CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-627

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-627 **CHEM.REVIEW # 3** **REVIEW DATE: 02-MAR-05**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	15-FEB-05	15-FEB-05(EDR)	25-FEB-05

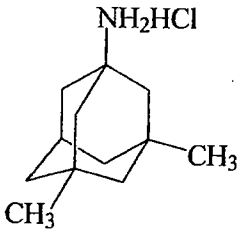
NAME & ADDRESS OF APPLICANT: Forest Laboratories Inc
235 East 42nd Street
New York, NY 10017

DRUG PRODUCT NAME
Proprietary: Namenda (memantine HCl) Oral Solution
Nonproprietary/USAN: Memantine HCl
Code Name/#: none
Chem.Type/Ther.Class: 1S/NMDA antagonist/2013060

PHARMACOL.CATEGORY/INDICATION: Moderate to severe AD

DOSAGE FORM: Oral Solution
STRENGTHS: 2 mg/mL of hydrochloride
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
1-amino-3,5-dimethyladamantane hydrochloride
$C_{12}H_{21}N.HCl$
Molecular weight 215.77
CAS # 41100-52-1 (HCl); 19982-08-2 (base)



SUPPORTING DOCUMENTS: IND 21,487 (Forest); 21,627 (Forest – oral solution); 33,392 (Forest - spasticity), 32,021 (Merz – bladder disfunction)

RELATED DOCUMENTS: none

REMARKS/COMMENTS: The amendment provides submitted electronically a new, revised labeling for both forms of drug product (tablets & OS). The strength of 2 mg/mL is to be marketed (initially 2 and 4 mg/mL). The requested instructions on how to use the dosing device has been provided and is acceptable.
The revisions address the clinical part of the document. The CMC information remains unchanged from February, 2004.

CONCLUSIONS & RECOMMENDATIONS: No CMC impact of the submission was noted, no CMC objections to labeling changes. The approval of NDA 21-627 is recommended.

cc:
Orig. NDA 21-627
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MRHeimann
HFD-810/JESimmons/HBPatel
R/D Init by:MRH/JES/HBP

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\N21627R.003.doc

54 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 1041

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

/s/

Janusz Rzeszotarski
3/14/05 01:40:57 PM
CHEMIST

Martha Heimann
3/14/05 02:26:55 PM
CHEMIST
Signed for Dr. John E. Simmons.

NDA 21-627 CHEMISTRY REVIEW

NDA 21-627

Namenda (Memantine Hydrochloride) Oral Solution

Forest Laboratories, Inc.

Chemistry Review
W. Janusz Rzeszotarski, Ph.D.
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. **NDA #** 21-627

2. **REVIEW #:** 3

3. **REVIEW DATE:** 02-MAR-2005

4. **REVIEWER:** W. Janusz Rzeszotarski, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	01-MAY-03

6. **SUBMISSION(S) BEING REVIEWED: An amended submission.**

Submission(s) Reviewed	Document Date
Original	01-MAY-03
Amendment (BZ)	03-JUL-03
Amendment (BL)	08-AUG-03
Amendment (BL)	29-DEC-03
Amendment (BL)	10-FEB-04
Amendment (BZ)	15-FEB-05

7. **NAME & ADDRESS OF APPLICANT:**

Name: Forest Laboratories, Inc.
Address: Harborside Financial Center
Jersey City, NJ 07311

Representative: Esin Kosal, Ph.D.
Telephone: 201-386-2126

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary: Namenda Oral Solution
   b) Non-Proprietary: No USP monograph; DS: Memantine Hydrochloride (USAN)
   c) Code Name/# none
   d) Chem. Type/Submission Priority: 3S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Treatment of moderate to severe Alzheimer's Disease

11. **DOSAGE FORM:** Oral Solution

12. **STRENGTH/POTENCY:** 2 mg/mL of memantine hydrochloride

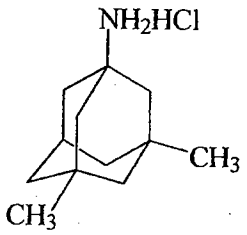
13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** __X__ **Rx** ___ **OTC**

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) **NO**

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

1-amino-3,5-dimethyladamantane hydrochloride
$C_{12}H_{21}N.HCl$
Molecular weight 215.77 (**215.76 USAN**)
CAS # 41100-52-1 (HCl); 19982-08-2 (base)



16. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			3	Adequate	12-JAN-2001	
	III			3	Adequate	26-SEP-2000	
	III			3	Adequate	24-FEB-2003	
	III			3	Adequate	01-SEP-1999	
	III			3	Adequate	22-MAY-2000	
	III			3	Adequate	06-OCT-2003	
	III			3	Adequate	19-DEC-2003	
	III			3	Adequate	09-MAR-1992	

[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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	33,392 AT 23-DEC-1997	Forest – Spasticity of Various Origin
IND		
NDA	21-487 AP 16-OCT-2003	Forest – Tablets (AD)

18. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Not reviewed		
EES	Acceptable	24-JUL-2003	OC
Pharm/Tox	Approvable	24-FEB-04	Kathleen Haberny, Ph.D.
Biopharm	Biowaver granted/AP	06-FEB-04	Veneeta Tandon, Ph.D.
Methods Validation	Submitted		
EA	Approval	12-JAN-2004	W.Janusz Rzeszotarski, Ph.D.
Microbiology	Approval	22-AUG-2003	Brian Riley
DMETS	Namenda acceptable	15-JUL-03	Tia M. Harper-Velazquez, Ph.D.

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug substance, memantine hydrochloride, is well characterized and studied. This DS has been reviewed in detail in the review for NDA 21-487. Its specifications are modest but exceed the historical levels and are set based on qualification of —— known impurities present in toxicology batch R7206 from the above mentioned NDA. Both, the drug substance and the drug product, are stable but the stability data for the final formulation supports expiration dating to — months only. The sponsor either did not carry additional stability study or failed to amend the 15-FEB-05 application. The stability studies began in 2001 hence sufficient data should be available at the date of this review. In view of the above the approval of NDA 21-627 is recommended with the expiration date of — months. Once the additional stability data is accumulated the sponsor would be able to extend the expiration date and report the data in annual report. The overall recommendation of the OC is: Acceptable. The recommendation to approve was made in the two previous reviews and is hereby repeated.

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

N/A

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

Namenda Oral Solution will be provided in 2 mg/mL strength in 12 fl oz (360 mL) container. The standard room temperature storage is recommended and the expiration date of [redacted] months is recommended. The strength of 2 mg/mL is to be marketed (initially 2 and 4 mg/mL). The requested instructions on how to use the dosing device has been provided and are acceptable.

C. **Basis for Approvability or Not-Approval Recommendation**

A stable formulation and a proven stability of DS. The DS and drug product specifications justified. All manufacturing facilities acceptable.

III. Administrative

Chemist: W. Janusz Rzeszotarski, Ph.D./02-MAR-2005

ChemistryTeamLeader/ Date: Martha R. Heimann, Ph.D.

Project Manager / Date: Melina Griffis, R.Ph

NDA 21-627 CHEMISTRY REVIEW

NDA 21-627

Namenda (Memantine Hydrochloride) Oral Solution

Forest Laboratories, Inc.

Chemistry Review
W. Janusz Rzeszotarski, Ph.D.
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. **NDA #** 21-627

2. **REVIEW #:** 1

3. **REVIEW DATE:** 12-JAN-2004

4. **REVIEWER:** W. Janusz Rzeszotarski, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	01-MAY-03

6. **SUBMISSION(S) BEING REVIEWED: An amended submission.**

Submission(s) Reviewed	Document Date
Original	01-MAY-03
Amendment (BZ)	03-JUL-03
Amendment (BL)	08-AUG-03
Amendment (BL)	29-DEC-03

7. **NAME & ADDRESS OF APPLICANT:**

Name: Forest Laboratories, Inc.
Address: Harborside Financial Center
Jersey City, NJ 07311

Representative: Esin Kosal, Ph.D.
Telephone: 201-386-2126

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary: Namenda Oral Solution
   b) Non-Proprietary: Memantine Hydrochloride (USAN)
   c) Code Name/#
   d) Chem. Type/Submission Priority: 3S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Treatment of moderate to severe Alzheimer's Disease

11. **DOSAGE FORM:** Oral Solution

12. **STRENGTH/POTENCY:** 2 and 4 mg/mL

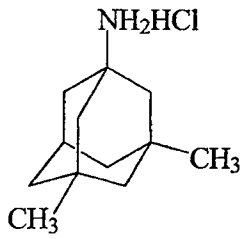
13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** **__X__Rx** **___OTC**

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) **NO**

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

1-amino-3,5-dimethyladamantane hydrochloride
$C_{12}H_{21}N.HCl$
Molecular weight 215.77 (**215.76 USAN**)
CAS # 41100-52-1 (HCl); 19982-08-2 (base)



16. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			3	Adequate	12-JAN-2001	
	III			3	Adequate	26-SEP-2000	
	III			3	Adequate	24-FEB-2003	
	III			3	Adequate	01-SEP-1999	
	III			3	Adequate	22-MAY-2000	
	III			3	Adequate	06-OCT-2003	
	III			3	Adequate	19-DEC-2003	
	III			3	Adequate	09-MAR-1992	

[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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	33,392 AT 23-DEC-1997	Forest – Spasticity of Various Origin
IND		
NDA	21-487 AP 16-OCT-2003	Forest – Tablets (AD)

18. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	In review		
EES	Acceptable	24-JUL-2003	OC
Pharm/Tox	In review		
Biopharm	In review		
Methods Validation	In preparation		
EA	Approval	12-JAN-2004	W.Janusz Rzeszotarski, Ph.D.
Microbiology	Approval	22-AUG-2003	Brian Riley
DMETS	In review		

Appears This Way
On Original

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug substance, memantine hydrochloride, is well characterized and studied. This API has been reviewed in detail in the review for NDA 21-487. Its specifications are modest but exceed the historical levels and are set based on qualification of — known impurities present in toxicology batch R7206 from the above mentioned NDA. Both, the drug substance and the drug product, are stable but the stability data for the final formulation supports expiration dating to ——— only. The sponsor either did not continue the stability study or failed to amend the application. The stability studies begun in 2001 hence sufficient data should be available at the date of this review. In view of the above the approval of NDA 21-627 is recommended with the expiration date of — months. Once the additional stability data is accumulated the sponsor would be able to extend the expiration date and report the data in annual report. The overall recommendation of the OC is: Acceptable. A copy of EES is attached.

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

N/A

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

Namenda Oral Solution will be provided in two strengths of 2 mg/mL and 4 mg/mL in three basic size containers of 120 mL, 360 mL and 480 mL with the CR-closure.equivalent. The standard room temperature storage is recommended and the expiration date of — months is recommended.

C. Basis for Approvability or Not-Approval Recommendation

A stable formulation and a proven stability of API. The API and drug product specifications justified. All manufacturing facilities acceptable.

III. Administrative

Chemist: W. Janusz Rzeszotarski, Ph.D./22-JAN-2004

ChemistryTeamLeader/ Date: Maryla E. Guzewska, Ph.D.

Project Manager / Date: Melina Griffis, R.Ph

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-627 **CHEM.REVIEW # 1** **REVIEW DATE: 12-JAN-04**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	01-MAY-03	02-MAY-03	10-MAY-03
Amendment (BZ)	03-JUL-03	07-JUL-03	07-JUL-03
Amendment (BL)	08-AUG-03	12-AUG-03	EDR
Amendment (BL)	29-DEC-03	31-DEC-03	EDR

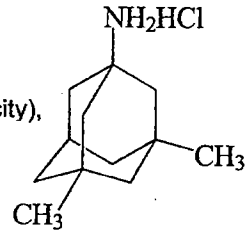
NAME & ADDRESS OF APPLICANT: Forest Laboratories Inc
235 East 42nd Street
New York, NY 10017

DRUG PRODUCT NAME
Proprietary: Namenda (Memantine HCl) Oral Solution
Nonproprietary/USAN: Memantine HCl
Code Name/#: none
Chem.Type/Ther.Class: 3S/NMDA antagonist/2013060

PHARMACOL.CATEGORY/INDICATION: Moderate to severe AD

DOSAGE FORM: Oral Solution
STRENGTHS: 2 and 4 mg/mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
1-amino-3,5-dimethyladamantane hydrochloride
$C_{12}H_{21}N.HCl$
Molecular weight 215.77 (**215.76 USAN**)
CAS # 41100-52-1 (HCl); 19982-08-2 (base)



SUPPORTING DOCUMENTS: IND 21,487 (Forest); 33,392 (Forest - spasticity), 32,021 (Merz – bladder disfunction), 54,045 ——— Tinnitus Forschungs – tinnitus), NDA 21-487 (Forest – tablets).
RELATED DOCUMENTS: none
REMARKS/COMMENTS: Originally developed by Merz. Formulated in different form and marketed in EU.
CONCLUSIONS & RECOMMENDATIONS: Batch-to-batch reproducibility proven. Stability under accelerated and real time conditions documented albeit for a limited period. The proposed specifications for drug substance and the drug product are modest but do not reflect the historical levels of impurities and degradants. A recommendation from OC issued as acceptable as of 24-JUL-2003. Recommend approval of NDA 21-627 with — months expiration date.

cc:
Orig. NDA 21-627
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\N21627NR.001.doc

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

/s/

Janusz Rzeszotarski
2/9/04 03:00:24 PM
CHEMIST

Maryla Guzewska
2/10/04 01:37:28 PM
CHEMIST
Recommend [redacted] months expiration period. Refer to Memorandum to NDA File in DFS