

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-323**

**ADMINISTRATIVE DOCUMENTS**  
**CORRESPONDENCE**



DEPARTMENT OF HEALTH & HUMAN SERVICES

David

Food and Drug Administration  
Rockville MD 20857

007 18 2001

William J. Burke, M.D.  
Professor and Vice Chair  
University of Nebraska Medical Center  
Department of Psychiatry  
985581 Nebraska Medical Center  
Omaha, Nebraska 68198-5580

Dear Dr. Burke:

Between September 19 and 21, 2001, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol SCT-MD-01) of the investigational drug Escitalopram, performed for Forest Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

ISI

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

FEI: 3001451216

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

If Headquarters classification is a different classification, explain why:

cc:

- HFA-224
- HFD-120 Doc.Rm. NDA#21-323
- HFD-120 Review Div.Dir. Katz
- HFD-120 MO Brugge
- HFD-120 PM David
- HFD-45 c/r/s GCP File #9411
- HFD-47 NK/GH
- HFR-SW350 DIB Woleske
- HFR-SW350 Bimo/Investigator Montgomery

r/d:(NK)(10/12/01)  
reviewed:AEH:(10/15/01)  
f/t:mb:(10/15/01)

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Reviewer Note to Rev. Div. M.O.

*Data acceptable.*

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application : NDA 21323/000 Sponsor: FOREST LABS  
Org Code : 120 PLAZA 3 STE 602  
Priority : 3S JERSEY CITY, NJ 07311

Stamp Date : 23-MAR-2001 Brand Name : ESCITALOPRAM 5/10/20MG TABLETS  
PDUFA Date : 21-AUG-2002 Estab. Name:  
Action Goal : Generic Name: ESCITALOPRAM 5/10/20MG  
District Goal: 24-NOV-2001 TABLETS  
Dosage Form: (TABLET)  
Strength : 5 MG, 10 MG, 20 MG

FDA Contacts: P. DAVID Project Manager (HFD-120) 301-594-2850  
L. ROCCA Review Chemist (HFD-810) 301-594-5357  
ID = 115238 Team Leader

Overall Recommendation: ACCEPTABLE on 17-JAN-2002 by P. LEFLER (HFD-324) 301-827-0062  
WITHHOLD on 29-NOV-2001 by GARCIA M

Establishment : CFN : 9616660 FEI : 3002806993  
FOREST LABORATORIES IRELAND LTD  
CLONSHAUGH, DUBLIN 17, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 16-NOV-01  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1523957 FEI : 1523957  
FOREST PHARMACEUTICALS INC  
5000 BROTHERTON ROAD  
CINCINNATI, OH 45209

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 17-JAN-02  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2419749 FEI : 2419749  
FOREST/INWOOD LABORATORIES  
300 303 320 321 330 PROSPECT STREET  
INWOOD, NY 11696

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 17-APR-01  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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Establishment : CFN : 2436283 FEI : 3000215868  
FOREST/INWOOD LABORATORIES  
500 COMMACK ROAD  
COMMACK, NY 11725

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 23-APR-01  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : 9613224 FEI : 3002807184  
H LUNDBECK A/S  
DK-4500 NYKOBING SJ, , DA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 15-OCT-01  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : 9613225 FEI : 3002807185  
H LUNDBECK A/S  
OTTILIAVE 9  
COPENHAGEN VALBY, , DA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 15-OCT-01  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA:

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Responsibilities:

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-JAN-02  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 29-NOV-01  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

Establishment :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 17-APR-01  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

Establishment :

FEI

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 17-APR-01  
Decision : ACCEPTABLE  
Reason : BASED ON FILE REVIEW

David  
Food and Drug Administration  
Rockville MD 20857

Susan G. Kornstein, M.D.  
Mood Disorders Institute  
700 West Grace Street, Suite 303  
Richmond, Virginia 23220

NOV 20

Dear Dr. Kornstein:

Between October 16 and 19, 2001, Ms. Candice J. Cortes, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol SCT-MD-01) of the investigational drug Escitalopram, performed for Forest Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Cortes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

FEI: 3003463790

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

If Headquarters classification is a different classification, explain why:

cc:

HFA-224  
HFD-120 Doc.Rm. NDA#21-323  
HFD-120 Review Div.Dir. Katz  
HFD-120 MO Brugge  
HFD-120 PM David  
HFD-45 c/r/s GCP File #10505  
HFD-47 NK/GH  
HFR-CE250 DIB Wagner  
HFR-CE250 Bimo Salisbury  
HFR-CE250 Investigator Cortes

r/d:(NK)(11/19/01) NJK  
reviewed:AEH:(11/20/01)  
f/t:mb:(11/20/01)

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Reviewer Note to Rev. Div. M.O.

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of

Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville MD 20857

**CLINICAL INSPECTION SUMMARY**

DATE: November 19, 2001

TO: Paul David, R.Ph., Senior Regulatory Project Manager  
Karen Brugge, M.D., Medical Officer  
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-323

APPLICANT: Forest Laboratories, Inc.

DRUG: Escitalopram Oxalate Tablets

CHEMICAL CLASSIFICATION: Type 3S

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Major Depressive Disorder

CONSULTATION REQUEST DATE: July 17, 2001

ACTION GOAL DATE: January 23, 2002

**I. BACKGROUND:**

Escitalopram (Lu 26-054) is the S-enantiomer of the selective serotonin reuptake inhibitor citalopram, which is currently marketed under the brand name of Celexa for depression. In this NDA, the sponsor has requested the use of escitalopram in major depressive disorder. Inspection assignments were issued on August 30, 2001 for three domestic sites, Burke, Khan and Kornstein for Protocol SCT-MD-01. The inspection was for the purpose of validating data in support of pending NDA 21-323.

**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*1 page*

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the data from these three domestic sites appear acceptable for use in support of the pending NDA.

There was no limitation to these inspections.

#### Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

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Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

#### CONCURRENCE:

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Antoine El-Hage, Ph.D., Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

cc:

NDA 21-323

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/c/r/s

HFD-47/Khin

HFD-47/Hajarian

HFD-45/RF

rd:NK:11/20/01

O:\WK\NDA21323 MDD CIS.DOC

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

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Michele Balser

11/20/01 03:50:12 PM

TECHNICAL

Original CIS was signed by Drs. Khin and ElHage on 11/20/01.

**APPEARS THIS WAY  
ON ORIGINAL**

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

<b>DATE RECEIVED:</b> 4/13/01	<b>DUE DATE:</b> 8/29/01	<b>OPDRA CONSULT:</b> 01-0084
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**TO:**

Russell Katz, M.D.  
 Director, Division of Neuropharmacological Drug Products  
 HFD-120

**THROUGH:**

Paul David  
 Project Manager, Division of Neuropharmacological Drug Products  
 HFD-120

<p><b>PRODUCT NAME:</b></p> <p>_____ ) and Lexapro (secondary)        (escitalopram oxalate tablets)        5 mg, 10 mg, and 20 mg</p> <p><b>NDA #:</b> 21-323</p>	<p><b>MANUFACTURER:</b> Forest Laboratories, Inc.</p>
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**SAFETY EVALUATOR:** Jennifer Fan, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a review of the proposed proprietary names \_\_\_\_\_ and "Lexapro" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**OPDRA RECOMMENDATION:**

OPDRA does not recommend the use of the proprietary name, \_\_\_\_\_, but has no objection to the use of the proprietary name "Lexapro".

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date.

<p>_____          Jerry Phillips, R.Ph.          Associate Director for Medication Error Prevention          Office of Post-Marketing Drug Risk Assessment          Phone: 301-827-3246          Fax: 301-443-5161</p>	<p>_____          Martin Himmel, M.D.          Deputy Director          Office of Post-Marketing Drug Risk Assessment          Center for Drug Evaluation and Research          Food and Drug Administration</p>
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Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B32  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** August 20, 2001  
**NDA NUMBER:** 21-323  
**NAME OF DRUG:** [REDACTED] ) and Lexapro (Secondary)  
(escitalopram oxalate tablets), 5 mg, 10 mg, and 20 mg  
**NDA HOLDER:** Forest Laboratories, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the tradenames [REDACTED], and "Lexapro" (secondary), regarding potential name confusion with other proprietary/established drug names.

PRODUCT INFORMATION

[REDACTED] "Lexapro" (escitalopram) is a selective serotonin reuptake inhibitor (SSRI) and is the pure S-enantiomer of the racemic bicyclic phthalane derivative citalopram (*Celexa*). Escitalopram is at least twice as potent as racemic citalopram and more than 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. The initial recommended dosage of [REDACTED] "Lexapro" is 10 mg once daily (morning or evening) for all patients and can be taken with or without food. Patients not responding to a 10 mg dosage may benefit from a dose increase to 20 mg after a minimum of one week. [REDACTED] "Lexapro" will be available as a 5 mg, 10 mg, and 20 mg tablet where the tablets are film coated, oval, and scored.

**II. RISK ASSESSMENT:**

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> as well as several FDA databases<sup>4</sup> for existing drug names which sound alike or look alike to [REDACTED] and "Lexapro" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database<sup>5</sup> and the data provided by Thomson &

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

<sup>2</sup> American Drug Index, 42<sup>nd</sup> Edition, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>4</sup> The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

Thomson's SAEGIS™ Online Service<sup>6</sup> were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted two sets of three prescription analysis studies each consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names            and "Lexapro". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with            and "Lexapro". These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose	Other**
<u>          </u> /Lexapro	Escitalopram Oxalate (Anti-depressant/SSRI – Rx) Tablet: 5 mg, 10 mg, and 20 mg	10 mg once a day	
Celexa	Citalopram HBr (Anti-depressant /SSRI – Rx) Tablet: 20 mg and 40 mg Oral Solution: 10 mg/5 mL	20 mg once a day	S/A, L/A per OPDRA
Relenza	Zanamivir (Anti-viral – Rx) Powder for inhalation (diskhaler device): 5 mg	2 inhalations twice a day.	S/A per OPDRA
Zyprexa (also Zyprexa Zydis)	Olanzapine (Anti-psychotic – Rx) Tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg Tablet (orally disintegrating): 5 mg and 10 mg	<i>Schizophrenia:</i> 5 to 10 mg once daily.  <i>Bipolar mania:</i> 10 to 15 mg once daily.	S/A per OPDRA
Loprox	Ciclopirox (Anti-fungal – Rx) Cream and Lotion: 0.77%	Apply to affected areas twice daily, morning and evening.	S/A per OPDRA
Avapro	Irbesartan (Anti-hypertesion – Rx) Tablet: 75 mg, 150 mg, and 300 mg	150 mg once daily with or without food.	S/A per OPDRA
Lescol/Lescol XL	Fluvastatin Sodium	Reduction goal of ≥ 25%	S/A per OPDRA

<sup>6</sup> WWW location <http://www.thomson-thomson.com>.

Product Name	Dosage form(s), Generic name	Usual adult dose	Other
Lexapro	Escitalopram Oxalate (Anti-depressant/SSRI - Rx) Tablet: 5 mg, 10 mg, and 20 mg	10 mg once a day	
	(Anti-hyperlipidemic - Rx) Capsule: 20 mg and 40 mg Tablet (Lescol XL): 80 mg	LDL cholesterol level: Capsule: 40 mg once or twice a day. Tablet: 80 mg once a day in the evening.  Reduction goal of < 25% LDL cholesterol level: 20 mg once or twice a day.	
Cipro/Cipro I.V.	Ciprofloxacin (Anti-Infective - Rx)  Tablet: 100 mg, 250 mg, 500 mg, and 750 mg Oral Suspension: 5 g/100 mL (5%) and 10 g/100 mL (10%) Injection (Cipro I.V.): 200 mg and 400 mg	Dosing and frequency varies according to disease state.	S/A per OPDRA
		*Frequently used, not all-inclusive	**S/A(Sound-alike), L:A (Look-alike)

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

Studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of “” and “Lexapro” and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 85 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for “” and “Lexapro” (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

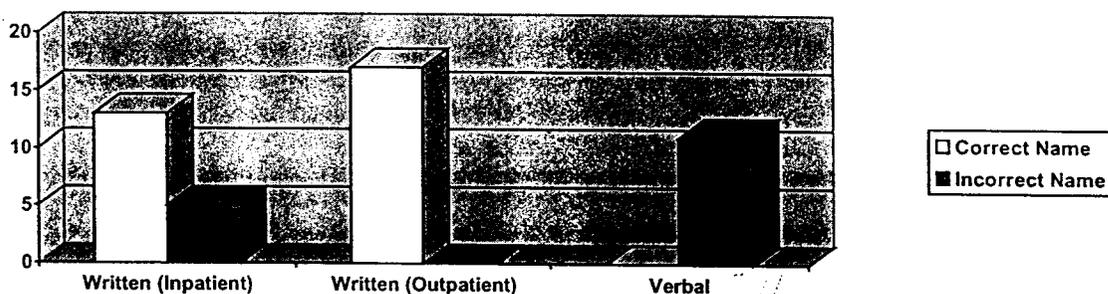
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient:  QD	Outpatient:  .ng
Outpatient:  5 mg Sig: i po QD	Take 1, by mouth, once a day.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<b>"Lexapro"</b>	
<i>Inpatient:</i> Lexapro 5 mg qd	<i>Outpatient:</i> Lexapro 5 mg
<i>Outpatient:</i> Lexapro 5 mg Sig: i po qd #30	Take 1, by mouth, once a day. #30

2. Results:

A. Results of the \_\_\_\_\_ studies are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written: Inpatient	28	18 (64%)	13 (72%)	5 (28%)
Written: Outpatient	27	17 (63%)	17 (100%)	0 (0%)
Verbal: Outpatient	30	11 (37%)	0 (0%)	11 (100%)
Total	85	46 (54%)	30 (65%)	16 (35%)



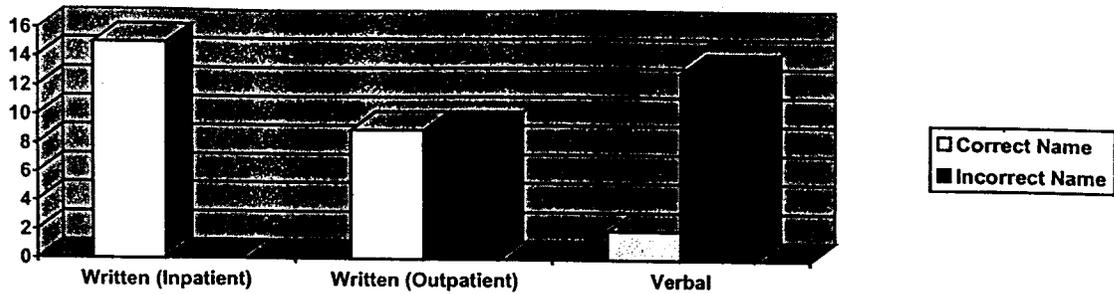
Among the written inpatient prescriptions, 5 (28%) out of 18 respondents interpreted \_\_\_\_\_ incorrectly. All 5 respondents interpreted \_\_\_\_\_ as *Vorexa*.

Among the written outpatient prescriptions, none (0%) of the 17 respondents interpreted \_\_\_\_\_ "incorrectly. One respondent commented that \_\_\_\_\_ " may sound similar to *Celexa*, an antidepressant medication.

Among the verbal outpatient prescriptions, 11 (100%) out of 11 respondents interpreted \_\_\_\_\_ incorrectly. Interpretations included *Relexa*, *Valex*, *Voloxitin*, *Rolexin*, *Velexa*, and *Rolexa*. One respondent, who interpreted \_\_\_\_\_ as *Relexa*, commented that the prescription may not be for *Relexa* since the dosing on the prescription was not correct for *Relexa*.

B. Results of the "Lexapro" studies are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Lexapro"	Incorrectly Interpreted
Written: Inpatient	30	15 (50%)	15 (100%)	0 (0%)
Written: Outpatient	28	18 (64%)	9 (50%)	9 (50%)
Verbal: Outpatient	27	15 (56%)	2 (13%)	13 (87%)
Total	85	48 (56%)	26 (54%)	22 (46%)



Among the written inpatient prescriptions, none (0%) of the 15 respondents interpreted “Lexapro” incorrectly.

Among the written outpatient prescriptions, 9 (50%) out of 18 respondents interpreted “Lexapro” incorrectly. Interpretations included *Cexapro*, *Cexapio*, and *Laxapro*.

Among the verbal outpatient prescriptions, 13 (87%) out of 15 respondents interpreted “Lexapro” incorrectly. Interpretations included *Lexiprel*, *Lexipril*, *Lexipro*, *Luxipro*, *Luxapril*, *Luxapro*, *Lexepro*, and *Lexepril*.

### C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name ‘ — ’ and “Lexapro”, the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such proprietary drug names include *Relenza*, *Zyprexa*, *Celexa*, *Loprox*, *Avapro*, *Cipro*, and *Lescol*.

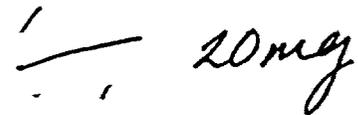
*Relenza* is the proprietary drug name for zanamivir and is indicated for the treatment of uncomplicated acute illness due to influenza A and B virus in adults and children  $\geq 7$  years of age who have been symptomatic for  $\leq 2$  days. It is available in a 5 mg strength powder that is inhaled through a *Diskhaler*. The recommended dosage is 2 inhalations twice a day. *Relenza* and ‘ — ’ sound similar since the “r” and the “v”, when pronounced over the telephone, can sound similar. This can be seen in the verbal portion of the OPDRA study where 5 respondents interpreted ‘ — ’ as *Relexa*, 1 respondent interpreted it as *Rolexin*, and another respondent interpreted it as *Rolexa*. *Relexa* sounds quite similar to *Relenza*. One respondent commented that the difference in dosing between the two drugs was a factor in ruling out *Relenza*. Also, another pronunciation similarity is the “za” in *Relenza* and the “xa” in ‘ — ’. They both have the same route of administration (oral) and share the same strength (5 mg). Even though they do sound similar, have the same route of administration, and share the same strength, there is a difference in dosage form (tablet vs. powder for inhalation and *Diskhaler*) and dosing directions (Take 1 tablet by mouth once a day vs. Take 2 inhalations twice a day). Due to these differences, there would be a decreased potential risk for a medication error between these two drug products.

*Zyprexa* is the proprietary drug name for olanzapine and is indicated for the treatment of schizophrenia and short-term treatment of acute manic episodes associated with Bipolar I disorder. It is available as a 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg as well as a 5 mg and 10 mg orally disintegrating tablet. The recommended dosage is 5 to 15 mg once a day depending on the disease state. The two drug names are similar due to the “exa” endings of both drug names. Also, both have the same dosage form (tablet), the same route of administration (oral), share the same strengths (5 mg, 10 mg, and 20 mg), and have the same dosing regimen and recommended dose (10 mg once a day). If *Zyprexa* was mistakenly given instead of

\_\_\_\_\_ then the patient's depression would not be treated. Also, the patient would be exposed to certain unnecessary side effects such as tardive dyskinesia, Neuroleptic Malignant Syndrome, orthostatic hypertension, seizures, dysphagia, dry mouth, and somnolence. If \_\_\_\_\_ was mistakenly dispensed instead of *Zyprexa*, the patient's schizophrenia and/or mania would not be treated. Also, the patient would be exposed to certain unnecessary side effects such as activation of mania/hypomania, hyponatremia, nausea, and insomnia.

*Celexa* is the proprietary drug name for citalopram hydrobromide and is indicated for the treatment of depression. It is available as a 20 mg and 40 mg tablet as well as a 10 mg/5 mL oral solution. *Celexa* is a racemic mixture of citalopram whereas \_\_\_\_\_ is the S-enantiomer of citalopram. \_\_\_\_\_ looks similar to *Celexa* when scripted (see below) and also sounds similar. Both proprietary drug names end in "lexa". The two drug products have the same dosage form (tablet), the same route of administration (oral), share the same strength (20 mg), and have the same dosage regimen (once a day). Even though these two products belong to the same drug class, a patient's depression may not be adequately treated if he/she receives the wrong medication. If a patient receives 20 mg of \_\_\_\_\_ instead of 20 mg of *Celexa*, the dose may be too high for the patient and could expose the patient to side effects such as nausea and dry mouth. If a patient receives *Celexa* instead of \_\_\_\_\_, the patient's depression would not be adequately treated, and the patient could experience side effects that would not be seen if the patient was taking \_\_\_\_\_.

*Writing Sample:*

  
\_\_\_\_\_ 20 mg

  
Celexa 20 mg

*Loprox* is the proprietary name for ciclopirox and is indicated in the treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*; cutaneous candidiasis (moniliasis) due to *C. albicans*; tinea (pityriasis) versicolor due to *M. furfur*. This drug product is available in a 0.77% cream and lotion. *Loprox* sounds somewhat similar to "Lexapro" since both start with the "l" sound as well as contain the "x" and the "pro" sound. However, the difference in dosage form and directions of use would distinguish the two drug products so that the potential risk of medication errors between these two products would be low.

*Avapro* is the proprietary name for irbesartan and is indicated for the treatment of hypertension. It is available as a 75 mg, 150 mg, and 300 mg tablet and is generally taken as once a day with or without food. *Avapro* sounds similar to "Lexapro" since both proprietary drug names end in "apro". Both also have the same dosage form (tablet), the same dosage regimen (once a day), and the same route of administration (oral). However, there are no overlapping strengths between the drug products. Since both drug products have multiple strengths, the prescriber would need to indicate the strength on the prescription. The strengths are the distinguishable factors that can decrease the potential risk of a medication error between these two products.

*Cipro* is the proprietary name for ciprofloxacin and is indicated the treatment of infections caused by a variety of microorganisms. It is supplied as a 100 mg, 250 mg, 500 mg, and 750 mg

tablet as well as a 5 g/100 mL and 10 g/100 mL oral suspension. It is also available as a 200 mg and 400 mg IV injection. The dosing depends on the patient's disease state. "Lexapro" sounds somewhat similar to *Cipro*. If a practitioner verbally transmits "Lexapro" over the telephone, the receiver of that prescription may not be able to hear the "le" portion of the name and instead may hear the "xapro" portion of the name, which sounds like *Cipro*. Even though these two products share the same dosage form (tablet) and route of administration (oral), there are no overlapping strengths, which will decrease the potential risk of a medication error occurring.

*Lescol* is the proprietary name for fluvastatin sodium and is indicated for the treatment of hypercholesterolemia, mixed dyslipidemia, and to slow the progression of coronary atherosclerosis in patients with coronary heart disease. It is available as a 20 mg and 40 mg capsule where the recommended dosage for the capsule is 20 to 40 mg once a day. *Lescol* sounds somewhat similar to "Lexapro" since both proprietary names begin with the "le" sound, and they also share a "k" sound in the middle of the proprietary name. Even though there were no positive hits in the verbal portion of the OPDRA study, 9 (60%) respondents out of 15 included an "l" at the end of the name (*Lexiprel*, *Luxapril*, *Lexipril*, and *Lexepri*). However, "Lexapro" can be distinguished from *Lescol* due to its additional syllable, the "xa" sound, and the "pro" ending. In the verbal portion of the OPDRA study, all the respondents included their interpretation of the "xa" sound in "Lexapro". Both products share the same route of administration (oral: tablet vs. capsule) and the same strength (20 mg). Both drug products can be taken once a day. Because of the differences in the proprietary drug names, the potential risk of medication errors between these two proprietary drug names is low.

The established name of this drug product, escitalopram oxalate, is very similar to *Celexa*'s established name, citalopram. There would be possible confusion between these products if the prescriber uses the established name on the prescription instead of the proprietary name. Please see above for the comparison between *Celexa* and

From the above information, OPDRA does not recommend in the use of the proprietary name, \_\_\_\_\_, but has no objection to the proprietary name, "Lexapro".

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

#### A. GENERAL COMMENT

1. The 10 mg and 20 mg container labels and carton labeling were not submitted. The following comments also pertain to the 10 mg and 20 mg labels and labeling.

#### B. CONTAINER LABEL (5 mg; bottle of 30, 100, and 1000; blister foil)

1. The proprietary drug name and the established name should be prominent on the label.
2. The established name should be at least ½ the size of the proprietary name in accordance to 21 CFR 201.10(g)(2).
3. The statement "Tablets – 5 mg" is duplicative information and is not necessary.
4. The "5 mg" should appear prominently and differentiated between the other strengths (10 mg and 20 mg). A different color for each strength may be used to highlight the strength of the drug product.
5. The net quantity statement (30 Tablets, etc.) should appear away from the tablet strength. It may be placed under the name and address of the sponsor, in the lower right-hand corner of the label.
6. On the side panel, the statement "See package insert for full prescribing information" should be

revised to read "Usual Dosage: 10 mg once a day. See package insert for further prescribing information."

7. On the blister foil, the statement "5 mg" should appear prominently on the label and distinguishable from the other strengths in addition to the statement "Equivalent to 5 mg escitalopram."

C. CARTON LABELING (10 x 10 Blister Box, 8 boxes x 7 tablets Blister Box, 1 x 7 Blister Box)

*10 x 10 Blister Box*

1. The Back Panel (assuming that this is the main panel) should refer to the above comments (section III(B)) 1, 2, 4, 5, 6, and 7.
2. The "Rx Only" on the Top Panel should be on the Back (Main) Panel.

*8 Boxes x 7 Tablets Blister Box*

1. On the 8 boxes x 7 tablets Blister Box, the statement "Rx only – See package insert for full prescribing information" should be revised to state "Rx Only".
2. The Usual Dosage statement should state "Usual Dosage: 10 mg once a day. See package insert for further prescribing information."
3. Please refer to the above comment (section III(B)) 1, 2, 4, 5, 6, and 7 for the Main Panel.

*1 x 7 Blister Box*

1. On the Front Panel, please refer to the above comment (section III(B)) 1, 2, 4, and 7.
2. On the Back Panel, please revise the statement "See package insert for full prescribing information" to state "Usual Dosage: 10 mg once a day. See package insert for further prescribing information."

D. PACKAGE INSERT

1. OPDRA has no comments on the package insert.

**APPEARS THIS WAY  
ON ORIGINAL**

V. RECOMMENDATIONS:

- A. OPDRA does not recommend the use of the proprietary name, '←', but has no objection to the use of the proprietary name, "Lexapro".
- B. OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.
- C. We recommend consulting Dan Boring (of the USAN council and LNC) for the proper designation of the established name.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

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Jennifer Fan, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

---

Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY  
ON ORIGINAL**

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

/s/

-----  
Jennifer Fan  
8/31/01 09:38:18 AM  
PHARMACIST

Jerry Phillips  
8/31/01 09:40:32 AM  
DIRECTOR

Martin Himmel  
9/4/01 12:27:09 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

Application: NDA 21323/000  
Stamp: 23-MAR-2001  
Regulatory Due: 23-JAN-2002  
Applicant: FOREST LABS  
PLAZA 3 STE 602  
JERSEY CITY, NJ 07311  
Priority: 3S  
Org Code: 120

Action Goal:  
District Goal: 24-NOV-2001  
Brand Name: ESCITALOPRAM 5/10/20MG TABLETS  
Estab. Name:  
Generic Name: ESCITALOPRAM 5/10/20MG TABLETS

Dosage Form: (TABLET)  
Strength: 5 MG, 10 MG, 20 MG

Application Comment: ESCITALOPRAM TABLETS ARE INTENDED FOR THE TREATMENT OF DEPRESSION. ESCITALOPRAM IS THE (+) S-ISOMER OF THE RACEMATE, CITALOPRAM, (CELEXA, NDA 20-822), WHICH WAS APPROVED ON JULY 17, 1998 FOR THE TREATMENT OF DEPRESSION. (on 17-APR-2001 by L. ROCCA (HFD-810) 301-594-5357)

FDA Contacts: P. DAVID (HFD-120) 301-594-2850 , Project Manager  
L. ROCCA (HFD-810) 301-594-5357 , Review Chemist  
ID = 115238 , Team Leader

Overall Recommendation: WITHHOLD on 29-NOV-2001 by M. GARCIA (HFD-322) 301-594-0095  
ACCEPTABLE on 17-JAN-2002 by P. LEFLER (HFD-324) 301-827-0062

Establishment: 9616660

FOREST LABORATORIES IRELAND LTD  
CLONSHAUGH, DUBLIN 17, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

Profile: TCM OAI Status: NONE

Estab. Comment: THE DRUG PRODUCT WILL BE MANUFACTURED BY FOREST AT THEIR CLONSHAUGH, DUBLIN FACILITY. UPON RECEIPT OF DS FOREST PERFORMS SPECIFIC ID TESTING BY IR & STEREOCHEMICAL INTEGRITY BY CHIRAL HPLC USING PROCEDURES PROVIDED BY LUNDBECK. THE ESCITALOPRAM OXALATE IS RELEASED FOR MANUFACTURING BASED ON COA FROM LUNDBECK & CONFIRMATION OF IDENTITY BY FOREST. DRUG PRODUCT RELEASE TESTING WILL BE CONDUCTED AT FOREST'S CLONSHAUGH, DUBLIN FACILITY. (on 24-APR-2001 by L. ROCCA (HFD-810) 301-594-5357)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
SUBMITTED TO DO	17-APR-2001	PS			EGASM
ASSIGNED INSPECTION	20-APR-2001	PS			EGASM
INSPECTION SCHEDULED	15-JUN-2001		03-AUG-2001		IRIVERA
INSPECTION PERFORMED	06-AUG-2001		02-AUG-2001		EGASM
DO RECOMMENDATION	15-NOV-2001			ACCEPTABLE	GARCIAM
OC RECOMMENDATION	16-NOV-2001			INSPECTION ACCEPTABLE	GARCIAM
				DISTRICT RECOMMENDATION	

Establishment: 1523957

FOREST PHARMACEUTICALS INC  
5000 BROTHERTON ROAD  
CINCINNATI, OH 45209

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: POTENTIAL OAI

Estab. Comment: DRUG PRODUCT WILL BE PACKAGED IN UNIT DOSE AND LABELED AT FOREST'S CINCINNATI FACILITY. (on 17-APR-2001 by L. ROCCA (HFD-810) 301-594-5357)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
OC RECOMMENDATION	17-APR-2001			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	
DO RECOMMENDATION	17-JAN-2002			ACCEPTABLE	SEASTHAM
				BASED ON FILE REVIEW	
WE ARE NOT AWARE OF ANY REASON TO WITHHOLD APPROVAL OF THIS FACILITY FOR PACKAGING AND LABELING OF TABLET PRODUCTS INTO UNIT DOSES.					
OC RECOMMENDATION	17-JAN-2002			ACCEPTABLE	ALCOCKP
				DISTRICT RECOMMENDATION	
POTENTIAL OAI DOES NOT APPEAR TO APPLY TO PACKAGING AND LABELING OF UNIT DOSE - SEE DISTRICT RECOMMENDATION. CONCUR WITH DISTRICT. UF 1-23-02					

Establishment: 2419749

FOREST/INWOOD LABORATORIES  
300 303 320 321 330 PROSPECT STREET  
INWOOD, NY 11696

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL

OAI Status: NONE

Estab. Comment: DRUG PRODUCT STABILITY TESTING WILL BE CONDUCTED AT FOREST'S  
INWOOD NY FACILITY. (on 17-APR-2001 by L. ROCCA (HFD-810) 301-594-  
5357)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
OC RECOMMENDATION	17-APR-2001			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Establishment: 2436283

FOREST/INWOOD LABORATORIES  
500 COMMACK ROAD  
COMMACK, NY 11725

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM

OAI Status: NONE

Estab. Comment: DRUG PRODUCT WILL BE PACKAGED IN BOTTLES & LABELED AT FOREST'S  
COMMACK, NY FACILITY. (on 17-APR-2001 by L. ROCCA (HFD-810) 301-  
594-5357)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
SUBMITTED TO DO	17-APR-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	19-APR-2001	PS			LFARINA
DO RECOMMENDATION	23-APR-2001			ACCEPTABLE	LFARINA
				BASED ON FILE REVIEW	
OC RECOMMENDATION	23-APR-2001			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 9613224

H LUNDBECK A/S  
DK-4500 NYKOBING SJ, , DA

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN

OAI Status: NONE

Estab. Comment: MANUFACTURING FACILITY FOR ESCITALOPRAM OXALATE. (on 17-APR-2001  
by L. ROCCA (HFD-810) 301-594-5357)

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
SUBMITTED TO DO	17-APR-2001	GMP			EGASM
ASSIGNED INSPECTION	'23-APR-2001	PS			EGASM
INSPECTION SCHEDULED	17-JUL-2001		18-SEP-2001		IRIVERA
INSPECTION PERFORMED	02-OCT-2001		21-SEP-2001		IRIVERA
NO FD-483 WAS ISSUED. FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	12-OCT-2001			ACCEPTABLE	GARCIA
OC RECOMMENDATION	15-OCT-2001			INSPECTION ACCEPTABLE	GARCIA
				DISTRICT RECOMMENDATION	

Establishment: 9613225

H LUNDBECK A/S  
OTTILIAVE 9  
COPENHAGEN VALBY, , DA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: MANUFACTURING FACILITY FOR ESCITALOPRAM OXALATE. THE ESCITALOPRAM OXAPATE API IS RELEASED TO FOREST BY H. LUNDBECK A/S AT THEIR QC FACILITY AT COPENHAGEN-VALBY, DENMARK. (on 17-APR-2001 by L. ROCCA (HFD-810) 301-594-5357)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
SUBMITTED TO DO	17-APR-2001	PS			EGASM
ASSIGNED INSPECTION	'20-APR-2001	PS			EGASM
INSPECTION SCHEDULED	17-JUL-2001		21-SEP-2001		IRIVERA
INSPECTION PERFORMED	21-SEP-2001		21-SEP-2001		GARCIA
DO RECOMMENDATION	12-OCT-2001			ACCEPTABLE	GARCIA
OC RECOMMENDATION	15-OCT-2001			INSPECTION ACCEPTABLE	GARCIA
				DISTRICT RECOMMENDATION	

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA:

Responsibilities: \_\_\_\_\_

Profile: CSN OAI Status: NONE

Estab. Comment: \_\_\_\_\_

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
SUBMITTED TO DO	17-APR-2001	PS			EGASM
ASSIGNED INSPECTION	'20-APR-2001	PS			EGASM
INSPECTION SCHEDULED	17-JUL-2001		09-AUG-2001		IRIVERA
INSPECTION PERFORMED	13-AUG-2001		09-AUG-2001		IRIVERA
DO RECOMMENDATION	11-OCT-2001			WITHHOLD	GARCIA
				PEND REG ACTION - WARNING LTR	

UNTITLED LETTER ISSUED 10/3/01

OC RECOMMENDATION	11-OCT-2001	WITHHOLD	GARCIAM
		WARNING LETTER ISSUED	
DO RECOMMENDATION	10-JAN-2002	ACCEPTABLE	GARCIAM
		ADEQUATE FIRM RESPONSE	
OC RECOMMENDATION	10-JAN-2002	ACCEPTABLE	GARCIAM
		DISTRICT RECOMMENDATION	

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

Profile: CTL OAI Status: NONE

Estab. Comment: \_\_\_\_\_

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
SUBMITTED TO DO	17-APR-2001	GMP			EGASM
ASSIGNED INSPECTION	20-APR-2001	GMP			EGASM
INSPECTION SCHEDULED	02-OCT-2001		24-OCT-2001		IRIVERA
INSPECTION PERFORMED	25-OCT-2001		23-OCT-2001		GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE	GARCIAM
				INSPECTION	
OC RECOMMENDATION	29-NOV-2001			ACCEPTABLE	GARCIAM
				DISTRICT RECOMMENDATION	

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

Profile: CTL OAI Status: NONE

Estab. Comment: \_\_\_\_\_

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
OC RECOMMENDATION	17-APR-2001			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

Profile: CTL OAI Status: NONE

Estab. Comment: \_\_\_\_\_

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-APR-2001				ROCCAL
OC RECOMMENDATION	17-APR-2001			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ

ACCORDING TO MPQAS, LAST GMP WAS 2/00, ACCEPTABLE.

**APPEARS THIS WAY  
ON ORIGINAL**

## ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21323/000	Priority: 3S	Org Code: 120
Stamp: 23-MAR-2001 Regulatory Due: 23-JAN-2002	Action Goal:	District Goal: 24-NOV-2001
Applicant: FOREST LABS HARBORSIDE FINANCIAL CENTER PLAZA 3 STE 602 JERSEY CITY, NJ 07311	Brand Name: ESCITALOPRAM 5/10/20MG TABLETS	Established Name:
	Generic Name: ESCITALOPRAM 5/10/20MG TABLETS	Dosage Form: TAB (TABLET)
	Dosage Form: TAB (TABLET)	Strength: 5 MG, 10 MG, 20 MG
FDA Contacts: P. DAVID (HFD-120)	301-594-2850	, Project Manager
L. ROCCA (HFD-810)	301-594-5357	, Review Chemist
ID = 115238		, Team Leader

Overall Recommendation:

**WITHHOLD on 29-NOV-2001 by M. GARCIA (HFD-322) 301-594-0095**

Establishment: 9616660	DMF No:
FOREST LABORATORIES IRELAND I	AADA No:
CLONSHAUGH, DUBLIN 17, , EI	

Profile: TCM	OAI Status: NONE	Responsibilities: FINISHED DOSAGE
Last Milestone: OC RECOMMENDATION		MANUFACTURER
Milestone Date: 16-NOV-2001		FINISHED DOSAGE RELEASE
Decision: ACCEPTABLE		TESTER
Reason: DISTRICT RECOMMENDATION		

Establishment: 1523957	DMF No:
FOREST PHARMACEUTICALS INC	AADA No:
5000 BROTHERTON ROAD	
CINCINNATI, OH 45209	

Profile: TCM	OAI Status: POTENTIAL OAI	Responsibilities: FINISHED DOSAGE PACKAGER
Last Milestone: OC RECOMMENDATION		
Milestone Date: 17-APR-2001		
Decision: ACCEPTABLE		
Reason: BASED ON PROFILE		

Establishment: 2419749	DMF No:
FOREST/INWOOD LABORATORIES	AADA No:
300 303 320 321 330 PROSPECT STREE	
INWOOD, NY 11696	

Profile: CTL	OAI Status: NONE	Responsibilities: FINISHED DOSAGE STABILITY
Last Milestone: OC RECOMMENDATION		TESTER
Milestone Date: 17-APR-2001		
Decision: ACCEPTABLE		



FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

MANUFACTURER

Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **11-OCT-2001**  
Decision: **WITHHOLD**  
Reason: **WARNING LETTER ISSUED**

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Establishment: \_\_\_\_\_ DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: \_\_\_\_\_  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **29-NOV-2001**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Establishment: 1 \_\_\_\_\_ DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: \_\_\_\_\_  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **17-APR-2001**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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Establishment: \_\_\_\_\_ DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: \_\_\_\_\_  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **17-APR-2001**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON FILE REVIEW**

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## MEMORANDUM

DATE: January 21, 2002

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-323

SUBJECT: Action Memo for NDA 21-323, for the use of Lexapro (escitalopram oxalate) in patients with Major Depressive Disorder (MDD)

NDA 21-323, for the use of Lexapro (escitalopram oxalate) in patients with Major Depressive Disorder (MDD), was submitted by Forest Laboratories, Inc., on 3/23/01. Escitalopram is the S-isomer of racemic citalopram, a selective serotonin reuptake inhibitor (SSRI) approved for the treatment of patients with MDD; the S-isomer is presumed to be responsible for most of the anti-depressant effect of citalopram. At the time of the original submission, the application included the results of 2 randomized controlled trials in patients with MDD, as well as required pre-clinical, biopharmaceutic, and chemistry data (given that this is an isomer of an approved racemate, the pre-clinical requirements were limited). Several months after the original submission, the sponsor submitted the results of 2 additional randomized controlled trials. The Division had previously informed the sponsor that a single controlled trial demonstrating the effectiveness of escitalopram would be sufficient for a finding of substantial evidence of effectiveness.

The clinical review team (Dr. Karen Brugge, medical officer, Dr. Ohidul Siddiqui, statistician, and Dr. Thomas Laughren, psychiatric drugs team leader) have concluded that one of the two studies submitted with the original application is "positive" (this parallel group study included arms treated with escitalopram 10 and 20 mg/day, citalopram 40 mg/day, and placebo). In this study, there was no appreciable difference seen between the 10 and 20 mg escitalopram groups. In the second study, which included an escitalopram arm (flexible dose between 10-20 mg/day), a citalopram arm (flexible dose between 20-40 mg/day), and placebo, neither of the active treatment arms were distinguished from placebo. While Dr. Brugge briefly described the results of the 2 studies submitted after the initial submission, Dr. Laughren points out that they were submitted too late in the review process for the team to perform an independent analysis. As he notes, since only a single study was required, and the sponsor has submitted such a study with the original submission, these additional trials need not be reviewed at this time. I agree.

Dr. Paul Roney, pharmacology reviewer, notes findings of cardiac injury in the rat at escitalopram doses of 80 and 120 mg/kg/day; ratios of the NOEL to the maximum recommended human dose (20 mg/day) for these findings are

between 8-18, based on Cmax. He suggests that the pathology is related to the Cmax of S-citalopram. In these studies, a given dose of escitalopram resulted in Cmax levels of S-citalopram somewhat greater than S-citalopram levels resulting from twice the dose of the racemate (which would provide an equivalent dose of S-citalopram), and the AUC of S-citalopram at the escitalopram doses associated with the pathology were perhaps greater than those seen after the equivalent dose of S-citalopram given as the racemate.

Dr. Lorenzo Rocca, the chemist, initially recommended that the application not be approved. This recommendation was based on a recommendation made by the Office of Compliance in their 11/29/01 Establishment Evaluation Request (EER) Summary Report. This recommendation in turn is based on a "Withhold" decision made on 10/11/01 pertaining to deficiencies noted on an inspection of \_\_\_\_\_, one of three drug substance manufacturers listed in the application. A Warning Letter issued on the same date; the contents of this letter, as well as the specific deficiencies that form the basis of the decision and letter are not available to me at this time.

However, this site was subsequently found to be acceptable by the Office of Compliance on 1/17/02, and, therefore, this is no longer a problem.

## **COMMENTS**

I agree with the clinical review team that the sponsor has presented a single controlled trial that is "positive" and that this establishes substantial evidence of effectiveness. As noted above, I also agree that the studies submitted subsequent to the original submission (which the sponsor alleges are also "positive") need not be reviewed at this time. Had they been negative on face (with positive findings for the active control group), this would have been worrisome, but this is not the case.

I also agree with Dr. Laughren that several of the labeling statements suggested by Dr. Brugge (related to GI bleeding and discontinuation symptoms) need not be included in labeling at this time, for the reasons outlined by Dr. Laughren (there is no specific signal for this drug, and we are in the process of determining if these are class effects of the SSRIs).

I also agree that there are no safety issues that would preclude approval, although a final decision will await the sponsor's response to our 11/30/01 request for additional analyses to address the issue of possible QTc prolongation.

I am somewhat troubled, however, by the findings of cardiac injury in the rat (a 13 week toxicology study in the rat was the longest toxicology study required). These findings are essentially absent from the racemate-treated groups, and while it is true that the Cmax levels of S-citalopram at 80 mg/kg of escitalopram

(the lowest dose at which the pathology is seen) are greater than those after a 160 mg/kg dose of the racemate, they are not substantially greater (2700 nmol/l vs 2000 nmol/l, respectively), and the AUCs are also not appreciably different (19,000 nmol.hr/l vs 22,000 nmol.hr/l) This is also true for levels of the 2 primary metabolites. I am not convinced, therefore, based on these data, that the pathology can be explained easily by differences in plasma levels of S-citalopram.

This is worrisome because we have relied upon these relatively short-term "bridging" studies with escitalopram to reassure us that the pathology seen with escitalopram is, for all intents and purposes, equivalent to that seen with the racemate, and that, therefore, the full panoply of pre-clinical toxicology assessments done for the racemate can substitute for that which is expected to be seen with escitalopram. This clearly seems not to be the case; that is, there appear to be findings of toxicological significance seen after administration of escitalopram that are not present when a dose of the racemate equivalent to the same dose of escitalopram is given, and the finding seems not to be explainable by differences in S-citalopram (or metabolite) levels derived from either escitalopram or the racemate.

It is possible, for example, given the finding of cardiac injury at 13 weeks at 80 mg/kg/day (and also at 2 months in a separate study designed to characterize the relationship between plasma levels and pathology; in this study, a dose related increase in pathology was seen at doses of 80 and 120 mg/kg/day of escitalopram), that we might expect to see similar pathology emerge at lower doses of escitalopram with longer durations of exposure; at this time, however, this is unknown, because longer duration toxicology studies were not required, and not performed. Further, by my calculations, the safety margin for the no-effect AUC in rats (associated with the 40 mg/kg/day dose in the 13 week study) compared to the maximum human dose (20 mg/day) is about 2. As noted above, this may turn out to be a considerably smaller margin with longer duration treatment in the rat. To the extent that this may be a signal of injury in humans, it may be particularly problematic in this case, given the specific toxicity seen, and the difficulties entailed in monitoring for a similar lesion in humans.

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These considerations suggest, it seems to me, that relying on the long-term toxicology seen with the racemate to predict the long-term toxicity of escitalopram may not be appropriate. For this reason, we will ask the sponsor to address this issue (it should be noted, though, that, according to Dr. Rosloff, supervisory pharmacologist, the lack of any hyperplasia in the 13 week study would generally be taken as a sign that carcinogenicity may not be a major concern, although I do wonder how well supported this conclusion is).

For the reasons stated above, therefore, I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

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Russell Katz  
1/23/02 07:49:06 AM  
MEDICAL OFFICER

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**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** December 27, 2001

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approvable Action for  
Escitalopram tablets for the treatment of major depressive disorder (MDD)

**TO:** File NDA 21-323  
[Note: This overview should be filed with the 3-23-01  
original submission.]

**1.0 BACKGROUND**

Escitalopram is a selective serotonin reuptake inhibitor. It is the S-enantiomer of racemic citalopram, which is currently approved and marketed for depression in an immediate release tablet, i.e., Celexa (NDA 20-822, originally approved for depression on 7-17-98). Essentially all of the serotonin reuptake blocking activity of the racemate resides in the S-enantiomer, thus independent development of the S-enantiomer for MDD was a rational undertaking. The proposed dose range for escitalopram in MDD is 10 to 20 mg/day.

We did not hold an EOP2 meeting with the sponsor, however, we did communicate in a 4-22-98 letter that a single adequate and well-controlled efficacy trial in MDD would be sufficient to support an efficacy claim for the S-enantiomer of racemic citalopram, assuming that racemic citalopram had been shown to be effective in MDD. We held a preNDA meeting with the sponsor on 11-14-00, and although we generally agreed with the plan for an NDA submission, we had considerable discussion regarding what safety data would be submitted with the NDA. We provided further clarification in a 12-11-00 letter that, unless efficacy data from the ongoing relapse prevention trial with escitalopram were submitted with the original NDA, it would be necessary to submit these data subsequent to an approval action, i.e., as a supplement.

This NDA required reviews by the CMC, pharmacology/toxicology, biopharmaceutics, and clinical groups. The CMC review was conducted by Lorenzo Rocco, Ph.D. The pharmacology/toxicology review was conducted by Paul Roney, Ph.D. The biopharmaceutics review was conducted by Iftekhar Mahmood, Ph.D. The primary review of the efficacy and safety data was done by Karen Brugge, M.D., from the clinical group. Ohidul Siddiqui, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under \_\_\_\_\_, which was originally submitted 5-27-99. The original NDA was submitted 3-23-01. A 7-12-01 update to the NDA included a safety update, data sets for two European efficacy studies, and revised labeling. A 10-19-01 update included long-term safety data from a relapse prevention trial.

We decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

## **2.0 CHEMISTRY**

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

Forest had initially proposed two possible tradenames for this product, i.e., \_\_\_\_\_ (primary) and Lexapro (secondary), and they were informed in a 9-26-01 letter that OPDRA considered the name \_\_\_\_\_ unacceptable. The secondary name Lexapro was given tentative approval.

## **3.0 PHARMACOLOGY**

I am not aware of any pharmacology/toxicology concerns that would preclude an approvable action on this NDA.

## **4.0 BIOPHARMACEUTICS**

The pharmacokinetics of escitalopram have been adequately characterized and I am not aware of any biopharmaceutics concerns that would preclude an approvable action on this NDA.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Overview of Studies Pertinent to Efficacy**

Our review of efficacy was based on the results of 2 double-blind, randomized, 8-week, placebo-controlled, parallel group US trials (MD-01 and MD-02) in adult outpatients meeting DSM-IV criteria for major depressive disorder (MDD). The original submission also included study reports for two placebo-controlled European trials in MDD (99001 and 99003). However, this submission did not include data sets for these two studies, nor did it mention them in the ISE. The labeling included with the original submission mentioned only the one positive US study (MD-01). Since we had previously informed the sponsor that a single positive study would be sufficient to gain approval for escitalopram, we filed the application and initiated a review that would focus only on studies MD-01 and MD-02. Subsequently, in the 7-12-01 safety update, the sponsor included data sets for the two European studies, and provided an updated label that now included mention of these two studies as positive trials in clinical trials section. While Dr. Brugge has provided comments on these two studies in her review, and considers them positive, these studies have not been reviewed by Dr. Siddiqui, and I will not further comment on them. We have included bracketed comments in our proposed labeling suggesting that the sponsor submit the results from these two studies in a supplement postapproval if they wish to have them included in labeling.

### 5.1.2 Summary of Studies Pertinent to Efficacy Claims

#### 5.1.2.1 Study MD-01

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (35 US sites) comparing escitalopram immediate release tablets (10 or 20 mg/day, taken as a single pm dose), citalopram immediate release tablets (40 mg/day, taken as a single pm dose), and placebo in adult outpatients meeting DSM-IV criteria for MDD. Patients were started at 10 mg (for escitalopram) or 20 mg (for citalopram), and doses were increased to the assigned dose at the end of the first week (for the 20 mg escitalopram and the citalopram groups). There were roughly 120 patients per each of the 4 groups in the sample analyzed (n=485), with the % completing to 8 weeks ranging from 74 to 80%. The patients were about 2/3 female, about 85% Caucasian, and the mean age was 40 years.

While the assessments included MADRS, HAMD, CGI, and others, the primary outcome was change from baseline to endpoint in MADRS total score, and I will comment only on that outcome. As is usually the case, the ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup MADRS assessment. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. If the overall analysis was significant, pairwise comparisons of active drug groups with placebo were made. The overall analysis for MADRS was highly significant ( $p < 0.0001$ ), as were all the pairwise comparisons of active drug vs placebo (in both LOCF and OC analyses):

#### Efficacy Results on MADRS Total Score for MD-01 (LOCF)

	Baseline MADRS	Δbaseline MADRS	[P-value(vs pbo)]
Escitalopram 10 mg	28.0	-12.8	0.0007
Escitalopram 20 mg	28.9	-13.9	<0.0001

<b>Citalopram 40 mg</b>	<b>29.2</b>	<b>-12.0</b>	<b>0.04</b>
<b>Placebo</b>	<b>29.5</b>	<b>-9.4</b>	

While not described here, results on various secondary endpoints also generally favored both escitalopram and citalopram over placebo. A gender analysis on the MADRS primary outcome revealed no gender interaction.

Comment: Both Drs. Brugge and Siddiqui considered this a positive study, and I agree.

### 5.1.2.2 Study MD-02

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (22 US sites) comparing escitalopram immediate release tablets (10 to 20 mg/day, taken as a single pm dose), citalopram immediate release tablets (20 to 40 mg/day, taken as a single pm dose), and placebo in adult outpatients meeting DSM-IV criteria for MDD. Patients were started at 10 mg (for escitalopram) or 20 mg (for citalopram), and doses were increased to the higher dose as early as week 3, as needed. There were roughly 125 patients per each of the 3 groups in the sample analyzed (n=375), with the % completing to 8 weeks ranging from 77 to 83%. The patients were about 50% female, about 83% Caucasian, and the mean age was 42 years. The mean escitalopram dose for completers was 17.6 mg/day.

While the assessments included MADRS, HAMD, CGI, and others, the primary outcome was change from baseline to endpoint in MADRS total score, and I will comment only on that outcome. As is usually the case, the ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup MADRS assessment. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. If the overall analysis was significant, pairwise comparisons of active drug groups with placebo were made. The overall analysis for MADRS was not even close to significant, nor were any of the pairwise comparisons of active drug vs placebo:

#### Efficacy Results on MADRS Total Score for MD-02 (LOCF)

	<b>Baseline MADRS</b>	<b>Δbaseline MADRS</b>	<b>[P-value(vs pbo)]</b>
<b>Escitalopram 10-20 mg</b>	<b>28.7</b>	<b>-12.9</b>	<b>0.251</b>
<b>Citalopram 20-40 mg</b>	<b>28.3</b>	<b>-13.0</b>	<b>0.151</b>
<b>Placebo</b>	<b>28.8</b>	<b>-11.2</b>	

While it's not possible to explain this outcome, it is worth noting that the placebo effect is quite large, and may provide some insight into why neither active drug group separated from placebo.

Comment: Both Drs. Brugge and Siddiqui considered this a failed study, and thus uninterpretable, and I agree.

### 5.1.3 Comment on Other Important Clinical Issues Regarding Escitalopram for MDD

### Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 2 studies we considered in this development program, only study MD-01 is pertinent to the issue of dose response. In that study, there appeared to be no advantage in the 20 mg escitalopram dose over the 10 mg dose, and this finding should be reflected in labeling. On the other hand, even in the absence of such evidence, I have no objection to a suggestion in labeling that patients not responding at a 10 mg dose may be advanced to 20 mg, as long as it is made clear that the available data do not support any advantage of the higher dose in the average patient.

### Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, age, and race. There was no indication of differences in response based on these variables, however, there was likely not adequate power to detect such differences.

### Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the MADRS observed in study MD-01 was similar to that seen in other positive antidepressant trials, and I consider this a sufficient effect to support an antidepressant claim for this product.

### Duration of Treatment

There were no data presented in this supplement pertinent to the question of the long-term efficacy of escitalopram, however, a supplement supporting longer-term efficacy for this S-enantiomer, based on a randomized withdrawal study that has now been completed, was submitted during the course of this review.

#### **5.1.4 Conclusions Regarding Efficacy Data**

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term antidepressant efficacy for escitalopram. As noted, we had previously agreed that a single positive study would, in combination with a demonstration of efficacy of the citalopram racemate, be sufficient to support such a claim. The issue of longer-term efficacy has been addressed by a supplement that is now under review. Assuming \_\_\_\_\_, I see no need to ask for a pediatric study with escitalopram.

#### **5.2 Safety Data**

Dr. Brugge's safety review of this NDA was based predominantly on an integrated database submitted in a 7-12-01 safety update and consisting of a pooling of escitalopram safety data for all of the completed

trials, along with safety data as of a 2-1-01 cutoff date for ongoing trials. Additional information considered in this safety review were available from a 10-19-01 update based on data from a randomized withdrawal trial.

As of the 2-1-01 cutoff date, there were approximately 2500 escitalopram exposures, including about 700 subjects receiving treatment for at least 6 months and about 100 receiving treatment for at least a year. Overall, this exposure represented approximately 645 exposure years with escitalopram. Most of the exposure was in the 10-20 mg/day range.

Given our prior knowledge of the risks associated with the racemic citalopram, the focus in the safety review was on any differences between the recognized safety profile for racemic citalopram with that observed with escitalopram.

### 5.2.1 Overview of Adverse Event Profile for Escitalopram in MDD

Overall, the adverse events profile for escitalopram in MDD was similar to that observed for citalopram in MDD receiving this drug. However, Dr. Brugge focused on three safety issues that may impact on labeling for this product:

#### 5.2.1.1 QT Prolongation

A pooled analysis of ECG data for the 4 short-term, placebo-controlled depression trials with escitalopram revealed a slight decrease in heart rate (HR) for both escitalopram and citalopram vs placebo, and also a suggestion of a slight tendency for QTc prolongation, as follows:

Pooled Analysis of ECG Data (4 depression trials for escitalopram)  
(Mean change from baseline)

	Placebo (n=540)	Escitalopram (n=650)	Citalopram (n=367)
Heart Rate	+0.3 bpm	-2.3 bpm	-2.4 bpm
QT(msec)	-0.2	+7.5	+7.6
QTc (msec)	+0.8	+2.0	+1.6

[Not clear what correction was used; Bazett would have underestimated the effect, given the tendency to slow heart rate.]

No escitalopram patients met the criterion of > 500 msec for either QT or QTc, and no patients discontinued for abnormal ECG, arrhythmia, or syncope.

There was a similar finding suggestive of QTc prolongation with escitalopram and citalopram in a PK study (98107), with mean change from baseline in QTc as follows:

CT 20 mg	+4 msec
CT 60 mg	+10 msec
SCT 10 mg	-1 msec
SCT 30 mg	+11 msec

Comment: While these data are suggestive of only a modest QTc effect for escitalopram, we need more information to more fully evaluate this weak signal. We have asked Forest in an 11-30-01 request to provide more information about the methods for collecting and analyzing QT data from their escitalopram studies, and asked that they use an appropriate technique for adjusting for heart rate. As of this time, we have not received a response to this request. While I do not feel this information is necessary prior to taking an approvable action, it will be needed prior to taking any final action.

#### **5.2.1.2 GI Bleeding with SSRIs**

There has been a longstanding concern that SSRIs as a class may be associated with an increased risk of bleeding, possibly related to effects of these drugs on platelet aggregation due to the SSRI primary effect. Several of the SSRIs already have Precautions statements noting this potential risk, based on spontaneously reported cases. There have been several epidemiological studies supporting the possibility of such an association, and we are in the midst of collecting more systematic data on this question from individual SSRI sponsors, including Forest, in regard to the Celexa database. An analysis of the escitalopram database has apparently not yielded any signal of such an association for escitalopram, at least not yet. Nevertheless, Dr. Brugge has proposed that we require Forest to include a statement noting this potential in the escitalopram label.

Given the fact that there is not yet such a statement in Celexa labeling, and the fact that we are in the midst of trying to look more systematically at this question, I am not inclined to insist on adding such a statement to escitalopram labeling, especially since there appears to be no signal of such a risk emerging from the premarketing database for this drug. Of course, this database is very limited. If we become convinced that there is a clear class risk of such bleeding events for all SSRIs based on our more systematic exploration clinical trials data, we can at that time ask Forest to include a class statement regarding this risk.

#### **5.2.1.3 Potential for Discontinuation Emergent Symptoms with SSRIs**

Dr. Brugge raised the possibility that escitalopram may be associated with discontinuation emergent adverse events, as have been seen with several other SSRIs. In fact, we are in the midst of initiating a broader exploration of this potential problem in the clinical trials databases for the various SSRIs. Apparently, there was no signal for such events in the somewhat limited escitalopram database. Dr. Brugge has suggested the possibility of requiring standard language warning of such events for escitalopram. However, I am not inclined to ask for such a statement, given the lack of a specific signal for this drug and the fact that we are

in the processing of initiating a larger exploration across various SSRIs in attempt to identify whether or not there is a class problem.

### **5.2.2 Conclusions Regarding Safety of Escitalopram in MDD**

There were no new safety findings to suggest a substantially different safety profile for escitalopram compared to that observed for racemic citalopram, and no basis for substantially different labeling for escitalopram compared to racemic citalopram, from the standpoint of safety. However, as noted, we still need the requested information regarding QT prolongation, and this information could impact on labeling.

### **5.3 Clinical Sections of Labeling**

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

### **6.0 WORLD LITERATURE**

Dr. Brugge reviewed the literature reports provided by the sponsor. Apparently none of the reports for escitalopram included any safety information. Reports were also provided for citalopram, but none included any new or unexpected serious adverse events that would impact on labeling.

### **7.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, escitalopram is not approved for the treatment of MDD anywhere at this time. We will ask for an update on the regulatory status of escitalopram for the treatment of MDD in the approvable letter.

### **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take this NDA to the PDAC.

### **9.0 DSI INSPECTIONS**

Inspections were conducted at 3 sites for escitalopram studies, and it is my understanding that all 3 audits were classified as NAI. Thus, the data for these studies are deemed acceptable.

## **10.0 LABELING AND APPROVABLE LETTER**

### **10.1 Final Draft of Labeling Attached to Approvable Package**

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's most recent draft dated 10-19-01.

### **10.2 Foreign Labeling**

Escitalopram is not approved for the treatment of MDD anywhere at this time.

### **10.3 Approvable Letter**

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that Forest has submitted sufficient data to support the conclusion that escitalopram tablets are effective and acceptably safe in the treatment of MDD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:

Orig NDA 21-323

HFD-120

HFD-120/TLaughren/RKatz/KBrugge/PDavid

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Thomas Laughren  
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MEDICAL OFFICER

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## **MEMORANDUM**

**DATE:** August 10, 2002

**FROM:** Director  
Division of Neuropharmacological Drug Products/HFD-120

**TO:** File, NDA 21-323

**SUBJECT:** Action Memo for NDA 21-323, for the use of Lexapro (escitalopram) in patients with Major Depressive Disorder (MDD)

NDA 21-323, for the use of Lexapro (escitalopram), the active S-isomer of the approved racemic citalopram, in patients with Major Depressive Disorder (MDD), was submitted by Forest Laboratories, Inc., on 3/23/01. An Approvable letter was issued on 1/23/02. There were 2 non-routine requests in the letter: 1) we asked for additional cardiac data, given a signal of potential QTc prolongation seen in a clinical pharmacology study, and 2) a justification for our reliance on the results of a 13 week rat study with escitalopram to successful bridge to the full pre-clinical work-up done with citalopram. The sponsor submitted a full response on 2/20/02.

The sponsor's submissions have been reviewed by Dr. David Gan, safety team clinical reviewer (review dated 7/12/02), Dr. Judy Racoosin, safety team leader (review dated 7/29/02), Dr. Gerard Boehm, safety reviewer (review dated 7/24/02), Dr. Karen Brugge, medical reviewer (review dated 4/2/02), Dr. Paul Roney, pharmacologist (review dated 7/22/02), and Dr. Thomas Laughren, psychiatric drugs team leader (memo dated 8/14/02).

In this memo, I will briefly review the sponsor's resubmission, and offer support for the action to be taken.

### **QT Prolongation**

Dr. Brugge's review described results of a multiple dose clinical pharmacology study (Study 98107) which appeared to reveal a signal for QTc prolongation. Specifically, EKGs taken after doses of escitalopram 10 and 30 mg, and citalopram 20 and 60 mg, were reported to yield the following findings (change from baseline):

**Escitalopram**

10 mg	-1 msec
30 mg	11 msec

**Citalopram**

20 mg	4 msec
60 mg	10 msec

Primarily on the basis of this finding, we asked the sponsor to provide additional data on the QT interval, including reports of relevant cardiac events in the post-marketing experience for citalopram.

Drs. Gan and Racoosin have reviewed the cardiac data.

According to the sponsor, the mean changes from baseline in the controlled trials yielded the following results (change from baseline, using Fredericia correction):

Placebo (N=592)	Escitalopram (N=715)	Citalopram (N=408)
0.5 msec	3.9 msec	3.7 msec

EKGs in these studies were not done in any systematic temporal relation to dosing (the drug is given once a day; the half-life is about 30 hours).

Further clarification of the results of Study 98107 was received from the sponsor.

Specifically, in this study, patients were randomized to receive a maximum dose of either 10 mg or 30 mg. The patients who were to receive the 30 mg dose first received 10 mg for 3 days, 20 mg for 3 days, and 30 mg for 17 days. Single EKGs were taken 24 hours after the first day of 10 mg (at C<sub>min</sub>), and 24 hours after the last day of 30 mg (at C<sub>min</sub>). The following results on change from baseline were seen:

	Escitalopram 10 mg	Escitalopram 30 mg
Day 2	11 msec	15 msec (at 10 mg)
Day 24	5 msec	19 msec
Day 34	6 msec	10 msec

The sponsor makes several points in relation to these results:

The pre-drug QT interval data were very unstable. Specifically, the results presented above were based on a change from baseline determined by a single EKG one day before dosing. A single screening EKG done anywhere from 2 to 28 days before dosing differed from the baseline EKG by +4 msec for both dose groups. Further, the sponsor notes, there were marked differences among the various off-drug EKGs.

Specifically, EKGs were taken at screening (as described above), baseline (one day before dosing in each Period), and Day 34 (10 days after the last dose in each period). The following chart displays the mean QTc intervals at each of these time points:

Screening	Baseline, PD 1	Day 34, PD 1	Baseline, PD 2	Day 34, PD 2
371 msec	362 msec	371	374	377

The sponsor suggests that this degree of variability makes interpretation of this study problematic, as does the fact that only single EKGs were taken at any time point. Further, they note, there was a 15 msec increase from baseline after the first 10 mg dose in the 30 mg dose group, a finding that is entirely inconsistent with all other data at this dose. Finally, they note that there was no concurrent placebo control group.

In addition, the sponsor reports (in a facsimile submission dated 8/5/02), that the mean plasma concentration in the 30 mg patients in this study at the time of the EKGs described above was about 30 ng/ml. They examined the QTc intervals in patients from the controlled trial who had plasma levels obtained at the time of their last visit, at the time of an EKG. A total of 60 patients had a plasma level greater than 25 ng/ml at that time, with a mean of about 40 ng/ml. In these patients the mean change from baseline in QTc duration was about 2.8 msec, compared to an increase of 1.6 msec in placebo patients.

EKGs were performed intentionally at Tmax in 2 studies. Study 98106 was a single dose study in which a dose of 20 mg was given. EKGs performed at 4 hours after drug administration revealed no important changes. Study 99166 also examined single doses of 10, 20, and 30 mg. In this study, the change from baseline for all doses was negative at 4 hours after dosing.

Dr. Racoosin describes the post-marketing reports of relevant cardiac events with citalopram, which has been marketed in Europe since 1989, and the US since 1998.

There have been several reports (N=14) of torsades de pointes, but only one appeared to be relatively well documented and un-confounded (a 44 year old

woman in Denmark who developed an episode after 2 months of treatment with citalopram; the drug was discontinued, with no additional information).

There have, in addition, been a number of reports of QT prolongation, with at least one reporting a QT interval of 580 msec (in a woman who fainted in association with this measurement at a citalopram dose of 409 mg; with subsequent reduction of the citalopram dose to 20 mg, no further events were reported). Many of these reports were either of confounded cases, or provided too little detail to be reasonably sure that the event was significant. In addition, a number of cases of QT prolongation were reported in overdose, many of these also being difficult to interpret. However, there were 12 cases in overdose in which no other drug ingestion was reported. The mean dose in these patients was about 1000 mg of citalopram.

There have also been a number of post-marketing reports of other ventricular arrhythmias, many of which were difficult to assess.

### **Pharmacology**

At the time of the Approvable letter, we had concerns about findings in the key 60 day rat study, which examined the effects of escitalopram and citalopram. Specifically, we noted evidence of cardiac injury at the 80 mg/kg/day dose of escitalopram that was not seen at the 160 mg/kg/day dose of citalopram. This finding was not due to higher levels of s-citalopram (or metabolites) in the escitalopram group at this dose compared to the s-citalopram levels in the citalopram group. This differential effect raised questions about the propriety of relying on the citalopram pre-clinical studies to support the safety of escitalopram.

Dr. Roney has reviewed the sponsor's response and found it acceptable. Briefly, the sponsor notes that while cardiac pathology was seen in the 160 mg/kg/day citalopram group, the relatively mild nature (compared to that seen in the 80 mg/kg/day escitalopram group) was related to the relatively brief exposure to the 160 mg/kg/day dose. Specifically, there were 4 early deaths at this dose (within the first 9 days of dosing), which resulted in the dose being reduced to 100 mg/kg/day. Therefore, animals in this group were treated with a dose, for most of the study, that was not comparable to 80 mg/kg/day of escitalopram (in fact, cardiac toxicity was seen in these 4 briefly treated animals at 160 mg/kg/day). With continued treatment at 100 mg/kg/day, cardiac toxicity emerged. Given these facts, Dr. Roney concludes that the sponsor has offered a satisfactory response to our concerns, and that the results of this study justify our reliance upon the pre-clinical evaluation of citalopram to support the approval of escitalopram.

## Comments and Conclusions

The sponsor has responded to our request for additional information about the potential for escitalopram to prolong the QT interval with additional analyses and clarifications about the primary source of our concern, Study 98107. They point out that this study also documented an increase in QTc duration of about 15 msec after a single 10 mg dose, a finding entirely inconsistent with all other data in the application. This finding, coupled with the variability in off-drug QTc durations and the lack of a placebo control, suggests to the sponsor that the 19 msec increase from baseline seen in the 30 mg group is unreliable. Additionally, the data from several hundred patients in the controlled trials suggest a very modest (if any) effect on the QT duration, as does the fact that there is no evidence that citalopram is associated with QTc prolongation.

I agree that the data from Study 98107 do not support a definitive conclusion that escitalopram is associated with an important prolongation of the QT interval. There is considerable variability, and the finding of a 15 msec increase in the QTc after a single 10 mg dose, a dose we do believe is not associated with a meaningful QT prolongation, does speak to the instability of the measurement of the QTc duration in this study. Further, the sponsor's documentation that mean plasma levels in the controlled trials greater than those seen at the 30 mg dose in Study 98107 were not associated with prolongation of the QTc interval also suggests that there is no documented stable signal of QT prolongation.

While it is true that the EKGs taken during the controlled trials were not taken in any systematic temporal relation to dosing, the long-half life of the drug would suggest that the timing of the EKG after dosing is not critical (the C<sub>min</sub> at steady state is about 50% of the C<sub>max</sub>, and, if the patients took their daily dose, as is typical, in the morning, it is likely that the EKGs done in the controlled trials were performed closer to C<sub>max</sub> than to C<sub>min</sub>). In addition, the lack of a known QT prolongation effect with citalopram (which at a marketed dose of 40 mg provides the equivalent of 20 mg of escitalopram) provides further reassurance of a lack of a meaningful effect on the QT of the maximum effective dose of escitalopram.

One could argue that despite the variability seen in Study 98107, the 19 msec prolongation seen at the 30 mg dose is still a finding needing further evaluation. That is, even though the results may appear to be unreliable, this fact does not firmly establish that the 19 msec prolongation is inaccurate.

This is strictly true, but I believe that the weight of the other evidence establishes that there is no important QTc prolongation at therapeutic doses of escitalopram, and that further evaluation need not be performed. However, I also believe that it would be important to further the relationship between higher doses and the QT interval. Toward that end, I believe we should ask the firm to submit, as a Phase 4 commitment, the details of their analysis of the plasma level-QT relationship at the higher doses/levels.

With regard to the pharmacology concern raised in the Approvable letter, I believe this issue has been adequately addressed.

For the reasons stated above, then, I will issue the attached Approval letter, with appended labeling.

Russell Katz, M.D.

**APPEARS THIS WAY  
ON ORIGINAL**

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

/s/

-----  
Russell Katz  
8/14/02 02:59:29 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** August 14, 2002

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approval Action for  
Escitalopram tablets for the treatment of major depressive disorder (MDD)

**TO:** File NDA 21-323  
[Note: This overview should be filed with the 2-20-02 response to our 1-23-02  
approvable letter.]

In our 1-23-02 approvable letter, we requested the following:

- A safety update
- A regulatory status update
- A world literature update
- A justification for why we should rely on citalopram chronic toxicity data as a basis for predicting chronic toxicity for escitalopram
- Agreement on dissolution method and specifications
- Agreement on final labeling

Forest responded to these issues in their 2-20-02 submission.

**Safety Update**

-We had asked Forest to focus on SAEs in their safety update. Dr. Brugge reviewed the response and concluded that no new safety information that would impact on an approval action or on labeling was revealed from this update. I agree.

**QTc Prolongation**

-This was an unresolved issue at the time of the approvable action. While an analysis of pooled ECG data from 4 clinical trials in depression revealed only a small increase from baseline in QTc (about 3-4 msec vs placebo), associated with both citalopram and escitalopram, a phase 1 study (98107) suggested a dose dependent effect with a roughly 10-11 msec effect for a 30 mg escitalopram dose and a 60 mg citalopram dose. We asked the sponsor for additional data and information about their methods in a 11-30-01 letter, and they responded with submissions dated 12-19-01, 1-9-02, 2-20-02,

and 5-28-02. These data have been reviewed by Drs. Gan and Racoosin from the safety group. Dr. Racoosin summarized the important findings as follows:

- There was a signal for QTc prolongation and sudden death in dogs in association with citalopram, that was thought to be due to the DDCT metabolite which is prevalent in dogs but present at much lower levels in humans.
  - While the ECG data from the clinical trials did not reveal much of a signal for QTc prolongation, these trials were likely not sensitive to detecting this effect, and therefore, we initially felt that more weight needed to be placed on the ph 1 study that did suggest an effect at a somewhat higher than recommended dose of 30 mg of escitalopram.
  - An evaluation of postmarketing reports for citalopram also suggested the possibility of QTc prolongation. There were overdose cases of both QTc prolongation and TdP. There were also several reports of QTc prolongation in association with therapeutic doses of citalopram.
  - On the basis of these aggregated findings, Dr. Racoosin initially recommended a Precautions statement that alerted clinicians to this potential problem and advised against the use of escitalopram in patients with known QTc prolongation or uncorrected hypokalemia. The proposed statement also recommended caution when escitalopram is used in patients with proarrhythmic conditions, e.g., bradycardia or myocardial ischemia, or in patients already taking drugs that prolong the QTc.
- We provided draft final labeling to Forest, including the cautionary language regarding a QTc effect, and in response, they provided additional data and an argument for why we should not rely on the results from study 98107:

-Regarding study 98107:

-There was no placebo control in this study. 17 normals were titrated with escitalopram as follows:

- 10 mg for 3 days
- 20 mg for 3 days
- 30 mg for 17 days

-There were 2 ECGs for each subject prior to dosing, i.e., at screening and at baseline, and a post-washout baseline 10 days after the last dose

-There were 2 ECGs for each subject after dosing began, i.e., on the morning of day 2 (24 hours after the initial 10 mg dose) and 24 hours after the last dose of 30 mg, on day 24.

-Thus the ECGs were obtained at Cmin, not Cmax

-The pattern of mean ECG changes was unusual:

- 9 msec decrease from screening to baseline
- 15 msec increase from baseline to the 10 mg Cmin
- 19 msec increase from baseline to the 30 mg Cmin
- 12 msec increase from baseline to post-washout baseline

-The sponsor argues that this pattern is marked by instability that cannot be explained and by a clear lack of dose response

-Comment: I agree that these data are difficult to interpret.

-Study MD-01:

-The sponsor also conducted an additional analysis of ECG data from study MD-01, the clinical trial supporting the efficacy of escitalopram. Since the mean escitalopram

concentration in the 30 mg group in study 98107 was about 32 ng/ml, the sponsor set a cutoff of 25 ng/ml to divide patients from study MD-01 into those with low and high concentrations. 60 patients met the criterion for having high levels, and the mean concentration in this group was about 41 ng/ml. The mean increase from baseline in QTc in this group was only 2.8 msec, compared to an increase of 1.2 msec in placebo patients in that study.

-Only ECG's obtained within 24 hours of the last dose were included in the analysis.

-It is important to note that, in the worst case for this study, the ECGs would have also been obtained at Cmin, as in study 98107, but most likely many were somewhere between Cmax and Cmin, since timing was random.

-Thus, there was essentially no QTc effect in MD-01 at concentrations that were actually higher than reported to be associated with a 19 msec increase in study 98107

-Study 99166:

-This was a SD PK study including doses of 10, 20, and 30 mg. ECGs were obtained at 4 hours. All 3 dose groups were compared with baseline, and for each, the reported increase was 8 msec, again, not easily interpretable, but not suggestive of dose response.

-**Comment:** The sponsor argues that these data do not support strong labeling language regarding the isolated and hard to explain findings in study 98107. We discussed these findings with the sponsor on 8-6-02, and there was general agreement that this study is problematic and should not be included in labeling. However, we have included a summary of the ECG findings from the phase 3 trials and a mention of the postmarketing cases of QTc prolongation and TDP for citalopram. I feel that this level of summarization of the ECG data is sufficient, given the data we have in hand. However, it would be useful to have, at some point, a well-designed clinical pharmacology study to examine this question for all the SSRIs, i.e., a placebo-controlled, head-to-head comparison, at Cmax for all drugs. However, I do not feel this is necessary prior to the approval of this product.

#### **Regulatory Status Update**

-Thus far, escitalopram has been approved in Sweden and Switzerland, and applications a \_\_\_\_\_

#### **World Literature Update**

-Literature searches from the previous cutoff date (11-30-01) up to 2-5-02 were conducted for both citalopram and escitalopram, and this information was reviewed by Dr. Brugge. No important new safety information that would impact on an approval action or on labeling was revealed from this search.

#### **Justification for Reliance on Citalopram Chronic Toxicity Data**

-Paul Roney has provided an acceptable rationale for why we should rely on citalopram chronic toxicity data as a basis for predicting chronic toxicity for escitalopram.

#### **Agreement on Dissolution Method and Specifications**

-Forest has accepted our proposed dissolution method and specifications.

added the proposed language to labeling.

, thus, we have not

**Agreement on Final Labeling**

-We reached final agreement on labeling with the sponsor on 8-14-02.

**CONCLUSIONS AND RECOMMENDATIONS**

I believe that Forest has submitted sufficient data to support the conclusion that escitalopram tablets are effective and acceptably safe in the treatment of MDD. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:  
Orig NDA 21-323  
HFD-120  
HFD-120/TLaughren/RKatz/KBrugge/PDavid

**DOC: MEMESCIT.AP1**

**APPEARS THIS WAY  
ON ORIGINAL**

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

/s/

-----  
Thomas Laughren  
8/14/02 12:00:15 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

**NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST**

NDA <u>21-323</u>	
Drug <u>Lexapro (escitalopram) 5, 10, and 20 mg</u> Tablets	Applicant <u>Forest</u>
RPM <u>Paul David</u>	Phone <u>x4-5530</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s) _____	
Application classifications: Chem Class _____ Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>1-23-02</u> Secondary <u>1-23-02</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:
  - User Fee Paid
  - User Fee Waiver (attach waiver notification letter)
  - User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert) .....	X
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling? .....	<input type="checkbox"/> Yes (include review) <input checked="" type="checkbox"/> No
Immediate container and carton labels .....	N/A
Nomenclature review .....	N/A
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.
  
- Exception for review (Center Director's memo)..... N/A
- OC Clearance for approval..... N/A

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)  Materials requested in AP letter
- ◆ Post-marketing Commitments
  - Agency request for Phase 4 Commitments..... N/A
  - Copy of Applicant's commitments .....
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No
  - Copy of Press Release or Talk Paper.....
- ◆ Patent
  - Information [505(b)(1)] ..... X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary .....
- ◆ Debarment Statement .....
- ◆ Financial Disclosure
  - No disclosable information ..... X
  - Disclosable information – indicate where review is located .....
- ◆ Correspondence/Memoranda/Faxes .....
- ◆ Minutes of Meetings ..... X
  - Date of EOP2 Meeting None
  - Date of pre NDA Meeting 11-14-00
  - Date of pre-AP Safety Conference N/A
- ◆ Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- ◆ Federal Register Notices, DESI documents .....

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... X
- ◆ Clinical review(s) and memoranda .....
- ◆ Safety Update review(s) .....
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred Pediatric Page..... See Deferral Letter
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable X

- ◆ Statistical review(s) and memoranda ..... X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) ..... N/A  
     Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ◆ DSI Audits ..... X  
     ■ Clinical studies □ bioequivalence studies .....

**CMC INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ CMC review(s) and memoranda ..... X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... X
- ◆ DMF review(s) ..... X
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... X
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ◆ Facilities Inspection (include EES report) ..... X  
     Date completed 11-29-01 ..... □ Acceptable ■ Not Acceptable
- ◆ Methods Validation ..... □ Completed ■ Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Pharm/Tox review(s) and memoranda ..... X
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A
- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21323 Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFY 120 Trade and generic names/dosage form: Escitalopram Action: AP  AE  NA

Applicant Forest Therapeutic Class 2020100

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate \_\_\_\_\_ inadequate   
Proposed indication in this application Major Depressive Disorder

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION. IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?  Yes (Continue with questions) \_\_\_\_\_ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)  
 Neonates (Birth-1month)  Infants (1month-2yrs)  Children (2-12yrs)  Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.  
 (1) Studies are ongoing, \_\_\_\_\_  
\_\_\_\_\_ (2) Protocols were submitted and approved.  
\_\_\_\_\_ (3) Protocols were submitted and are under review.  
\_\_\_\_\_ (4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? \_\_\_\_\_ Yes  No  
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Clinical Team Leader (e.g., medical review, medical officer, team leader)

1-17-02

Signature of Preparer and Title

Date

Orig NDA/BLA # \_\_\_\_\_  
HP \_\_\_\_\_ /Div File  
NDA/BLA Action Package  
HFD-960/ Peds Team  
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

APPEARS THIS WAY  
ON ORIGINAL



*Escitalopram Tablets*

NDA # 21-323

**Pediatric Deferral**

**APPEARS THIS WAY  
ON ORIGINAL**



FAX: 201-524-9711

Phone: 201-386-2126

February 15, 2001

Russell Katz, M.D., Director  
Division of Neuropharmacological Drug Products  
Food and Drug Administration  
CDER, HFD-120, Woodmont II  
Document Control Room, 4<sup>th</sup> Floor  
1451 Rockville Pike  
Rockville, MD 20852

CENTER FOR DRUG EVALUATION  
AND RESEARCH

FEB 20 2001

RECEIVED HFD-120

IND: \_\_\_\_\_  
Serial: 120  
Product: Escitalopram (Lu 26-054) Tablets (5, 10, and 20 mg).  
Contents: General Correspondence,  
REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES.

Dear Dr. Katz:

Forest Laboratories, Inc. requests a deferral of the requirement to perform pediatric studies in the NDA for escitalopram tablets for the treatment of depression (NDA 21-323).

Due to the fact that the first clinical trials for escitalopram have not yet been evaluated by the FDA for safety and efficacy in adults, this deferral is requested for all pediatric age groups.

This pediatric deferral was discussed at the pre-NDA meeting for NDA 21-323 held on November 14, 2000. The division noted that such a deferral would be acceptable and pointed out that the pediatric development plan for escitalopram would also be dependent on the results and FDA action on the pediatric studies currently being conducted with Celexa (citalopram). The Pediatric Study Request Letter (dated April 28, 1999) for Celexa requested that the results of the pediatric studies be submitted by April 28, 2002. After the FDA has reviewed the results of the Celexa studies Forest will negotiate with the Division regarding an optimal pediatric development program for escitalopram and the final date for the submission of pediatric study reports.

Thank you for your time and consideration. If there are any questions related to this IND, please contact me at (201) 386-2126.

Sincerely,

Daniel T. Coleman, Ph.D.  
Manager, Regulatory Affairs

FOREST LABORATORIES, INC.  
PLAZA THREE, SUITE 602

HARBORSIDE FINANCIAL CENTER  
JERSEY CITY, NJ 07311



*Escitalopram Tablets*

*NDA # 21-323*

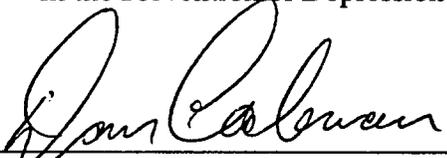
**Claimed Exclusivity**

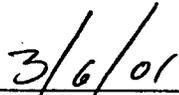
## CLAIMED EXCLUSIVITY

Pursuant to 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(4), Forest Laboratories, Inc. claims 5 years exclusivity for Escitalopram Tablets which contain 5, 10 or 20 mg of escitalopram as the active ingredient.

As set forth in 21 CFR 314.108(a), Forest Laboratories, Inc. certifies that this application contains the following new clinical investigations that were conducted by Forest Laboratories to demonstrate the safety and efficacy of Escitalopram Tablets and are essential to support approval of this application:

- SCT-MD-01: Fixed Dose Comparison of the Safety and Efficacy of Lu 26-054, Citalopram, and Placebo in the Treatment of Major Depressive Disorder
- SCT-MD-02: Flexible Dose Comparison of the Safety and Efficacy of Lu 26-054, Citalopram, and Placebo in the Treatment of Major Depressive Disorder.
- SCT-MD-03: Placebo-Controlled Evaluation of the Safety and Efficacy of Lu 26-054 in the Prevention of Depression Relapse.

  
\_\_\_\_\_  
Daniel T. Coleman, Ph.D.  
Manager, Regulatory Affairs

  
\_\_\_\_\_  
Date

**APPEARS THIS WAY  
ON ORIGINAL**



*Escitalopram Tablets*

NDA # 21-323

**Patent Certification**

**APPEARS THIS WAY  
ON ORIGINAL**

# Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53 for  
NDA # 21-323

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: N/A
- Active Ingredient(s): escitalopram oxalate
- Strength(s): 5, 10 and 20 mg
- Dosage Form: Tablet
- Approval Date: N/A

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**U.S. Patent Number: Re. 34,712**

**Expiration Date: June 8, 2009**

**Type of Patent: Drug Substance(Active Ingredient)**

**Name of Patent Owner: H. Lundbeck A/S**

**U.S. Agent: Gordon W. Hueschen**

---

The undersigned declares that the above stated United States Patent Number Re. 34,712 covers the composition, formulation and/or method of use of escitalopram oxalate. This product is the subject of this application for which approval is being sought.



Daniel T. Coleman, Ph.D.  
Manager, Regulatory Affairs  
Forest Laboratories, Inc.

3/6/01  
Date.

Phone: (201) 386-2126