

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204168Orig1s000

CHEMISTRY REVIEW(S)



NDA 204,168

**Levomilnacipran HCl (20mg, 40mg, 80mg and 120mg) SR Capsule
Forest Research Institute Inc.**

**Pei-I Chu, Ph.D.
Office of New Drug Quality Assessment DPA1
For Division of Psychiatry Drug Products**

Review of Chemistry, Manufacturing, and Controls

Chemistry Review Data Sheet

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 204,168
2. REVIEW # 2
3. REVIEW DATE: June 25, 2013
4. REVIEWER: Pei-I Chu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

September 24/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Research Institute
Address: Harborside Financial Center, Plaza V, Jersey
City, NJ 07311
Representative: Ann Howell
Telephone: 201-427-8740

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

a) Proprietary Name: (b) (4)

b) Non-Proprietary Name (USAN): levomilnacipran (base) and levomilnacipran hydrochloride (salt)

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Norepinephrine(NE) and serotonin (5-HT) reuptake inhibitor

Chemistry Review Data Sheet

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20mg, 40mg, 80mg, 120mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed
 Not a SPOTS product

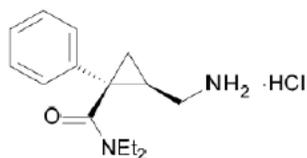
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (1S,2R)-2-(aminomethyl)-N,N-diethyl-1-Phenylcyclopropanecarboxamide hydrochloride

Molecular Formula: C₁₅H₂₂N₂O•HCl

Molecular Weight: 282.81 g/mol

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	1	Adequate	9/10/2012	
	III		4				Sufficient information in application
	III		4				Sufficient information in application
	III		1	Adequate	4/16/2012		
	II		1	Adequate	Pending EES Info	CMC info is adequate	
	III		4				Sufficient information in application
	IV		4				(b) (4)
	III		4				Sufficient information in application
	III		1	Adequate	3/21/2012		
	III		4				Sufficient information provided
	III		1	Adequate	1/09/2012		
	III		1	Adequate	10/02/2012		
	III		4				Sufficient information in application

Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

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	104483	Commercial

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	acceptable	06/24/2013	Office of compliance
Pharm/Tox	acceptable	06/17/2013	Arippa Ravindran
Biopharm	acceptable	05/20/2013	Akm Khairuzzaman
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
DMEPA	acceptable	06/06/2013	Louis Flowers
EA	NA		
Microbiology	NA		

Chemistry Review Section

The Chemistry Review for NDA 204168**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

This NDA is recommended for approval from the CMC perspective since the Office of Compliance makes the acceptable recommendation of the facilities in EES.

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

PEI-I CHU
06/25/2013

RAMESH K SOOD
06/25/2013

NDA 204,168

**Levomilnacipran HCl (20mg, 40mg, 80mg and 120mg) SR Capsule
Forest Research Institute Inc.**

**Pei-I Chu, Ph.D.
Office of New Drug Quality Assessment DPA1
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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 204,168
2. REVIEW # 1
3. REVIEW DATE: June 12, 2013
4. REVIEWER: Pei-I Chu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

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September 24/2012

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d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

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

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Chemistry Review Data Sheet

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13. ROUTE OF ADMINISTRATION: Oral

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 SPOTS product – Form Completed
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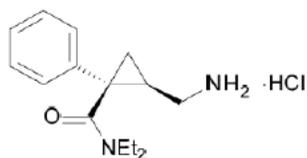
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	III		4				Sufficient information in application
	III		1		Adequate	3/21/2012	
	III		4				Sufficient information provided
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EES	Pending		Office of compliance
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Biopharm	acceptable	05/20/2013	Akm Khairuzzaman
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
DMEPA			
EA	NA		
Microbiology	NA		

Chemistry Review Section

The Chemistry Review for NDA 204168**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 204168 has been reviewed for the chemistry, manufacturing, and controls section. An information request letter was sent to the sponsor on 2/15/2013. Adequate responses from the sponsor have been received on 3/06/2013. Office of Regulatory Affairs has completed the inspections of all the manufacturing facilities in March 2013. This NDA will be recommended for approval from the CMC perspective after Office of Compliance makes the final recommendation of the facilities in EES,

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

None as per this review.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product**

The drug product (b) (4) was formulated as a sustained release (SR) capsule formulation intended for once-daily oral administration. The commercial drug products are supplied in HPMC capsules imprinted in black ink. Upon opening the capsule, the contents inside are off-white to yellow colored beads. The drug product is a sustained release capsule containing 20, 40, 80, or 120 mg of levomilnacipran with a total capsule weight of 89, 148, 264, or 379 mg, respectively. The drug products were prepared by (b) (4)

Up to 18 months of stability data at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH storage conditions have been generated. Based on the stability data of the NDA registration batches, a shelf-life of 24 months is recommended for Levomilnacipran SR Capsules, 20 mg, 40 mg, 80 mg, and 120 mg in the commercial packaging configurations when stored at controlled room temperature.

Drug Substance

Sevella® (also known as milnacipran and F2207) was approved by the Food and Drug Administration (FDA) for the management of fibromyalgia on 14 Jan 2009. Levomilnacipran (1S, 2R) is the more active of the two enantiomers present in the

Chemistry Review Section

racemate Savella. Levomilnacipran HCl has an aqueous solubility of 0.7 g/mL. The pH of the 1% w/v aqueous solution is between 5.2 and 5.9. The melting point of the compound is about 192°C. The ionization constant (pKa) of levomilnacipran HCl at 25°C is reported to be approximately 9.65 and logP neutral to be 1.64. Only one polymorphic form of levomilnacipran HCl is reported. Levomilnacipran HCl (F2695) drug substance was determined to be a BCS Class 1 (high solubility - high permeability) compound. It is stable under ambient and accelerated storage conditions and is not hygroscopic. Degradation studies of levomilnacipran HCl in solution show that the drug substance undergoes degradation at extreme acidic and alkaline conditions. However, the levomilnacipran HCl drug substance is not sensitive to oxidative conditions or light. The drug substance information has been provided in DMF (b) (4) DMF (b) (4) will receive an adequate status when Office of Compliance updated the manufacturing facility EES status to "overall compliant."

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

The drug should be initiated at 20mg once daily for two days and then increased to 40mg once daily. An increment of 40mg is allowed at intervals of not less than 2 days to a maximum recommended dose of 120mg once daily.

C. Basis for Approvability or Not-Approval Recommendation

The approval of this NDA will be determined by the adequacy of the IR response from the sponsor and the status of the facility inspection.

II. Administrative**A. Reviewer's Signature**

Pei-I Chu, Ph.D.

Endorsement Block

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Tele Chhagan, Ph.D.
Chemistry Branch Chief :	Ramesh Sood, Ph.D.
Chemistry Project Manager :	Teshara Bouie

C. CC Block

Orig. NDA-204168

(b) (4)

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/s/

PEI-I CHU
06/24/2013

RAMESH K SOOD
06/24/2013

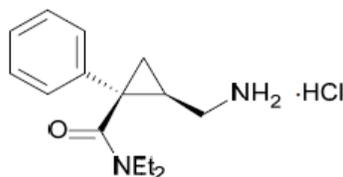
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch I)
Initial Quality Assessment
NDA 204168

OND Division: Division of Psychiatry Products
NDA: 204168
Applicant: Forest Laboratories Inc.
NDA Filing Category: 505(b)(1)
Letter Date: 25-SEP-12
Stamp Date: 25-SEP-12
PDUFA Date: 25-JUL-13
Proposed Trade Name: not provided
Established Name: levomilnacipran (base) and levomilnacipran hydrochloride (salt)
Dosage Form: sustained-release capsule
Strengths: 20 mg, 40 mg, 80 mg, and 120 mg
Route of Administration: Oral
Indication: Treatment of Major Depressive Disorder (MDD)
Assessor: Chhagan G. Tele, Ph.D.
ONDQA Fileability: Yes

Background

The applicant submitted this NDA under section 505(b)(1) in an e-CTD format seeking approval for levomilnacipran hydrochloride (F2695) sustained release capsules 20 mg, 40 mg, 80 mg, and 120 mg once daily for the treatment of MDD. Levomilnacipran HCl will be initiated at 20 mg once daily as a starting titration dose. Levomilnacipran HCl inhibits both norepinephrine (NE) and 5-hydroxytryptamine (serotonin [5-HT]) reuptake in vitro and in vivo and is approximately 2-fold more potent at inhibiting NE reuptake than 5-HT reuptake transporters. Levomilnacipran is the more active of the 2 enantiomers present in the racemate of milnacipran which was approved by the FDA on 14-JAN-2009 for the management of fibromyalgia under the trade name Savella® (NDA 022256, film coated tablets, Cypress Bioscience Inc., Approved, 14-JAN-2009). The chemistry, manufacturing, and controls information of drug substance is the subject of the current IND 104483 (allowed 08-MAR-2009) for the clinical evaluation for the treatment of MDD. The clinical development program for levomilnacipran HCl consisted of 5 short-term placebo-controlled studies and 2 long-term studies (1 open-label and 1 randomized-withdrawal). Several meetings (End of Phase 2, Pre-NDA CMC specific, Pre-NDA clinical, and Type C (b) (4)) have been held with the sponsor prior to submission of the NDA to discuss the drug development program. Minutes of these meetings can be found in DARRTS and should be read by the reviewer. The reviewer needs to bridge any changes and agreements evolved from the meetings, amendments, and annual reports submitted during the drug development. The applicant provided Quality Overall Summary in the submission.

Structure of levomilnacipran hydrochloride



Chemical Name (USAN 2011): (1*S*,2*R*)-2-(Aminomethyl)-*N,N*-diethyl-1-phenylcyclopropane carboxamide monohydrochloride

Drug Substance

Levomilnacipran hydrochloride drug substance CMC information is cross-referenced to DMF (b) (4) [LoA dated 25-MAY-2012, (b) (4)]. The drug substance will be manufactured commercially and tested (release and stability) by (b) (4). DMF (b) (4) will need to be reviewed and found adequate to support NDA.

Levomilnacipran hydrochloride is white to almost white crystalline powder. The chemical structure elucidation of levomilnacipran HCl (F2695) drug substance has been confirmed by elemental analysis and different techniques of molecular spectroscopic analysis such as ultraviolet (UV) absorption spectroscopy, ¹H and ¹³C nuclear magnetic resonance (NMR), infrared (IR) absorption spectroscopy and X-ray powder diffraction (XRPD). Levomilnacipran hydrochloride crystalline structure and the related physicochemical properties have been characterized to provide definitive evidence for the proposed chemical structure. The physicochemical characteristics of the drug substance are defined by appearance, solubility, pH, specific optical rotation, dissociation constant, partition coefficient, hygroscopicity, particle size analysis.

Solid form screening studies demonstrated that Levomilnacipran hydrochloride drug substance exists in a single (b) (4) polymorphic form. During the drug product manufacturing process, the drug substance is (b) (4)

[Redacted]

Based on the stability data of the drug substance, the applicant has proposed retest date of (b) (4) for the drug substance when stored in the proposed container closure system. Reviewer need to evaluate the quality and quantity of the stability data for the granting of the proposed retest period for the drug substance.

Drug Product

Levomilnacipran hydrochloride drug product have been formulated into four strengths, 20 mg, 40 mg, 80 mg, and 120 mg sustained-release HPMC capsules differentiated by capsule color, capsule size, and capsule marking. The drug products are prepared by filling HPMC capsules dose proportionally with levomilnacipran SR beads.

Optimized formulations were selected for scale-up and process optimization studies using a design of experiments (DOE). An overall risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product critical quality attributes (CQAs). The results of the initial formulation risk assessment are provided. The reviewer needs to review the adequacy of the risk assessment of formulation components.

[Redacted]

Drug product capsules were manufactured and released tested at the Forest Laboratories Ireland, Ltd., Clonshaugh, Dublin, Ireland and (b) (4) using equipment of the same design and operating principle as that for the commercial manufacture process. Drug product stability testing will be done at the Forest Research Institute, Inc., Farmingdale, NY. Microbiological testing will be done at the (b) (4). Drug product packaging will be done at the Forest Pharmaceuticals, Inc., Cincinnati, Ohio (blister/bottle), (b) (4) and (b) (4).

Validated analytical methods are provided for the determination of ID, assay, and content uniformity (HPLC), chiral purity and ID (chiral HPLC), degradation products (UPLC), residual solvents (GC), (b) (4) and dissolution (HPLC). The reviewer needs to look for the adequacy of the validation parameters.

The capsules are packaged in HDPE bottles and unit-dose (b) (4) blister packs. The blisters consist of film- (b) (4) (b) (4) (b) (4) aluminum foil.

Specification proposed for release of lixivaptan capsule are description, ID, assay, content uniformity, degradation product, dissolution, (b) (4), and microbial testing. The dissolution test method is performed in accordance with USP <711> using the (b) (4) to determine the amount of drug substance released from the capsules. The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA Biopharmaceutics reviewer.

Batch analyses from three NDA registration batches manufactured at Forest Laboratories Ireland Limited and three NDA registration batches manufactured at (b) (4) are provided. Levomilnacipran SR beads batches were manufactured at commercial-scale batch size (b) (4) at both facilities. Levomilnacipran SR Capsules, 20 mg, 40 mg, 80 mg, and 120 mg manufactured for NDA registration purpose were encapsulated within one-tenth of the commercial-scale batch sizes and were packaged in the proposed marketing container closure system.

The formal stability study of the NDA registration batches of Levomilnacipran SR Capsules, 20 mg, 40 mg, 80 mg, and 120 mg was conducted for three batches of the highest and lowest strengths (20 mg and 120 mg) and two batches of the intermediate strengths (40 mg and 80 mg) on long-term stability program for each commercial packaging configuration. Detailed information of stability study for the three NDA registration batches of each strength manufactured at Forest Laboratories Ireland, Limited at 18 months long-term (25°C/60% RH), 12 months intermediate (30°C/65% RH) and 6 months accelerated (40°C/75% RH) storage conditions of the ongoing stability programs are provided. Similarly information of stability study for the three NDA registration batches of each strength manufactured at (b) (4) at 3 months long-term (25°C/60% RH), intermediate (30°C/65% RH) and accelerated (40°C/75% RH) storage conditions of the ongoing stability programs are provided.

Stability tests include: description, assay, chiral purity, degradation products, dissolution, (b) (4) and microbiology monitored in the stability program using validated, stability-indicating test methods. The sponsor also provided photostability results and indicated that Levomilnacipran SR capsules do not need protection from light exposure since the product is not photosensitive. The reviewer needs to confirm this statement on the provided data.

Based on stability data an expiration dating period of (b) (4) is proposed for Levomilnacipran SR capsules packaged in HDPE bottles in 30-capsule count and 90-capsule count and unit-dose blister configuration when Store at 25° C (77° F); excursions permitted between 15° C and 30° C (59° F and 86° F).

Critical Review Issues

Drug Substance

- The NDA applicant references DMF (b) (4) (b) (4) for CMC information on Levomilnacipran HCl. DMF (b) (4) will need to be evaluated and found acceptable to support this NDA.
- Control strategy of potential impurities (including potential process impurities, potential genotoxic impurities) in the drug substance was discussed at both CMC specific and pre-NDA meetings held with the sponsor prior to submission of the NDA. The reviewer needs to bridge any changes and agreements evolved from these meetings, amendments, and annual reports submitted during the drug development.

Drug Product

- The compatibility of the excipients used in the drug product will need to be evaluated.
- Need to evaluate the adequacy of the information provided on non-compendial inactive components (capsule shells and ink).
- Risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product critical quality attributes (CQAs). The results of the initial formulation risk assessment are provided. The reviewer needs to evaluate the adequacy of the risk assessment.

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Need to evaluate the possibility of the agglomeration of Levomilnacipran in a capsule as a function of time and how such agglomeration could impact drug product dissolution and in vivo performance.
- Need to evaluate the proposed in-process controls and associated acceptance criteria in manufacturing of the drug product.
- The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA Biopharmaceutics reviewer.
- NDA submission contains no nanoscale materials. However, the reviewer should indicate that no nanoscale materials are present (see MAPP 5015.9 entitled, "Reporting Format for Nanotechnology—Related Information in CMC Review.")
- In the proposed labeling, the reviewer needs to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally, reviewer need to confirm that all the excipients used in the drug product formulation are included.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. NDA submission does not have QbD elements (no design space, PAT, RTRT, reduced end-product testing etc.). However, it does contain an extensive pharmaceutical development section and design of experiments in Step 2 of the drug substance synthesis.

A claim for categorical exclusion under 21 CFR §25.31 (b) is provided in Module 1. In accordance with 21 CFR 25.15(d) and 21 CFR 25.31(b), Forest Laboratories, Inc. claims a categorical exclusion from the requirement for an Environmental Assessment or Environmental Impact Statement. In addition, the applicant states that to the best of their knowledge, no extraordinary circumstances exist that would preclude this claim for categorical exclusion. The approval of this application increases the use of the active moiety (levomilnacipran HCl), but the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb [REDACTED] (b) (4). The calculation of the Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment is provided

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The ONDQA PM submitted all manufacturing, testing, and packaging sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The ONDQA Biopharmaceutics team has to be consulted for review of the dissolution method and specification (Biopharmaceutics reviewer has not been assigned yet). It is recommended that the microbiology staff be consulted for evaluation of the microbiological controls.

**PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA**

NDA Number: 204168	Applicant: Forest Laboratories Inc.	Stamp Date: 25-SEP-12
Drug Name: levomilnacipran hydrochloride SR Capsule	NDA Type: Standard	Filing:

CMC Reviewer: Pei-I Chu, Ph. D.
Biopharmaceuticals Reviewer: not assigned yet

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Applicant claims categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			Biopharmaceutics reviewer needs to assess related sections
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?			Biopharmaceutics reviewer needs to assess related sections
35.	Is the dissolution test part of the DP specifications?			
36.	Does the application contain the dissolution method development report?			
37.	Is there a validation package for the analytical method and dissolution methodology?			
38.	Does the application include a biowaiver request?			
39.	Does the application include a IVIVC model?			
40.	Is information such as BCS classification mentioned, and supportive data provided?			
41.	Is there any <i>in vivo</i> BA or BE information in the submission?			

K. FILING CONCLUSION				
	Parameter	Yes	No	Comment
42.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			
45.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

Chhagan Tele

04-OCT-12

Name of Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

Ramesh Sood

Name of Branch Chief
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

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

/s/

CHHAGAN G TELE
10/09/2012

RAMESH K SOOD
10/09/2012

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 204168/000
 Reg. Code: 130
 Priority: 5
 Receipt Date: 25-SEP-2012
 DUFA Date: 25-JUL-2013
 Action Goal:
 District Goal: 26-MAY-2013

Sponsor: FOREST LABS INC
 PLAZA V STE 1900
 JERSEY CITY, NJ 07311
 Brand Name: (b) (4) levomilnacipran hydrochloride
 Estab. Name:
 Generic Name: Levomilnacipran (F2695)

Product Number; Dosage Form; Ingredient; Strengths
 001; CAPSULE; LEVOMILNACIPRAN HYDROCHLORIDE; 20MG
 002; CAPSULE; LEVOMILNACIPRAN HYDROCHLORIDE; 40MG
 003; CAPSULE; LEVOMILNACIPRAN HYDROCHLORIDE; 80MG
 004; CAPSULE; LEVOMILNACIPRAN HYDROCHLORIDE; 120MG

DA Contacts:	P. CHU	Prod Qual Reviewer	3017963887
	T. BOUIE	Product Quality PM	3017961649
	J. TOURE	Regulatory Project Mgr (HFA-130)	3017965419
	C. TELE	Team Leader	3017961762

Overall Recommendation:

ACCEPTABLE	on 24-JUN-2013	by J. WILLIAMS	()	3017964196
PENDING	on 10-OCT-2012	by EES_PROD		
PENDING	on 10-OCT-2012	by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

MF No: AADA:
 Responsibilities: FINISHED DOSAGE MANUFACTURER
 Profile: CAPSULES EXTENDED RELEASE OAI Status: NONE
 Next Milestone: OC RECOMMENDATION
 Milestone Date: 27-DEC-2012
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

FDA ORDER LEO
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: CAPSULES EXTENDED RELEASE OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-OCT-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: FEI: (b) (4)
(b) (4)

MF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: CAPSULES EXTENDED RELEASE OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-OCT-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
