CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206439Orig1s000

CHEMISTRY REVIEW(S)

NDA 206439

MDX-8704 (Memantine HCl ER/ donepezil HCl fixed dose combination capsules 28/10mg and 14/10mg)

Forest Laboratories Inc.

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

Review of Chemistry, Manufacturing, and Controls

Reference ID: 3633270

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Chemistry Review Section

Chemistry Review Data Sheet

1. NDA 206439

2. REVIEW # 1

3. REVIEW DATE: September 23, 2014

4. REVIEWER: Pei-I Chu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	February 26, 2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest laboratories, Inc.
Address:	Harborside Financial Center, Plaza V, Suite 1900, Jersey City, USA, 07311
Representative:	Kathleen Waldron
Telephone:	201-386-2115

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

a) Proprietary Name: Namzaric
b) Non-Proprietary Name (USAN): MDX-8704 (memantine HCl extended release/donepezil HCl capsules)
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority:

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9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: memantine: an orally active N-methyl-D-aspartate (NMDA) receptor antagonist, donepezil: an orally active reversible acetylcholinesterase inhibitor

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 28mg memantine HCl ER/10mg donepezil HCl and 14mg memantine HCl ER/10mg donepezil HCl

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

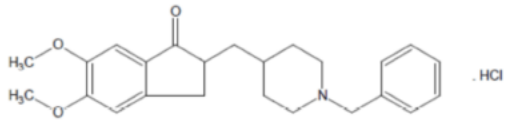
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: **donepezil hydrochloride**
(±)-2,3-dihydro-5,6-dimethoxy2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride

(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride

Molecular Formula: $C_{24}H_{29}NO_3 \cdot HCl$
Molecular Weight: 415.95 g/mol

Structural Formula



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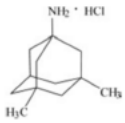
Chemistry Review Section

Chemical Name: memantine hydrochloride(salt)

1-Amino-3,5-dimethyladamantane hydrochloride

1-Amino-3,5-dimethyltricyclo[3.3.1.1^{3,7}] decane hydrochloride

Molecular Formula: $C_{12}H_{21}N{\cdot}HCl$
Molecular Weight: 215.77 g/mol

Structural Formula: 

17. RELATED/SUPPORTING DOCUMENTS:

Reference ID: 3633270

Chemistry Review Section

A. DMFs:

DMF#	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Completed	Comments
(b) (4)	IV		(b) (4)	1	Adequate	09/25/2013	
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			1	Adequate	12/10/2012	
	III			4			Sufficient information in application
	III			1	Adequate	09/10/2012	Sufficient information in application
	III			4			Sufficient information in application
	III						Sufficient information in application
	IV			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	IV			4			Sufficient information in application
	IV			1	Adequate	08/08/2013	
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	IV			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in

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			closures				application
(b) (4)	III		(b) (4)	4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	I			1	Adequate	09/09/2014	

[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)

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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22525	Commercial
NDA	21720	Commercial
NDA	21487	Commercial

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	DATE	**REVIEWER**
Biometrics	NA	NA	
EES	Acceptable	05/30/2014	Office of compliance
Pharm/Tox	NA	NA	NA
Biopharm	Pending		Eradiri Okpo
LNC	NA	NA	NA
Methods Validation	NA	NA	NA
OPDRA	NA	NA	NA
DMEPA	TBD		Moukhtara, Aline M.
EA	NA	NA	NA
Microbiology	Acceptable	05/06/2014	Bryan Riley

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The Chemistry Review for NDA 206439

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

MDX-8704 is a combination product of capsules containing two approved active ingredients (memantine and donepezil). Except for the dissolution specification, NDA 206439 has been reviewed for the chemistry, manufacturing and controls section. The Office of Compliance has determined that the drug substance, drug product and packaging facilities are acceptable based on profile. The approval from a CMC perspective is contingent upon an acceptable recommendation from the Biopharm reviewer for the dissolution specification. A separate memo will be put in DARRTS with final CMC recommendation on the adequacy of the dissolution specification and product shelf life.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product (MDX 8704)

The drug product, memantine HCl ER/donepezil HCl (MDX8740) capsules, is developed as an oral capsule formulation containing a fixed dose combination of memantine HCl extended release (ER) (b) (4) and donepezil HCl (b) (4). The memantine ER (b) (4) have been manufactured commercially for Namenda XR® capsules which were approved in NDA 22525. They are sugar sphere (b) (4) Donepezil is commercially available as tablets (Aricept®). The donepezil HCl (b) (4) formulation developed for MDX 8704 is similar to the Aricept tablet formulation which was approved in NDA 21720. The excipients consist of (b) (4) Most of the excipients used in the donepezil HCl (b) (4) have been used in the approved Aricept® tablet.

The manufacturing process for memantine HCl ER/donepezil HCl capsules consists of (b) (4) distinct stages: (b) (4)

Both Memantine strengths (b) (4) are encapsulated from a common ER (b) (4) formulation. (b) (4). Memantine HCl ER/Donepezil HCl Capsules, 14 mg/10 mg, are a locked, size 2 light green opaque capsules, with black 'FL 14/10' radial imprint on the cap. Memantine HCl ER/Donepezil HCl Capsules, 28 mg/10 mg are locked, size 1 blue

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opaque capsules, with black 'FL 28/10' radial imprints on the caps. The commercial product is available in HDPE bottles with (b) (4) caps (b) (4).

Forest has provided 12 month stability data and a complete regression analysis within 120 days post-submission of the original NDA. With the update, Forest has request a drug product shelf life of 18 months.

From the CMC perspective, the product quality risk is low. The memantine XR component of this product has been manufactured using the same commercial process as in the approved NDA 22525. The donepezil (b) (4)

Drug Substance

Donepezil HCl, USP is off-white to cream colored crystalline powder with a melting point of 219.0°C to 220.5°C. The water solubility at pH 7 is 0.15g/mL. DMF (b) (4) has been filed by the drug substance manufacturer (b) (4). This DMF has been reviewed and found to be adequate. The applicant has referred to DMF (b) (4) for all manufacturing, control, testing and stability of the donepezil HCl drug substance.

Memantine hydrochloride drug substance is currently approved for Namenda® tablets (NDA 21487), Namenda® Oral Solution (NDA 21627) and Namenda® XR extended release capsules (NDA 22525). It is a white (b) (4) powder with a melting point of greater than 220°C (b) (4) The solubility at pH 7 is 43.6 mg/mL.

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Risk Assessment – Memantine HCl and Donepezil HCl XR Capsules

From Initial Quality Assessment			Review Assessment		
Product Attribute/CQA	**Factors That Can Impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comment**
Assay (memantine), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	The applicant developed the memantine (b) (4) manufacturing process and gained commercial batch experience at the proposed manufacturing site. The formulation, manufacturing process and container closure selected will ensure that acceptable assay and stability will be obtained.	Acceptable	Any changes in the manufacturing process parameters could affect the assay and dissolution profile of the memantine ER (b) (4)
Assay (donepezil), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	The applicant has conducted DOE study to (b) (4) The capsules were 100% weight inspected.	Acceptable	The assay and dissolution profile of the donepezil may be affected (b) (4) used.
Physical stability memantine), solid state	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Excipients selected for the memantine ER (b) (4) were the same as the approved Namenda XR commercial product developed by Forest. Manufacturing process parameters and batch size were the same as the Namenda XR capsule .	Acceptable	The drug product is stable. Any changes of manufacturing process parameters could affect the dissolution profile of the memantine ER (b) (4).
Physical stability (donepezil), solid state	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Excipient compatibility study was conducted during development. Product stability data has been collected. The process was scaled up to the commercial size. Process parameters selected based on DOE study	Acceptable	The drug product is stable. Any changes (b) (4) process parameters could affect the dissolution profile of the donepezil (b) (4).
Content uniformity (memantine)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	Process parameters selected were based on previous manufacturing experience of the same product, release and stability data.	Acceptable	The drug substance (b) (4) to ensure acceptable content uniformity and dissolution

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Risk Assessment – Memantine HCl and Donepezil HCl XR Capsules

From Initial Quality Assessment			Review Assessment		
Product Attribute/CQA	**Factors That Can Impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comment**
Content uniformity (donepezil)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	The drug loading in the donepezil (b) (4) [redacted] Process parameters selected were based on DOE study. The commercial equipment is considered the same as the registration batch according to SUPAC	Acceptable	The (b) (4) [redacted] to ensure adequate content uniformity and dissolution profile.
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The applicant follows c-GMP procedure to maintain the facility and manufacture the product. Microbial data will be monitored at release and annually	Acceptable	Follow c-GMP procedure and adequately maintain the manufacturing facility
Dissolution (donepezil)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4) [redacted] The dissolution profile of the donepezil (b) (4) should meet specification due to its high solubility and the (b) (4) [redacted]	Acceptable	Refer to Biopharmaceutics Review
Dissolution (memantine),	• Formulation • Raw materials (rate controlling polymers) • API sources • Process parameters • Scale/equipment • Site	Medium	(b) (4) [redacted] The product will be packaged in HDPE bottles. (b) (4) [redacted]	Acceptable	If changes in the container closure system are to be made, adequate stability/dissolution data should be provided since the dissolution profile may be affected by the package components selected.
Alcohol dose dumping (memantine)	• Formulation • Process parameters • Scale/equipment • Site	High	Even though the product has a pronounced effect in dose dumping with 40% alcohol, clinical trials suggested that the adverse events were mild for doses up to 100mg	Acceptable	Refer to Biopharmaceutics Review

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

The drug (memantine HCl extended-release and donepezil HCl) capsules 28/10 mg is for use in patients currently stabilized on memantine HCl (10 mg twice daily or 28 mg extended-release once daily) and donepezil HCl 10 mg. The drug (memantine HCl extended-release and donepezil HCl) capsules 14/10 mg is for use in patients with severe renal impairment currently stabilized on memantine HCl (5 mg twice daily or 14 mg extended-release once daily) and donepezil HCl 10 mg.

C. Basis for Approvability or Not-Approval Recommendation

From the perspective of chemistry, manufacturing and controls, this application is recommended for approval pending the recommendation of the biopharmaceutics reviewer. The applicant has addressed all issues raised through information requests and the Office of Compliance has rendered an acceptable recommendation.

II. Administrative

A. Reviewer's Signature

Pei-I Chu, Ph.D.

B. Endorsement Block

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Martha Heimann, Ph.D.
Chemistry Branch Chief:	Olen Stephens, Ph.D.
Chemistry Project Manager :	Teshara Bouie

C. CC Block

Orig. NDA 206439

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

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

/s/

PEI-I CHU
09/24/2014

OLEN M STEPHENS
09/24/2014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 206439/000	**Sponsor:**	FOREST LABS INC
Org. Code:	120		PLAZA V STE 1900
Priority:	4		JERSEY CITY, NJ 07311
Stamp Date:	26-FEB-2014	**Brand Name:**	MEMANTINE HC1 EXTENDED RELEASE AND DONEP
PDUFA Date:	26-DEC-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	MEMANTINE HC1 EXTENDED RELEASE AND DONEP
District Goal:	27-OCT-2014	**Product Number; Dosage Form; Ingredient; Strengths**	

001; CAPSULE; DONEPEZIL HYDROCHLORIDE; 10MG
001; CAPSULE; MEMANTINE HYDROCHLORIDE; 14MG
002; CAPSULE; DONEPEZIL HYDROCHLORIDE; 10MG
002; CAPSULE; MEMANTINE HYDROCHLORIDE; 28MG

FDA Contacts:	P. CHU	Prod Qual Reviewer		3017963887
	T. BOUIE	Product Quality PM		3017961649
	T. WHEELOUS	Regulatory Project Mgr	(HFD-120)	3017961161
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	ACCEPTABLE	on 30-MAY-2014	by T. SHARP	()	3017963208
	PENDING	on 14-MAR-2014	by EES_PROD		
	PENDING	on 14-MAR-2014	by EES_PROD		

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

(b) (4)

DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	CAPSULES, MODIFIED RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-MAR-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: **AADA:**

Responsibilities: (b) (4)

Profile: CAPSULES, MODIFIED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

E: shment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** 2436921 **FEI:** 1000521508

FOREST LABORATORIES INC

FARMINGDALE, , UNITED STATES 117353900

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

M. ne Date: 17-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** 9616660 **FEI:** 3002806993

FOREST LABORATORIES IRELAND, LTD.
CLONSHAUGH BUSINESS AND TECHNOLOGY PARK

DUBLIN 17, CLONSHAUGH, IRELAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CAPSULES, MODIFIED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

FOREST PHARMACEUTICALS INC

CINCINNATI, , UNITED STATES 45209

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: CAPSULES, MODIFIED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

E shment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-MAR-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		