopram is approximately 23-25 hours. The systemic clearance is approximately 0.5 L/min.
- Elderly (>65) vs. young adults: The PK values are similar between the young and elderly after a single dose. At steady state the AUC and half-life of escitalopram increases by 50% in the elderly as compared to the young.
- Gender: No significant gender effect was observed. For escitalopram, a longer T_{max} was seen in male subjects (5.9 hours) vs. female subjects (4.1 hours); C_{max} was only slightly higher in males than in females (30.3 vs. 23.0 ng/mL), and AUC was higher (506 vs 401 ng•hr/mL) in females than males (difference disappeared when normalized based on body weight). For S-DCT there was also no statistical difference in the pharmacokinetic parameters between male and female subjects.
- Renal Impairment: In patients with mild to moderate renal function impairment oral clearance of citalopram was reduced by 17% compared to normal subjects; no adjustment of dosage for such patients is recommended

Drug Interactions:

- Metoprolol - Administration of 20 mg/day escitalopram for 21 days resulted in a 50% increase in the peak plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of escitalopram and metoprolol had no clinically significant effects on blood pressure or heart rate.
- Desipramine and Other Tricyclic Antidepressants (TCAs) - Coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 50% increase in desipramine concentrations. The clinical significance of this finding is unknown.

B. Current Submission

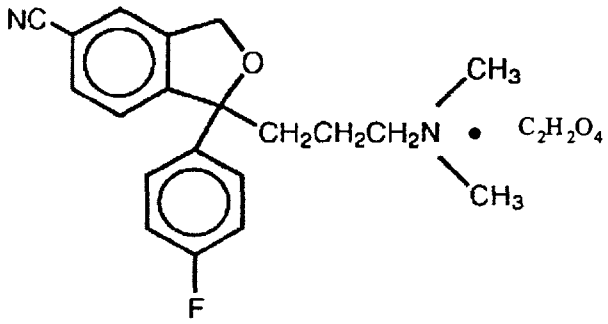
The current NDA (21-365) is for an escitalopram oxalate oral solution that contains 5 mg/5mL of escitalopram. The sponsor is requesting approval of Escitalopram Oral Solution indicated for the ——— of major depressive disorders. The sponsor refers to NDA for the ESC tablet formulation (NDA 21-323) and the approved citalopram tablet formulation (NDA 20-822) for information on the basic pharmacokinetics, drug-drug interaction studies, as well as clinical efficacy and safety. The Clinical Pharmacology and Biopharmaceutics portion of NDA 21-323 (tablet formulation) has been reviewed and found to be acceptable by the Office of Clinical Pharmacology and Biopharmaceutics. Bioequivalence of the oral solution to this tablet formulation has been demonstrated in Study SCT-PK-06. The batch of tablets used as a reference in this study was also used in two pharmacokinetic studies and one clinical study in support of NDA 21-323. Minor formulation changes for the oral solution formulation should not affect the performance of this product *in vivo*.

V. Question Based Review

A. General Attributes

A.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor. The structure and physical properties of escitalopram oxalate are shown below:



Structural Formula:	$C_{20}H_{21}FN_2O \cdot C_2H_2O_4$
Chemical Name:	(+) 1-(3dimethylaminopropyl)-1-(4fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Code name:	LU-26-054
Molecular Weight:	414 —
Solubility:	sparingly soluble in water and ethanol and freely soluble in methanol and DMSO
Apparent Permeability:	The permeability of escitalopram has not been reported

Escitalopram is the S-enantiomer of the racemic compound citalopram. Escitalopram is a white to slightly yellow powder. Escitalopram will be marketed as a 5 mg/5 mL oral solution. The product is formulated as follows:

Escitalopram Oxalate	— mg/mL
Sorbitol, USP ——	— mg/mL
Citric Acid, USP	— mg/mL
Sodium Citrate, USP	— mg/mL
Malic Acid, NF	— mg/mL
Propylene Glycol, USP	— mg/mL
Methylparaben, NF	— mg/mL
Propylparaben, NF	— mg/mL
Natural Peppermint flavor # —	— mg/mL
Purified Water, USP	— mL

A.2. Why was the S-enantiomer chosen to be developed into a separate product?

The pharmacological effect of citalopram resides in the S-enantiomer. The S-enantiomer, escitalopram, is twice as potent as racemic citalopram and more than 100 times as potent as the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. The firm decided to market the tablet formulation of escitalopram for major depression. An NDA for escitalopram oxalate 5, 10 and 20 mg tablets (NDA 21-323) has been submitted and found acceptable by the Office of Clinical Pharmacology and Biopharmaceutics. The oral solution was developed as an alternative to the tablet formulation for patients who either prefer the oral solution to the tablet or for patients who may have difficulty in swallowing tablets.

A.3. What is the proposed mechanism of drug action and therapeutic indication?

Escitalopram oral solution is indicated for the treatment of major depression in adults. The mechanism of action of citalopram 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).

A.4. What is the proposed route of administration?

Escitalopram oral solution is formulated to be taken orally.

B. Clinical Pharmacology

B.1. What are the dose and the dosing regimen and are there any unresolved dosing or administration issues?

The dose and the dosing regimen, 10 mg/day given orally will remain consistent with the escitalopram tablet dosing.

C. General Biopharmaceutics

C.1. Was bioequivalence demonstrated for the ESC oral solution when compared to the tablet formulation?

Yes, study SCT-PK-06 demonstrated that ESC 2mg/mL oral solution and the ESC tablet formulation were bioequivalent when given as a single, 20 mg dose, under fasting conditions based on 90% confidence intervals computed using log transformed data. Confidence intervals for ESC were between 92% and 103% for C_{max}, 92% to 103% for AUC_{0-t} and 92% to 104% for AUC_{0-inf}.

C.2. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The pivotal clinical trial was completed with the tablet formulation. The 2 mg/mL oral solution is bioequivalent to the tablet batch (Batch #99034C) used as the reference in two pharmacokinetic studies (SCT-PK 02 and SCT-PK-04) and one clinical study (SCT-MD-01) submitted in support of approval of NDA 21-323.

206 ***C.3. Were there any formulation changes made during drug development?***

207 Yes, the to-be-marketed formulation was not used in the bioequivalence study (SCT-PK-
208 06). Both the proposed commercial formulation (1 mg/mL) and the formulation used in the
209 bioequivalence study (2mg/mL) are similar with the exception of the active pharmaceutical
210 ingredient, escitalopram oxalate, and the antioxidant, malic acid. The proposed commercial
211 formulation contains 1 mg/mL of escitalopram. The lot used in the bioequivalence study
212 contained 2 mg/mL. The level of malic acid was [redacted] to a level to sufficiently
213 protect ESC from oxidation. The two formulations are shown below.
214

	To-Be –Market Formulation		Lot #00201-B[1]	
	Mg/mL	% w/v	Mg/mL	% w/v
Escitalopram Oxalate	[redacted]		[redacted]	
Sorbitol Solution, USP 70%	[redacted]		[redacted]	
Citric Acid, USP	[redacted]		[redacted]	
Sodium Citrate, USP	[redacted]		[redacted]	
Malic Acid, NF	[redacted]		[redacted]	
Glycerin, USP	[redacted]		[redacted]	
Propylene Glycol, USP	[redacted]		[redacted]	
Methylparaben, NF	[redacted]		[redacted]	
Propylparaben, NF	[redacted]		[redacted]	
Natural Peppermint Flavor	[redacted]		[redacted]	
Purified water, USP	[redacted]		[redacted]	

1. Oral solution formulation administered in the bioequivalence study (SCT-PK-06)

215

216 ***C.4. Is the dose proportionality shown in the dose range of 10 to 30 mg?***

217 Yes, a dose proportionality study using the 10-mg tablet formulation in both young and
218 elderly healthy volunteers demonstrated that the 10, 20 and 30-mg doses are proportional.
219 Using a standard linear regression model [log (Cmax or AUC $_{0\text{-inf}}$)=log(a) + b*log(dose) and
220 accepting the hypothesis of proportionality of b=1], dose proportionality was established for
221 escitalopram for both C_{max} and AUC $_{0\text{-inf}}$ parameters.

222 **D. Analytical Section**

223 ***D.1. Were the correct moieties identified and properly measured?***

224 Yes, the major metabolites of ESC, S-demethylcitalopram (S-DCT) and S-
225 didemethylcitalopram (S-DDCT) were identified. S-DCT is approximately one-third of the
226 parent compound and S-DDCT is approximately one-twentieth of the parent compound. In
227 vitro studies have shown that escitalopram is 7-fold and 27-fold more potent than S-DCT
228 and S-DDCT respectively, suggesting that the metabolites do not contribute significantly to
229 the antidepressant action of ESC. Both Escitalopram (ECS) and S- Demethylcitalopram (S-
230 DCT) were analyzed.

231 ***D.2. What bioanalytical methods were used to assess concentrations?***

232 [redacted]
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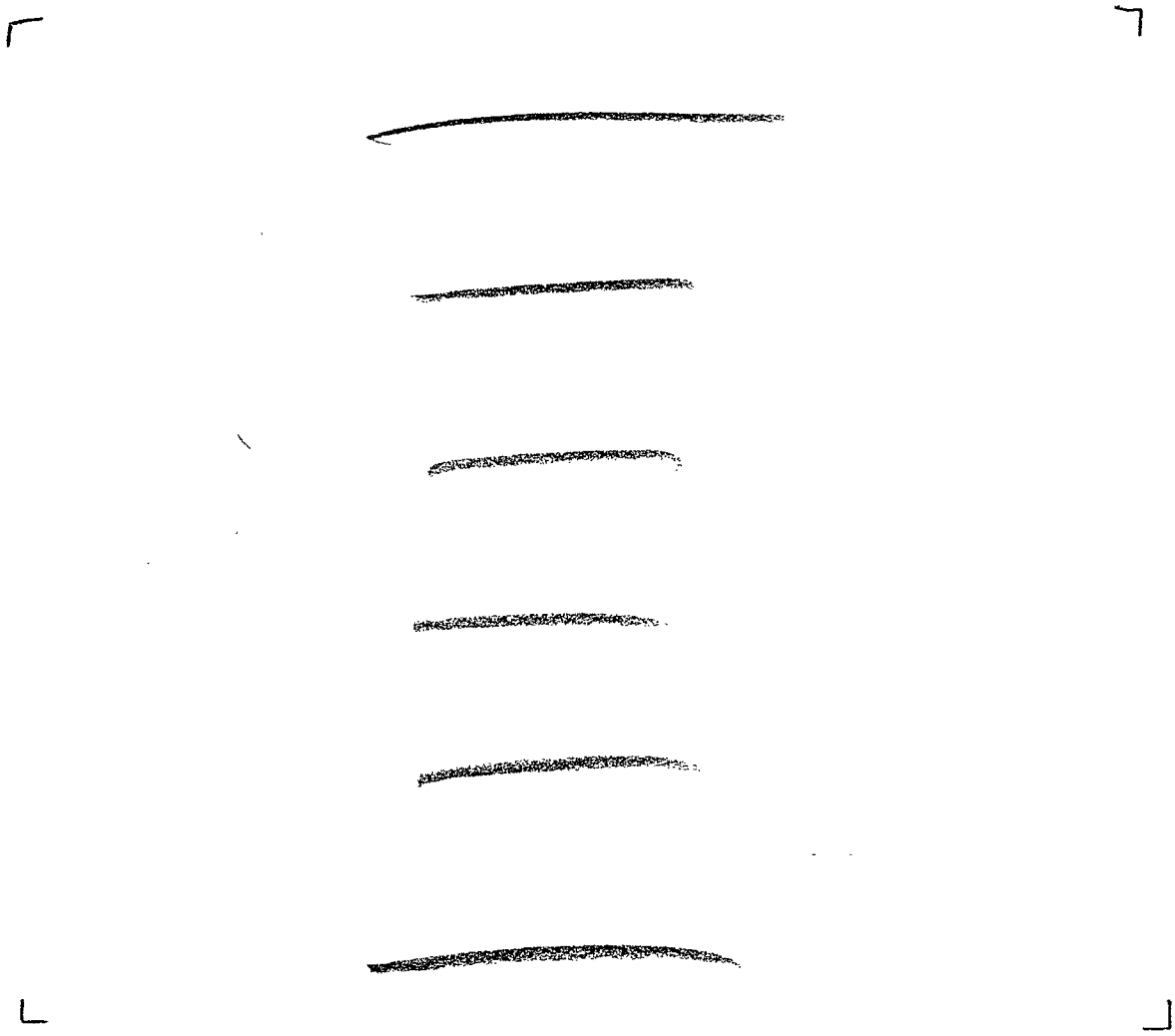


E. Establishment Inspection

E.1. Did the establishment inspection report reveal any deficiencies which may affect the outcome of the bioequivalence studies submitted by the firm?

No, although there were minor violations, there was nothing in the establishment inspection report from DSI that would make the outcome of the biostudies invalid. DSI conducted an audit of the clinical and analytical portions of Study SCT-PK-06 at [redacted] [formerly [redacted] (5/28/02 to 6/04/02) (clinical portion) and Forest Laboratories (3/26/02 to 3/28/02) (analytical portion). The clinical site was cited for not reporting QTc values on the ECG printouts. The sponsor substituted QTc values using Bazett's correction [QTc=QT√60/HR). A Form 483 was issued to Forest Laboratories for the following:

- Failure to submit stability data of escitalopram in solution and human plasma. The firm stated that they would include all relevant stability data in the NDA submissions in the future. The stability data of escitalopram will be reported in the next NDA update (June 2002).

- Failure to investigate and resolve the shifting of retention times for escitalopram and its metabolites (This finding does not invalidate the results of the study.)
- Failure to exclude subjective criterion of selecting outliers based on study personnel's discretion. The firm responded that they would revise the SOP.
- Failure to follow the SOP for calibrating the freezer temperature within the specified limits (The freezer was inspected during the study and was at the appropriate temperature).

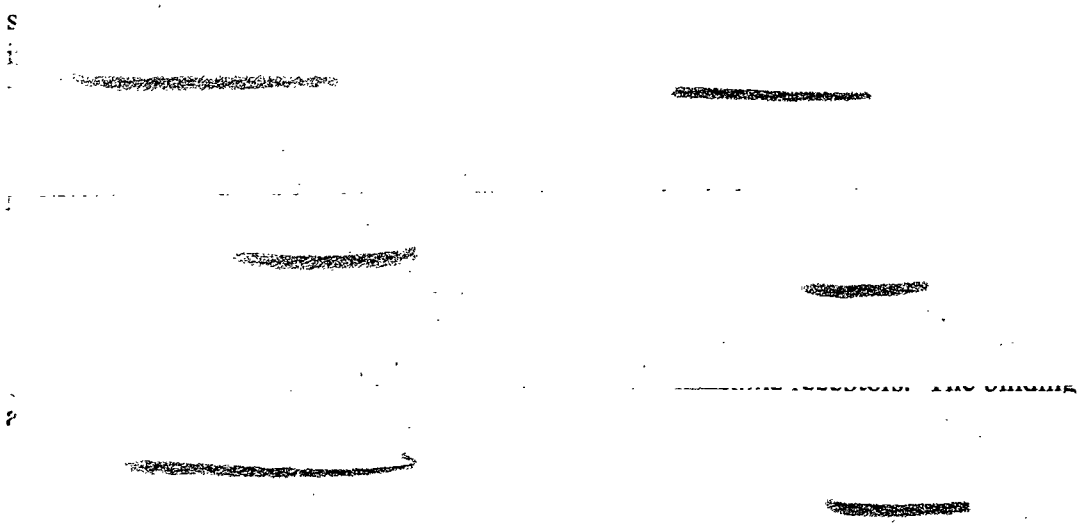
On August 1, 2002, Forest Laboratories responded to the FDA Form 483 regarding submission of stability data by submitting two stability reports to N21-365 as agreed to at the time of the inspection. This seems reasonable.

VI. Clinical Pharmacology Labeling

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram,



Pharmacokinetics

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma, [redacted] 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Absorption and Distribution

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg.

The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination

Following oral administration of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta- adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^- and Ca^{++} channels.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Population Subgroups

Age - Escitalopram pharmacokinetics in subjects ≥ 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. [redacted] increased by approximately 50% in elderly subjects and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients (see Dosage and Administration).

Gender - In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. [redacted]

[redacted], there were no differences in AUC, C_{max}, and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients (see Dosage and Administration).

Reduced renal function - In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, -2D6, -2C9, -2C19, and -2E1. [redacted]

Conclusion:

The change to the Clinical Pharmacology section of the labeling to incorporate the information regarding ESC solution is acceptable. Rest of the Clin. Pharm. Section should be made identical to the approved label of ESC tablets. ESC oral solution will be incorporated into the labeling for the approved escitalopram oxalate tablets.

VII. Appendices

A. Individual Study Review

A.1. Study SCT-PK-06 (Bioequivalence Study)

Title:

A Single-Dose, Open Label, Randomized, Two-Way Crossover, Bioequivalence Study Comparing Escitalopram Tablets (20 mg) with Escitalopram Oral Solution (20 mg) In Human Volunteers

Objective:

The objective of this study was to compare the rate and extent of absorption of 20 mg ESC oral solution with 20 mg ESC tablet formulation and to demonstrate the bioequivalence of these two products.

Principal Investigator:

[redacted]

Clinical Site:

[redacted]

Clinical Laboratory Analysis

[redacted]

Bioanalytical Laboratory

Forest Laboratories, Inc.
220 Sea Lane
Farmingdale, NY 11735

Pharmacokinetic Analysis

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Formulations:
Escitalopram 20 mg Tablets, Lot 99034C, manufactured March 1999 (batch size not given)
Escitalopram Oral Solution (10 mg/5 mL); Lot 00201-B; manufactured February 2000 (batch size not given)

Study Dates:
August 12, 2000 to October 5, 2000

Study Design:
This was single-center, open-label, single dose, randomized, two-way crossover study in 18 healthy Hispanic male and female subjects (18-35 yrs). Each subject received a single dose of ESC 20 mg oral solution and a single dose of ESC 20 mg tablet in a randomized order, separated by an interval of 14 days. Each dose was administered with 240 mL of water after an overnight fast of at least 10 hours.

Sample Collection:
Blood samples were collected from each subject at 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0, 96.0, 120.0, 144.0, and 168.0 hours post-drug administration

Analytical Method Performance
A suitable validated and [redacted] was used for the analysis of ESC and its metabolite, S-DCT, in plasma samples. QC samples at [redacted] were analyzed along with each batch of study samples.

[redacted]

Pharmacokinetic Computations and Statistical Analysis

Using GLM procedure in SAS, analysis of variance (ANOVA), was performed on Ln-transformed AUC_{0-t}, AUC_{0-} and C_{max} and on untransformed Tmax and t1/2 at the significance level of 0.05. The intra-subject coefficient of variation (CV) , ratio of means (Treatment A/Treatment B) based on the geometric means from the ANOVA, and the 90% geometric confidence interval were calculated for the natural log-transformed AUC_{0-t}, AUC_{0-} and C_{max}..

Pharmacokinetic Results:

Based on a comparison of the rate and extent of absorption, Escitalopram Oral Solution and Escitalopram tablets are bioequivalent under fasting conditions. The mean plasma ESC data is shown in Figure 1 and the S-DCT data is shown in Figure 2.

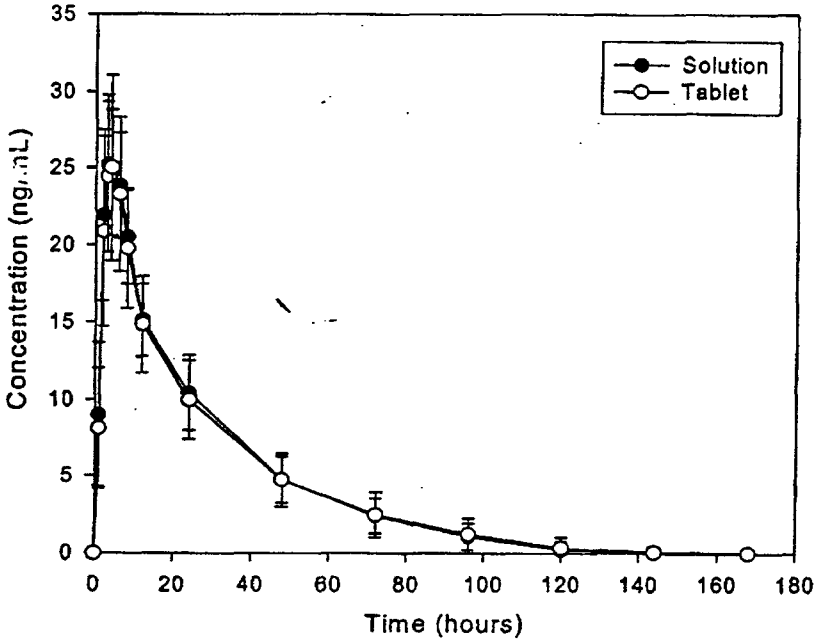


Figure 1: Plasma concentrations (mean [SD]) of Escitalopram after administration of 20 mg tablet and 10 mL solution (10mg/5mL) in healthy young male and female subjects.

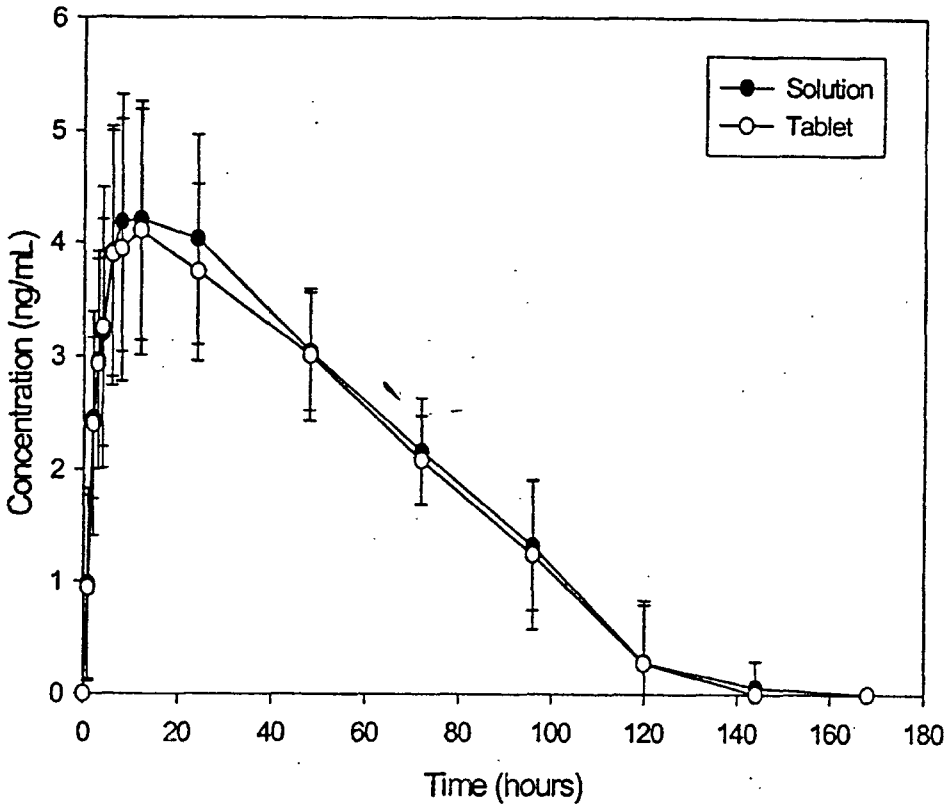


Figure 2: Plasma concentrations (mean [SD]) of S-DCT after administration of 20 mg tablet and 10 mL solution (10 mg/5mL) in healthy young male and female subjects.

The statistical results are summarized in the following Table.

SCT-PK-06: Pharmacokinetic parameters (Mean±SD) of ESC after a Single Dose of Escitalopram 20 mg Oral Solution and Tablet in Young Healthy Subjects			
PK parameters	Oral solution (N=18)	Tablet (N=18)	90% CI
Cmax (ng/mL)	26.2± 4.2	25.8± 5.7	92-103
AUC0-t (ng•hr/mL)	699.1± 165.8	687.9± 206.9	92-103
AUC0-inf (ng•hr/mL)	746.1± 170.1	741.7± 218.5	92-104
			p-values
Tmax (hr)	3.9± 1.4	3.7± 1.2	0.657
t ½ (hr)	23.0± 5.8	24.6± 6.3	0.160
CL/F (L/hr)	28.5± 8.3	29.4± 9.5	0.341
Vz/F (L)	898.2± 141.6	974.1± 118.2	0.040

SCT-PK-06: Pharmacokinetic parameters (Mean ± SD) of S-DCT after a Single Dose of Escitalopram 20 mg Oral Solution and Tablet in Young Healthy Subjects			
PK parmeters	Oral solution (N=18)	Tablet (N=18)	90% CI*
Cmax (ng/mL)	4.5± 1.1	4.3± 1.1	90-101
AUC0-t (ng•hr/mL)	288.4± 61.1	272.9± 54.2	91-99
AUC0-inf (ng•hr/mL)	377.5± 55.8	363.2± 68.3	90-102
			p-values
Tmax (hr)	13.0± 6.4	13.1± 7.3	0.952
t ½ (hr)	47.2± 14.3	45.7± 13.6	0.690
* CI is the ratio of the Oral Solution over the Tablet			

Gender Effect:

The data from Study SCT-PK-06 was evaluated for a gender effect. The data for the 9 male and 9 female subjects enrolled in the study were combined (oral solution and tablet formulation) and the pharmacokinetic parameters for each group (18 males and 18 females) were evaluated. The data for the mean pharmacokinetic parameters of escitalopram and S-demethylcitalopram following administration of a 20-mg dose of escitalopram oxalate are shown in the following figures (Figure 3 and 4) and summarized in the following table.

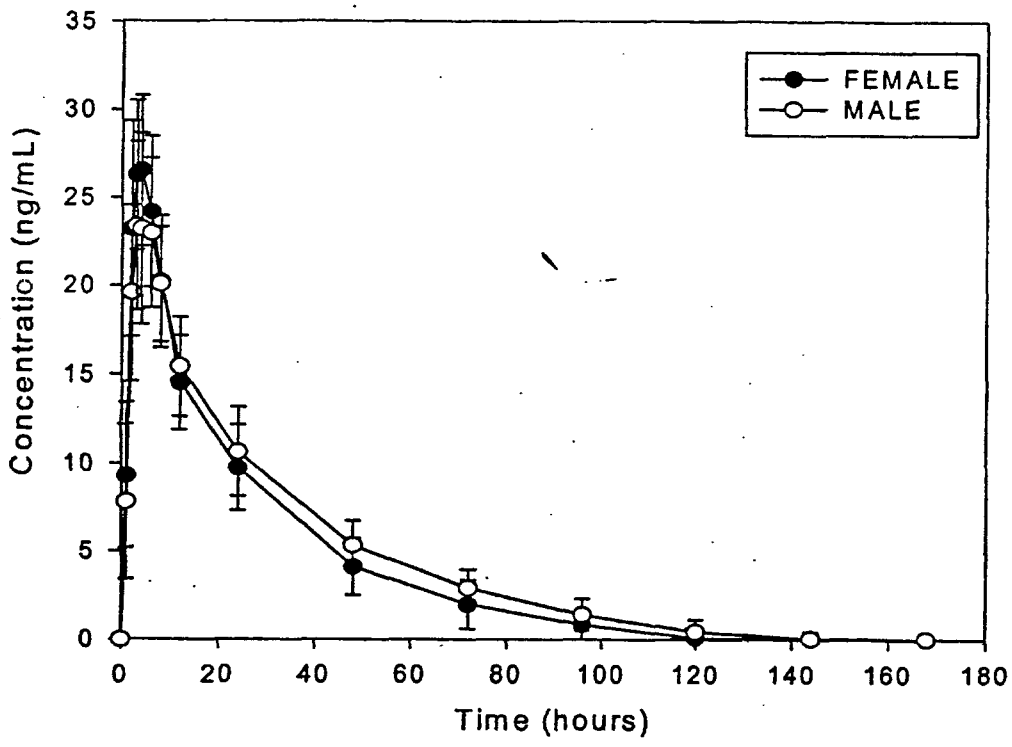


Figure 3: Plasma concentrations of escitalopram after administration of 20 mg escitalopram in healthy female vs. male subjects.

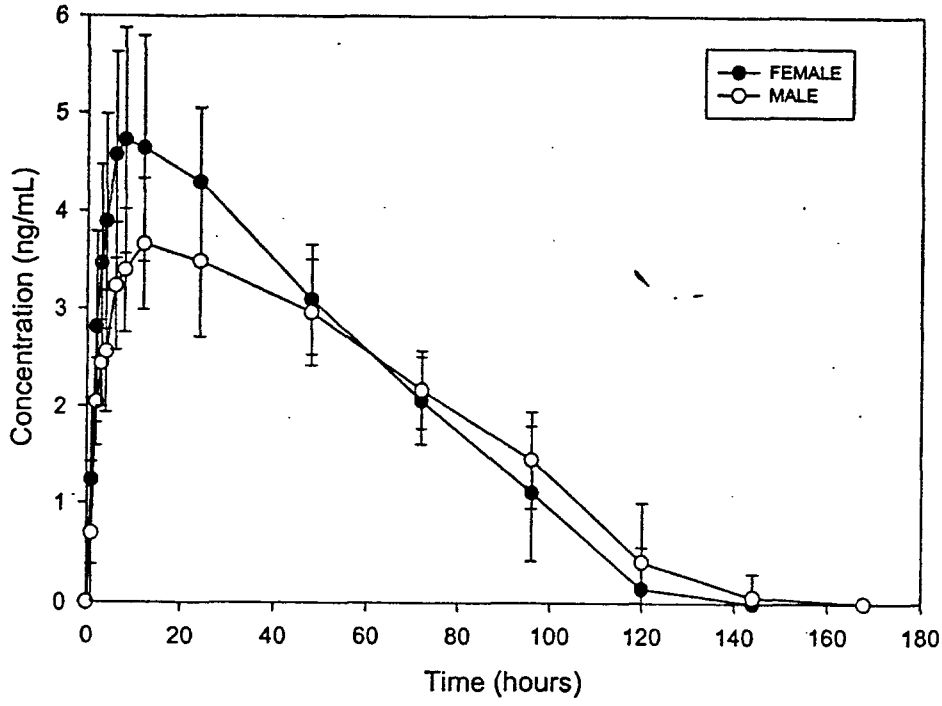


Figure 4: Plasma concentrations of S-demethylcitalopram after administration of 20 mg of escitalopram in healthy female vs. male subjects.

Comparison of mean pharmacokinetic parameters for female versus male subjects			
PK parameter	Females (n=18)	Males (n=18)	p-value
Escitalopram			
Cmax (ng/mL)	27.6 ± 5.1	24.5 ± 5.1	0.620
AUC0-t (ng•hr/mL)	654.5 ± 185.5	732.5 ± 180.9	0.217
AUC0-inf (ng•hr/mL)	703.9 ± 196.9	783.8 ± 185.8	0.226
Tmax (hr)	3.7 ± 1.3	3.9 ± 1.3	0.529
t ½ (hr)	22.1 ± 6.5	25.5 ± 5.1	0.094
S- Demethylcitalopram			
Cmax (ng/mL)	5.0 ± 1.1	3.8 ± 0.8	0.001
AUC0-t (ng•hr/mL)	290.0 ± 65.4	271.3 ± 61.5	0.339
AUC0-inf (ng•hr/mL)	372.6 ± 66.9	368.1 ± 58.3	0.834
Tmax (hr)	11.7 ± 7.1	14.4 ± 6.3	0.229
t ½ (hr)	41.3 ± 11.3	51.6 ± 14.4	0.025

Conclusion:

Study SCT-PK-06 demonstrated that the ESC tablets and the 10 mL ESC solution (2mg/mL), each given as a 20 mg total dose, are bioequivalent under single-dose fasting conditions based on the 90% confidence intervals for the pharmacokinetic parameters Cmax, AUC0-t and AUC 0-inf for ESC and S-demethylcitalopram of 80-125%,
No gender effects were found for T_{max}, C_{max}, t ½ , AUC_{0-t}, and AUC 0-inf for escitalopram.
No gender effects were found for T_{max}, AUC_{0-t}, and AUC_{0-inf} values for S-demethylcitalopram, however t ½ and C_{max} values were significantly different statistically between males and female groups with a decrease in t ½ of 32% and an increase in C_{max} of 20% in female versus male subjects.

SUMMARY DATA WAS SUBMITTED FOR THE FOLLOWING STUDY (STUDY 99166) WHICH WAS CONDUCTED IN NORTHERN IRELAND. STUDY DATES, LOT NUMBER AND INFORMATION ABOUT THE PERFORMANCE OF THE ANALYTICAL METHOD FOR SERUM SAMPLES WERE NOT PROVIDED. THE FULL REPORT WAS SUBMITTED PREVIOUSLY IN N21-323.

A.2. Study 99166 (Dose Proportionality Study)

Title:

An Open, Single-Dose, Randomized, Three-Way Crossover Pharmacokinetic Study in Healthy young and elderly Volunteers Investigating the Dose Proportionality of Lu26-054 following Administration of a 10, 20, and 30 mg Dose.

Principal Investigator:

[redacted]

Objective:

The primary objective of the trial was to determine the dose proportionality of 10, 20 and 30 mg of ESC in two separate groups, 18-45 years and 65 or more years. The secondary objective was to compare the pharmacokinetic data in young and elderly subjects.

Formulations:

Escitalopram Oxalate 10mg Tablets, Batch PD1287, given as a 10, 20 and 30 mg dose.

Study dates:

February 28, 2000 to June 16, 2000

Study Design

This was a single-center, single-dose, open randomized, three-way crossover study in 18 healthy elderly subjects (9 males and 9 females ≥65 years of age) and 18 healthy young (9 males; 9 females 18-45 years of age) subjects. Each subject received 3 single doses of 10, 20 and 30 mg of escitalopram, each separated by a 17-21 day washout period.

Sample Collection:

Blood samples were collected at frequent intervals over a 24 hour period after dose administration.

Analytical Method Performance

No information was provided on the performance of the analytical method. Serum samples were analyzed.

Pharmacokinetic Computations and Statistical Analysis

A non-linear power model relating the pharmacokinetic parameters of primary interest to dose as a power function was used to assess dose proportionality. Estimates of the slope of the proportionality plots were derived by performing a linear regression of the log transformed pharmacokinetic parameter (y) on the log transformed dose: log (*y*) = log (*a*) + *b*x log (dose), where *a* is the proportionality factor and *b* is a power function parameter. In this model, dose proportionality was obtained when the estimates of *b* were not statistically significant different from one.

Pharmacokinetic Results:

The mean PK parameters of ESC and S-DCT following a single dose administration of 10, 20 and 30 mg escitalopram tablets in healthy young and elderly subjects are given in the following table:

Pharmacokinetic Parameters (Mean± SD) of **ESC** following a single Dose Administration of 10, 20 and 30 mg Escitalopram Tablets in Healthy Young and Elderly Subjects			
	10 mg	20 mg	30 mg
Young Subjects (N=15)			
C_{max} (ng/mL)	9.1±2.8	18.8±3.3	27.4±5.5
Tmax (hr)	4.1±1.5	4.3±1.6	3.4±1.0
AUC0-t (ng•hr/mL)	245.9±105.4	533.3±171.6	820.7±307.8
$AUC_{0\text{-}inf}$ (ng•hr/mL)	295.9±114.5	580.7±177.5	873.9±315.3
$T_{½}$ (hr)	25.0±7.0	24.2±6.6	24.9±6.8
CL/F (L/hr)	38.5±13.5	37.8±12.2	38.9±14.2
V_z/F (L)	1304±368	1266±191	1294±329
Elderly Subjects (N=14)			
C_{max} (ng/mL)	8.3±2.1	16.8±4.8	25.6±5.7
Tmax (hr)	5.2±1.1	4.6±1.4	5.5±2.4
AUC0-t (ng•hr/mL)	334.8±161.2	674.8±306.2	1075±502.5
$AUC_{0\text{-}inf}$ (ng•hr/mL)	398.0±178.1	751.3±346.5	1178±593.7
$T_{½}$ (hr)	37.4±9.8	37.0±11.6	37.0±10.4
CL/F (L/hr)	30.0±13.0	33.7±18.8	31.6±15.8
V_z/F (L)	1478±375	1616±729	1510±411
Pharmacokinetic Parameters (Mean± SD) of **S-DCT** following a Single Dose Administration of 10, 20 and 30 mg Escitalopram Tablets in Healthy Young and Elderly Subjects			
	10 mg	20 mg	30 mg
Young Subjects (N=15)			
C_{max} (ng/mL)	1.8±0.6	3.6±1.1	5.3±1.4
Tmax	21.2±11.2	20.9±12.5	18.5±9.6
AUC0-t (ng•hr/mL)	90.9±36.6	282.8±58.0	433.9±103.7
$AUC_{0\text{-}inf}$ (ng•hr/mL)	210.5±22.3	392.3±66.4	553.8±124.5
$t_{½}$ (hr)	60.9±17.4	62.1±16.0	59.5±16.6
MR [1]	0.98±0.27	0.76±0.23	0.74±0.29

Elderly Subjects (N=14)			
C_{max} (ng/mL)	1.4±0.4	2.6±0.7	3.9±0.8
Tmax	26.3±9.7	27.2±14.5	23.9±13.7
AUC0-t (ng•hr/mL)	72.9±28.2	233.7±90.3	392.3±75.4
$AUC_{0\text{-}inf}$ (ng•hr/mL)	220.7±39.4	393.6±71.4	524.9±94.9
$t_{½}$ (hr)	83.8±23.0	77.0±17.4	75.1±21.1
MR_1	0.55±0.15	0.63±0.23	0.55±0.22
1: Metabolic Ratio: $AUC_{0\text{-}inf}$, S-DCT/$AUC_{0\text{-}inf}$, ESC			

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572 The effect of age is seen in the following figure
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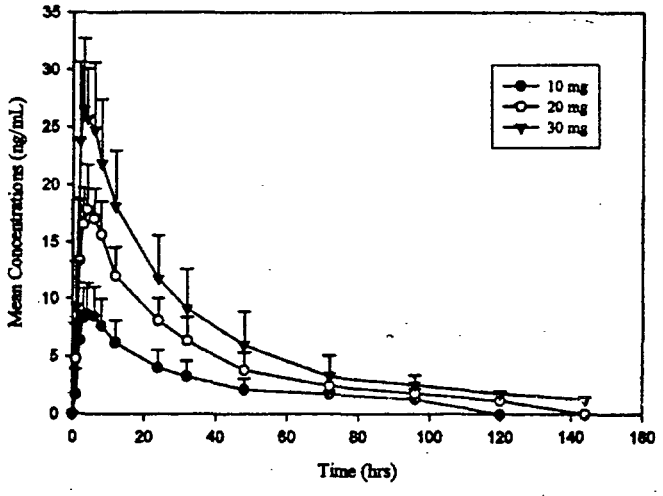
Mean Serum Concentrations of Escitalopram Following a Single Dose Administration of Escitalopram 10, 20 and 30 mg Tablets in Healthy Young Subjects



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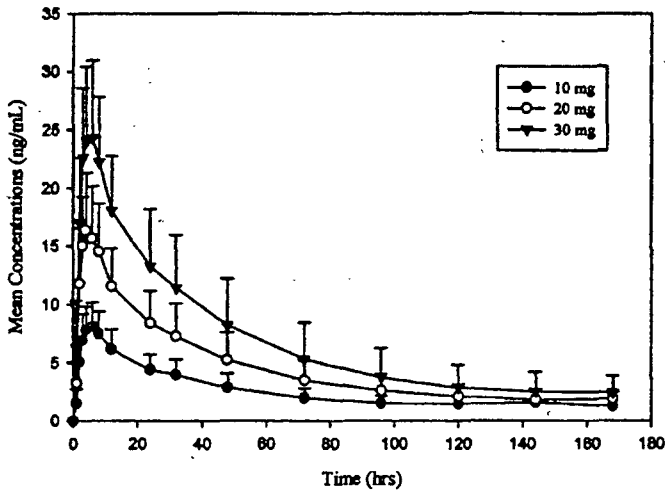
Mean Serum Concentrations of Escitalopram Following a Single Dose Administration of Escitalopram 10, 20 and 30 mg Tablets in Healthy Elderly Subjects



The 95% confidence intervals (CI) for slopes (power parameter ***b***) of the proportionality plots for $AUC_{0\text{-}inf}$ and C_{max} for escitalopram are summarized in the following Table.

95% confidence intervals of the slopes of the proportionality plots of escitalopram for AUC0-inf and Cmax			
Age Group	Gender	Power parameter ***b***	95% CI
Young	Men	0.981	[0.895; 1.066]
Young	Women	1.001	[0.893; 1.110]
Elderly	Men	0.959	[0.767; 1.151]
Elderly	Women	0.963	[0.917; 1.010]
Young	Men	1.024	[0.888; 1.160]
Young	Women	1.031	[0.908; 1.155]
Elderly	Men	1.022	[0.825; 1.219]
Elderly	Women	1.023	[0.965; 1.081]

Conclusions:

Using a standard linear regression model [log (Cmax or AUC $_{0\text{-}inf}$)=log(a) + b*log(dose) and accepting the hypothesis of proportionality of b=1], dose proportionality was established for escitalopram for both C_{max} and AUC $_{0\text{-}inf}$ parameters. ESC was rapidly absorbed, with peak plasma concentration occurring between 3-5 hours. The $AUC_{(0\text{-}inf)}$ and Cmax values of ESC increased linearly and proportionally with dose. In general, AUC $_{0\text{-}inf}$ values were larger in the elderly compared to the young subjects. A gender difference in Cmax and AUC was observed only in elderly subjects.

Mean Cmax values of escitalopram were similar in the young and elderly subjects. Maximum serum concentrations of escitalopram were obtained at approximately 2 to 6 hours for young and 3 to 8 hours for elderly subjects. The mean AUC $_{0\text{-}inf}$ values obtained in the elderly subjects were larger than those in the young subjects. The overall mean t ½

values of escitalopram were significantly longer in the elderly (37.0+11.6 hrs) compared to those in the young subjects (24.2± 6.6 hrs) for the 20 mg dose.
For S-DCT, dose proportionality was established for Cmax but the slope (b) was less than unity for AUC $_{0\text{-inf}}$. Maximum serum concentrations of S-DCT were obtained at approximately 8 to 34 hours for young and 10 to 42 hours in the elderly subjects. The overall mean t ½ values of S-DCT were significantly longer in the elderly (77.2± 19.6 hrs) compared to those in the young subjects (60.8± 16.1 hours).

The results support the approved pharmacokinetic labeling that states "The multiple dose pharmacokinetics of escitalopram oxalate are linear and dose proportional in a dosing range of 10-30 mg/day" and "After a single dose, the plasma escitalopram levels were similar in the young and the elderly subjects. At steady state, escitalopram AUC and half-life were increased by approximately 50% in elderly subjects. 10 mg is the recommended dose for elderly patients."

B. Proposed Labeling

The package insert for escitalopram oxalate oral solution, based upon the proposed package insert for NDA 21-323 amended 10/19/01, appears as follows:
Name of Product™
(escitalopram oxalate)

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Draft Labeling
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/s/

Carol Noory
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Ramana S. Uppoor
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BIOPHARMACEUTICS

APPEARS THIS WAY
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