CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-525

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: June 14, 2010

From: Martha R. Heimann, Ph.D., CMC Lead, ONDQA/DNDQA-1

To: NDA 22-525

Subject: **Overall Compliance and CMC Recommendations:**
NDA 22-525 Namenda XR (memantine HCl) Extended Release Capsules

The CDER Office of Compliance (OC) issued an overall 'Acceptable' recommendation for NDA 22-525 on May 27, 1010. A copy of the establishment evaluation report is attached. Dr. Sherita McLamore's review for this NDA, dated May 25, 2010, recommends approval of the application, pending an acceptable OC recommendation. Based on Dr. McLamore's review, and the Compliance recommendation, the Office of New Drug Quality Assessment recommends approval of NDA 22-525.

cc: Orig., NDA 22-525
DNP/T. Wheelous
DNDQA-1/R. Sood
DNDQA-1/M. Heimann
DNDQA-1/S. McLamore
DNDQA-1/T. Bouie

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

/ :ation:	NDA 22525/000	**Sponsor:**	FOREST LABS
Org. Code:	120		PLAZA 5 STE 1900
Priority:	3		JERSEY CITY, NJ 07311
Stamp Date:	21-AUG-2009	**Brand Name:**	NAMENDA XR(MEMANTINE HCL)ER CAPSULES
PDUFA Date:	21-JUN-2010	**Estab. Name:**	
Action Goal:		**Generic Name:**	MEMANTINE HCL
District Goal:	22-APR-2010	**Product Number; Dosage Form; Ingredient; Strengths**	001; CAPSULE, EXTENDED RELEASE; MEMANTINE HYDROCHLORIDE; 7MG 002; CAPSULE, EXTENDED RELEASE; MEMANTINE HYDROCHLORIDE; 14MG 003; CAPSULE, EXTENDED RELEASE; MEMANTINE HYDROCHLORIDE; 21MG 004; CAPSULE, EXTENDED RELEASE; MEMANTINE HYDROCHLORIDE; 28MG

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	M. HEIMANN	Team Leader	301-796-1678

Overall Recommendation: ACCEPTABLE on 27-MAY-2010 by M. STOCK (HFD-320) 301-796-4753

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

DMF No: **AADA:**

N :nsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-SEP-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 2436921	**FEI:** 1000521508	
	FOREST LABORATORIES INC 220 SEA LANE		
	FARMINGDALE, NY 117353900		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-SEP-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:**	**FEI:**	
	FOREST LABORATORIES INC 500 COMMACK ROAD		
	COMMACK, NY 11725		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
Profile:	CAPSULES EXTENDED RELEASE	**OAI Status:**	NONE
L ilestone:	OC RECOMMENDATION		
Milestone Date:	17-SEP-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9616660	**FEI:** 3002806993	
	FOREST LABORATORIES IRELAND LTD CLONSHAUGH BUSINESS AND TECHNOLOGY PARK		
	CLONSHAUGH, DUBLIN 17, , IRELAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CAPSULES EXTENDED RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-MAY-2010		
Decision:	ACCEPTABLE		
Rr n:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 1523957 **FEI:** 1523957

FOREST PHARMACEUTICALS INC
5000 BROTHERTON RD

CINCINNATI, OH 452091105

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Profile: CAPSULES EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-OCT-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 2436283 **FEI:** 3004422109

FOREST RESEARCH INSTITUTE
49 MALL DRIVE

COMMACK, NY 117255722

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-OCT-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-SEP-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

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

/s/

MARTHA R HEIMANN
06/14/2010

NDA 22-525

Namenda® XR (memantine Hydrochloride) Extended Release Capsules

Forest Research Institute, Inc.

Sherita D. McLamore, Ph.D.

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-525

2. REVIEW: #2

3. REVIEW DATE: May 19, 2010

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	August 21, 2009
Amendment	November 2, 2009
Amendment	April 2, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	April 26, 2010
Amendment	April 16, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harborside Financial Center Plaza V, Suite 1900 Jersey City, New Jersey 07311
Representative:	Michael P. Niebo
Telephone:	201-386-2046

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Namenda® XR Extended Release Capsules
b) Non-Proprietary Name (USAN): memantine hydrochloride
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Alzheimer disease

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 7 mg, 14 mg, 21 mg and 28 mg

13. ROUTE OF ADMINISTRATION: oral

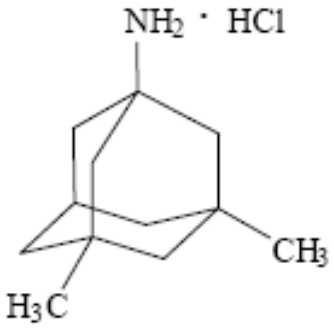
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Name: 1-amino-3,5-dimethyladamantane hydrochloride
Molecular Formula: $C_{12}H_{21}N \cdot HCl$
Molecular Weight: 215.76



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4			
	IV			4			
	IV			4			
	IV			4			
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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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
NDA	21-487	Namenda® (memantine hydrochloride) Tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Pending
Pharm/Tox	N/A	N/A	
ONDQA Biopharm	Acceptable	Acceptable	Sandra Suarez, Ph. D.
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable		Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 22-525

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 22-525 is approvable. The approval from a CMC perspective is contingent upon an acceptable recommendation from the Office of Compliance. A separate memo will be put in DARRTS with final CMC recommendation after the Office of Compliance has provided their final recommendation.

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(s) and Drug Substance(s)

The drug substance, Memantine hydrochloride is a white, (b) (4) with a faintly bitter taste. The molecular formula and molecular weight of the drug substance are $C_{12}H_{21}N \cdot HCl$ and 215.76, respectively. The drug substance will be manufactured and packaged by (b) (4) The applicant cross referenced NDA 21-487 for all information pertaining to the manufacture and control of the drug substance. NDA 21-487 was approved for the treatment of Alzheimer disease in October 2003.

The drug product, Namenda® XR memantine hydrochloride Extended Release Capsules is a once a day treatment for moderate to severe dementia of the Alzheimer's type. Memantine hydrochloride was approved for the treatment of Alzheimer's disease under NDA 21-487. The approved product is available in 5 and 10 mg doses as a standard immediate release tablet. The current drug product is a capsule filled with (b) (4) beads which will be available in four different strengths, 7 mg, 14 mg, 21 mg and 28 mg. The beads are sugar spheres that are coated with (b) (4) before being filled into gelatin capsules. The 7 mg drug product is a yellow, opaque capsule imprinted with black "FLI 7 mg". The 14 mg drug product is a dark green, opaque capsule body and yellow cap imprinted with black "FLI 14 mg". The 21 mg drug product is a dark green, opaque capsule body and white to off-white cap imprinted with black "FLI 21 mg". The 28 mg drug product is a dark green, opaque capsule imprinted with white "FLI 28 mg".

All strengths of the drug product are manufactured from a common blend and differ only in the quantity of extended release beads. The drug product will be manufactured by Forest Laboratories of Ireland. All strengths will be packaged in 30 and 90 count 60 cc HDPE bottles with child resistant induction seal closures and in blister packs. The blisters packs consist of a film (b) (4)

The applicant has requested a 24-month shelf life for the drug product. The applicant submitted 24 months of long term and 6 months of accelerated stability data for the drug product in bottles and blisters. The stability protocol includes a bracketed approached with testing at 0, 3, 6, 9, 18, 24 and 36 months. The bracketed designs includes three batches each of the 7 mg and 28 mg capsules and one batch each of the 14 mg and 21 mg capsules in all three packaging configurations. The applicant has demonstrated that the drug product can be adequately stored (i.e. all data within specifications) at 25º C/60%RH for 24 months in both of the proposed container closure systems. At the time tested, the related substances were well below the level of specification limit and there were virtually no deviations in the assay. The dissolution results were within the proposed acceptance criteria. The ONDQA Biopharmaceutics team was consulted for review of the biowaiver request, the IVIVC model, and the proposed dissolution test acceptance criteria. The ONDQA biopharmaceutics team found the proposed IVIVC model acceptable and granted the waiver request of the *in vivo* bioequivalence requirements for the drug product. However, the review team concluded that the proposed dissolution specifications were not acceptable. As such, the ONDQA biophram team recommended that the applicant adopt new dissolution acceptance criteria. The data was reviewed and compared to the ONDQA proposed dissolution acceptance criteria and all results were acceptable and within the proposed limits. In the April 16, 2010 amendment, the applicant agreed to adopt the revised release/stability dissolution specifications.

All sites were submitted to the Office of Compliance in September of 2009. With the exception of the drug product manufacturer, Forest Laboratories, (FEI: 3002806993), all sites have been found acceptable based on profile or on the District recommendation. Forest Laboratories, Ireland has been assigned inspection and the final recommendation form the Office of Compliance is pending.

The applicant has provided adequate data to support the request 24-month shelf life. Thus, pending an acceptable recommendation form the Office of Compliance, the applicant will granted a 24- month expiry.

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

The drug product is an extended release formulation memantine hydrochloride. The drug product has maximum daily dose of 28 mg and is being developed for the treatment of Alzheimer's disease. The drug product will be packaged in either in 30-count and 90-count presentations in 60 cc, white, square HDPE bottles or in blister

packs containing 28 capsules per pack. The bottles will be capped with 33 mm child-resistant caps (CRC) made of HDPE with (b) (4) liners and (b) (4) induction inner seals. The 28 count blisters pack consists of film composed of (b) (4) heat sealed to a (b) (4) aluminum foil.

C. Basis for Approvability or Not-Approval Recommendation

Approvability of NDA 22-525 from a Chemistry standpoint is contingent upon an acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
RSood

C. CC Block

Orig. NDA 22-525
Division File

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

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/s/

SHERITA D MCLAMORE
05/25/2010

RAMESH K SOOD
05/25/2010

NDA 22-525

Namenda® XR (memantine Hydrochloride) Extended Release Capsules

Forest Research Institute, Inc.

Sherita D. McLamore, Ph.D.

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-525

2. REVIEW: #1

3. REVIEW DATE: April 14, 2010

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
n/a	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 21, 2009
Amendment	November 2, 2009
Amendment	April 2, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harborside Financial Center Plaza V, Suite 1900 Jersey City, New Jersey 07311
Representative:	Michael P. Niebo
Telephone:	201-386-2046

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Namenda® XR Extended Release Capsules
b) Non-Proprietary Name (USAN): memantine hydrochloride
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Alzheimer disease

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 7 mg, 14 mg, 21 mg and 28 mg

13. ROUTE OF ADMINISTRATION: oral

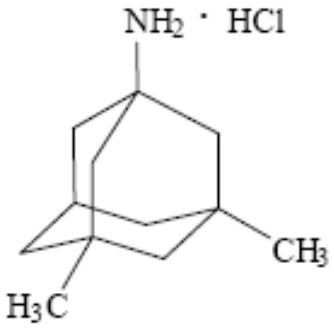
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Name: 1-amino-3,5-dimethyladamantane hydrochloride
Molecular Formula: $C_{12}H_{21}N \cdot HCl$
Molecular Weight: 215.76



17. RELATED/SUPPORTING DOCUMENTS:

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	III			4	n/a		N/A
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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
NDA	21-487	Namenda® (memantine hydrochloride) Tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Pending
Pharm/Tox	N/A	N/A	
ONDQA Biopharm	Pending	Pending	Sandra Suarez, Ph. D.
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable		Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 22-525

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 22-525 is approvable. The approval from a CMC perspective is contingent upon an acceptable recommendation from the Office of Compliance and an adequate response to the Biopharm deficiency communicated in the April 6, 2010 IR Letter and to the following CMC comment:

In your April 2, 2010 response, you indicated that Microbial testing will be performed on the validation batches and the first three commercial batches of each strength the drug product at release. You further indicate that if all batches show no microbial growth, the Microbial testing will be removed from the specification and the updated specification will be included in the next Annual Report. Please be advised that that in the absence of providing justification, microbial limit testing should be performed at release and on stability. *Moreover, removing a test from the regulatory specification is not an annual reportable change. As such, we suggest that you provide acceptable scientific justification for removing the microbial limit test and submit this change post-approval in the form of a Prior Approval supplement.*

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(s) and Drug Substance(s)

The drug substance, Memantine hydrochloride is a white, crystalline solid with a faintly bitter taste. The molecular formula and molecular weight of the drug substance are $C_{12}H_{21}N{\cdot}HCl$ and 215.76, respectively. The drug substance will be manufactured and packaged by (b) (4) . The applicant cross referenced NDA 21-487 for all information pertaining to the manufacture and control of the drug substance. NDA 21-487 was approved for the treatment of Alzheimer disease in October 2003.

The drug product, Namenda® XR memantine hydrochloride Extended Release Capsules is a once a day treatment for moderate to severe dementia of the Alzheimer's type. Memantine hydrochloride was approved for the treatment of Alzheimer's disease under NDA 21-487. The approved product is available in 5 and 10 mg doses as a standard immediate release tablet. The current drug product is a

capsule filled with [redacted] (b) (4) beads which will be available in four different strengths, 7 mg, 14 mg, 21 mg and 28 mg. The beads are sugar spheres that are coated with an [redacted] (b) (4) before being filled into gelatin capsules. The 7 mg drug product is a yellow, opaque capsule imprinted with black "FLI 7 mg". The 14 mg drug product is a dark green, opaque capsule body and yellow cap imprinted with black "FLI 14 mg". The 21 mg drug product is a dark green, opaque capsule body and white to off-white cap imprinted with black "FLI 21 mg". The 28 mg drug product is a dark green, opaque capsule imprinted with white "FLI 28 mg".

All strengths of the drug product are manufactured from a common blend and differ only in the quantity of extended release beads. The drug product will be manufactured by Forest Laboratories of Ireland. All strengths will be packaged in 30 and 90 count 60 cc HDPE bottles with child resistant induction seal closures and in blister packs. The blisters packs consist of a film [redacted] (b) (4)

The applicant has requested a 24-month shelf life for the drug product. The applicant submitted 24 months of long term and 6 months of accelerated stability data for the drug product in bottles and blisters. The stability protocol includes a bracketed approached with testing at 0, 3, 6, 9, 18, 24 and 36 months. The bracketed designs includes three batches each of the 7 mg and 28 mg capsules and one batch each of the 14 mg and 21 mg capsules in all three packaging configurations. The applicant has demonstrated that the drug product can be adequately stored (i.e. all data within specifications) at 25º C/60%RH for 24 months in both of the proposed container closure systems. At the time tested, the related substances were well below the level of specification limit and there were virtually no deviations in the assay. The dissolution results were within the proposed acceptance criteria. The ONDQA Biopharmaceutics team was consulted for review of the biowaiver request, the IVIVC model, and the proposed dissolution test acceptance criteria. The ONDQA biopharmaceutics team found the proposed IVIVC model acceptable and granted the waiver request of the *in vivo* bioequivalence requirements for the drug product. The review team further concluded that the proposed dissolution specifications were not acceptable. As such, the ONDQA biophram team recommended that the applicant adopt new dissolution acceptance criteria (see page 22 of this review). The data was reviewed and compared to the ONDQA proposed dissolution acceptance criteria and all results remained acceptable. To date the applicant has not responded to the Biopharm request gto revised the dissolution specifications. As such, we will defer on making a decision on the expiry until the applicant has responded.

All sites were submitted to the Office of Compliance in September of 2009. With the exception of the drug product manufacturer, Forest Laboratories, (FEI: 3002806993), all sites have been found acceptable based on profile or on the District

recommendation. Forest Laboratories, Ireland has been assigned inspection and the final recommendation form the Office of Compliance is pending.

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

The drug product is an extended release formulation memantine hydrochloride. The drug product has maximum daily dose of 28 mg and is being developed for the treatment of Alzheimer's disease. The drug product will be packaged in either in 30-count and 90-count presentations in 60 cc, white, square HDPE bottles or in blister packs containing 28 capsules per pack. The bottles will be capped with 33 mm child-resistant caps (CRC) made of HDPE with (b) (4) liners and (b) (4) induction inner seals. The 28 count blisters pack consists of film composed of (b) (4) aluminum foil.

C. Basis for Approvability or Not-Approval Recommendation

Approvability of NDA 22-525 from a Chemistry standpoint is contingent upon the applicant adopting the proposed dissolution specification outlined in the April 6, 2010 IR letter, an adequate response to the new CMC comment outlined in this review and an acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
RSood

C. CC Block

Orig. NDA 22-525
Division File

67 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

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/s/

SHERITA D MCLAMORE
04/14/2010

MARTHA R HEIMANN
04/14/2010
for Ramesh Sood

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-525
Applicant:	Forest Laboratories, Inc.
Stamp Date:	21-Aug-2009
PDUFA Date:	21-Jun-2010
Trademark:	Namenda XR®
Established Name:	memantine hydrochloride
Dosage Form:	Extended release capsule
Route of Administration:	Oral
Indication:	Alzheimer's disease
PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒ Pending applicant's response to filing issues	
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

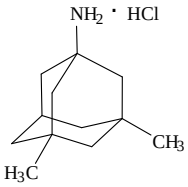
Namenda® (memantine hydrochloride) Tablets are currently approved for treatment of Alzheimer's disease under NDA 21-487, which was approved in 2003. The approved product is a conventional immediate release tablet available in two strengths, 5 mg and 10 mg. The recommended dosage is 10 mg administered bid, with the 5 mg strength used for dose titration. A lower dose, 5 mg bid, is recommended for patients with severe renal impairment.

The current NDA provides for a memantine hydrochloride extended release capsule formulation to be available in four strengths, 7 mg, 14 mg, 21 mg and 28 mg. The recommended target dose is 28 mg/day, with the lower capsule strengths used for dose titration. A lower dose, 14 mg/day, is recommended for patients with severe renal impairment. It is noted that the proposed labeling for Namenda XR® Capsules recommends that patients who are currently on a regimen of 10 mg twice daily of the immediate release tablets be switched to 28 mg/day of the extended release capsule formulation. Similarly, substitution of 14 mg/daily of the extended release capsule formulation for 5 mg bid of the immediate release tablet is recommended for patients with severe renal impairment.

Drug Substance

The active ingredient in Namenda XR® Tablets, memantine hydrochloride (chemical name: 1-amino-3,5-dimethyladamantane hydrochloride), is a well characterized small molecule with molecular formula $C_{12}H_{21}N$•HCl and molecular weight 215.76.

The chemical structure of memantine HCl is:



Memantine HCl is a (b) (4), odorless substance with a faintly bitter taste. It is water soluble (b) (4) The pH of a 1% aqueous solution is between (b) (4) It is classified as providing high solubility/high permeability (Class I) under the BCS classification system. The compound does not melt, but sublimes above (b) (4) The ionization constant (pKa) is approximately (b) (4) and logP is (b) (4) Only one (b) (4) modification of Memantine HCl is reported.

The bulk drug substance is manufactured under NDA 21-487, which is cross-referenced for CMC information. Information in the current NDA is limited to a summary of the manufacturing facilities and drug substance specification approved under NDA 21-487.

Drug Product

The proposed dosage form is an extended release capsule containing 7 mg, 14 mg, 21 mg, or 28 mg of memantine hydrochloride in the following presentations:

7 mg	Size 4, yellow, opaque capsule imprinted with black "FLI 7 mg" on the cap
14 mg	Size 4, dark green, opaque capsule body and yellow cap imprinted with black "FLI 14 mg"
21 mg	Size 4, dark green, opaque capsule body and white to off-white cap imprinted with black "FLI 21 mg"
28 mg	Size 3, dark green, opaque capsule imprinted with white "FLI 28 mg"

Namenda XR® Capsules will be packaged in 30 count or 90 count 60 cc white, square, HDPE bottles with child resistant induction sealed closures. The capsules will also be packaged in (b) (4)/aluminum blister packs.

The Namenda XR® extended release capsule formulations consist of hard gelatin capsules filled with memantine HCl extended release beads. The beads are (b) (4), consisting of sugar spheres that are coated with ar (b) (4) drug layered beads. The drug layered beads are coated with (b) (4) coated beads. The (b) (4) The capsules of the four strengths are manufactured from a common blend of ER beads and are dose proportional.

The components and composition of Namenda XR® Capsules are summarized in the applicant's Tables 1.1- 1 and 1.1- 2, which are shown below.

Table 1.1-1. Components and Composition of Memantine HCl ER Beads, (b) (4)

Component	*Function*	*Quality Standard*	*Theoretical Weight (mg/capsule)*
Memantine HCl	Active ingredient	Reference: NDA 21-487	(b) (4)
Sugar Spheres (b) (4)		NF	
(b) (4)		USP/NF	
Talc	Anti-adherent	USP/NF	
(b) (4)		USP/NF	
		Per DMF[a]	
		USP/NF	
		Per DMF[b]	
		USP/NF	
Total (Memantine HCl ER Beads,			(b) (4)

a DMF No (b) (4)
b DMF No

Table 1.1-2. Components and Quantitative Composition of Memantine HCl ER Capsules, 7 mg, 14 mg, 21 mg and 28 mg

Component	*Function*	*Quality Standard*	*Theoretical Weight (mg/capsule)*			
			7 mg	*14 mg*	*21 mg*	*28 mg*
Empty Gelatin Capsule[a]	Capsule shell	DMF[b]	(b) (4)			
Memantine HCl ER Beads (b) (4)	Bead	In process control[c]				
Total Weight[d]			**82.25**	**126.50**	**170.74**	**224.99**

a Actual capsule shell weight may vary per the range provided in the vendor specification
b DMF No (b) (4) nd DMF No. (b) (4)
c Reference Section 3.2.P.3.4
d Actual capsule batch size will depend on the measured capsule shell weight and assay results for the beads

Capsule components are commonly used as excipients in solid oral dosage forms. All components of the extended release beads comply with compendial (USP/NF) requirements or are manufactured from compendial excipients. Qualitative formulation information for the (b) (4) and (b) (4) coatings is provided in the submission; the manufacturer's DMFs are cross-referenced for additional information.

The proposed commercial memantine HCl extended release bead formulation differs slightly from the phase 3 clinical formulation and is manufactured at a different site. The differences between the clinical and commercial formulations are summarized in the applicant's Table 3.2.P.2.2.1-3, which is shown on the following page. The applicant indicates that bioequivalence of the clinical Phase 3 and commercial formulations was shown in Study MEM-PK-17, which was performed on the 28 mg strength. A biowaiver for the lower strengths is requested.

Table 3.2.P.2.2.1-3. Memantine HCl ER Beads: Comparison of Commercial and Clinical Formulations

	Clinical Study	*MEM-PK-17 MEM-PK-18 MEM-PK-23*	*MEM-PK-17 MEM-MD-50 MEM-MD-51 MEM-MD-54*
	Manufacturing Site	*Forest Ireland*	*Forest Inwood*
	Bead Formulation	*Release 3* (b) (4)	*Release* (b) (4)
	Formulation Type	*Commercial*	*Clinical*
Process	*Ingredients*	*Theoretical Wt. (mg/g)*	*Theoretical Wt. (mg/g)*
	Sugar spheres, NF (b) (4) (b) (4)		(b) (4)
(b) (4)	Memantine HCl	158.2	158.5
			(b) (4)
	Talc, USP/NF		(b) (4)
	(b) (4)	-	-
			(b) (4)
Total (Memantine HCl ER Beads)		1000	1000

1 (b) (4) is removed during the manufacturing process

Memantine HCl ER capsules will be manufactured by Forest Laboratories at the Clonshaugh, Dublin facility in Ireland. Namenda XR® Capsules are manufactured and coated using conventional manufacturing processes, i.e., (b) (4) Process controls (b) (4) are typical for a bead in capsule formulation.

The proposed regulatory specifications for Namenda XR® Capsules are shown on the following page. The proposed analytical procedures are relatively straight-forward. Memantine HCl *Assay*, *Content uniformity* and *Identity* are determined using a single (b) (4) HPLC method (b) (4) . *Related substances* are determined using a (b) (4) method that also serves as a second identification method. Dissolution is determined using USP Apparatus I (baskets) at 100 rpm in pH 1.2 NaCl/HCl buffer. Dissolution results are quantitated using an HPLC method that is similar to the assay method. It is noted that the applicant proposes relatively wide acceptance criteria for the dissolution test based on an IVIVC model that is submitted in the application.

Table 1.1-1. Specifications for Memantine HCl ER Capsules

Test	*Acceptance Criteria*		*Test Method*
Description*	7 mg	Locked, size (b) (4) yellow, opaque capsule. Imprinted with black "FLI 7 mg" on the cap. Upon opening the capsule, contents inside should confirm the presence of white to off-white beads.	PRD-TM-ANL-00011
	14 mg	Locked, size (b) (4) dark green, opaque capsule body and yellow cap imprinted with black "FLI 14 mg. Upon opening the capsule, contents inside should confirm the presence of white to off-white beads	
	21 mg	Locked, size (b) (4) dark green, opaque capsule body and white to off-white cap imprinted with black "FLI 21 mg". Upon opening the capsule, contents inside should confirm the presence of white to off-white beads	
	28 mg	Locked, size (b) (4) dark green, opaque capsule. Imprinted with white "FLI 28 mg" on the cap.Upon opening the capsule, contents inside should confirm the presence of white to off-white beads	
Identification (GC)	Sample conforms to standard		PRD-TM-ANL-00147
Identification (HPLC)	Sample conforms to standard		PRD-TM-ANL-00139
Content Uniformity	Conforms to current USP <905> *Uniformity of Dosage Units*		PRD-TM-ANL-00139
Assay*	(b) (4) Label Claim		PRD-TM-ANL-00139
Degradation Products*			PRD-TM-ANL-00147
(b) (4)	(b) (4)		
Unspecified (each)			
Total (Specified and Unspecified)			
Dissolution*[1]	1 hour: 4 hours: 8 hours: 12 hours:	(b) (4)	PRD-TM-ANL-00140

* Bolded tests are for stability evaluation

[1] Complies with USP <711> Dissolution, Extended-Release Dosage Forms Acceptance Table 2.

The NDA stability package includes long-term stability data through 18 months and accelerated data through 6 months for three pilot-scale batches of lowest and highest strengths (7 mg and 28 mg capsules). A bracketing approach is employed and the applicant provides long-term stability data through 18 months and accelerated data through 6 months for one pilot-scale batch each of the intermediate 14 mg and 21 mg capsule strengths. All batches were manufactured at the Forest Ireland commercial facility and packaged in the proposed commercial packaging presentations. A 24-month shelf life is proposed based on statistical analysis of the long-term assay results.

Critical issues for review

*Drug Substance: N*o critical issues can be identified based on information provided in the NDA.

*Drug Product: N*o critical issues can be identified based on information provided in the NDA. It is noted however that the Pharmaceutical Development Section generally contains brief narratives of the development process. The applicant provided minimal supporting data in this section of the application.

Deficiencies and navigability problems were noted during the initial assessment. The application fails to contain executed batch record as required under 21 CFR §314.50(d)(1)(ii)(b). Several sections of the application lack hyperlinks to the referenced supporting documentation. The lack of executed batch records is a potential filing issue that should be easily corrected.

Additional issues

Administrative: The Namenda® XR Capsule is a new dosage form and approval of this application may be expected to increase use of the active moiety, memantine hydrochloride. The firm has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of Namenda XR Capsules is provided in the submission. The facilities listed in Attachment 1 were entered into EES on 08-Sep-2009.

Labeling/Established Name: The active ingredient in Namenda XR® Capsules, memantine hydrochloride, is the hydrochloride salt and labeled potency is based on content of the salt. Therefore, there is no issue of consistency between the established name (memantine hydrochloride extended release capsules) and the labeled potency.

Comments for 74-Day Letter

There are no comments for the 74 day letter. It is recommended that the following issues be communicated to the applicant as soon as possible in order to allow the firm to correct these deficiencies prior to the 45-day filing meeting.

1) *21 CFR §314.50(d)(1)(ii)(b) requires submission of executed batch records for drug product batches used to conduct bioavailability or bioequivalence studies, or primary stability studies. The application does not contain the required batch records. At the minimum, you should provide an executed batch record for manufacture of the Memantine HCl MR Beads and one batch record that is representative of the encapsulation process.*

2) *We have identified the following problems that make navigation and review of the CMC section of the application difficult for the reviewer.*

a) The following issues are applicable to the 3.2.P [Drug Product] sections for all capsules strengths:

Module	***Comment***
3.2.P.2.5 Microbiological Attributes	*This section is not present.*
3.2.P.2.6 Compatibility	*This section is not present.*
3.2.P.3.5 Process Validation and/or Evaluation	*This section is not present.*
3.2.P.4.1 Specifications	*Tables 3.2.P.4.1.1–1 and 3.2.P.4.1.1–2 cross reference multiple SOPs. Links the supporting documents are not provided.*
3.2.P.4.2 Analytical Procedures	*This section references SOP 6.3.145. No link is provided.*
3.2.P.5.1 Specification(s)	*Table 3.2.P.5.1-1 does not contain links to referenced analytical procedures.*
3.2..P.5.2 Analytical Procedures	*Table 3.2.P.5.2-1 does not contain links to referenced analytical procedures.*
3.2.P.5.3 Validation of Analytical Procedures	*Table 3.2.P.5.3-1. does not contain links to referenced analytical procedures or method validation reports*
3.2.P.5.4 Batch Analyses	*Table 3.2.P.5.4.1-1 does not contain links to referenced batch analysis results.*
3.2.P.5.5 Characterization of Impurities	*Tables 3.2.P.7.1.1-1, 3.2.P.7.1.2-1 and 3.2.P.7.1.3-1 do not contain links to referenced supporting documentation.*
3.2.P.8.3 Stability Data	*Dissolution data tables are provided in 4 point Times New Roman font. This is not legible on screen or when printed.*

b) The 3.2.P [Drug Product] subsections for the 14 mg, 21 mg and 28 mg capsules strengths contain numerous references to the corresponding sections of the 3.2.P section for the 7 mg strength but no links are provided.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective provided the applicant adequately addresses the deficiencies noted above.

The drug substance is manufactured under an approved NDA. The extended release formulation is relatively simple and there are no QbD aspects to the submission. Assignment of CMC portion of the NDA to a single reviewer is recommended. The ONDQA Biopharmaceutics team should be consulted for review of the biowaiver request, IVIVC model, and proposed dissolution test acceptance criteria.

Martha R. Heimann, Ph.D. _____
Pharmaceutical Assessment Lead Date

Ramesh Sood, Ph.D. _____
Branch Chief Date

ATTACHMENT 1

Manufacturing Establishment for Namenda® XR Capsules

Facility Information	Function
(b) (4)	Manufacture, testing, and stability testing of the commercial drug substance **Note: Facility will be withdrawn by the firm.**
	Manufacture, testing, and stability testing of the commercial drug substance
	Manufacture, testing, and stability testing of the commercial drug substance
Forest Laboratories, Ireland, Ltd. Clonshaugh Business & Technology Park Dublin 17, Ireland FEI: 3002806993	Manufacture and release testing of drug product, acceptance testing of drug substance
Forest Laboratories, Inc. 500 Commack Road Commack, NY 11725 FEI: 3000215868	Drug product packaging and labeling
Forest Pharmaceuticals, Inc. 5000 Brotherton Road Cincinnati, OH 45209 CFN: 1523957	Drug product packaging and labeling
Forest Laboratories, Inc. 220 Sea Lane Farmingdale, NY 11735 CFN: 2436921	Drug product release and stability testing
Forest Laboratories, Inc. 49 Mall Drive Commack, NY 11725 FEI: 3003997569	Drug product release and stability testing

ATTACHMENT 1

Manufacturing Establishment for Namenda® XR Capsules

Facility Information	Function
Forest Laboratories, Ireland, Ltd. Clonshaugh Business & Technology Park Dublin 17, Ireland FEI: 3002806993	Drug product release and stability testing
(b) (4)	Microbiological testing of raw materials **Note: Not entered into EES**
	Physical and chemical testing of raw materials **Note: Not entered into EES**
	Physical and chemical testing of raw materials **Note: Not entered into EES**

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Numbers: 22-525 **Applicant: Forest Laboratories** **Stamp Date: 21-Aug-2009**

Drug Name: Memantine HCl extended release capsules **NDA Type: Standard**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		Executed batch records were not provided.
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	NA		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes, pending amendment of the application to include the required executed batch records

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D.
Branch Chief, DPA 1, ONDQA Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

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

/s/

MARTHA R HEIMANN
09/10/2009

RAMESH K SOOD
09/10/2009