

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
22-525**

OTHER REVIEW(S)

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-525
APPLICANT	Forest Laboratories, Incorporated
DRUG NAME	NAMENDA XR (memantine hydrochloride)
SUBMISSION DATE	August 21, 2009
SEALD REVIEW DATE	June 17, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

21 Pages Withheld IN full Immediately After This Page as (b)(4)
Draft Labeling.

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/

DEBRA C BEITZELL
06/23/2010
SEALD comments sent to DNP on 6/17/10

LAURIE B BURKE
06/23/2010

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A single-dose oral neurotoxicity study in female rats with memantine in the presence and absence of donepezil at a maximum tolerated dose. The study should be conducted in at least 10 animals per group. Doses of memantine should range from one estimated to result in an AUC (0-24 hr) similar to that observed at steady state at the maximum recommended clinical dose of NAMENDA XR, up to a maximum tolerated dose. Two positive control groups should be included, one treated with 30 mg/kg i.p. memantine + 10 mg/kg i.p. donepezil (for comparison to the results of Creeley et al., 2008) and one treated with 3 mg/kg i.p. MK-801. Neurohistopathology should be assessed at 48 hours after dosing using standard cupric silver staining methods, and should include examination of all brain regions shown to be affected by Creeley et al. (2008) and/or in Study MEM-TX-27. Toxicokinetic analyses of memantine and donepezil should be performed for the oral and i.p. treated groups.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/

SALLY U YASUDA

06/17/2010

PMR/PMC development template

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information	
NDA # 22-525	
Proprietary Name: Namenda XR Established/Proper Name: memantine hydrochloride Dosage Form: extended release capsules Strengths: 28 mg	
Applicant: Forest Laboratories, Inc. Agent for Applicant (if applicable): Michael P. Niebo, Michael.niebo@frx.com 201-386-2046	
Date of Application: August 20, 2009 Date of Receipt: August 21, 2009 Date clock started after UN: n/a	
PDUFA Goal Date: June 21, 2009	Action Goal Date (if different): May 28, 2010
Filing Date: October 20, 2009 Date of Filing Meeting: October 9, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3	
Proposed Indication(s): treatment of moderate to severe dementia of the Alzheimer's type	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
List referenced IND Number(s): 33,392	
PDUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/> YES

<i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i> If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i> Comments:	<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES # years requested: 3</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p>

<p>1. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>			<p>X YES</p>
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
21627	MEMANTINE HYDROCHLORIDE	U-539	4-11-2015
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p>Format and Content</p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<p><input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)</p> <p>X CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)</p>	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<p>X YES</p>	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<p>X YES</p>	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<p>X YES</p> <p>X YES</p>
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<p>X YES</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible</p> <p><input type="checkbox"/> English (or translated into English)</p> <p><input type="checkbox"/> pagination</p> <p><input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<p>X YES</p>
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<p>X Not Applicable</p>
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p>Not Applicable</p>
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<p>X YES</p>
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act</i></p>	<p>X YES</p>

<p>section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p>
Pediatrics	
<p>PREA <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>Comments:</p>	<p><input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p>	<p><input checked="" type="checkbox"/> NO</p>

<p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p>Comments:</p>	
Prescription Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<p><input type="checkbox"/> Not applicable</p> <p><input checked="" type="checkbox"/> Package Insert (PI)</p> <p><input type="checkbox"/> Patient Package Insert (PPI)</p> <p><input type="checkbox"/> Instructions for Use</p> <p><input type="checkbox"/> MedGuide</p> <p><input checked="" type="checkbox"/> Carton labels</p> <p><input type="checkbox"/> Immediate container labels</p> <p><input type="checkbox"/> Diluent</p> <p><input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p>
<p>Package insert (PI) submitted in PLR format?</p> <p>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p>Comments: 3/15/10 in DARRTS</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p>
<p>REMS consulted to OSE/DRISK?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> Outer carton label</p> <p><input type="checkbox"/> Immediate container label</p> <p><input type="checkbox"/> Blister card</p> <p><input type="checkbox"/> Blister backing label</p> <p><input type="checkbox"/> Consumer Information Leaflet (CIL)</p> <p><input type="checkbox"/> Physician sample</p> <p><input type="checkbox"/> Consumer sample</p> <p><input type="checkbox"/> Other (specify)</p>
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES</p> <p>Date(s):</p> <p><input type="checkbox"/> NO</p>
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: IND 33392, NDA</p>	<p>X YES</p> <p>Date(s):</p> <p>January 7, 2008</p>
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<p>X NO</p>

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 13, 2009

NDA/BLA #: 22525

PROPRIETARY/ESTABLISHED NAMES: Namenda XR (memantine hydrochloride)

APPLICANT: Forest Labs

BACKGROUND:

This is an application for 7 mg, 14 mg, 21 mg, and 28 mg of an extended release formulation of an already approved product. The approved product is NDA 21487 Namenda immediate release 5 mg and 10mg tablets for use in moderate to severe dementia of the Alzheimer's type.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Teresa Wheelous, R. Ph.	Y
	CPMS/TL:	Robbin Nighswander	N
Cross-Discipline Team Leader (CDTL)	Ranjit Mani, M.D.		Y
Clinical	Reviewer:	Ranjit Mani, M.D	Y
	TL:	Ranjit Mani, M.D	Ranjit Mani, M.D
OSE	Reviewer:	Laurie Kelly	Y
	TL:	Melina Griffis	N

Clinical Pharmacology	Reviewer:	Veneeta Tandon	
	TL:	Raman Baweja, Ph.D.	Y
Biostatistics	Reviewer:	Jingyu Luan, Ph.d.	
	TL:	Kun Jin, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Hawver, Ph.D.	
	TL:	Lois Freed, Ph.D.	Y
Product Quality (CMC)	Reviewer:	Sherita McLamore, Ph.D.	Y
	TL:	Martha Heimann, Ph.D.	Y
Bioresearch Monitoring (DSI)	Reviewer:	Antoine El Hage	N
	TL:		
Other reviewers	OCP / PK – Dr. Huixia Zhang OCP/PK/Pharmacometrics – Hao Zhao		

OTHER ATTENDEES:

Biopharmaceutics – Sandra Suarez, Ph.D.

Lisa Mathews – Maternal Health

505(b)(2) filing issues?	X Not Applicable
Per reviewers, are all parts in English or English translation?	X YES

Electronic Submission comments	X Not Applicable
CLINICAL	X FILE
• Clinical study site(s) inspections(s) needed?	X YES
• Advisory Committee Meeting needed?	X NO
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	X Not Applicable
CLINICAL PHARMACOLOGY Comments: Sponsor should submit complete in vitro dose-dumping alcohol effect study report	<input type="checkbox"/> FILE X Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	X YES
BIostatISTICS	X FILE
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: Refer to already approved Namenda products	X FILE
PRODUCT QUALITY (CMC)	X FILE
• Categorical exclusion for environmental assessment (EA) requested?	X YES
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
• Sterile product?	X NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Russell Katz, M.D.	
GRMP Timeline Milestones: Mid-cycle meeting 1/14/10, Complete primary & secondary reviews 1/21/10, 4-21-10 PeRC, 5-0- 10 Labeling, 6-21-10 Sign off	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
X	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>X Review issues have been identified for the 74-day letter. List (optional):</p> <p>X Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
X	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22525

ORIG-1

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NAMENDA XR(MEMANTINE
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/s/

TERESA A WHEELOUS

03/23/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 30, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Melina Griffis, RPh, Team Leader
Kellie Taylor, Pharm.D., MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Namenda XR (Memantine Hydrochloride) 7 mg, 14 mg, 21 mg, and
28 mg Capsules

Application Type/Number: NDA 022525

Applicant: Forest Laboratories, Inc.

OSE RCM #: 2009-1915

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1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed container labels, carton labeling, and insert labeling for Namenda XR and identified areas of vulnerability that can lead to medication errors. We provide recommendations in Section 5 that aim at reducing the risk of medication errors with regard to the proposed product labels and labeling.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Namenda immediate release tablets are currently marketed, therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on November 10, 2009, to identify medication errors involving Namenda or memantine hydrochloride.

The MedRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” were used as search criteria for Reactions. The search criteria used for Products were active ingredients “memantine” and “memantine hydrochloride,” trade name “Namenda” and verbatim substance search “memantine%” and “namenda%.” No date limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

2.2 LABEL AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the labels and labeling submitted as part of the August 21, 2009 submissions (see Appendices A, B, C, D, E, F, G, and H). In addition, DMEPA reviewed container labels and carton labeling for all currently marketed Namenda products (see Appendix I, J, K, L, M, N, O, and P). These were reviewed so that comparisons could be made across the product line.

3 RESULTS

3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The AERS search conducted on November 10, 2009, yielded 89 cases. Of these cases, 87 were excluded from further evaluation because these cases do not describe a medication error or do not describe an error related to the label or labeling or the product specifically. The irrelevant cases pertained to the following:

- Report of an adverse drug reaction unrelated to a medication error (n=20)
- Report of an accidental exposure to medication by a child (n=2)
- Product quality complaint about a generic product making a patient feel ill (n=1)
- Report of accidental exposure that led to adverse drug reactions, but it is unclear from the report how the patient received the suspect medication (n=1)
- Wrong patient error where one patient received another patient’s medicine (n=2)
- Improper dose errors, including accidental and intentional overdoses, where labels and labeling

were not contributing factors (n=55)

- Report of a potential error which described that imprint codes on the tablet may lead to error, however, no error attributed to confusion between imprint codes has been reported (n=1)
- Wrong drug errors where possible name confusion, and not labels and labeling, may have been a contributing factor or the contributing factor(s) are undetermined (n=5). These cases were evaluated in the proprietary name review for Namenda XR (OSE Review # 2009-1914).

The remaining two cases are relevant to this review and describe improper dose errors associated with the use of Namenda (see Appendix Q for ISR numbers):

- In one case, the patient was supposed to follow titration pak dosing but instead initiated the medication at 15 mg daily and continued on this dose.
- One case was reported by a physician and noted that the patient's wife observed a medication error further described as the patient taking memantine 5 mg daily since initiation instead of following standard titration dosing. After the error was detected, the patient followed the directions on the professional sample patient starter kit which titrate patients up to a dose of 10 mg twice daily according to the physician.

Neither of the improper dose cases reported a cause of error or contributing factors.

3.2 LABEL AND LABELING

The label and labeling risk assessment findings indicate the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. It was determined that the labels and labeling need improvement in the following areas: clarification in the dosage and administration section of labeling that Namenda XR should not be crushed, divided, or chewed, more differentiation between the four available strengths of Namenda XR, and more differentiation between Namenda and Namenda XR product lines which utilize overlapping colors. Our recommendations are further explained in Section 5 below.

4 DISCUSSION

Our search of the FDA AERS database identified two cases of improper dose errors where labeling may have been a contributing factor. One case involved the Namenda titration pak and the other case involved the Namenda patient starter kit. However, neither case specifically cited the labeling as a contributing factor to the error. Review of the Namenda titration pak and patient starter kit labels identified little similarity in overall design to the proposed labels for the Namenda XR titration pack and patient starter kit. Considering the Applicant is submitting entirely new labels and labeling for Namenda XR, DMEPA reviewed the current proposed labels and labeling to ensure that patient directions are not vulnerable to confusion that can lead to medication errors.

Our review of the labels and labeling identified the need for more visual differentiation within the Namenda XR product line as well as between the Namenda and Namenda XR product line in order to avoid selection errors. Additionally, we identified the need for clarification in the dosage and administration section of the insert labeling in order to avoid improper administration errors. We will address these in our recommendations in Section 5 below.

5 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container labels and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 5.1 Comments to the Division. We request the recommendations for the carton labeling and

container label in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

5.1 COMMENTS TO THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Dosage and Administration Subsection

In order to help minimize the risk of administration errors, we recommend including the statement “Namenda XR should be swallowed whole and should not be divided, chewed, or crushed.”

B. FULL PRESCRIBING INFORMATION

1. Dosage and Administration Subsection

See Comment A (1) above.

5.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENTS FOR LABELS AND LABELING

1. In accordance with 21 CFR 201.10(g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. The proprietary name as presented incorporates the use of a (b) (4) for the “XR” portion. The (b) (4) used for the “XR” portion mimics the (b) (4) that is used in the graphic and is not well contrasted with its background, which diminishes its prominence. The “XR” in the proposed presentation can be overlooked and the Namenda XR may be mistakenly dispensed as namenda. Revise all labels and labeling so that the coloring of the “XR” portion is uniform with the rest of the proprietary name.
3. As currently presented, the (b) (4) color used to differentiate the 14 mg strength is the same (b) (4) used in the proprietary name as well as the (b) (4) utilized for Namenda 10 mg strength. In addition, the (b) (4) color used to designate the 28 mg strength is similar to the (b) (4) color of the trade dress and Namenda 5 mg strength. The overlapping color schemes among these products minimize the strength differentiation among the available product strengths of Namenda and Namenda XR. Utilize a unique color for each of these strengths that is not one of the colors already used to differentiate other strengths, taking into consideration the entire Namenda product line. These colors should be carried through to all labels and labeling for the Namenda XR product line, including the Titration Pack and the Patient Starter Kit.
4. We recognize that the 30 count and 90 count bottles are unit-of-use for this product.

Please ensure these bottles utilize child-resistant closures to comply with the Poison Prevention Packaging Act of 1970.

B. RETAIL CONTAINER LABELS FOR 30 AND 90 COUNT BOTTLES (7 mg, 14 mg, 21 mg, and 28 mg)

1. Since the Namenda XR product line uses the same layout and background, we are concerned that selection errors may occur if the presentation of strength is not prominent and well differentiated within the Namenda XR product line. Consider enlarging the color boxing on the principle display panel similar to that utilized in the strength presentation of your Namenda retail container labels in order to more adequately differentiate between the available strengths.
2. As currently presented, the (b) (4) is located directly beneath the strength presentation and may be difficult to find on the label. Move the (b) (4) to the upper right hand corner so it is more easily identified.

C. RETAIL UNIT DOSE CARTON LABELING (7 mg, 14 mg, 21 mg, and 28 mg)

1. See comment B(1) and B(2) above.
2. Remove the (b) (4) on the back panel of the carton. (b) (4) is typically used to highlight and bring prominence to important information. As currently presented, the (b) (4) is used to highlight manufacturer information. In addition, the (b) (4) color is the same as that used to designate the 14 mg strength. Therefore, as currently proposed, the (b) (4)ing is inappropriately applied.
3. Add the strength designation to the back panel of the carton to improve identification of the strength.

D. RETAIL UNIT DOSE BLISTER LABELS (7 mg, 14 mg, 21 mg, and 28 mg)

As currently presented, the differentiation between the strengths is minimal. We acknowledge your use of (b) (4) in your strength presentation; however, we recommend incorporating the use of color or other means to add more visual differentiation between the four available strengths.

E. RETAIL TITRATION PACK

The highlighting of the weeks should utilize the same colors as those used for strength differentiation to maintain consistency and help patients as they transition from the titration pack to retail bottles.

F. PROFESSIONAL SAMPLE UNIT DOSE CARTON LABELING (7 mg, 14 mg, 21 mg, and 28 mg)

1. See comment B(1) and B(2) above.
2. See comment C(2) and C(3) above.
3. Ensure a lot number and expiration date is included on the labeling, preferably not on the

principle display panel to minimize crowding.

G. PROFESSIONAL SAMPLE UNIT DOSE BLISTER LABELS (7 mg, 14 mg, 21 mg, and 28 mg)

1. As currently presented, the strength presentation is not adequately prominent. Relocate the strength presentation box directly beneath the presentation of the proprietary name and the established name.
2. The prominence of the manufacturing statement should be minimized so that the proprietary name, established name, and strength presentation are the most prominent information on the label.
3. Ensure a lot number is included on the label.

H. PROFESSIONAL SAMPLE PATIENT STARTER KIT

1. Delete the term (b) (4) from professional samples in accordance with 64 FR 67720.
2. As there is no difference between the Kit and the Pack configurations, there is no need to differentiate the professional sample from the trade package with terminology other than “Professional Sample – Not for Sale”. Delete the term (b) (4) from the package and change the name to “Titration Pack”.
3. See comment E above.
4. See comment F(3) above.

20 Pages withheld in full immediately after this page as (b)(4) Draft Labeling.

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/

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03/30/2010

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03/30/2010

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