CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-365

CHEMISTRY REVIEW(S)

NDA 21-365

Lexapro® (escitalopram oxalate) Oral Solution (5mg/5mL)

Forest Laboratories, Inc.

Lorenzo Rocca, Ph.D.
HFD-120

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Table of Contents

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Chemistry Review Data Sheet

1. NDA 21-365

2. REVIEW: 1

3. REVIEW DATE: August 5, 2002

4. REVIEWER: Lorenzo Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Original NDA	November 2, 2001
N(C) Amendment	December 17, 2001
N(BC) Amendment	June 27, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harborside Financial Center Plaza Three, Suite 602 Jersey City, NJ 07311
Representative:	John Baiano, Ph.D. Associate Director of CMC Regulatory Affairs
Telephone:	201-386-2118

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Lexapro®
   b) Non-Proprietary Name (USAN): Escitalopram oxalate
   c) Code Name/# (ONDC only):Lu 26-054
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3 (New Formulation)
      - Submission Priority: S (Standard)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 5mg/5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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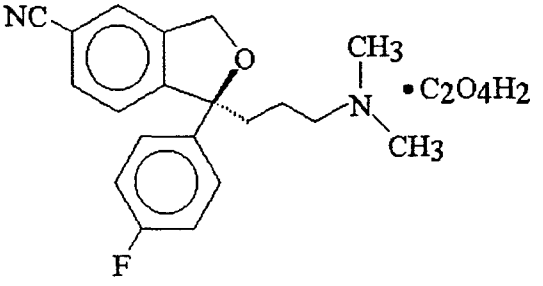
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate

Molecular Formula: $C_{20}H_{21}FN_2O \bullet C_2H_2O_4$ (oxalate salt)

Molecular Weight: 414.4 (oxalate salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

MF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	H. Lundbeck	Drug Substance	3	Adequate	July 10, 2001	N/A
	III	[redacted]	[redacted]	3	Adequate	Nov. 13, 1999	N/A
	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	IV	[redacted]	[redacted]	3	Adequate	Sept. 1, 1999	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,523	Original IND Lu 26-054-Oral Solution

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES[1]	All Sites Acceptable	7/3/02	Office of Compliance
Pharm/Tox	Review Pending	N/A	Paul L. Rooney, Ph.D.
Biopharm	Consult Pending	11/15/01	Ray Baweja, Ph.D.
LNC	USAN available	N/A	N/A
Methods Validation	Submission Pending	N/A	Lorenzo Rocca, Ph.D.
OPDRA	Proprietary name "Lexapro" found acceptable for Escitalopran Tablets	2/27/02	Jerry Phillips, R.Ph.
EA	Categorical Exclusion Granted	N/A	Lorenzo Rocca, Ph.D.
Microbiology	Approvable	7/10/02	Stephen Langille, Ph.D.

[1] FDA CDER EES Detail Report is appended to this review.

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The Chemistry Review for NDA 21-365

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-365 is deficient. The applicant needs to adequately respond to the following CMC deficiencies.

- Please provide the FDA with a list of the equipment (i.e., equipment type and manufacturer) used to manufacture, package and label Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL.
- Please provide the FDA with the COAs for the following batches of escitalopram oral solution: Lot #'s 00906, 01001, 00601, 00604 and 00605.
- Please include, as part of the regulatory release specifications, a chiral assay for determining the enantiomeric purity of Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL. Please provide the FDA with a copy of the regulatory release chiral test method and the validation results, which demonstrates the methods suitability for its intended use.
- Please provide the FDA with the LOD/LOQ for the identified degradation products (i.e., [redacted] and [redacted] when analyzed for by the HPLC method [redacted]
- Please provide the FDA with a description (e.g., lot #, manufacturer) of the citalopram HBr and the [redacted] reference materials, which are used by Forest Laboratories to perform release testing of Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL.
- Please correct Tables 2-2 and/or Table 2-3 in Section 4.5.11 of NDA 21-365 to correctly describe the Packaging Configuration used for drug product stability samples.
- Based on the available stability data the FDA recommends lowering the proposed specifications for the impurities [redacted] and [redacted] from [redacted] and [redacted] to [redacted] and [redacted] respectively. These specifications are identical to the currently approved specifications for these impurities in the product Celexa® (citalopram HBr) Oral Solution 10mg/5mL.
- Please provide the FDA with a copy of the chiral normal phase HPLC method used to evaluate the enantiomeric purity of escitalopram oxalate oral solution 5mg/5mL and 10mg/5mL stability samples. Please include data (e.g., chromatograms), which validates this chiral normal phase HPLC method for its intended use.
- The FDA notes Forest's decision to [redacted] Please commit to testing the primary stability samples for enantiomeric purity for the proposed expiry date (i.e., 24

months). Please note that data supporting enantiomeric purity of the drug product is expected for the full expiry period.

- Please provide the FDA with the development history which led to the proposed commercial formulation for Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL.
- Please provide the FDA with the exact categorical exclusion (i.e., 21CFR reference) that is claimed by Forest Laboratories, Inc for the manufacture of Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL. Please state whether, to the applicant's knowledge, any extraordinary circumstances exist (21 CFR25.15(d)) concerning the manufacture of Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL.

Please note that on July 15, 2002 NDA 21-365 was found approvable for microbiology. Forest Laboratories will need to adequately address the microbiology deficiencies before NDA 21-365 can be approved for CMC. The NDA 21-365 microbiology deficiencies are described in Dr. Stephen Langille' (HFD-805) NDA 21-365 Product Quality Microbilogy Review, dated July 15, 2002.

The Office of Compliance has found acceptable, from a cGMP standpoint, both the supplier of Escitalopram oxalate drug substance and the manufacturer of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL The FDA CDER EES Detail Report is appended to this review.

Submission of the NDA 21-365 methods validation package, to the appropriate FDA testing laboratory, is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Lexapro® (escitalopram oxalate) Oral solution 5mg/5mL is a non–sterile, clear, colorless to opalescent liquid, essentially free of foreign matter, with a peppermint aroma. The Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is equivalent to 1mg escitalopram/mL. The commercial drug product will be packaged in the following package configuration: [redacted]240cc [redacted] bottle [redacted]

The drug substance is the S-(+)-enantiomer of racemic citalopram. The racemic citalopram chemical entity and the chemical synthesis of racemic citalopram have been developed and patented by H. Lundbeck (Copenhagen, Denmark). Lundbeck first introduced racemic citalopram as an antidepressant in Denmark in 1989. Forest Laboratories markets the HBr salt of racemic citalopram formulated as a 120cc (4oz) or

240cc (8 oz) 10mg/5mL oral solution (NDA 21-046, submitted November 2, 1998, approved December 22, 1999). The citalopram molecule contains one asymmetric carbon with the clinical activity residing in the S-(+) stereoisomer. S-citalopram oxalate (Lu 26-054-O) was discovered and patended by H. Lundbeck who has licensed the drug to Forest Laboratories. The method of synthesis of S-citalopram oxalate is based on the synthesis of racemic citalopram HBr. The manufacture of racemic citalopram HBr is described in Lundbeck's Type II DMF — The desired S-enantiomer is obtained using

The manufacture of S-citalopram oxalate is described in Lundbeck's Type II DMF — The Escitalopram Oxalate drug substance is released for manufacturing escitalopram oxalate oral solution based on the COA from H. Lundbeck and confirmation of drug substance identity and stereochemical integrity by Forest Laboratories Ireland (Dublin, Ireland), and then conformation of identity for escitalopram and oxalate by the drug substance manufacturer Forest Pharmaceuticals (St. Louis, MO). Forest Laboratories Ireland will perform, at minimum, 1

The drug substance release specifications provide adequate control of the identity, quality and purity of the drug substance used to manufacture Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL. Drug substance stability is performed by H. Lundbeck, and is described in H. Lundbeck's Type II DMF — Lundbeck's Type II DMF — was reviewed (see DMF — Chemistry Review 3, July 10, 2001) by Lorenzo Rocca Ph.D. (HFD-120), and was found adequate to support NDA 21-323. No changes to DMF — are reported since it was last found adequate. Therefore DMF — remains adequate to support the manufacture of Escitalopram Oxalate drug substance for the manufacture of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL.

Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is manufactured using excipients which are USP/NF grade, and one non-compendial excipient namely Natural Peppermint Flavor — Natural Peppermint Flavor — has previously been approved for use in the racemic product Celexa® (citalopram HBr) Oral Solution 10mg/5mL (NDA 21-046, approved December 22, 1999). As in the case of the approved racemic product, Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is formulated using methylparaben/propylparaben as preservatives. In addition, Lexapro® (escitalopram oxalate) Oral Solution is formulated using a citric acid/sodium citrate buffer and malic acid as an antioxidant. NDA 21-365 was submitted, on March 8, 2002, to HFD-805 for microbiology consult. On July 15, 2002, Dr. Stephen Langillie (HFD-805) found NDA 21-365 approvable for microbiology.

An escitalopram 2 mg/mL oral solution was used by the sponsor in their clinical trials (IND 60,523) to demonstrate single dose bioequivalency of the escitalopram 2 mg/ml oral solution to a single of escitalopram 20 mg tablet. This study showed that the pharmacokinetic parameters C_{MAX} and AUC for the two formulations fell within the acceptance criteria of 80-125% demonstrating bioequivalency of both dosage forms. The

proposed 1 mg/mL commercial formulation for escitalopram oral solution is identical to the 2 mg/mL clinical escitalopram oral solution with the exception that the level of active was reduced and the anti-oxidant (malic acid) level was reduced by —— The latter change was made because it afforded an antioxidant level that was sufficient to protect escitalopram from oxidation. Three commercial scale demonstration lots (Lot No: 00906, 00907, 01001) of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL have been manufactured at the commercial site of manufacture, and are currently on stability. The differences between the clinical and commercial formulations are not deemed, from a chemistry standpoint, to cause concern that compatibility studies are needed.

Escitalopram oxalate is a chiral drug substance. ICH stability studies (up to 9 months for the 5mg/5mL commercial product and 12 months for the 2mg/mL clinical formulation) have not shown any significant change in the products chiral assay. The specifications of the known degradation products and unidentified impurities are consistent with the current ICH guidelines. However, based on the available stability data the sponsor will be asked to tighten regulatory release specifications for the identified degradation prodcuts (i.e., —— —— and ——— . In addition, the sponsor will be asked to set a regulatory release specification for the enantiomeric purity of Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL.

Based on the stability data (i.e., up to 18-months controlled room temperature (25°±2°C/60±5%RH) and 6-months accelerated (40°±2°C/75±5%RH)) submitted for Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL, packaged as intended for commercial distribution, a 24-month expiration period (shelf-life) is acceptable when stored at 25°C (77°F) (excursions permitted to 15°C to 30°C (59°F to 86°F)).

B. Description of How the Drug Product is Intended to be Used

Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL was developed for patients who would prefer a liquid formulation to a tablet or for those patients who may have difficulty swallowing tablets. The recommended dose of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is 10 mg once daily for all patients. Patients not responding to a 10 mg dose may benefit from a dose increase to 20 mg after a minimum of one week.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-365 is not approvable for CMC. The not approval recommendation is based on the following major chemistry issues:

- Forest Laboratories needs to adequately respond to several CMC deficiencies, which are described under *Chemistry Assessment* Section VIII titled **DRAFT DEFICIENCY LETTER**.
- On July 15, 2002 NDA 21-365 was found approvable for microbiology. Forest Laboratories will need to adequately address all microbiology deficiencies before NDA 21-365 can be approved for CMC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date
TOliver (TL)/Date
PDavid(PM)/Date

C. CC Block

Orig. NDA 21-365
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/TOliver

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(A)

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

49 pages

(A)

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

/s/

Lorenzo Rocca
8/5/02 02:00:02 PM
CHEMIST

Thomas Oliver
8/6/02 05:45:53 AM
CHEMIST

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APPEARS THIS WAY
ON ORIGINAL

CDER CHEMISTRY REVIEW TEMPLATE CDER

Chemistry Assessment Section

NDA 21-365

Lexapro® (escitalopram oxalate) Oral Solution (5mg/5mL)

Forest Laboratories, Inc.

Lorenzo Rocca, Ph.D.
HFD-120

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Table of Contents

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Chemistry Review Data Sheet

1. NDA 21-365

2. REVIEW: 2

3. REVIEW DATE: November 4, 2002

4. REVIEWER: Lorenzo Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	November 2, 2001
Chemistry Review #1	August 6, 2002
Approvable Letter	September 5, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Original NDA	November 2, 2001
N(C) Response to Chemistry Info. Request	December 17, 2001
N(BC) Amendment(Drug Product Stability Update)	June 27, 2002
N(BC) Response to Microbiology Info. Request	August 19, 2002
N000(AZ) Complete Response to Approvable Letter	October 2, 2002

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ON ORIGINAL

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harborside Financial Center Plaza Three, Suite 602 Jersey City, NJ 07311
Representative:	John Baiano, Ph.D. Associate Director of CMC Regulatory Affairs
Telephone:	201-386-2118

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Lexapro®
   b) Non-Proprietary Name (USAN): Escitalopram oxalate
   c) Code Name/# (ONDC only):Lu 26-054
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3 (New Formulation)
      - Submission Priority: S (Standard)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 5mg/5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____SPOTS product – Form Completed

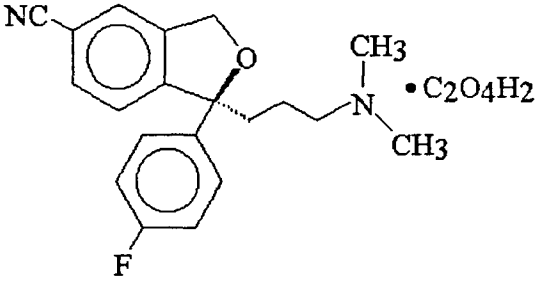
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate

Molecular Formula: $C_{20}H_{21}FN_2O \bullet C_2H_2O_4$ (oxalate salt)

Molecular Weight: 414.4 (– oxalate salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	H. Lundbeck	Drug Substance	3	Adequate	July 10, 2001	N/A
	III			3	Adequate	Nov. 13, 1999	N/A
	III			4	Adequate	N/A	N/A
	III			4	Adequate	N/A	N/A
	III			4	Adequate	N/A	N/A
	III			4	Adequate	N/A	N/A
	III			4	Adequate	N/A	N/A
	III			4	Adequate	N/A	N/A
	III			4	Adequate	N/A	N/A
	IV			3	Adequate	Sept. 1, 1999	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,523	Original IND Lu 26-054-Oral Solution

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES[1]	All Sites Acceptable	7/3/02	Office of Compliance
Pharm/Tox	Recommend for Approval	5/23/02	Paul L. Rooney, Ph.D.
Biopharm	Recommend for Approval	8/20/02	Carol Noory, Ph.D.
LNC	USAN available	N/A	N/A
Methods Validation	Submission Pending	N/A	Lorenzo Rocca, Ph.D.
OPDRA	Proprietary name "Lexapro" found acceptable for Escitalopran Tablets	2/27/02	Jerry Phillips, R.Ph.
EA	Categorical Exclusion Granted	11/4/02	Lorenzo Rocca, Ph.D.
Microbiology	Recommend for Approval	9/19/02	Stephen Langille, Ph.D.

[1] FDA CDER EES Detail Report is appended to this review.

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The Chemistry Review for NDA 21-365

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-365 is no longer deficient because the applicant has adequately responded to the CMC deficiencies in the FDA Approvable Letter dated September 5, 2002 (see NDA 21-365 Complete Response to Approvable letter dated October 2, 2002).

Please note that on July 15, 2002 NDA 21-365 was found approvable for microbiology. Forest Laboratories has adequately addressed the microbiology deficiencies. Please see Dr. Stephen Langille's (HFD-805) NDA 21-365 Product Quality Microbilogy Review #2, dated September 19, 2002. NDA 21-365 is recommended for approval from the standpoint of microbial product quality.

The Office of Compliance has found acceptable, from a cGMP standpoint, both the and the manufacturer of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL. Please see NDA 21-365 Chemistry Review #1, dated August 6, 2002, for a copy of the FDA CDER EES Detail Report.

Submission of the NDA 21-365 methods validation package, to the appropriate FDA testing laboratory, is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Lexapro® (escitalopram oxalate) Oral solution 5mg/5mL is a non-sterile, clear, colorless to opalescent liquid, essentially free of foreign matter, with a peppermint aroma. The Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is equivalent to 1mg escitalopram/mL. The commercial drug product will be packaged in the following package configuration: 240cc bottle.

The drug substance is the S-(+)-enantiomer of racemic citalopram. The racemic citalopram chemical entity and the chemical synthesis of racemic citalopram have been developed and patented by H. Lundbeck (Copenhagen, Denmark). Lundbeck first introduced racemic citalopram as an antidepressant in Denmark in 1989. Forest

Laboratories markets the HBr salt of racemic citalopram formulated as a 120cc (4oz) or 240cc (8 oz) 10mg/5mL oral solution (NDA 21-046, submitted November 2, 1998, approved December 22, 1999). The citalopram molecule contains one asymmetric carbon with the clinical activity residing in the S-(+) stereoisomer. S-citalopram oxalate (Lu 26-054-O) was discovered and patended by H. Lundbeck who has licensed the drug to Forest Laboratories. The method of synthesis of S-citalopram oxalate is based on the synthesis of racemic citalopram HBr. The manufacture of racemic citalopram HBr is described in Lundbeck's Type II DMF —— The desired S-enantiomer is obtained using

The manufacture of S-citalopram oxalate is described in Lundbeck's Type II DMF —— . The Escitalopram Oxalate drug substance is released for manufacturing escitalopram oxalate oral solution based on the COA from H. Lundbeck and confirmation of drug substance identity and stereochemical integrity by Forest Laboratories Ireland (Dublin, Ireland), and then conformation of identity for escitalopram and oxalate by the drug substance manufacturer Forest Pharmaceuticals (St. Louis, MO). Forest Laboratories Ireland will perform, at minimum,

The drug substance release specifications provide adequate control of the identity, quality and purity of the drug substance used to manufacture Lexapro® (escitalopram oxalate) Oral Solution, 5mg/5mL. Drug substance stability is performed by H. Lundbeck, and is described in H. Lundbeck's Type II DMF —— Lundbeck's Type II DMF —— was reviewed (see DMF —— Chemistry Review 3, July 10, 2001) by Lorenzo Rocca Ph.D. (HFD-120), and was found adequate to support NDA 21-323. No changes to DMF —— are reported since it was last found adequate. Therefore DMF —— remains adequate to support the manufacture of Escitalopram Oxalate drug substance for the manufacture of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL.

Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is manufactured using excipients which are USP/NF grade, and one non-compendial excipient namely Natural Peppermint Flavor —— Natural Peppermint Flavor —— has previously been approved for use in the racemic product Celexa® (citalopram HBr) Oral Solution 10mg/5mL (NDA 21-046, approved December 22, 1999). As in the case of the approved racemic product, Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is formulated using methylparaben/propylparaben as preservatives. In addition, Lexapro® (escitalopram oxalate) Oral Solution is formulated using a citric acid/sodium citrate buffer and malic acid as an antioxidant. NDA 21-365 was submitted, on March 8, 2002, to HFD-805 for microbiology consult. On September 19, 2002, Dr. Stephen Langille (HFD-805) recommended NDA 21-365 for approval from the standpoint of microbial product quality.

An escitalopram 2 mg/mL oral solution was used by the sponsor in their clinical trials (IND 60,523) to demonstrate single dose bioequivalency of the escitalopram 2 mg/ml oral solution to a single of escitalopram 20 mg tablet. This study showed that the

pharmacokinetic parameters C_{MAX} and AUC for the two formulations fell within the acceptance criteria of 80-125% demonstrating bioequivalency of both dosage forms. The proposed 1 mg/mL commercial formulation for escitalopram oral solution is identical to the 2 mg/mL clinical escitalopram oral solution with the exception that the level of active was reduced and the anti-oxidant (malic acid) level was reduced by [redacted]. The latter change was made because it afforded an antioxidant level that was sufficient to protect escitalopram from oxidation. Three commercial scale demonstration lots (Lot No: 00906, 00907, 01001) of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL have been manufactured at the commercial site of manufacture, and are currently on stability. The differences between the clinical and commercial formulations are not deemed, from a chemistry standpoint, to cause concern that compatibility studies are needed.

Escitalopram oxalate is a chiral drug substance. ICH stability studies (up to 9 months for the 5mg/5mL commercial product and 12 months for the 2mg/mL clinical formulation) have not shown any significant change in the products chiral assay. The specifications of the known degradation products and unidentified impurities are consistent with the current ICH guidelines. The sponsor submitted updated drug product stability data at 25°C/60%RH for their proposed market formulation (e.g., 5mg/5mL) in the intended commercial packaging (see NDA 21-365 Amendment, June 27, 2002). **Based on the stability data (i.e., up to 18-months controlled room temperature (25°±2°C/60±5%RH) and 6-months accelerated (40°±2°C/75±5%RH)) submitted for Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL, packaged as intended for commercial distribution, a 24-month expiration period (shelf-life) is acceptable when stored at 25°C (77°F) (excursions permitted to 15°C to 30°C (59°F to 86°F)).**

B. Description of How the Drug Product is Intended to be Used

Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL was developed for patients who would prefer a liquid formulation to a tablet or for those patients who may have difficulty swallowing tablets. The recommended dose of Lexapro® (escitalopram oxalate) Oral Solution 5mg/5mL is 10 mg once daily for all patients. Patients not responding to a 10 mg dose may benefit from a dose increase to 20 mg after a minimum of one week at 10mg/day dosing.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-365 is recommended for approval from a CMC standpoint. The approval recommendation is based on the following:

- Forest Laboratory has responded adequately to all CMC deficiencies listed in the Agency Approvable Letter dated September 5, 2002
- Forest Laboratories has responded adequately to all microbiological deficiencies listed in NDA 21-365 Product Quality Microbiology Review #1, dated July 15, 2002.
- The applicant has provided adequate information to assure the identity, strength, quality and purity of the drug product. All facilities involved in the manufacture and control of the drug substance and drug product were found to have acceptable cGMP.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date
TOliver (TL)/Date
PDavid(PM)/Date

C. CC Block

Orig. NDA 21-365
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/TOliver

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/s/

Lorenzo Rocca
11/1/02 05:49:49 PM
CHEMIST

Thomas Oliver
11/4/02 08:02:57 AM
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(B)

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

35 pages

(B)