CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206439Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206439	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Namzaric (proposed tradename) Established/Proper Name: memantine HCL extended release & donepezil Dosage Form: Capsule Strengths: 14/10 mg and 28/10 mg		
Applicant: Forest Laboratories Inc.		
Date of Receipt: February 26, 2014		
PDUFA Goal Date: December 26, 2014	Action Goal Date (if different): December 10, 2014	
RPM: Teresa Wheelous		
Proposed Indication(s): Alzheimer's Disease		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 20-690 Aricept (donepezil)	FDA previous findings of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Bioequivalence of the FDC to the individual components (Namenda XR and Aricept) and serves as the bridge between the proposed new drug product and the listed drug, Aricept.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO X

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Aricept	20-690	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A X YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO X

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO X
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO X
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides a fixed dose combination formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):
There is no unexpired exclusivity for this NDA product.

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

X 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

In accordance with the Federal Food Drug and Cosmetic Act (FDCA) and 21 C.F.R. §314.50 (i)(1)(i), the following "Paragraph I Certification" is hereby provided for our Section 505(b)(2) New Drug Application for memantine HCI extended release and donepezil HCI fixed dose combination

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

TERESA A WHEELOUS
12/23/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 206439

Application Type: New NDA

Name of Drug/Dosage Form: TRADENAME (memantine hydrochloride extended release and donepezil hydrochloride) capsules 14mg /10 mg and 28 mg/10 mg

Applicant: Forest Laboratories, Inc.

Receipt Date: February 26, 2014

Goal Date: December 26, 2014

1. Regulatory History and Applicant's Main Proposals

The sponsor of this new fixed dose combination product, is also the originator for one of the two approved product components, memantine HCl extended release, NDA 22525. The other ingredient, donepezil HCl, is referenced making this a 505b2 application. The memantine HCl extended release product labeling received a SEALD review, and is the basis of the sponsor's fixed dose product labeling.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 30, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *aligned left*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: ***DBL check to see if correct***

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *2.1 "G" (Guidelines) needs capitalized; 7.2 "O" (Other) needs capitalized*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: ***Need to check***

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *TOC reflects omission as instructed, 8.2 is omitted*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *In 8.6, 8.7 and 12.3, cross reference for Dosage and Administration should state 2.2, not 2.*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

    Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

    Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

TERESA A WHEELOUS
12/23/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 16, 2014
To:	Billy Dunn, M.D. Acting Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Robin Duer, MBA, BSN, RN Acting Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Mathilda Fienkeng, PharmD, Team Leader **Office of Prescription Drug Promotion (OPDP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline M. Moukhtara, RN, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	NAMZARIC (memantine HCl and donepezil HCl)
Dosage Form and Route:	extended-release capsules for oral use
Application Type/Number:	NDA 206,439
Applicant:	Forest Research Institute, Inc.

1 INTRODUCTION

On February 26, 2014, Forest Research submitted for the Agency's review an Original New Drug Application for NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on May 9, 2014, for DMPP and OPDP to review the Applicant's proposed PPI for NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules.

2 MATERIAL REVIEWED

- Draft NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules PPI received on February 26, 2014, and received by DMPP on December 4, 2014.
- Draft NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules PPI received on February 26, 2014, and received by OPDP on December 4, 2014.
- Draft NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules Prescribing Information (PI) received on February 26, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on December 4, 2014.
- Draft NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules Prescribing Information (PI) received on February 26, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on December 4, 2014.
- Approved Aricept (donepezil HCl) comparator labeling dated September 6, 2013.
- Approved Namenda (memantine HCl) comparator labeling dated October 24, 2013.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/16/2014

ALINE M MOUKHTARA
12/16/2014

ROBIN E DUER
12/16/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 16, 2014

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Teresa Wheelous, Senior Regulatory Project Manager
Division of Neurology Products (DNP)

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP draft full Prescribing Information (PI) and Container/Carton Label comments for NAMZARIC (memantine HCl and donepezil HCl) extended-release capsules, for oral use

NDA: 206439

On May 9, 2014, DNP consulted OPDP to review the draft package insert (PI), patient labeling (PPI), and carton and container labeling for the original NDA submission for Namzaric (memantine HCl and donepezil HCl) extended-release capsules.

PI and PPI:
OPDP reviewed the draft substantially complete version of the PI titled "Sponsor 060214 Namzaric label" obtained on December 11, 2014 from the DNP Sharepoint. OPDP's comments on the draft PI are provided below.

The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the draft PPI under a separate cover on December 16, 2014.

Carton and Container Labeling Comment:
OPDP reviewed the December 8, 2014, carton and container labeling (attached), and has the following comment:

- While the font size used for the established name may be half the size of the trade, OPDP is concerned that the prominence and disparate font styles of the trade name and established names in the presentations do not meet the regulatory requirements. Therefore, we recommend revising the proposed established name on the carton labeling to be in accordance with 21 CFR 201.10 (g)(2) which states that, "[t]he 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."

If you have any questions, please contact Aline Moukhtara (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
12/16/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 10, 2014

TO: William Dunn, M.D.
Director
Division of Neurology Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 206439, Memantine ER/Donepezil Capsules sponsored by Forest Laboratories, Inc., USA

At the request of the Division of Neurology Products (DNP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the analytical portion of the following bioequivalence study:

Study #: MDX-PK-104
Study Title: "A single center, randomized, open label, two way crossover, single dose study evaluating the bioequivalence of memantine HCl fixed dose combination (MDX-8704) versus co-administered Namenda XR™ and Aricept® in healthy subjects"

The analytical site inspection for the above study was conducted by Iram Hassan (ORA, NYK-DO) and Gajendiran Mahadevan, Ph.D. (OSI) between August 11 and 15, 2014 at **Forest Research Institute, Inc., Farmingdale, NY.** The inspection included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's staff and management.

At the conclusion of the inspection, Form FDA 483 was issued (**Attachment-1**). The firm responded to Form DFA 483 on September 8, 2014 (**Attachment-2**). The Form FDA 483, the firm's response to Form FDA 483, and our evaluation follow.

1) **Failure to accurately report all method validation experiments conducted for measurements of memantine and donepezil in plasma. Specifically, prestudy method validation run IDs #3, 4, 5, 11, and 12 were assigned Watson Run ID numbers, but not reported in the summary of analytical runs (Table 31 of method validation report PRD-RPT-BDM-00608).**

In the response to the observation, the firm noted that these runs were preparatory evaluations of standards and QC samples captured under the same Watson LIMS folder as the validation, but not part of the method validation runs themselves. However, the firm submitted a revised and updated validation report including all analytical runs associated with the validation of method_354, including runs 3, 4, 5, 11, and 12. As a corrective action, the firm revised SOP PRD-SOP-BDM-00014 to require all runs conducted under the Watson LIMS method validation folder to be reported in the validation report under "Summary of Analytical Runs."

DBEGLPC Assessment:

In the opinion this reviewer, the firm's corrective actions are acceptable. This observation does not affect the data integrity.

2) **Failure to adequately demonstrate inter-run (inter-batch) accuracy and precision of the memantine/donepezil analytical method at the lower limit of quantitation (LLOQ). Specifically, the accuracy and precision at the LLOQ (0.5/0.5 ng/mL) was demonstrated only once on April 15, 2013 (Run ID #13).**

In the response to the observation, the firm stated that they demonstrated inter-run accuracy and precision of memantine and donepezil (0.5/0.5 ng/mL) at the LLOQ during method validation in accordance with the 2001 Guidance for Industry: Bioanalytical Method Validation. This demonstration was done with calibration standards at the LLOQ and not QC samples independent of the calibration curve.

The firm failed to fully validate the analytical method and the accuracy and precision of memantine and donepezil concentrations at the LLOQ. However, the low, mid, and high QCs used during sample analysis performed with acceptable accuracy and precision (e.g., 98.44%/95.31%, 98.44%/98.44%, and 96.88%/96.88% of the low, mid, and high QCs for memantine/donepezil, respectively passed during sample analysis) to determine memantine and donepezil concentrations at or near the LLOQ. Thus, this observation does not affect the data integrity.

Recommendations:

Following the inspection and review of the firm's response, the data were found to be reliable. Thus, this DBGLPC reviewer recommends that the data from study MDX-PK-104 be accepted for Agency review.

Gajendiran Mahadevan, Ph.D.
GLP Branch, DBGLPC, OSI

Final Classification:

VAI: Forest Research Institute, Inc., Farmingdale, NY
FEI: 1000521508

CC:
OSI/DBGLPC/Taylor/Bonapace/Dasgupta/Mahadevan/Dejernett/Fenty-Stewart/Nkha/Johnson
OSI/DBGLPC/Haidar/Skelly/Choi

CDER/OND/DNP/Dunn/Wheelous

ORA/NYK-DO/Frankovic/Hassan

Draft: GM 09/17/2014
Edit: AD 11/7/2014; CB 11/7/2014

OSI File: BE6702; O:\BE\EIRCOVER\206439.bio.me

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/Forest Novum Pharmaceutical, Las Vegas, NV/NDA 206439_Memantine

FACTS: 8766717

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/s/

GAJENDIRAN MAHADEVAN
11/14/2014

ARINDAM DASGUPTA
11/14/2014

CHARLES R BONAPACE
11/14/2014

WILLIAM H TAYLOR
11/14/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 30, 2014
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 206439
Product Name and Strength:	Namzaric (memantine and donepezil) extended-release capsules 14 mg/10 mg, 28mg/10 mg
Product Type:	Multi-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Forest Research Institute, Inc.
Submission Date:	February 26, 2014
OSE RCM #:	2014-486
DMEPA Primary Reviewer:	Justine Harris, RPh
DMEPA Acting Team Leader:	Tingting Gao, PharmD

1 REASON FOR REVIEW

This review responds to a request from DNP for DMEPA to review the proposed container labels, Prescribing Information (PI), and patient instructions for Namzaric (memantine/donepezil) for areas of vulnerability that could lead to medication errors.

(b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B - N/A
Previous DMEPA Reviews	C -N/A
Human Factors Study	D - N/A
ISMP Newsletters	E - N/A
Other	F - N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Memantine extended-release (Namenda XR) and donepezil (Aricept) are currently marketed as single ingredient products. Namzaric is a combination product containing these two active ingredients. Therefore, we compared the current marketed label and labeling of Namenda XR[1] to the proposed labels and labeling for Namzaric and determined that the proposed labels and

[1] Namenda XR container labels. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=710f523f-0158-4639-8ce7-57598247d48c

labeling for Namzaric are well differentiated from the currently marketed Namenda XR label and labeling.

Our evaluation determined the proposed label and labeling for Namzaric could be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Specifically, both the container label and the PI lack unit of measure (mg) following the memantine component of this combination product. (b) (4) In addition, in the Patient Package Insert, instructions should be included for the patient regarding how to avoid potential (b) (4) of the capsules. Lastly, since there is one recommended dose (i.e., once daily), this recommended dose should be added to the container label.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the proposed labels and labeling can be improved to increase the readability and prominence of important information, increase clarity, and add information necessary for the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information

1. We recommend adding a unit of measure immediately following all numbers, as appropriate. For example, in Section 2.2, Recommended Dosing, revise "TRADENAME (b) (4)" to read "TRADENAME 28 mg/10 mg." Include the unit of measure for both drugs of this combination product throughout the labeling, i.e. 14 mg/10 mg, 28 mg/10 mg.

2. (b) (4)

B. Patient Package Insert

3. In the section *"How should TRADENAME be stored?"* include instructions on how to prevent potential (b) (4), such as, "(b) (4)"

4.2 COMMENTS FOR FOREST RESEARCH INSTITUTE, INC.

A. Container Labels

1. Replace “Tradename” with the conditionally acceptable name “Namzaric.”

2. Include the units for both drug components in the product strength statement. Revise to state ‘14 mg/10 mg’ and ’28 mg/10 mg’.

3. Since there is one recommended dose (i.e., once daily), include the recommended dose on the label in accordance with 21 CFR 201.55. For example:
   Usual dosage: Take 1 capsule once daily, see package insert for full Prescribing Information”

4. Relocate the statement “ (b) (4) ” above the statement “Dispense in tight, light resistant container...” so that these two related statements are near each other. In other words, switch the places of (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Namzaric that Forest Research Institute, Inc. submitted on February 27, 2014

Table 2. Relevant Product Information for Namzaric	
Active Ingredient	memantine HCl /donepezil HCl
Indication	Treatment of moderate to severe dementia of the Alzheimer's type
Route of Administration	oral
Dosage Form	extended-release capsules
Strength	○ 14 mg memantine/10 mg donepezil HCl ○ 28 mg memantine/10 mg donepezil HCl
Dose and Frequency	The usual dosage is 28 mg/10 mg once daily. The maximum daily dose is 28 mg/10 mg. For patients with severe renal impairment a dose of 14 mg/10 mg once daily is recommended.
How Supplied	○ The 14 mg/10 mg capsule product will be available in 30-count and 90 count bottles ○ The 28 mg/10 mg capsule product will be available in 30-count and 90-count bottles
Storage	This product should be stored at 25° C (77°F); excursions permitted between 15°C - 30° C (59°F - 86°F). (b) (4)
Container Closure	HDPE bottles with (b) (4) caps.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Namzaric labels and labeling submitted by Forest Research Institute, Inc.

- Container labels (submitted February 26, 2014, Appendix G.2)
- Full Prescribing Information (submitted May 29, 2014, no image)
- Patient Information (submitted May 29, 2014, no image)

G.2 Label and Labeling Images

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE HARRIS
09/30/2014

TINGTING N GAO
10/01/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 24, 2014

TO: William H. Dunn, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation I

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Recommendation to accept clinical data from NDA 206-439, Memantine ER/Donepezil capsules sponsored by Forest Laboratories, Inc., N.J., without clinical site inspection

On April 23, 2014, the Division of Neurology Products (DNP) requested inspections of the clinical and analytical sites for the following study conducted from April 26, 2013 to June 25, 2013:

Study number: **MDX-PK-104**
Study Title: "A single-center, randomized, open-label, two-way crossover, single-dose study evaluating the bioequivalence of memantine HCl extended release and donepezil HCl fixed-dose combination (MDX-8704) versus co-administered Namenda XR™ and Aricept® in healthy subjects"

Clinical site: PPD Phase I Clinic
7551 Metro Center Drive, Suite 200
Austin, TX 78744

OSI declines to inspect PPD Phase I Clinic, Austin, TX **for the reasons presented below:**

OSI inspected the above clinical site four times during the last two years for the following applications:

1. NDA (b) (4) for clinical portions of a bioequivalence study conducted from (b) (4)
2. NDA (b) (4) for clinical portions of relative bioavailability studies conducted from (b) (4)
3. NDA (b) (4) for clinical portions of a pharmacokinetic study om (b) (4)
4. NDA (b) (4) for clinical portions of bioequivalence studies conducted from (b) (4)

The audits included a thorough review of study records, study protocol compliance, informed consent documents of human subjects, institutional review board, and case report forms, examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff. The inspections during and since the conduct of study MDX-PK-104 did not find significant changes in operations at PPD. Therefore, the conduct of these studies was representative of the conduct of study MDX-PK-104. **No significant adverse observations were identified during the previous inspections. The previous inspectional outcomes provide assurance that the site conducted study MDX-PK-104 without significant irregularities.**

Considering the consistent inspectional history of the clinical site and our finite resources for conducting inspections, this reviewer concludes that **the data from the clinical portion of study MDX-PK-104 are acceptable for further Agency review without an onsite inspection at PPD Phase I Clinic, Austin, TX.**

Please note that inspection of the analytical site will be conducted as requested.

Should you have questions or wish to have further discussion with our staff, please feel free to contact Ms. Shila Nkah, OSI Project Manager, at 301-796-8347.

Jyoti B. Patel, Ph.D.
Pharmacologist
BE Branch, DBGLPC, OSI

DARRTS cc:
OSI/Kassim
OSI/DBGLPC/Taylor/Dejernett/Nkah/Fenty-Stewart/Johnson
OSI/DBGLPC/GLPB/Bonapace/Dasgupta
OSI/DBGLPC/BB/Patel/Choi/Haidar/Skelly
CDER/OND/ODEI/DNP/Eradiri/Wheelous/Dunn

Email cc:
ORADALBIMO@fda.hhs.gov/ Martinez/Bias (BIMO)/Turcovski (DIB)

Draft: JBP 07/21/2014
Edit: MFS 7/22/2014, WHT 7/22/2014

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/PPD Phase I Clinic, Austin, TX

OSI file #: BE 6702; file name: 206439.for.mem-don.CANCL.doc
FACTS: 8766717

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/s/

JYOTI B PATEL
07/24/2014

SAM H HAIDAR
07/24/2014

WILLIAM H TAYLOR
07/25/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 24, 2014

TO: Director, Investigations Branch
Dallas District Office
4040 N. Central Expressway, Suite 300
Dallas, TX 75204

Director, Investigations Branch
New York District Office
158-15 Liberty Avenue
Jamaica, NY 11433

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER PDUFA NDA, High Priority Data Validation Inspection,** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 206-439
DRUG: Memantine ER/Donepezil capsules
SPONSOR: Forest Laboratories, Inc., Jersey City, NJ

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence (BE) study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to September 06, 2014.**

Do not reveal information about the applicant/sponsor, application number, study to be inspected, drug names, or the study investigator to the sites prior to the start of the

inspection. The sites will receive this information during the inspection opening meeting.

The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the clinical inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.

Study number: **MDX-PK-104**
Study Title: "A single-center, randomized, open-label, two-way crossover, single-dose study evaluating the bioequivalence of memantine HCl extended release and donepezil HCl fixed-dose combination (MDX-8704) versus co-administered Namenda XR™ and Aricept® in healthy subjects"

Clinical Site: PPD Phase I Clinic
7551 Metro Center Drive, Suite 200
Austin, TX 78744
TEL: (512)447-2985

Investigator: Matthew M. Medlock, M.D.

SECTION A – RESERVE SAMPLES

Because this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., investigator site) is responsible for randomly selecting and retaining reserve samples from each shipment of drug product provided by the sponsor for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf).

During the clinical site inspection, please:

☐ Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.

☐ If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant/sponsor, manufacturer, and packager. Additionally, verify that the site notified the applicant/sponsor, in writing, of the storage location of the reserve samples.

☐ Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.

☐ Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

☐ Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.

☐ Compare the study report in the NDA submission to the original documents at the site.

☐ Check for under-reporting of adverse events (AEs).

☐ Check for evidence of inaccuracy in the electronic data capture system.

☐ Check reports for the subjects audited.

- o Number of subject records reviewed during the inspection:_____
- o Number of subjects screened at the site:_____
- o Number of subjects enrolled at the site:_____
- o Number of subjects completing the study:_____

☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

☐ Confirm that site personnel followed SOPs during study conduct.

☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.

☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

☐ Other comments:

_____

_____

_____

SECTION C – ANALYTICAL DATA AUDIT

Analytical Site: **Forest Research Institute, Inc.**
Bioanalytical Department
220 Sea Lane
Farmingdale, NY
TEL: (631)501-5300; (b) (4)
FAX: (631)501-5400

Investigator: Irina Konstantinovskaya

Methodology: LC-MS/MS

During the analytical site inspection, please:

☐ Examine all pertinent items related to the analytical method used for the measurement of memantine and donepezil concentrations in human plasma.

☐ Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.

☐ Determine if the site employed a validated analytical method to analyze the subject samples.

☐ Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.

☐ Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.

☐ Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.

☐ Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.

☐ Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.

☐ Examine correspondence files between the analytical site and the Applicant/sponsor for their content.

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and

also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible. Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.

DBGLPC POC: Jyoti Patel, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-301-796-4617
Fax: 1-301-847-8748
E-mail: jyoti.patel@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Choi/Patel/Dejernett
OSI/DBGLPC/Bonapace/Mada
CDER/OND/ODEI/DNP/Eradiri/Wheelous/

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ORANYKBIMO@fda.hhs.gov/ Sacco/Hansen/Matthias (BIMO)/Daurio (DIB)
Draft: JBP 04/23/2014
Edit: YMC 04/23/2014; SHH 04/24/2014

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ Forest Research Institute, Inc., NJ/Clinical Sites/PPD Phase I Clinic, Austin, TX

OSI file #: BE 6702; assignment file name: bio206439
FACTS: 8766717

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

/s/

JYOTI B PATEL
04/24/2014

SAM H HAIDAR
04/24/2014