

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-487

Chemistry Review(s)

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

NDA #: 21-487

CHEM.REVIEW # 2

REVIEW DATE: 15-OCT-03

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	24-SEP-03	25-SEP-03	25-SEP-03
Amendment	03-OCT-03	06-OCT-03	06-OCT-03
Amendment	14-OCT-03	15-OCT-03	15-OCT-03

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

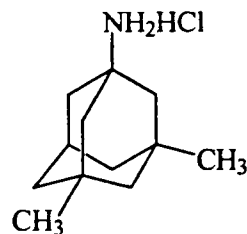
DRUG PRODUCT NAME
Proprietary: Namenda(memantine HCl) Tablets
Nonproprietary/USAN: Memantine HCl
Code Name/#: none
Chem.Type/Ther.Class: 1S/NMDA antagonist/2013060

PHARMACOL.CATEGORY/INDICATION: Moderate to severe AD

DOSAGE FORM: Tablets
STRENGTHS: 5, 10, 15, 20 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx _____ OTC

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

1-amino-3,5-dimethyladamantane hydrochloride
C₁₂H₂₁N.HCl
Molecular weight — 215.76 USAN)
CAS # 41100-52-1 (HCl); 19982-08-2 (base)



SUPPORTING DOCUMENTS: IND 21,487 (Forest); 33,392 (Forest -

RELATED DOCUMENTS: none

REMARKS/COMMENTS: Reedited labels of all commercial presentations. The 15 and 20 mg tablets have been deleted from the How Supplied section of the Package Insert. The big logo ("Phenix") on the Patient Starter Kit was moved to the side and the list of its content printed in its place. The DMETS recommendations have been implemented.

CONCLUSIONS & RECOMMENDATIONS: In present form the labels and the package insert are fully acceptable. Recommend approval of NDA 21-487 with 18 months expiration date.

cc:
Orig. NDA 21-487
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

1S/

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\N21487R.002.doc



NDA 21-487 CHEMISTRY REVIEW



NDA 21-487

[Trade Name Not Established] (Memantine Hydrochloride) Tablets

Forest Laboratories, Inc.

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

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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA # 21-487
2. REVIEW #: 1
3. REVIEW DATE: 18-AUG-2003
4. REVIEWER: W. Janusz Rzeszotarski, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	31-JUL-02

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission (RS)	19-DEC-02
Amendment (BZ)	10-JAN-03
Amendment (BC)	13-MAR-03
Amendment (BC)	19-MAR-03
Amendment (BC)	25-JUN-03
Amendment (BZ)	01-JUL-03
Amendment (BC)	11-JUL-03
Amendment (BC)	06-AUG-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: Not established
- b) Non-Proprietary: Memantine Hydrochloride (USAN)
- c) Code Name/#
- d) Chem. Type/Submission Priority: 1S

9. LEGAL BASIS FOR SUBMISSION: N/A

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

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5, 10, 15, 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

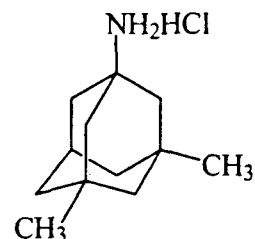
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-amino-3,5-dimethyladamantane hydrochloride

$C_{12}H_{21}N.HCl$

Molecular weight (215.76 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	01-OCT-2000	
	IV			3	Adequate	27-SEP-2000	
	IV			3	Adequate	25-APR-2002	
	IV			3	Adequate	05-AUG-1999	
	III			3	Adequate	22-MAY-2001	
	III			3	Adequate	27-SEP-2000	
	III			4	N/A	Not in	
	III			4	N/A	Not in	
	III			3	Adequate	14-MAR-2001	
	III			3	Adequate	12-APR-1996	
	III			3	Adequate	09-AUG-1999	
	III			3	Adequate	09-AUG-1999	
	III			3	Adequate	18-JUN-1999	
	III			3	Adequate	30-MAY-2003	
	III			3	Adequate	16-FEB-2003	

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 –
IND		
NDA		

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	Acceptable	04-AUG-2003	W.Janusz Rzeszotarski, Ph.D.
Microbiology	In review		
DMETS	In review		

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry part has not been altered on subsequent resubmission of 19-DEC-2002. The drug substance, memantine hydrochloride, is well characterized and studied. Its specifications are modest but exceed the historical levels and are set based on qualification of three known impurities present in toxicology batch R7206. Both, the drug substance and the drug product, are stable but the stability data for the final formulation supports expiration dating to 18 months only. In view of the above the approval of NDA 21-487 is recommended with the expiration date of 18 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 and a copy of EES is attached.

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

N/A *NING*

II. Summary of Chemistry Assessments

Memantine is an uncompetitive, moderate affinity antagonist of N-methyl-D-aspartate (NMDA) receptor. Its proposed mode of action in Alzheimer's Disease is to decrease the excessive glutamate transmission attenuating the excitotoxic neuronal destruction.

A. Description of the Drug Product and Drug Substance

Drug Product. The film coated tablets of 5mg, 10 mg, 15 mg and 20 mg strength consist of compendial inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; talc, USP; and magnesium stearate, _____. The _____ coatings are similarly composed of compendial and FD&C ingredients. The iron oxide black is the only exception. Its specifications and testing is done under the JPE (Japanese Pharmaceutical Excipients) methodology which has been reviewed and approved in the _____ DMF _____. The developmental formulations varied in the ratio of the inactive ingredients only and their use in clinical studies was fully warranted.

The tablets will be packaged in _____ bottles of 60 to 2000 tablets. The blister presentations will be provided to healthcare professionals only as titration pack, starter kits and maintenance pack. Commercial distribution of these samples may include from _____ per card.

The bottle configurations are white opaque, oblong-, square- and round-shaped, wide mouth bottles of _____

Blister packs are made _____ supplied by _____
backed with _____ supplied by _____

The results of 12 month stability studies of the validation batches in commercial packaging forms prove that the drug product is stable and support the request for 18 months expiration dating.

Drug Substance. Memantine hydrochloride has two chiral carbon atoms at positions 3 and 5.

L

3. If
necessary, the specification for _____ should be reevaluated after a significant number of commercial scale batches have been tested. The sponsor's claim that the justification for the memantine drug substance related substance specifications is based upon historical levels found in scale up and commercial scale batches is incorrect. The levels of related substances in found in batch R7206 used in the mouse micronucleus and carcinogenicity studies once again do not support the claim. The acceptable justification comes from the Table 4.4-11, which provides the levels of the related substances in batch R7206 and the Table 4.4-12, which provides the calculations of the acceptable human daily intake based upon the mouse micronucleus and the rat and mouse carcinogenicity studies. No need for particle size spec - high permeability.

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

Memantine hydrochloride tablets will be provided in ^{four} strengths equivalent to 5, 10, 15, 20 mg base in numerous packaging configurations. The standard room temperature storage is recommended and the expiration date of 18 months is justified.

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./18-AUG-2003

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 #: 21-487

CHEM.REVIEW # 1

REVIEW DATE: 18-AUG-03

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Resubmission	19-DEC-02	19-DEC-02	19-DEC-02
Amendment	10-JAN-03	13-JAN-03	16-JAN-03
Amendment	13-MAR-03	14-MAR-03	18-MAR-03
Amendment	19-MAR-03	20-MAR-03	24-MAR-03
Amendment	25-JUN-03	26-JUN-03	30-JUN-03
Amendment	01-JUL-03	02-JUL-03	07-JUL-03
Amendment	11-JUL-03	14-JUL-03	16-JUL-03
Amendment	06-AUG-03	06-AUG-03	07-AUG-03

NAME & ADDRESS OF APPLICANT:

Forest Laboratories Inc
235 East 42nd Street
New York, NY 10017

DRUG PRODUCT NAME

Proprietary:

[Not established](memantine HCl) Tablets

Nonproprietary/USAN:

Memantine HCl

Code Name/#:

none

Chem.Type/Ther.Class:

1S/NMDA antagonist/2013060

PHARMACOL.CATEGORY/INDICATION:

Moderate to severe AD

DOSAGE FORM:

Tablets

STRENGTHS:

5, 10, 15, 20 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

XXXXX Rx _____ OTC

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

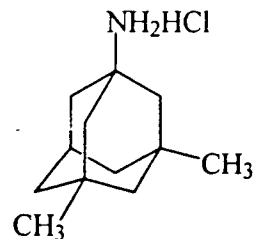
1-amino-3,5-dimethyladamantane hydrochloride

C₁₂H₂₁N.HCl

Molecular weight (215.76 USAN)

CAS # 41100-52-1 (HCl); 19982-08-2 (base)

SUPPORTING DOCUMENTS: IND 21,487 (Forest); 33,392 (Forest -



RELATED DOCUMENTS: none

REMARKS/COMMENTS: Originally developed by Merz. Co-formulated with donepezil in EU. Main body of submission poorly translated from German. Obsolete testing and measuring methods very limited process controls. Numerous minor issues have been resolved by the listed above amendments.

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. They are based on qualification of three known impurities present in toxicology batch R7206. The facilities added in 01-JUL-03 amendment have been recommended as acceptable (See the copy of EER attached). The trade name has not been established. Minor correction needed for package insert: the molecular weight in the package insert has to conform to USAN (215.76 instead — Recommend approval of NDA 21-487 18 months expiration date.

cc:

Orig. NDA 21-487

HFD-120

HFD-120/WJRzeszotarski

HFD-120/MGriffis

HFD-120/MEGuzewska

R/D Init by:MEG

151

W. Janusz Rzeszotarski, Ph.D., Chemist

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Redacted 73

pages of trade

secret and/or

confidential

commercial

information

pp. 9-81

**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
8/20/03 09:18:48 AM
CHEMIST

Maryla Guzewska
8/20/03 02:19:39 PM
CHEMIST